BAHIANA
ESCOLA DE MEDICINA E SAÚDE PÚBLICA

Programa de Pós-Graduação em Medicina e Saúde Humana

Valor Prognóstico de Parâmetros Anatômicos e Funcionais Cardíacos no Cenário de Prevenção Cardiovascular Primária

Tese de Doutorado

Anderson da Costa Armstrong

Salvador-Bahia
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Tese apresentada ao curso de Pós-graduação em Medicina e Saúde Humana da Escola Bahiana de Medicina e Saúde Pública para obtenção do título de Doutor em Medicina

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Dedicatória

Dedico este trabalho a meus pais Vera e Marizon Armstrong, minha esposa Dinani Armstrong, meus filhos Anderson e Arthur Armstrong, meus demais familiares e amigos. Nada seria possível tampouco valeria a pena sem vocês ao meu lado.

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“In the End, we will remember not the words of our enemies, but the silence of our friends.”

“No final, nós nos lembraremos não das palavras dos nossos inimigos, mas do silêncio dos nossos amigos.”

Martin Luther King, Jr.

Resumo

INTRODUÇÃO As doenças cardiovasculares são importantes causas de morbidade e mortalidade. Estratégias de prevenção cardiovascular primária utilizando dados de ecocardiografia são potencialmente úteis à prática clínica, porém carecem de avaliação metodológica rigorosa. OBJETIVO O objetivo primário é testar a hipótese de que hipertrofia ventricular esquerda e remodelamento atrial esquerdo, mensurados em adultos jovens, são preditores de risco cardiovascular e oferecem valor incremental sobre os métodos tradicionais. Nos objetivos secundários, investigamos a relação das medidas de remodelamento com disfunção ventricular sistólica e diastólica, os determinantes longitudinais de remodelamento atrial e o perfil de reprodutibilidade das medidas ecocardiográficas de massa ventricular esquerda e dimensão atrial esquerda. MÉTODOS Esta tese foi realizada como fruto da parceria científica entre a Escola Bahiana de Medicina e Saúde Pública e o Hospital Johns Hopkins. Os dados foram obtidos a partir de grandes estudos de coorte prospectivos e de revisão sistemática da literatura. O remodelamento cardíaco foi avaliado a partir de medidas de massa ventricular esquerda, classificação de hipertrofia ventricular, medida linear anteroposterior do átrio esquerdo e da área atrial esquerda. Em relação ao objetivo primário, o valor incremental foi avaliado por predição independente, poder discriminatório, calibração e reclassificação de risco pelo *net reclassification improvement*. Em relação aos objetivos secundários, foi investigada a associação longitudinal de remodelamento cardíaco e risco cardiovascular com função ventricular através da fração de ejeção do ventrículo esquerdo e de um novo índice de relaxamento cardíaco. Determinantes do remodelamento atrial esquerdo ao longo de 20 anos foram avaliados em modelos multivariados. Parâmetros de precisão e acurácia das medidas ecocardiográficas foram testados. RESULTADOS Oito artigos científicos compõem a tese. Como resultado do objetivo primário, hipertrofia ventricular demonstrou valor incremental para risco cardiovascular por todos os métodos estatísticos avaliados, mas dimensão atrial falhou em reclassificar o risco da população estudada. Em relação aos objetivos secundários, hipertrofia ventricular relaciona-se com função sistólica após 20 anos e disfunção diastólica é preditora de eventos cardiovasculares. Pressão arterial e obesidade são os principais determinantes do remodelamento atrial em 20 anos. As medidas ecocardiográficas de dimensões cardíacas mostram robusto perfil de reprodutibilidade. CONCLUSÃO A utilização racional da medida de hipertrofia ventricular pode auxiliar na avaliação do risco cardiovascular primário de populações jovens, mas o valor da dimensão atrial na reclassificação de risco é incerto. Medidas ecocardiográficas de hipertrofia ventricular e remodelamento atrial esquerdos podem estar alterados em fases subclínicas das doenças cardiovasculares.

Palavras-chave: Remodelação ventricular esquerda. Remodelação atrial esquerda. Prevenção primária. Doenças cardiovasculares.

Abstract

BACKGROUND Cardiovascular diseases are major causes of morbidity and mortality. Strategies for primary cardiovascular prevention using echocardiography data are potentially useful in clinical practice, but lack rigorous methodological assessment. OBJECTIVE The primary objective is to test the hypothesis that left ventricular hypertrophy and left atrial remodeling, measured in young adults, are predictors of cardiovascular disease and provide incremental value over traditional methods for cardiovascular risk stratification. As secondary analysis, we investigate the relationship of measures of ventricular remodeling with cardiac dysfunction, and longitudinal determinants of atrial remodeling. In addition we also study the reproducibility profile of echocardiographic measurements of left ventricular mass and left atrial dimension. METHODS This thesis is a result of the scientific collaboration between Escola Bahiana de Medicina e Saude Publica and the Johns Hopkins Hospital. Data were obtained from large prospective cohort studies. Cardiac remodeling was assessed from measurements of left ventricular mass, left ventricular hypertrophy, anteroposterior left atrium diameter, and left atrial area. For the primary objective, we assessed independent prediction ability, discrimination, calibration, and the net reclassification improvement. For the secondary endpoints, we used left ventricular ejection fraction and a novel strain relaxation index to assess left ventricular systolic and diastolic function, respectively. Determinants of left atrial remodeling over 20 years were evaluated in multivariate models. Parameters of precision and accuracy of echocardiographic measurements were tested. RESULTS This thesis reports eight manuscripts. As a result of the primary endpoint, ventricular hypertrophy demonstrated incremental value for cardiovascular risk, but atrial dimension failed to reclassify the risk of the cohort. Regarding the secondary endpoints, ventricular hypertrophy relates to systolic dysfunction over 20 years, and diastolic dysfunction is a long-term predictor of cardiovascular events. Blood pressure and obesity are major determinants of atrial remodeling over 20 years. Echocardiographic measurements of cardiac dimensions show robust reproducibility profile. CONCLUSION A judicious use of information on left ventricular hypertrophy may assist the evaluation of primary cardiovascular risk in youth, but the value of atrial dimension in risk reclassification is uncertain. Echocardiographic measures of left ventricular hypertrophy and left atrial remodeling may be altered in subclinical stages of cardiovascular diseases.

Keywords: Left ventricular remodeling. Left atrial remodeling. Primary prevention. Cardiovascular diseases.

Lista de abreviaturas

ACC - *American College of Cardiology*

AHA - *American Heart Association*

ASC - área de superfície corpórea

ASE - *American Society of Echocardiography*

AUC - *areas under the receiver-operating characteristic curves*

CARDIA - *Coronary Artery Risk Development in Young Adults*

EUA - Estados Unidos da América

HR - *hazard ratio*

IMC - índice de massa corporal

MESA - *Multi-Ethnic Study of Atherosclerosis*

SUMÁRIO

1. Introdução

Doenças cardiovasculares são a causa número um de óbitos no mundo e fazem-se responsáveis por altos custos aos sistemas de saúde, tendo em vista a gravidade e a cronicidade normalmente relacionadas a tal tipo de afecção.[1,2] A melhor forma de combate à elevada morbidade das doenças cardiovasculares encontra-se na prevenção primária de eventos, buscando-se identificar – de forma precoce – indivíduos em risco cardiovascular elevado.[3] Diversos escores de risco e marcadores biológicos têm sido desenvolvidos no sentido de aprimorar a classificação de risco cardiovascular na prática clínica. No entanto, na publicação de novos marcadores de risco, nota-se de forma recorrente a ausência de rigidez metodológica científica que embase as conclusões defendidas por diversos autores.[4]

A falta de rigidez metodológica principalmente relacionada aos marcadores precoces de doença cardiovascular tem promovido conhecimento parcial acerca do papel de vários desses novos marcadores. Isso muitas vezes leva à superestimação do valor real que tais técnicas poderiam agregar à prática clínica.[4] Um otimismo exagerado para com novas técnicas pode aumentar os custos da assistência em saúde, sem necessariamente agregar valor assistencial. As inconsistências recorrentes nas publicações científicas de novos marcadores de risco cardiovascular levaram a *American Heart Association* (AHA) a emitir uma declaração científica regulamentando as normas para investigação e publicação dessas, baseando-se um uma rigorosa metodologia científica.[5] Em nossa tese, propusemo-nos a adotar os modelos rígidos de análise científica recomendados a fim de contribuirmos ao máximo para que parâmetros ecocardiográficos de remodelamento cardíaco subclínico possam vir a ser adequadamente utilizados na prática clinica diária.

Apesar das manifestações clínicas de doenças cardiovasculares usualmente se apresentarem em adultos de meia-idade, fases subclínicas se fazem presente em momentos precoces da vida. A correta detecção de risco cardiovascular em jovens adultos pode proporcionar a identificação adequada de indivíduos em risco elevado, os quais podem vir a beneficiar-se de intervenções precoces.[3] Entretanto, a detecção de risco cardiovascular nos adultos jovens é extremamente desafiadora. Ferramentas úteis em adultos com mais de 40 anos,

como o Escore de Risco Cardiovascular de Framingham,[6] não mostram desempenho satisfatório para estratificar jovens em risco de longo prazo para doenças cardiovasculares. [7]

A imagem cardiovascular possibilita a medida não invasiva do remodelamento cardíaco. Dentre as técnicas de imagem cardiovascular, a ecocardiografia caracteriza-se como método de baixo custo e de risco virtualmente nulo, com elevadas disponibilidade e versatilidade. A técnica ecocardiográfica do modo-M é bem estabelecida na literatura, tendo sido aplicada desde a década de 1970 para estimativa de massa ventricular esquerda e dimensão atrial esquerda. [8-10] Ambos massa ventricular esquerda e dimensão atrial esquerda têm demonstrado associação com risco cardiovascular,[11-13] mas ainda sem demonstrar benefício após uma análise metodológica rígida focada na população de jovens adultos. O objetivo principal do nosso trabalho foi preencher essas lacunas de conhecimento. Com isso, buscamos investigar o valor incremental que tais medidas ecocardiográficas poderiam agregar aos fatores de risco tradicionalmente utilizados na prática clínica.

O estudo CARDIA foi criado para investigar fatores de risco cardiovascular e o desenvolvimento de doenças cardiovasculares subclínicas, através do seguimento prospectivo de uma grande coorte bi-racial de jovens inicialmente saudáveis.[14] Os dois primeiros artigos que compõem a tese derivam do estudo CARDIA, os quais objetivaram responder as dúvidas existentes sobre o real papel da hipertrofia ventricular esquerda e da dimensão atrial esquerda no risco cardiovascular em idade adulta. O remodelamento cardíaco está relacionado à disfunção cardíaca sistólica e diastólica. As alterações cardíacas estruturais que caracterizam o processo de remodelamento costumam ser mensuradas através da dimensão das câmaras cardíacas. Dentre as diversas câmaras cardíacas, destacam-se as medidas de remodelamento das câmaras esquerdas, as quais são mais diretamente responsáveis pela circulação sistêmica. A hipertrofia ventricular esquerda, determinada através da medida da massa do ventrículo esquerdo, está envolvida como causa e consequência nos processos de remodelamento cardíaco que levam à disfunção ventricular tanto sistólica quanto diastólica. O átrio esquerdo, por sua vez, possui íntima relação com as pressões de enchimento do ventrículo esquerdo, as quais se refletem elevadas quando estabelecidos os diferentes graus de disfunção diastólica. Tanto mudanças na massa ventricular esquerda quanto na dimensão atrial esquerda podem estar presentes antes dos sintomas clínicos

de insuficiência cardíaca, mostrando-se potencialmente úteis na identificação precoce dessa afecção.[8,15,16]

Como objetivos adicionais secundários, utilizamos dados do estudo CARDIA para investigar em um outro artigo se a medida da massa ventricular esquerda aferida nos jovens guardaria relação com a disfunção ventricular sistólica de longo prazo. Analisando os dados longitudinais dessa coorte, pudemos também investigar a influência dos fatores de risco cardiovascular modificáveis sobre o remodelamento atrial ao longo de 20 anos de seguimento, o que deu origem a uma nova publicação científica. Olhando exclusivamente os dados sobre controle de qualidade e perfil de reprodutibilidade das medidas ecocardiográficas do estudo CARDIA em sua avaliação ecocardiográfica no ano 25, preparamos um outro manuscrito que demonstra importantes aspectos relativos à qualidade das medidas ecocardiográficas em grandes populações.

O *Multi-Ethnic Study of Atherosclerosis* (MESA)[17] foi outro grande estudo de coorte prospectivo financiado pelo *National Heart, Lung, and Blood Institute* nos EUA. A população do estudo MESA, de idade mais avançada em comparação à do estudo CARDIA, é mais afeita a apresentar alterações cardiovasculares subclínicas. A disfunção ventricular diastólica esquerda, por exemplo, é mais presente em idades mais avançadas.[18] Desse modo, utilizamos para um artigo científico a coorte do estudo MESA para investigar como objetivo secundário se a disfunção diastólica – conhecidamente relacionada ao remodelamento ventricular e atrial – agregaria valor incremental na predição de eventos clínicos. Também utilizando dados do estudo MESA, investigamos em um outro artigo científico como a medida ecocardiográfica da hipertrofia ventricular esquerda compara-se ao padrão ouro medido pela ressonância magnética e se essa relação é afetada pelos diversos métodos de indexação da massa ventricular esquerda.

A cooperação que culminou com esse trabalho teve início no período em que o autor esteve no Hospital Johns Hopkins para treinamento em técnicas de Imagem Cardiovascular avançadas, no contexto de aprimorar as atividades assistenciais e acadêmicas junto à Universidade Federal do Vale do São Francisco. Após o término de tal treinamento, a colaboração científica entre a Universidade Johns Hopkins e a Escola Bahiana de Medicina e Saúde Pública continuou ao longo do período do Programa de Doutorado em Medicina e Saúde Humana, refletindo-se no número de publicações decorrentes desse esforço.

Os esforços depreendidos nas investigações sobre remodelamento cardíaco renderam um convite para integrar o grupo de redação das diretrizes conjuntas da *American Society of Echocardiography* com a *European Association of Cardiovascular Imaging* para quantificação ecocardiográfica de câmaras cardíacas, as quais encontram-se em fases finais para publicação (Anexo I). Esse prestigioso convite vem como consequência do processo de aprendizado e acúmulo de experiências em que esteve inserida esta tese.

2. Revisão da Literatura

2.1. Avaliação de risco cardiovascular

O estudo *Framingham Heart Study* é um marco na epidemiologia cardiovascular, concebido e financiado nos EUA pelo *National Institutes of Health*, durante a primeira metade do século XX. [19] O próprio termo "fatores de risco" foi inicialmente apresentado à comunidade científica em uma publicação derivada do *Framingham Heart Study* em 1961.[20] Utilizando-se de parâmetros relativamente simples e usualmente disponíveis, escores de risco cardiovascular derivados do *Framingham Heart Study* foram incorporados com sucesso na prática clínica cotidiana.

Inicialmente, os escores de risco de Framingham voltavam-se a desfechos clínicos decorrentes apenas de doença arterial coronariana. [20-22] D'Agostino ET AL. seguiram por 12 anos 8.491 participantes do *Framingham Heart Study* com mais de 30 anos de idade e predominantemente caucasianos, a fim de desenvolver uma versão do Escore de Risco Cardiovascular de Framingham para estimativa de risco cardiovascular global em 10 anos. Nesta versão publicada em 2008, idade, níveis séricos de colesterol total e HDL-colesterol, pressão arterial sistólica, medicação anti-hipertensiva, tabagismo e presença de diabetes são utilizados para computar o risco cardiovascular global, adotando-se como desfecho clínico combinado o primeiro evento relacionado à doença arterial coronariana, acidente vascular encefálico, doença arterial obstrutiva periférica e insuficiência cardíaca.[6]

Tais versões do Escore de Risco Cardiovascular de Framingham têm sido validadas em diversos grupos étnicos.[23,24] No entanto, idade tem-se mostrado como principal parâmetro no cálculo do Escore de Risco Cardiovascular de Framingham, levando-o a subestimar risco cardiovascular de jovens adultos mesmo na presença de múltiplos fatores de risco.[7] Em 2009, Pencina ET AL. publicaram uma versão do Escore de Risco Cardiovascular de Framingham para estimativa de risco em 30 anos de jovens adultos do *Framingham Heart Study*. No entanto, esta nova versão utilizava-se como desfecho combinado a presença de doença arterial coronariana ou acidente vascular encefálico, divergindo do conceito de risco cardiovascular global defendido por D'Agostino no ano anterior.[25]

As duas principais sociedades científicas da área cardiovascular dos EUA, *American Heart Association* (AHA) e *American College of Cardiology* (ACC), emitiram recomendações conjuntas para a avaliação de risco cardiovascular no contexto da prevenção primária de adultos. Recomenda-se que profissionais de saúde avaliem seus pacientes para risco cardiovascular global como estratégia de prevenção primária a partir de 20 anos de idade.[3] No entanto, as limitações para aplicação do Escore de Risco Cardiovascular de Framingham global em jovens adultos dificultam a estratificação de risco para doenças cardiovasculares na população com menos de 30 anos de idade. Novas estratégias parecem ser necessárias a esta população para adequada estratificação de risco cardiovascular precoce.

A inclusão de novos marcadores aos parâmetros de risco já consagrados pelo Escore de Risco Cardiovascular de Framingham tem se mostrado iniciativa atrativa na literatura científica.[26,27] No entanto, a relevância clínica de grande parte dos marcadores propostos como complementares ao Escore de Risco Cardiovascular de Framingham parece não resistir ao escrutínio de uma avaliação metodológica rigorosa. [4,28,29] A necessidade de mais bem avaliar a introdução de novos marcadores aos parâmetros existentes levou ao desenvolvimento do conceito de reclassificação de risco, ou *net reclassification improvement*.[30] Diante do grande número de novos marcadores de risco cardiovascular sendo proposta, a AHA estabeleceu critérios bem definidos para que um novo marcador passe a ser considerado válido. O rigor metodológico passa a requerer análise estatística robusta compreendendo calibração de modelos estatísticos, valor preditor de risco independente dos parâmetros tradicionais, incremento na discriminação e poder de promover adequada reclassificação quando comparado aos parâmetros tradicionais.[5] Apesar de massa ventricular esquerda e dimensão atrial esquerda constituírem parâmetros tradicionais de ecocardiografia utilizados há décadas, nenhum deles foi submetido a uma avaliação que contemple os critérios recomendados pela AHA até o presente momento.

2.2. Massa ventricular esquerda

Apesar de massa ventricular esquerda também poder ser avaliada por outros métodos ecocardiográficos usando tecnologias bi- ou tridimensionais, o modo-M foi a primeira técnica a ser desenvolvida e persiste recomendada pela *American Society of Echocardiography* (ASE).[8,10] A técnica é bem estabelecida e baseia-se na aquisição de medidas lineares em modo-M do septo interventricular, cavidade interna do ventrículo esquerdo e parede posterior do ventrículo

esquerdo guiadas a partir de imagens bidimensionais em janela acústica para-esternal esquerda. Assumindo que o ventrículo esquerdo possui o formato de um elipsoide de revolução, utilizam-se as medidas lineares para calcular os volumes subepicárdicos e cavitário do ventrículo esquerdo. O volume miocárdico é, então, calculado pela subtração do volume subepicárdico do volume cavitário. Multiplicando-se o volume miocárdico pela densidade miocárdica (convencionada em 1,05 mg/dL) estima-se a massa ventricular esquerda, usando a fórmula recomendada pela ASE.[8,11]

A aquisição das imagens depende da qualidade da janela acústica do examinado e da experiência do examinador. Em alguns casos, identificar as interfaces entre epicárdio e pericárdio ou entre endocárdio e cavidade ventricular podem ser desafiadores. Ademais, em alguns casos é difícil atingir a correta aquisição da imagem linear de forma perpendicular ao septo interventricular. No entanto, a principal limitação do método encontra-se na necessidade de se estimar os volumes cardíacos (objeto tridimensional) a partir de medidas lineares. Com isso, o cálculo requer que se elevem ao cubo os valores mensurados, ampliando em magnitude possíveis erros de mensuração.[11,31-34] Com isso, a técnica por modo-M não é recomendada para estimar massa ventricular esquerda em pacientes com coração significativamente remodelado. No entanto, essa condição é incomum em jovens, sendo virtualmente inexistente nos indivíduos saudáveis.

Um bom perfil de reprodutibilidade tem sido publicado na literatura para estimativa de massa ventricular esquerda por modo-M. O estudo PRESERVE (*Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement*) avaliou a variabilidade intra-paciente repetindo ecocardiogramas em 183 hipertensos com hipertrofia ventricular esquerda. O coeficiente de correlação intra-classe para as medidas lineares foi de 0,87 para dimensão intracavitária, 0,85 para septo interventricular e 0,83 para parede posterior do ventrículo esquerdo.[35] Em outro estudo, as mesmas 24 imagens foram analisadas de forma independente por dois observadores experientes para massa ventricular esquerda, tendo sido reportada diferença média inter-observadores de 1,83 g e limites de concordância de 95% entre -48,8 g e 52,5 g.[36] Já a reprodutibilidade intra-observador foi avaliada em 21 indivíduos por Missouris ET AL., mostrando coeficiente de variação de 6,1% e intervalo de confiança de 95%

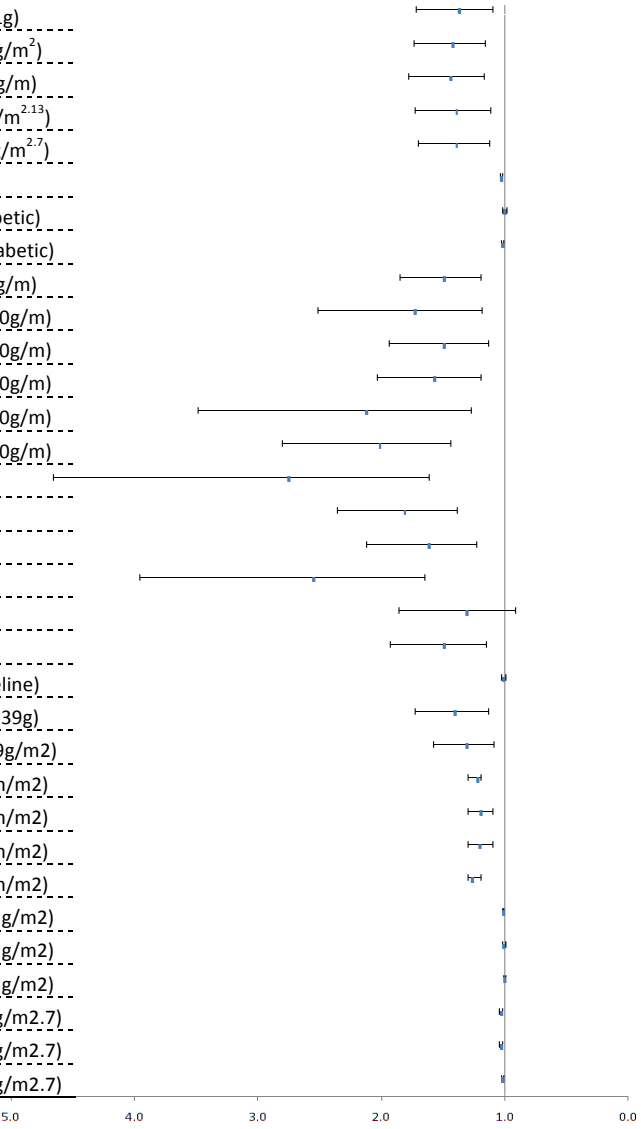
(IC95%) entre 3,9% e 8,3%.[32] No entanto, o perfil de reprodutibilidade em grandes estudos multicêntricos e os mecanismos de controle de qualidade são escassos na literatura mundial.

O aumento da massa ventricular esquerda pode ser relacionado a processo adaptativo ou patológico, sem limites claros entre ambos.[37] De fato, a elevação da massa ventricular esquerda parece ser o elemento mais importante no processo de remodelamento cardíaco e encontra-se intimamente relacionado ao processo de disfunção ventricular.[15] A associação entre massa ventricular esquerda e fatores de risco cardiovascular tem sido demonstrada na literatura. Mesmo em valores considerados dentro da normalidade pelos parâmetros atuais, elevação da massa ventricular esquerda é positivamente associada à pressão arterial sistólica, índice de massa corporal (IMC) e escore coronariano de cálcio por tomografia computadorizada.[38,39] Ao longo da vida, a elevação da massa ventricular esquerda parece não ser consequência inevitável do envelhecimento, mas sim determinada pelos valores de pressão arterial, tabagismo, presença de diabetes e peso corporal. Tais fatores de risco são comuns também no processo de disfunção sistólica e diastólica do ventrículo esquerdo. Adicionalmente, massa ventricular esquerda também está associada a aneurisma de aorta abdominal, espessura subcutânea subescapular, frequência cardíaca e atividade física.[12,40-46]

A habilidade da massa ventricular esquerda em predizer doenças cardiovasculares tem sido avaliada ao longo das décadas. Apesar de vários estudos consistentemente demonstrar relação entre massa ventricular esquerda e doenças cardiovasculares, costumam focar-se em populações de pacientes hipertensos e não costumam incluir adultos jovens em suas coortes. Em recente trabalho de revisão, coletamos 11 estudos reportando 33 modelos de regressão de Cox para investigação do poder preditor de massa ventricular esquerda em relação a doenças cardiovasculares.[11] A menor razão de risco encontrada (*hazard ratio* – HR) foi de 1,0 (IC 95% = 0,99; 1,02) para massa ventricular esquerda indexada por área de superfície corpórea em pacientes com diabetes como preditor de um desfecho combinado de morte cardiovascular, doença cardíaca isquêmica, insuficiência cardíaca, insuficiência renal terminal, doença arterial periférica e acidente vascular encefálico. [47] O maior HR encontrado foi de 2,8 (IC 95% = 1,6; 4,7) para massa ventricular esquerda determinando mortalidade geral em pacientes com insuficiência cardíaca (Figura I).[48]

Figura I – *Hazard ratios* e intervalos de confiança de 95% para estudos de coorte prospectiva usando ecocardiografia em modo-M para estimar massa ventricular esquerda como preditor de desfechos clínicos (modificado de Armstrong ET AL.[11])

Publicação	Normalização	Desfechos	Preditor
de Simone[49], 2005	Não usado	Combinado 1	MVE (71g)
	BSA		MVEi (38 g/m^2)
	Altura		MVEi (43 g/m)
	Altura$^{2.13}$		MVEi (25 g/m$^{2.13}$)
	Altura$^{2.7}$		MVEi (19 g/m$^{2.7}$)
de Simone[50], 2008	Altura$^{2.7}$	IC independente IM	MVEi
Eguchi[47], 2007	ASC	Combinado 2	MVEi (diabetic)
			MVEi (no diabetic)
Levy[51], 1990	Altura	HOMENS - Combinado 3	MVEi (50g/m)
		HOMENS - Morte por DCV	MVEi (per 50g/m)
		HOMENS - morte	MVEi (per 50g/m)
		MULHERES - Combinado 3	MVEi (per 50g/m)
		MULHERES - Morte DCV	MVEi (per 50g/m)
		MULHERES - morte	MVEi (per 50g/m)
Quiñones[48], 2000	Não usado	morte	MVE
		hospitalização DCV	MVE
Sundström[52], 2001	ASC	morte	MVEi
		Morte por DCV	MVEi
		Morbidade total	MVEi
		Morbidade por DCV	MVEi
Verdecchia[53], 1998	ASC	Combinado 4	MVE (baseline)
Verdecchia[54], 2001	ASC	Combinado 5	MVEi (per 39g)
Verdecchia[55], 2001	ASC	AVE, AIT	MVEi (per 29g/m2)
Verma[56], 2008	ASC	Combinado 6	MVEi (10gm/m2)
		morte	MVEi (10gm/m2)
		Morte por DCV	MVEi (10gm/m2)
		Morte ou hospitalização IC	MVEi (10gm/m2)
Zoccalli[57], 2001	ASC	morte	MVEi (per 1 g/m2)
		Morte por DCV	MVEi (per 1 g/m2)
		DCV	MVEi (per 1 g/m2)
	Altura$^{2.7}$	morte	MVEi (per 1 g/m2.7)
		Morte por DCV	MVEi (per 1 g/m2.7)
		DCV	MVEi (per 1 g/m2.7)



LEGENDA: combinado 1 - eventos cardiovasculares (CV) fatais e não fatais, incluindo morte súbita e outras mortes AVC, infarto do miocárdio (IM), acidente vascular cerebral (AVC), insuficiência cardíaca (IC) necessitando de hospitalização, insuficiência renal com necessidade de diálise, angina documentada, ataque isquêmico transitório (AIT), ou doença arterial obstrutiva periférica verificado por angiografia; Combinado 2 - Morte cardiovascular, doença isquêmica do coração, IC, doença renal terminal, doença arterial periférica e AVC; Combinado 3 - doença coronária, IC, AVC/AIT e claudicação intermitente; Combinado 4 - doença arterial coronariana, AVC, AIT cerebral, doença oclusiva aorto-ilíaca sintomática, oclusão trombótica de uma artéria da retina documentada, IC progressiva requerendo hospitalização e insuficiência renal com necessidade de diálise; Combinado 5 - IM fatal e não fatal, morte súbita cardíaca, AVC fatal e não fatal, outras mortes AVC, todas as causas de morte, IC grave que requer hospitalização e insuficiência renal grave com necessidade de diálise; Combinado 6 - ponto final da morte por causas AVC, reinfarto, IC , AVC , ou ressuscitação após parada cardíaca

2.3. Dimensão atrial esquerda

O átrio esquerdo é estruturalmente e funcionalmente vinculado ao ventrículo esquerdo. Em situações fisiológicas, o átrio funciona como reservatório durante a sístole ventricular, como conduto durante as fases iniciais da diástole e, na última fase da diástole ventricular, contrai-se auxiliando o enchimento do ventrículo. O remodelamento do átrio esquerdo é fortemente relacionado ao aumento nas pressões de enchimento do ventrículo esquerdo, servindo como importante indicativo da função diastólica do ventrículo esquerdo e demonstrando relação com risco cardiovascular. [8,58-60]

A mensuração da dimensão atrial esquerda por ecocardiografia em modo-M tem sido amplamente utilizada na prática clínica e em pesquisas científicas, constituindo em método de baixa complexidade e custo. Partindo de uma imagem bidimensional do eixo longo cardíaco em janela acústica para-esternal esquerda, orienta-se a aquisição da imagem linear em modo-M atravessando a raiz da aorta na altura do seio aórtico. Mede-se a dimensão atrial esquerda utilizando o diâmetro anteroposterior do átrio esquerdo partindo da parede posterior da raiz da aorta à parede posterior do átrio esquerdo, durante a fase final da sístole ventricular.[8]

Basear o tamanho de uma estrutura tridimensional como o átrio esquerdo em uma medida linear única é limitação intrínseca da dimensão atrial esquerda medida por ecocardiografia em modo-M. A simplicidade da medida facilita a precisão do método, porém ele perde em acurácia já que o átrio esquerdo por vezes apresenta crescimento excêntrico. Dessa forma, a medida linear anteroposterior do átrio esquerdo é menos confiável nos casos em que o aumento das dimensões não se dá de forma proporcional.[8,58] Esse risco é minimizado em adultos jovens saudáveis durante consulta para prevenção primária, tendo em vista a baixíssima prevalência esperada de remodelamento cardíaco nesse grupo específico da população. Tal limitação, entretanto, é reduzida pela utilização de medidas bidimensionais ou tridimensionais da dimensão atrial, como área e volume.[8]

Estudos transversais têm demonstrado a associação entre a dimensão atrial esquerda e outros fatores de risco cardiovascular. Como resultado da análise de 4.059 participantes do estudo CARDIA durante o quinto ano de seguimento da coorte, um perfil de risco cardiovascular mais favorável mostrou-se relacionado a menores valores de dimensão atrial esquerda. Ainda

nesse estudo, Gidding ET AL. mostraram que maiores valores de IMC, pressão artéria sistólica elevada, tabagismo, hiperglicemia, maior atividade física e menor frequência cardíaca associavam-se ao aumento da dimensão atrial esquerda.[12] IMC e pressão arterial sistólica também demonstraram forte associação com dimensão atrial esquerda nos 2.500 hipertensos não complicados estudados por Cuspidi ET AL.[61] e em 423 pacientes investigados por Tsang ET AL.[62] Apesar das relações mostradas nos estudos transversais, os determinantes de longo prazo da dimensão atrial esquerda em jovens ainda não são totalmente conhecidos.

Em 2.774 participantes do estudo CARDIA houve medida de dimensão atrial esquerda no ano de seguimento cinco e mensuração do escore de cálcio coronariano por tomografia computadorizada (um marcador de doença aterosclerótica coronariana) no ano de seguimento quinze. Nessa população de adultos jovens e saudáveis, foi demonstrado que o aumento dos valores de dimensão atrial esquerda está relacionado à quantidade de cálcio coronariano após 10 anos. Tal relação deu-se independentemente de fatores de risco tradicionais, como sexo, idade, etnia, IMC, pressão arterial sistólica, tabagismo, LDL-colesterol, HDL-colesterol e triglicerídeos.[14]

Apesar de em menor volume quando comparado a massa ventricular esquerda, a medida da dimensão atrial esquerda vem sendo utilizada com sucesso como preditor de eventos cardiovasculares ao longo dos anos. Essa relação é particularmente conhecida para os casos de fibrilação atrial e doença cerebrovascular.[62-70] No estudo LIFE, 939 pacientes hipertensos foram acompanhados com ecocardiogramas repetidos ao longo de 4,8 anos. Em modelos estatísticos ajustados para idade, massa ventricular esquerda, pressão arterial sistólica e Escore de Risco Cardiovascular de Framingham, valores de dimensão atrial esquerda elevados no início do seguimento foram relacionados com maior incidência de fibrilação atrial; enquanto a redução nos valores de dimensão atrial esquerda ao longo do seguimento esteve relacionada com redução no risco de eventos.[71] No entanto, a habilidade de dimensão atrial esquerda como preditor de eventos cardiovasculares globais - mais apropriados à prevenção primária em jovens – ainda é pouco conhecida.

3. Objetivos

3.1. Primário

1. Testar a hipótese de que hipertrofia ventricular esquerda e remodelamento atrial esquerdo, mensurados em adultos jovens, são preditores independentes de risco cardiovascular ao longo de duas décadas. Em se confirmando valor preditor independente, avaliar se estes parâmetros possuem valor preditor incremental ao modelo clínico tradicional – **Artigos # 1 e 2**.

3.2. Secundários

2. Testar a hipótese de que massa ventricular esquerda prediz desenvolvimento de disfunção ventricular esquerda em 20 anos de seguimento – **Artigo # 3**.
3. Testar a hipótese de que disfunção diastólica prediz insuficiência cardíaca e fibrilação atrial em 8 anos de seguimento – **Artigo # 4**
4. Identificar fatores de risco para crescimento atrial ao longo de 20 anos de seguimento – **Artigo # 5**

3.3. Terciários

5. Revisar a literatura sobre massa ventricular esquerda como preditora independente de eventos cardiovasculares e os efeitos da indexação sobre esse papel – **Artigo # 6**
6. Identificar a acurácia da medida de massa ventricular esquerda por ecocardiografia e os efeitos da indexação na definição de hipertrofia ventricular – **Artigo # 7**
7. Identificar a reprodutibilidade das medidas de massa ventricular esquerda e dimensão atrial esquerda no estudo CARDIA – **Artigo # 8**

4. Métodos

Esta tese foi realizada como fruto da parceria científica entre a Escola Bahiana de Medicina e Saúde Pública e o Hospital Johns Hopkins, dos quais se originam respectivamente o orientador e co-orientador do trabalho. Dois grandes estudos observacionais do tipo coorte prospectivo, o estudo CARDIA e o MESA, forneceram os dados utilizados nas análises dos artigos originais. Uma revisão sistemática com levantamento da literatura publicada na MEDLINE sobre o papel da hipertrofia ventricular esquerda na predição do risco cardiovascular também compõe os resultados apresentados.

O estudo *Coronary Artery Risk Development in Young Adults* (CARDIA) foi realizado nos Estados Unidos da América, sob coordenação do *National Heart, Lung, and Blood Institute*. Entre os anos de 1985 e 1986, 5.115 afrodescendentes e caucasianos moradores dos EUA, com idade entre 18 e 30 anos, foram incluídos na coorte do estudo CARDIA para seguimento prospectivo de longo termo. Os centros recrutadores foram distribuídos nas cidades de Birmingham, AL; Oakland, CA; Chicago, IL; e Minneapolis, MN. O recrutamento estratificou os participantes objetivando incluir números aproximadamente iguais de: (1) afrodescendentes e caucasianos; (2) homens e mulheres; (3) indivíduos com menos de 25 e 25 ou mais anos de vida; e (4) indivíduos com formação igual a ou menor que *high school education* (correspondente no Brasil ao ensino médio) e indivíduos com formação superior. Ecocardiogramas foram realizados na totalidade da população do estudo CARDIA em dois momentos, quinto e vigésimo quinto ano de seguimento da coorte. Neste último, o Hospital Johns Hopkins (Baltimore, Maryland, EUA) funcionou como laboratório central para todos os exames de ecocardiografia realizados e dispõe de acesso aos bancos de dados do estudo. Os dados disponíveis no estudo CARDIA mostram-se adequados à investigação do papel da ecocardiografia na detecção de alterações cardiovasculares subclínicas e na utilização de parâmetros ecocardiográficos para estratificação de risco cardiovascular em adultos jovens.

Entre julho de 2000 e agosto de 2002, 6.814 homens e mulheres sem doença cardiovascular aparente foram recrutados em seis cidades norte-americanas (Baltimore, Maryland; Chicago, Illinois; Forsyth, North Carolina; Los Angeles, Califórnia; New York, New York; St. Paul, Minnesota) para o estudo MESA.[17] Toda a coorte foi submetida a ressonâncias

magnéticas cardíacas no início do estudo e ao longo dos 10 anos de seguimento. O Hospital Johns Hopkins atuou como laboratório central para todas as ressonâncias magnéticas cardíacas utilizadas no estudo. Entre julho de 2005 e abril de 2007, uma parte da coorte foi submetida a exames de ressonância magnética cardíaca e a ecocardiogramas também no Hospital Johns Hopkins. Similar aos propósitos do estudo CARDIA, o estudo MESA também se propõe a estudar doenças cardiovasculares subclínicas, porém utiliza uma população de meia-idade no recrutamento.

A hipertrofia ventricular esquerda e a dimensão atrial esquerda estão entre os principais parâmetros conhecidos na investigação do remodelamento cardíaco, os quais compreendem o maior volume de evidências científicas publicadas no sentido de correlacionar remodelamento cardíaco a eventos cardiovasculares. Para investigar o papel de tais parâmetros no risco cardiovascular, utilizamos a técnica de mensuração da massa ventricular esquerda, da classificação para hipertrofia ventricular, do diâmetro anteroposterior do átrio esquerdo e da área atrial esquerda. As técnicas para mensuração que utilizamos nesta tese têm sido validadas e padronizadas ao longo das últimas décadas, com recomendações bem estabelecidas para sua aferição.[8,9]

Mesmo esses parâmetros tendo sido investigados por décadas, observamos que eram muitas a lacunas de conhecimento a serem exploradas. Particularmente, informação relevante à determinação do valor incremental de tais parâmetros pôde ser avaliada através das tabelas de reclassificação de risco cardiovascular e o cálculo do *net reclassification improvement*, conforme descrito por Pencina ET AL e recomendado pela *American Heart Association*.[5,30] Dessa forma, realizamos avaliação do valor de predição independente dos parâmetros de remodelamento cardíaco através de modelos de regressão de Cox e avaliação da capacidade discriminatória para risco cardiovascular pela computação de sensibilidade e especificidade através das curvas ROC, em modelos multivariados adequadamente calibrados. Como passo seguinte, realizamos os cálculos de reclassificação do risco cardiovascular utilizando as técnicas *net reclassification improvement*.

Os questionamentos principais desta tese complementam-se com um grande número de outras importantes dúvidas ainda existentes no campo. Dividimos, dessa forma, os esforços investigativos em vários artigos, hierarquizando os objetivos em principais, secundários e

terciários. As funções sistólica e diastólica do ventrículo esquerdo, enquanto parâmetros intimamente relacionados ao remodelamento cardíaco, foram investigados em análises longitudinais nas suas associações com remodelamento cardíaco e com risco cardiovascular. A função sistólica foi avaliada pela fração de ejeção do ventrículo esquerdo, parâmetro comumente aplicado na prática clínica.[8] Já a disfunção diastólica, medida de grande complexidade e inúmeras controvérsias,[16,72] requereu o desenvolvimento de um novo índice – *strain relaxation index* – que se utiliza de parâmetros relacionados aos gradientes pressóricos de enchimento ventricular e também às propriedades do tecido miocárdico. O remodelamento atrial esquerdo ao longo de 20 anos de seguimento foi avaliado em sua associação com conhecidos fatores de risco cardiovascular modificáveis no período.

Investigamos aspectos de precisão e acurácia das medidas de hipertrofia ventricular esquerda e de remodelamento atrial esquerdo através do acesso aos métodos de aquisição de imagens, interpretação de imagens, controle de qualidade e também à integralidade do banco de dados clínicos dos estudos CARDIA e MESA. Parâmetros de reprodutibilidade foram avaliados para medida de dimensão atrial esquerda no contexto do estudo CARDIA, tanto na aquisição e interpretação das imagens ecocardiográficas medidas por correlação intra-classe e coeficiente de variância, quanto nos métodos de treinamento, padronização e controle de qualidade. Mesma avaliação foi dedicada à massa ventricular esquerda, para qual avaliação de acurácia da medida e da classificação de hipertrofia frente ao padrão-ouro pela ressonância magnética foi avaliada por métodos de correlação e concordância que incluíram Gráficos de Bland-Altman, correlação linear, percentual de concordância e coeficiente Kapa.

Os sete pontos levantados em nossos objetivos têm como resultados os oito artigos científicos que compõem a tese. O objetivo principal deu como frutos dois artigos já aceitos para publicação. Cada um dos seis objetivos secundários e terciários resultou em mais um artigo científico redigido, sendo cinco destes já publicados em revistas internacionais. Cada artigo científico que compõe esta tese possui, naturalmente, sua própria sessão metodológica detalhada, sua apresentação de resultados e uma discussão dos méritos científicos encontrados. Na discussão desta tese, de forma complementar, buscamos demonstrar como os vários artigos aqui apresentados se interconectam na busca a importantes respostas relacionados ao remodelamento cardíaco em fases subclínicas.

5. Manuscritos e Publicações

Artigo 1 - Framingham score and LV mass predict events in young adults: CARDIA study. *Int J Cardiol 2014;172:350-5.*

Artigo 2 - Left atrial dimension and traditional cardiovascular risk factors predict 20-year clinical cardiovascular events in young healthy adults: the CARDIA study. *Eur Heart J Cardiovasc Imaging 2014. In press. Aceito para publicação.*

Artigo 3 - Relation of Left Ventricular Mass at Age 23 to 35 Years to Global Left Ventricular Systolic Function 20 Years Later: from the Coronary Artery Risk Development in Young Adults Study. *Am J Cardiol 2014;113:377-83.*

Artigo 4 - Diastolic function assessed from tagged MRI predicts heart failure and atrial fibrillation over an 8-year follow-up period: the multi-ethnic study of Atherosclerosis. *Eur Heart J Cardiovasc Imaging 2013. In press. Aceito para publicação.*

Artigo 5 - Association of early adult modifiable cardiovascular risk factors with left atrial size over a 20-year follow-up period: the CARDIA study. *BMJ open 2014;4:e004001.*

Artigo 6 - LV mass assessed by echocardiography and CMR, cardiovascular outcomes, and medical practice. *JACC Cardiovasc Imaging 2012;5:837-48.*

Artigo 7 - Left Ventricular Mass and Hypertrophy by Echocardiography and Cardiac Magnetic Resonance: The Multi-Ethnic Study of Atherosclerosis. *Echocardiography 2014;31:12-20.*

Artigo 8 - Quality Control and Reproducibility in M-mode, Two-dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year-25 Examination Experience. *Artigo submetido ao Journal of the American Society of Echocardiography. Em revisão.*

Objetivo Primário

Testar a hipótese de que hipertrofia ventricular esquerda e remodelamento atrial esquerdo, mensurados em adultos jovens, são preditores independentes de risco cardiovascular ao longo de duas décadas. Em se confirmando valor preditor independente, avaliar se estes parâmetros possuem valor preditor incremental ao modelo clínico tradicional

Artigo 1 - Framingham Global Cardiovascular Score and Left Ventricular Mass predict Cardiovascular Events in a Large Biracial Cohort of Young Adults: The CARDIA Study

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Framingham score and LV mass predict events in young adults: CARDIA study☆,☆☆

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ABSTRACT

Background: Framingham risk score (FRS) underestimates risk in young adults. Left ventricular mass (LVM) relates to cardiovascular disease (CVD), with unclear value in youth. In a young biracial cohort, we investigate how FRS predicts CVD over 20 years and the incremental value of LVM. We also explore the predictive ability of different cut-points for hypertrophy.
Methods: We assessed FRS and echocardiography-derived LVM (indexed by body surface area or height$^{2.7}$) from 3980 African–American and white Coronary Artery Risk Development in Young Adults (CARDIA) participants (1990–1991); and followed over 20 years for a combined endpoint: cardiovascular death; nonfatal myocardial infarction, heart failure, cerebrovascular disease, and peripheral artery disease. We assessed the predictive ability of FRS for CVD and also calibration, discrimination, and net reclassification improvement for adding LVM to FRS.
Results: Mean age was 30 ± 4 years, 46% males, and 52% white. Event incidence ($n = 118$) across FRS groups was, respectively, 1.3%, 5.4%, and 23.1% ($p < 0.001$); and was 1.4%, 1.3%, 3.7%, and 5.4% ($p < 0.001$) across quartiles of LVM (cut-points 117 g, 144 g, and 176 g). LVM predicted CVD independently of FRS, with the best performance in normal weight participants. Adding LVM to FRS modestly increased discrimination and had a statistically significant reclassification. The 85th percentile (≥116 g/m^2 for men; ≥96 g/m^2 for women) showed event prediction more robust than currently recommended cut-points for hypertrophy.
Conclusion: In a biracial cohort of young adults, FRS and LVM are helpful independent predictors of CVD. LVM can modestly improve discrimination and reclassify participants beyond FRS. Currently recommended cut-points for hypertrophy may be too high for young adults.

1. Introduction

Global cardiovascular (CV) risk tools, such as the Framingham risk score (FRS) [1], are recommended to assess risk in asymptomatic adults as young as age 20 years [2]. However, the FRS alone tends to underestimate event prediction in youth, even when multiple risk factors are present [3]. In addition, it is still unclear whether adding a risk marker to FRS may aid in young adult CV risk stratification.

Left ventricular mass (LVM) and hypertrophy (LVH) are markers of LV remodeling, recognized as important measures to assess clinical prognosis in hypertensive children, adolescents, and adults [4–6]. Both measurements have shown predictive power for CV events in diverse clinical settings [7,8]. Obesity is an important determinant of LVM and may

☆ All authors have read and approved submission of the manuscript, which has not been published and is not being considered for publication elsewhere in whole or in part in any language. On behalf of all authors, there is no relevant disclosure related to this manuscript.
☆☆ A preliminary version of these findings was presented on November 4th, during the 2012 American Heart Association scientific meetings (Los Angeles, CA), in the finals of the Elizabeth Barrett–Connor Investigator Award competition.

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interact with indexing methods, affecting the definition of LVH [7,9]. The best way to integrate LVM measures and LVH into clinical algorithms, however, is not established; particularly in youth [2,10].

In a biracial cohort of young adults followed over 20 years, we hypothesized that FRS would be a valuable tool to stratify CV risk and that adding information on LVM could aid in this risk stratification. Thus, in this study we aim 1) to assess the occurrence of CV events as predicted by the FRS in youth alone, 2) to assess the ability of LVM to predict CV events independent of the FRS, exploring the interactions of the various indexing methods with obesity, and 3) to investigate if LVM improves discrimination and effectively reclassifies young adults by adding prediction power to the FRS. Additionally, we explore the performance of currently recommended LVH cut-points for long-term event prediction in this biracial young cohort.

2. Methods

2.1. Study design and sample

The Coronary Artery Risk Development in Young Adults (CARDIA) study was previously described [11]. Briefly, 5115 African–American and white adults, aged between 18 and 30 years, were enrolled in 4 field centers (Birmingham, AL; Oakland, CA; Chicago, IL; and Minneapolis, MN) in 1985–1986 and followed prospectively. The CARDIA exam year-5 (1990 – 1991) was defined as baseline for the present study, when the entire cohort underwent echocardiography assessment. All subjects with interpretable echocardiography exam and complete data on covariates at CARDIA exam year-5 were included in this study. From the 4352 participants who attended the year-5 exam, 109 did not have echocardiography data and one withdrew consent from the study, 132 were missing data on the Framingham risk covariates, 126 were missing information on LVM, and 4 were missing body surface area, leaving 3980 in the analytic cohort. CARDIA exam Year-0 clinical characteristics for the analytic cohort and excluded participants are shown in Supplement Table S1. Informed consent was obtained from each participant, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the all centers' human research committee.

2.2. Echocardiography

All echocardiograms were performed on an Acuson cardiac ultrasound machine (Siemens) [12] by trained professionals, using a standardized method previously designed and available at the CARDIA website (http://www.cardia.dopm.uab.edu/exam-materials2). All studies were interpreted at a single reading center (University of California, Irvine) at the time of year-5 examination. LVM was measured from short-axis views, using 2D-guided M-mode echocardiography, leading-edge-to-leading-edge technique, as recommended by the ASE [13,14]. Reproducibility profile has been published for the original measurements and a recent reassessment [12,15]. LVM was indexed (LVMi) by BSA or height$^{2.7}$. BSA was computed using standardized weight/height measurements by the modified DuBois method [16,17]. Weight was measured with balance beam scales (the same type of scale in all centers) and height with a wall mounted stadiometer or vertical ruler. Additionally, unindexed LVM and LVM/height$^{1.7}$ were computed and reported in the supplemental material.

2.3. Follow-up and endpoint

Details of outcomes ascertainment processes have been described [18]. For this analysis, a combined endpoint of CV events, including cardiovascular death and nonfatal heart failure (HF), myocardial infarction (MI), stroke, transient ischemic attack (TIA), and peripheral artery disease (PAD) was the dependent variable.

The total follow-up period was 20 years, with median follow-up among those without CV events of 19.9 years. Participants were interviewed during their scheduled study examinations and by telephone yearly; vital status was checked by participant or proxy interview or by database searches at 6 month contacts between annual interviews. Participants were asked about overnight hospitalizations and outpatient procedures for treatment of cardiovascular conditions.

Medical records were requested for all suspected cardiovascular events. Death certificates were requested for all deaths; the protocol required requests for emergency services and emergency department records, next-of-kin and physician interviews for outpatient suspected cardiovascular deaths. Two members of the end-points committee reviewed each record, applying standard outcome definitions contained in a detailed adjudication manual, to classify events; disagreements were resolved by committee consensus.

MI was classified based on an algorithm using symptoms, cardiac biomarkers, and ECG findings [19]. HF required admission for new or decompensated heart failure, and classification was based on symptoms, signs, and imaging according to criteria developed by the Atherosclerosis Risk in Communities Study [20]. Stroke was adjudicated based on symptoms, physical findings, and imaging results, and published guidelines were used for subclassification [21–23]. TIA required one or more episodes of focal neurologic deficit, and imaging must have been negative for stroke regardless of symptom duration [23]. PAD was adjudicated based on symptomatic disease, ischemic ulcers, gangrene, and/or requiring intervention. Cardiovascular death included mortality with an underlying cause of atherosclerotic coronary heart disease, stroke, atherosclerotic disease other than coronary or stroke (e.g., abdominal aortic aneurysm), and non-atherosclerotic cardiac disease (e.g., non-ischemic cardiomyopathy and including hypertensive heart disease). Fatal atherosclerotic coronary heart disease included fatal MI and coronary heart disease using published recommendations [19].

2.4. Statistical analysis

Cox regression analysis assessed the performance of LVMi as an independent predictor of CV events, computing hazard ratios (HR) for the overall cohort and according to BMI groups (normal weight, overweight, and obese). For the analysis, we computed the first event in each participant. Statistical significance of the HRs was assessed with the Wald chi-square test. Areas under the receiver-operating characteristic curves (AUC) were also computed [24]. A nonparametric statistical test developed by DeLong et al. [24] was used to determine whether the AUCs for different models were significantly different. For the "FRS covariate" models, all covariates present in the calculation of the Framingham 10-year global cardiovascular risk score (FRS) [1] were individually included in multivariable models, adjusting also

Table 1
Participant characteristics at CARDIA exam year-5 (1990–91), overall and according to the BMI group.

Variable	Mean (SD)			
	Normal (n = 1986)	Overweight (n = 1153)	Obese (n = 743)	Overall (n = 3980)
Age	29.8 (3.7)	30.1 (3.6)	30.2 (3.7)	30.0 (3.6)
Height (m)	1.71 (0.09)	1.72 (0.10)	1.69 (0.09)	1.71 (0.09)
Weight (kg)	64.9 (9.1)	80.3 (9.8)	101.0 (17.4)	75.7 (18.1)
BSA (m^2)	1.74 (0.18)	1.90 (0.18)	2.06 (0.22)	1.84 (0.23)
Heart rate (beats/30 s)	33.8 (5.0)	33.7 (4.8)	35.0 (4.7)	34.1 (5.0)
Total cholesterol (mg/dL)	173.2 (33.0)	182.2 (34.1)	185.9 (35.3)	177.9 (34.2)
HDL cholesterol (mg/dL)	56.7 (14.0)	50.9 (13.5)	47.2 (12.5)	53.4 (14.2)
LDL cholesterol (mg/dL)	102.9 (30.9)	114.5 (31.6)	118.3 (32.3)	108.8 (32.0)
SBP (mm Hg)	105.6 (11.0)	109.1 (10.7)	111.6 (12.3)	107.7 (11.4)
DBP (mm Hg)	67.3 (9.5)	69.9 (9.5)	73.3 (10.4)	69.1 (9.9)
Cigarette/day	3.8 (7.6)	3.8 (8.0)	3.4 (7.0)	3.7 (7.6)
BMI (kg/m^2)	22.3 (1.7)	27.1 (1.4)	35.4 (5.2)	26.0 (5.7)
LVMi/height$^{2.7}$ ($g/m^{2.7}$)	32.4 (8.0)	36.5 (8.2)	41.7 (10.0)	35.2 (9.2)
LVMi/BSA (g/m^2)	78.5 (18.3)	83.1 (18.8)	83.6 (19.1)	80.6 (18.8)
Variable	Number of participants (%)			
	Normal (n = 1986)	Overweight (n = 1153)	Obese (n = 743)	Overall (n = 3980)
African–American ethnicity	782 (39.4)	584 (50.7)	512 (68.9)	1919 (48.2)
Male gender	878 (44.2)	640 (55.5)	278 (37.4)	1813 (45.6)
Diabetic participants	12 (0.6)	8 (0.7)	10 (1.4)	30 (0.8)
Use of anti-hypertensive medication	11 (0.6)	18 (1.6)	31 (4.2)	61 (1.5)

Legend: BMI—body-mass index; SD—standard deviation; SBP—systolic blood pressure; DBP—diastolic blood pressure; LVM—left ventricular mass; LVMi—left ventricular mass index.

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for race and gender. For the "calculated FRS" models, we modified the score as first described by D'Agostino et al. [1] to include age as a continuous variable and race. Net reclassification improvement was calculated to evaluate the added predictive ability for LVMi to the FRS [25]. Statistical significance of the net reclassification improvement was tested with Equation 9 in Pencina et al. [25]. Calibration was assessed by the Hosmer–Lemeshow test and indicated good calibration for all models (data not shown). In an exploratory additional analysis, we calculated HR and AUC for diverse LVH cut-points predicting events, using models adjusted for age, sex, and race. LVH cut-points included the currently ASE-recommended cut-points [14], gender-specific percentiles in our entire population, 95th race-specific percentiles of a healthy reference subgroup, and additional cut-points previously shown in the literature [26]. Additional information on statistical analysis is reported in the Supplements.

3. Results

Participant age ranged from 22 to 36 years at the CARDIA examination year 5. According to BMI classification, 49.9% of the participants were normal weight; 29.0% were overweight; 18.7% were obese; and 2.5% were underweight. Patient characteristics are shown in Table 1, according to the BMI group.

The combined endpoint of CV events was registered in 118 participants; 29 (24.6%) had cardiovascular death, 26 (22.0%) developed congestive heart failure, 29 (24.6%) myocardial infarction, 21 (17.8%) stroke, 9 (7.6%) TIA, and 4 (3.4%) participants developed PAD. Cardiovascular death was due to hypertension (8 participants); ischemic heart disease (7 participants); pulmonary heart disease (3 participants); cardiomyopathy (2 participants); cardiac dysrhythmias (3 participants); cerebrovascular disease (4 participants); and complication of heart diseases (2 participants). Information on participant characteristics according to the presence of events is shown in Supplement Table S2. Events were incident in 83 African–American participants

Table 2
Cox regression hazard ratios (HR) and areas under the receiver-operating characteristic curves (AUC) for LVM and the Framingham risk score (FRS).

Predictor	FRS covariates		Calculated FRS	
	HR (95% CI) *p*-value	AUC	HR (95% CI) *p*-value	AUC
LVM/height$^{2.7}$	1.15 (0.99, 1.35) 0.07	0.80*	1.18 (1.03; 1.35) 0.02	0.80*
LVM/BSA	1.18 (1.01, 1.38) 0.04	0.80*	1.21 (1.05; 1.39) 0.007	0.80**

Legend: LVM—left ventricular mass; BSA—body surface area; CI—confidence interval. HR refers to 1 standard-deviation increase. The "FRS covariate" models included: race, gender, age, HDL-cholesterol, total cholesterol, systolic blood pressure, treatment for hypertension, smoking status, and presence of diabetes. In the calculated FRS, the score is calculated as initially described by D'Agostino et al. modified to include age as a continuous variable and with further adjustment to race [1]. AUC for FRS covariates alone = 0.79 and for calculated FRS alone = 0.79.

* *p*-value < 0.05.

** *p*-value = 0.07, in both cases when comparing AUC between FRS alone and adding LVM index [24].

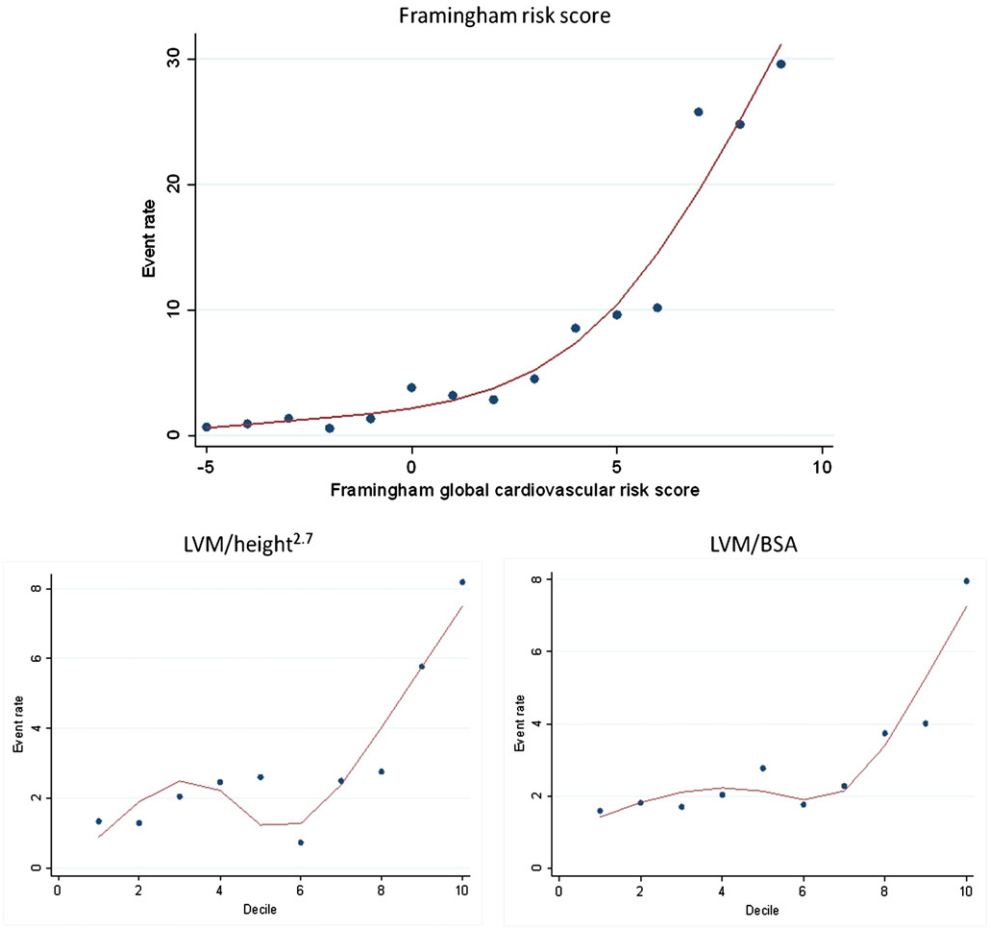

Fig. 1. Cubic spline fitted to show event rates for computed Framingham risk score plus age and across left ventricular mass deciles, according to indexation method. **Legend:** Framingham global cardiovascular risk score following D'Agostino et al. (2008) [1]; scores of ≥9 are pooled. Sample sizes in the Framingham point score categories are (point score: sample size): (−5: 141), (−4: 543), (−3: 441), (−2: 533), (−1: 592), (0: 439), (1: 409), (2: 278), (3: 216), (4: 173), (5: 103), (6: 49), (7: 23), (8: 20), and (≥9: 20), with maximum point score 13. LVM category refers to deciles of the distribution in the cohort; LVM—left ventricular mass; BSA—body-surface area.

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Table 3
Cox regression hazard ratios (HR) and areas under the receiver-operating characteristic curves (AUC) for cardiovascular event combined endpoint in normal, underweight, and obese participants.

Predictor	FRS covariates		Calculated FRS	
	HR (95% CI) *p*-value	AUC	HR (95% CI) *p*-value	AUC
LVM/height$^{2.7}$	1.55	0.87	1.54	0.85
Normal	(1.07; 2.22)	0.80	(1.13; 2.10)	0.80
Overweight	0.02	0.72	0.006	0.69
Obese	1.11		1.10	
	(0.79; 1.57)		(0.79; 1.53)	
	0.56		0.58	
	1.05		1.15	
	(0.82; 1.36)		(0.91; 1.45)	
	0.70		0.24	
LVM/BSA	1.43	0.87	1.51	0.85
Normal	(1.03; 1.98)	0.80	(1.12; 2.02)	0.80
Overweight	0.03	0.73	0.006	0.70*
Obese	1.07		1.07	
	(0.77; 1.49)		(0.80; 1.45)	
	0.67		0.64	
	1.14		1.24	
	(0.88; 1.48)		(0.98; 1.55)	
	0.33		0.07	

Legend: BMI—body-mass index; LVM—left ventricular mass; BSA—body surface area; CI—confidence interval. HR refers to 1 standard-deviation increase. The "FRS covariate" models included: race, gender, age, HDL-cholesterol, total cholesterol, systolic blood pressure, treatment for hypertension, smoking status, and presence of diabetes. In the calculated FRS, the score is calculated as initially described by D'Agostino et al. modified to include age as a continuous variable and with further adjustment to race [1]. AUC or FRS covariates alone were 0.86, 0.80, and 0.72 for normal, overweight, and obese respectively. AUC for calculated FRS alone were 0.85, 0.80, and 0.68 for normal, overweight, and obese respectively.

* *p*-value = 0.07, when comparing AUC between FRS alone and adding LVM index [24].

(4.3% of the total) and in 35 white participants (1.7% of the total). Normal BMI participants had 26 CV events (1.3%), while the overweight had 38 (3.3%), and the obese 34 CV events (4.6%). Unadjusted cumulative event rates according to the FRS point score and to LVM indexed by BSA and height$^{2.7}$ are shown in Fig. 1, demonstrating increasing event rates across the variables, with a tendency for steeper slopes at the higher levels of both FRS and indexed LVM.

Considering the entire cohort and adjusting for FRS covariates, the hazard ratios for CV events were slightly higher for LVM/BSA compared to LVM/height$^{2.7}$ (Table 2). Of note, African–American ethnicity was associated with higher hazard ratios for both LVMi: 2.28 (95% CI: 1.51, 3.45) for LVM/height$^{2.7}$ and 2.33 (95% CI: 1.55, 3.52) for LVM/BSA. Similar results were found for unindexed LVM or LVM/height$^{1.7}$ (Supplement Table S3). When the models were adjusted for the calculated FRS, race, and age, LVM and indices showed statistically significant independent event prediction ability. Both LVMi had modest increases in the AUC when added to the calculated FRS or the FRS covariates (Table 2). When the hazard ratios were computed according to the BMI group, the best performance was found for normal weight individuals, with similar performance for LVM/BSA or height-derived LVM indexing (Table 3; Supplement Table S3).

Both LVM indexing methods showed similar positive and statistically significant net reclassification improvement when added to FRS covariates (Table 4). Adding LVM/height$^{2.7}$ correctly downgraded risk in 189 (5%) participants that did not have events, and correctly reclassified 7 (6%) of those that had events to a higher risk group. Adding LVM/BSA moved 188 (5%) of participants that did not have events to a lower risk group, and reclassified 8 (7%) participants that had events to a higher risk group. The net reclassification improvement for LVM/height$^{2.7}$ was 0.13 ($p < 0.01$) and for LVM/BSA was 0.11 ($p = 0.02$).

The prevalence of LVH varied with the indexing process (Table 5). The results of the exploratory analysis regarding the best cut-point value to define LVH in our population are shown in Table 5 Compared to the current ASE-recommended values for LVM/height$^{2.7}$ and for LVM/BSA, overall, the 85th percentile achieved the highest AUC values (0.716 and 0.726, respectively) though they did not reach statistical significance ($p = 0.20$ and $p = 0.08$, respectively). The 85th percentile also had the highest HRs (2.89 and 3.00, respectively) overall.

4. Discussion

Both FRS and LVM are widely used in decision-making on adult patients, although their value as a global cardiovascular risk marker when assessed in early adulthood is not established. In a population based study of biracial young healthy adults, we showed that FRS had good performance for risk stratification over a 20-year follow-up (as opposed to 10 years for the Framingham score in older individuals). LVM assessed by echocardiography showed a modest but consistent additional predictive power to FRS, particularly in normal weight participants. This suggests that LVMi may be adequate to complement the FRS information in young individuals with other risk factors, in which FRS alone typically underestimates the CV risk burden. Further, the current cut-points for LVH were explored in a long-term perspective for predicting CV events in young adults and showed that current ASE-recommended cut-points appear to be too high for young adults.

D'Agostino and colleagues followed 8491 predominantly white subjects free of CV disease (mean age 49 years) over 12 years and described a more robust version of the FRS updated for global CV 10-year risk profile [1,3]. However, age is the major determinant of risk in the FRS and many young individuals with hypertension, obesity, and other risk factors have therefore a low global FRS predicted risk [3]. Since young individuals with chronic exposure to risk factors have a higher CV risk burden early in life, risk scores may underestimate risk in this age group [27].

The rates of cardiovascular events in young adults are a major concern [28]. Despite the low event rate (2.96% in 20 years) and the known racial- and age-related limitations, the calculated FRS performed well in CARDIA

Table 4
Reclassification table: absolute number of participants classified in each strata for Framingham risk score (FRS) components plus race *vs.* adding information on left ventricular mass (LVM) index.

	Risk category	No event ($n = 3862$)				Events ($n = 118$)			
		FRS				FRS			
		<2.5%	2.5 – 4.9%	5.0 – 9.9%	≥10%	<2.5%	2.5 – 4.9%	5.0 – 9.9%	≥10%
FRS + LVM/height$^{2.7}$	<2.5%	2517	92	2	0	24	8	0	0
	2.5 – 5.0%	112	583	64	1	1	18	7	0
	5.0 – 10%	0	60	259	30	0	6	15	7
	>10%	0	0	23	119	0	0	0	32
FRS + LVM/BSA	<2.5%	2514	94	3	0	24	8	0	0
	2.5 – 5.0%	117	576	66	1	3	16	7	0
	5.0 – 10%	0	72	253	24	0	5	18	5
	>10%	0	0	21	121	0	0	0	32

Legend: LVM—left ventricular mass; BSA—body surface area. Cut-points for risk groups were defined according to logistic regression models (see Methods for full description).

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Table 5
Age-, race, and sex-adjusted hazard ratios (HR) and areas under the receiver-operating characteristic curves (AUC) for current American Society of Echocardiography (ASE)-recommended cut-points for left ventricular hypertrophy (LVH) and for 85th, 90th, and 95th percentile cut-points of left ventricular mass (LVM) index.

LVH parameter (unit)	LVH cut-point value	Prevalence of LVH (%)	HR (95% CI)	AUC (*p*-value)
LVM/height$^{2.7}$ (g/m$^{2.7}$)				
ASE-recommended	≥49 M, ≥45 W	378 (9.5)	2.35 (1.51, 3.67)	0.705 (NA)
Liao [26], 1997 (sex specific)	≥50 M, 47 W	299 (7.5)	2.31 (1.44, 3.71)	0.702 (0.55)
Liao [26], 1997	≥51 M/W	216 (5.4)	2.24 (1.33, 3.78)	0.700 (0.51)
95% Reference group (race-specific)	≥44.6 B, ≥44.5C	551 (13.8)	2.70 (1.84, 3.97)	0.716 (0.16)
85th percentile	≥45.1 M, ≥42.9 W	587 (15.0)	2.89 (1.98, 4.22)	0.716 (0.20)
90th percentile	≥47.3 M, ≥45.9 W	399 (10.0)	2.90 (1.93, 4.37)	0.715 (0.07)
95th percentile	≥51.6 M, ≥51.2 W	200 (5.0)	2.26 (1.32, 3.87)	0.698 (0.39)
LVM/BSA (g/m^2)				
ASE-recommended	≥116 M, ≥96 W	318 (8.0)	2.53 (1.60, 4.01)	0.706 (NA)
Liao [26], 1997 (sex specific)	≥117 M, ≥104 W	197 (5.0)	2.26 (1.31, 3.90)	0.699 (0.38)
Liao [26], 1997	≥125 M/W	75 (1.9)	2.34 (1.08, 5.08)	0.698 (0.35)
95% reference group (race-specific)	≥103.6 B, ≥104.5C	395 (9.9)	2.70 (1.76, 4.14)	0.709 (0.77)
85th percentile	≥105.4 M, ≥89.5 W	598 (15.0)	3.00 (2.06, 4.37)	0.726 (0.08)
90th percentile	≥111.1 M, ≥94.8 W	399 (10.0)	2.06 (1.31, 3.24)	0.702 (0.31)
95th percentile	≥119.4 M, ≥101.8 W	200 (5.0)	2.12 (1.21, 3.73)	0.697 (0.25)

Legend: LVM—left ventricular mass; BSA—body surface area; HR—hazard ratio; CI—confidence interval; NA—not applicable; M—men; W—women; B—blacks; C—Caucasians. AUC *p* values refer to the difference in AUC from ASE-recommended cut-points [24].

with relative risk of nearly 20 for the highest 1% of FRS values compared to those with risk below 2.5% (Fig. 1). In this study, we computed the FRS in percentiles of risk as it is widely known and usually applied to patients in daily practice. To avoid statistical limitations, we also used the FRS covariates as independent variables in our models.

After adjustment for race, our findings support LVM as a risk marker that could add valuable information beyond the FRS in a young cohort of young adult Caucasian and African–American men and women. Prior studies investigating the predictive power of LVM including a biracial cohort were performed in older or sicker populations, have not used recently recommended risk reclassification methodology, and have a substantially shorter follow-up period when compared to the present report [7]. [29]

Heart size scales with body size and definitions of normality range should take into account variation associated with anthropometrics. The ASE currently provides cut-points for the diagnosis of LVH when LVM is indexed to height$^{2.7}$ or to BSA [14]. Obesity relates to LV remodeling and may interact with the indexing method [30]. Studies have reported that BSA indexing underestimates LVH prevalence among obese and overweight individuals [31,32]. Height based indexing seems to predict CV events similarly to BSA indexing in studies with low prevalence of obesity, but becomes superior as the prevalence of obesity increases [33,34].

Obesity plays a major role in cardiac geometry even in the absence of increased cardiometabolic risk and also influences LVM values early in life [35,36]. However, it is not clear when an adaptive increase in LVM becomes pathologic. Indexing LVM for body size attempts to overcome this problem; however, the best LVM indexing method that could adjust for adaptive increases but not pathologic increases in LVM remains under debate [10]. Indexing to height appears to show a better relation with lean body mass, but LVM/BSA is still used in the literature and is recommended by the ASE [7,14,37]. It is possible that the relationship of indexed LVM to events might be different in obese and non-obese young adults. As previously reported [33], LVM indexing methods had similar success across BMI groups in our study. The most robust results for the LVMi predicting CV events were among participants in the normal BMI group (Tables 2 and S2). The adaptive increase in LVM mediated by obesity is not present in normal weight participants; thus, increased LVM can be assumed to be pathologic rather than adaptive in these individuals.

Current cut-points for LVH are based on studies using middle-aged populations and do not use global CV event prediction as a parameter to define cut-points for LVH [14]. Clear cut-points for LVH in young adults may aid the general clinician in daily decision-making and therapeutic approach [7]. Our exploratory results suggest that the current ASE recommendation on LVH may not be the most appropriate for young adults. A more adequate cut-point could include lower values of LVM and be based on global events prediction ability.

4.1. Study limitations

We report a low event rate over the 20-year follow-up period, which may affect the statistical power of our survival assessment. However, the incidence rate seems adequate to the assessment of a healthy cohort of young individuals. LVM was calculated using an algorithm that computes M-mode echocardiography measurements, assuming that the heart is modeled as a prolate ellipsoid of revolution, limiting the use of this method in remodeled hearts. [7,14] However, remodeled hearts are rarely present in young healthy adults. Moreover, echocardiography is a validated and recommended method to assess LVM and LVH, with a reasonable profile for cost, versatility, acceptability, availability, and reproducibility. [4–6,14,38,39]

5. Conclusion

In African–American and White adults at ages 22 to 36 years, the FRS showed good performance predicting global cardiovascular events over

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20 years of follow-up. LVM can independently predict CV events, modestly improve discrimination, and also effectively reclassify participants beyond the FRS. Although modest, the additional value of LVM, particularly in those of normal weight may help to assess CV risk in young adults with multiple risk factors, typically underestimated by FRS alone. Different LVM indexing methods performed similarly for event prediction in our study. The results of our exploratory analysis for the 85th percentiles of LVM/height$^{2.7}$ and for LVM/BSA suggest that the currently ASE-recommended cut-points for LVH might be lowered for CV event prediction in young generally healthy individuals.

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All CARDIA sites' ethics committees have approved the research protocol, and informed consent has been obtained from all CARDIA participants. Dr. Lima and Dr. Armstrong had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.01.003.

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Objetivo Primário

Testar a hipótese de que hipertrofia ventricular esquerda e remodelamento atrial esquerdo, mensurados em adultos jovens, são preditores independentes de risco cardiovascular ao longo de duas décadas. Em se confirmando valor preditor independente, avaliar se estes parâmetros possuem valor preditor incremental ao modelo clínico tradicional

Artigo 2 - Left atrial dimension and traditional cardiovascular risk factors predict 20-year clinical cardiovascular events in young healthy adults: The CARDIA Study

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Left atrial dimension and traditional cardiovascular risk factors predict 20-year clinical cardiovascular events in young healthy adults: the CARDIA study

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Aims We investigated whether the addition of left atrial (LA) size determined by echocardiography improves cardiovascular risk prediction in young adults over and above the clinically established Framingham 10-year global CV risk score (FRS).

Methods and results We included white and black CARDIA participants who had echocardiograms in Year-5 examination (1990–91). The combined endpoint after 20 years was incident fatal or non-fatal cardiovascular disease: myocardial infarction, heart failure, cerebrovascular disease, peripheral artery disease, and atrial fibrillation/flutter. Echocardiography-derived M-mode LA diameter (LAD; $n = 4082$; 149 events) and 2D four-chamber LA area (LAA; $n = 2412$; 77 events) were then indexed by height or body surface area (BSA). We used Cox regression, areas under the receiver operating characteristic curves (AUC), and net reclassification improvement (NRI) to assess the prediction power of LA size when added to calculated FRS or FRS covariates. The LAD and LAA cohorts had similar characteristics; mean LAD/height was 2.1 $\pm$ 0.3 mm/m and LAA/height 9.3 $\pm$ 2.0 mm^2/m. After indexing by height and adjusting for FRS covariates, hazard ratios were 1.31 (95% CI 1.12, 1.60) and 1.43 (95% CI 1.13, 1.80) for LAD and LAA, respectively; AUC was 0.77 for LAD and 0.78 for LAA. When LAD and LAA were indexed to BSA, the results were similar but slightly inferior. Both LAD and LAA showed modest reclassification ability, with non-significant NRIs.

Conclusion LA size measurements independently predict clinical outcomes. However, it only improves discrimination over clinical parameters modestly without altering risk classification. Indexing LA size by height is at least as robust as by BSA. Further research is needed to assess subgroups of young adults who may benefit from LA size information in risk stratification.

Keywords Left atrial size • Cardiovascular events • Echocardiography • Young adults

Introduction

The assessment of cardiovascular (CV) risk is recommended in youth by using clinical parameters. However, the value of global risk scores (such as described in the Framingham Heart Study) in adults aged <30 years is unclear.[1,2] Left atrial (LA) structure and function relate to ventricular function.[3] CV mortality, myocardial infarction (MI), heart failure (HF), stroke, and atrial fibrillation have all been predicted by LA size in diverse populations.[4] However, the additional predictive value of LA size assessed in young adults over traditional risk factors is unclear.

Atrial dilatation is the major marker of LA remodelling, an adaptive process that relates to the duration and strength of the LA exposure to stressing factors. As the atrium enlarges, the remodelling mechanism involves microstructure alterations; markedly interstitial fibrosis and myocyte hypertrophy.[5] The importance of LA remodelling in young healthy adults, however, is not totally understood. In the

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Coronary Artery Risk Development in Young Adults (CARDIA) study of risk evolution in young adults, LA size has shown a strong relationship with traditional CV risk factors in both cross-sectional and longitudinal assessments, but relationships with incident events have not yet been reported.[6–8]

We hypothesized that LA size assessed in young healthy adults is associated with future CV events, independently of CV risk prediction provided by traditional risk factors. Using a large biracial cohort of the CARDIA study, we investigate the additional predictive value of LA diameter (LAD) and area (LAA) over the Framingham 10-year global CV risk score (FRS). Since the method of indexing LA size to body size has not been established, we tested the relative strength of different indexing methods on this CV event prediction.

Methods

Participant selection

As previously described, CARDIA is a prospective study that enrolled 5115 African-American and white adults (aged 18–30 years) from four US Field Centers (Birmingham, AL; Oakland, CA; Chicago, IL; and Minneapolis, MN) in 1985–86.[9] The entire cohort underwent echocardiograms at follow-up Year-5 examination (1990–91); this was defined as baseline for the present study. We included participants with interpretable echocardiograms and complete data on covariates at baseline. Of the 4352 participants who attended the Year-5 examination, 109 did not have echocardiography data and one withdrew consent from the study. In the remaining 4242 participants, 132 were missing covariate data, 28 missing LAD, and 1670 missing information on LAA. LAA assessment is more complex than M-mode diameter and requires optimal 2D images. In CARDIA Year-5 examination, echocardiograms were focused to assess cardiac structure and function using an M-mode technique; this reduced the number of interpretable 2D exams. This left 4082 participants in the analytic cohort for LAD and 2412 for LAA analysis.

Echocardiography

Echocardiographic exams were performed using an Acuson™ cardiac ultrasound system (Siemens Healthcare, Erlangen, Germany), as previously reported for the CARDIA study.[10] The images were analysed at a single Reading Center (University of California, Irvine, CA, USA) and followed standard recommendations.[11] Parasternal long-axis 2D views were used to guide the assessment of M-mode anteroposterior diameter of the LA, and the areas were acquired from a 2D four-chamber view, both measured at the point of maximum atrial volume (*Figure 1*). LA measurements were indexed by height or body surface area (BSA).

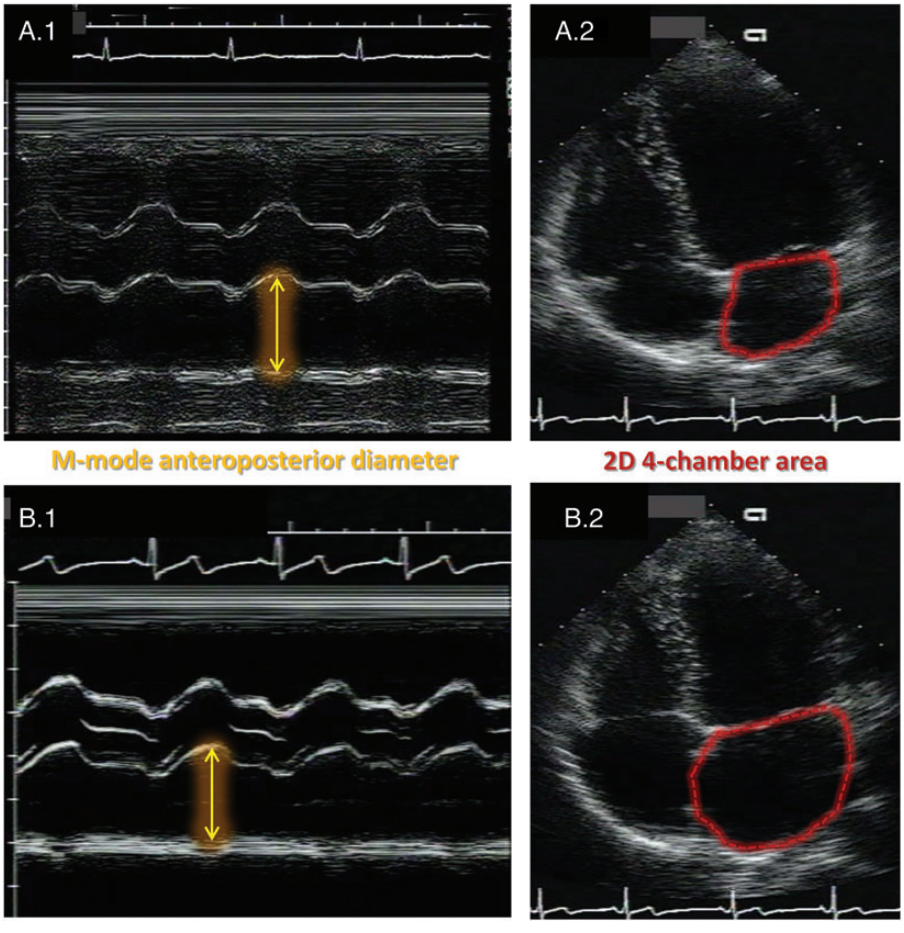

Figure 1 Illustrative representation of the LA size assessment in two participants in the CARDIA follow-up Year 5. Participant A had normal findings and B showed eccentric LA remodelling. Note that the M-mode anteroposterior diameters are similar in both participants (A.1 and B.1), but the 2D areas are markedly different (A.2 and B.2).

Other variables

Assessment methods for risk factor variables have been described for the CARDIA study.[12] Briefly, the use of anti-hypertensive medication and smoking status were self-reported, assessed using questionnaires. Systolic blood pressure (SBP) was the average of the last two measurements (total of three). Diabetes was defined based on CARDIA examination Years 0, 2, and 5 by the presence of one of the following criteria: history of hypoglycaemic medication use or fasting glucose $\geq$126 mg/dL.

Cardiovascular outcomes

To assess CV risk in young asymptomatic adults, all major CV events should be taken into account in a global assessment of risk.[1] We used a combined endpoint that included CV death, non-fatal MI, HF, cerebrovascular disease (stroke or transient ischaemic attack—TIA), peripheral artery disease, and atrial fibrillation/flutter (AFib). These events include the ones described in the FRS original publication,[2] adding AFib due to its high relevance in LA remodelling.[5]

Participants were interviewed during their scheduled study examinations and by telephone yearly regarding hospitalizations and outpatient procedures. Vital status was checked every 6 months. Inpatient and outpatient medical records and/or death certificates were requested and reviewed by two members of the endpoints committee during the process of adjudication for CV events. Atrial fibrillation or flutter cases were identified based on participants' medical records using a combination of physician documentation of atrial fibrillation or flutter, electrocardiogram tracings and reports, and cardioversion attempts, and documentation of appropriate anti-arrhythmic medication use in the setting of an arrhythmia history. All records were reviewed by two members of the endpoint committee which applied standard outcome definitions contained in a detailed adjudication manual to classify events. Committee consensus resolved eventual disagreements. For the other outcomes, the ascertainment process has been previously described in details.

Statistical analysis

We assessed the performance of LAA and LAD as predictors of CV events in multivariable analyses adjusted for traditional CV risk factors. The FRS is widely used to estimate CV risk in clinical settings using as traditional risk factors: gender, age, BMI, total cholesterol, HDL cholesterol, SBP, use of anti-hypertensive medication, diabetes status, and smoking status. To assess the independent predictive ability of LA size, we adjusted our analysis to the calculated FRS (computing the score) and also ran the same analysis using the FRS covariates independently included in multivariable models (not computing the score). To compute the FRS, we calculated the per cent of risk as first described by D'Agostino *et al.*,[2] but modified the original calculation to include age as a continuous variable in the models (because the CARDIA participants are younger than the ones used in the FRS original publication).

The hazard ratios (HRs) of a 1 standard deviation (SD) difference of LA atrial size were assessed by a multivariable Cox regression analysis adjusted for race and[1] the computed FRS plus age; or[2] the FRS covariates. Receiver operating characteristic (ROC) curves were used to determine the differences in discrimination to predict CV events. The discrimination improvement for the areas under the ROC curves (AUC) was assessed using the method of DeLong *et al.*[13] All models had good calibration as indicated by the Hosmer–Lemeshow test (data not shown). Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated as first described by Pencina *et al.*[14] to evaluate the added predictive ability for LA size to the traditional risk factors.

To calculate the reclassification performance, logistic regression models were used to define four risk groups according to FRS results with or without adding LA size information. The risk groups were defined in each model based on the predicted risk $<$2.5%, 2.5–5.0%, 5.0–$<$10.0%, and $\geq$10% in 20 years, in accordance with advice to select risk categories for reclassification tables that are clinically meaningful.[15] NRI is strongly influenced by the cut-points used for risk stratification, and the most meaningful cut-points for LA size for young adults have not been established. Previous reports used older populations to establish clinically meaningful categories cut-points, but these were thought to be not adequate to a young healthy population as in CARDIA due to a very different base risk for events. Reclassification tables were built and risk groups (for FRS covariates with or without LA information) were cross-tabulated, according to the presence of incident event during the study follow-up period. After LA size information is added to the FRS, a correct reclassification occurs when a participant who did not have an event moves to a lower risk category or when a participant who had an event moves to a higher risk category.

Results

CARDIA participants who attended the Year-5 examination and underwent echocardiography were included in the study (*Table 1*). The mean $\pm$ SD values of LAD indexed to height and BSA were 2.07 $\pm$ 0.27 mm/m and 1.93 $\pm$ 0.24 mm/m^2, respectively. The LAA indexed by height and BSA was, respectively, 9.25 $\pm$ 1.97 mm^2/m and 8.66 $\pm$ 1.74 mm^2/m^2.

Participants were followed in average 19.4 $\pm$ 2.3 years for those who did not have any events. Of the 4082 participants in the LAD cohort, 149 (3.7%) had events: 25.5% CV death, 24.2% non-fatal MI, 17.5% HF, 2.7% peripheral arterial disease, 5.4% TIA, 16.1% stroke, and 8.7% AFib. In the assessment of LAA as a predictor of CV events (n = 2412), 77 (3.2%) participants had events: 24.7% CV death, 28.6% non-fatal MI, 15.6% HF, 2.6% peripheral arterial disease, 3.9% TIA, 15.6% stroke, and 9.1% AFib.

Results for LA dimension

We analysed the independent ability of LAD to predict long-term CV events, adjusted for the calculated FRS or the FRS covariates (*Table 2*). The HRs ranged from 1.19 (95% CI 1.02, 1.39) for LAD/BSA adjusted for the calculated FRS to 1.34 (95% CI 1.12, 1.60) for LAD/height adjusted for FRS covariates. A modest increase in the AUC was found for adding LAD to FRS; in this regard, LAD/height had a slightly superior performance when compared with LAD/BSA (*Table 2*). Although not reaching statistical significance, a trend was found favouring AUC for LAD/height when compared with LAD/BSA (P = 0.13 for models using FRS covariates and P = 0.08 for models using the calculated FRS).

The reclassification tables for adding LAD indexed by height or BSA are summarized in *Table 3*, showing the number of participants reclassified according to the presence or absence of CV event over the 20-year follow-up period. Of the 3933 participants who did not have incident events, 344 (8.8%) were correctly down reclassified when LAD was indexed to height and 280 (7.1%) when LAD was indexed to BSA. Among the 149 participants who had events over the follow-up period, 13 (8.7%) were correctly up reclassified for LAD/height and 9 (6.0%) for LAD/BSA. No statistically significant NRI for LAD plus FRS compared with FRS covariates alone was

Table 1 Participant characteristics at the CARDIA study examination Year 5, overall and in the analytic cohorts for LAD and LAA

Variables	Overall cohort (n = 4352) Mean (SD)	LAD cohort (n = 4082) Mean (SD)	LAA cohort (n = 2412) Mean (SD)
Age (years)	30 (4)	30 (4)	30 (4)
BMI (kg/m^2)	26 (6)	26 (6)	25 (5)
SBP (mmHg)	108 (12)	108 (12)	107 (11)
Total chol (mg/dL)	178 (34)	178 (34)	176 (33)
HDL-C (mg/dL)	53 (14)	53 (14)	53 (14)
	%	%	%
White race	51	52	51
Male gender	45	46	48
Current smoker	29	28	28
Anti-HTN medication	1.6	1.5	1.3
Diabetes	0.9	0.8	0.7

SD, standard deviation; BMI, body-mass index; SBP, systolic blood pressure; LAD, left atrial diameter assessed by M-mode echocardiography; LAA, left atrial area assessed by 2D four-chamber echocardiography; total chol, total cholesterol; HDL-C, high-density lipoprotein cholesterol; anti-HTN medication, anti-hypertensive medication.

Table 2 Cox regression HRs and AUC for LAD predicting CV events (n = 4082; 151 events)

Predictor	FRS covariates		Calculated FRS	
	HR (95% CI)	AUC (95% CI)	HR (95% CI)	AUC (95% CI)
LAD/height	1.34 (1.12, 1.60)	0.774 (0.735, 0.812)	1.28 (1.10, 1.50)	0.768 (0.728, 0.808)
LAD/BSA	1.26 (1.07, 1.48)	0.770 (0.731, 0.809)	1.19 (1.02, 1.39)	0.761 (0.720, 0.801)

HR refers to 1 SD increase. AUC for FRS covariates alone = 0.767 (0.727, 0.807) and for calculated FRS alone = 0.759 (0.718, 0.800). The FRS covariates includes: gender, age, BMI, total cholesterol, HDL, SBP, use of anti-hypertensive medication, diabetes status, and smoking status.
LAD, left atrial diameter; BSA, body surface area; CI, confidence interval; FRS, Framingham 10-year global CV risk score.

found; the NRI values were 0.033 (P = 0.31) and 0.018 (P = 0.53) for LAD/height and LAD/BSA, respectively. A trend in significance was found for IDI, LAD/height had an IDI of 0.0053 (P = 0.09), and LAD/BSA had an IDI of 0.0040 (P = 0.08).

Results for LAA

LAA was assessed as an independent CV event predictor, after adjustment to the calculated FRS or the FRS covariates (*Table 4*). The Cox regression HRs for both indexing methods were statistically significant, ranging from 1.36 (95% CI 1.09, 1.70) for BSA indexation adjusted for the calculated FRS to 1.43 (95% CI: 1.13, 1.80) for indexing LAA by height and adjusting for FRS covariates. No statistical significance was found comparing AUC for LAA indexed by height or BSA (P = 0.61 for models using FRS covariates and P = 0.57 for models using the calculated FRS).

Reclassification tables for adding LAA to risk factors are reported in *Table 5*. Of the 2335 participants who did not have incident events, 246 (10.5%) were correctly down reclassified by adding LAA/height to FRS and 229 (9.8%) by adding LAA/BSA. Among the 77 who had events over the follow-up period, 11 (14.3%) and 12 (15.6%) were correctly up reclassified when LAA was indexed to height and BSA, respectively. Similar to LAD, LAA did not show statistically significant NRI values; the computed NRIs were 0.050 (P = 0.40) and 0.055 (P = 0.36) for LAA indexed by height and BSA, respectively. No significant value was found for IDI regarding LAA, LAA indexed by height had IDI = 0.0047 (P = 0.26), and indexed by IDI = 0.0053 (P = 0.20).

Discussion

We assessed the 20 prediction power for CV events of LAA and LAD in a large bi-racial cohort of young adults. As recommended by the American Heart Association, reclassification statistics were applied to estimate how LA size could aid in risk stratification for young adults.[16] LA size measurements independently predicted clinical outcomes but only modestly improved discrimination and showed no improvement in risk classification. Different indexing methods for LA size were tested for event prediction. In this regard, indexing LAD and LAA by height was slightly better than those by BSA.

CV disease is a rising concern worldwide, frequently presenting as the mortality in the first manifestation of CV disease.[17] The ability to identify high CV risk individuals is essential for planning primary prevention strategies.[1] Young asymptomatic subjects may benefit from early CV risk stratification, but the traditional risk assessment tools

Table 3 Reclassification table: absolute number of participants classified in each risk strata of FRS covariates vs. adding information on LAD

Risk category	No event (n = 3933)				Events (n = 149)			
	FRS + LAD/height				FRS + LAD/height			
	<2.5%	2.5–4.9%	5.0–9.9%	≥10%	<2.5%	2.5–4.9%	5.0–9.9%	≥10%
FRS								
<2.5%	2076	136	0	0	25	5	0	0
2.5–4.9%	195	698	113	3	4	30	3	0
5.0–9.9%	1	107	362	40	0	5	27	5
≥ 10%	0	1	40	161	0	0	1	44
	FRS + LAD/BSA				FRS + LAD/BSA			
FRS								
<2.5%	2100	111	1	0	27	3	0	0
2.5–4.9%	159	755	93	2	3	32	2	0
5.0–9.9%	0	90	391	29	0	4	29	4
≥10%	0	0	31	171	0	0	1	44

LAD, left atrial diameter; BSA, body surface area; FRS, Framingham 10-year global CV risk score.

Table 4 Cox regression HRs and AUC for LAA predicting CV events (n = 2412; 78 events)

Predictor	FRS covariates		Calculated FRS	
	HR (95% CI)	AUC (95% CI)	HR (95% CI)	AUC (95% CI)
LAA/height	1.43 (1.13, 1.80)	0.784 (0.734, 0.834)	1.39 (1.12, 1.73)	0.766 (0.712, 0.819)
LAA/BSA	1.42 (1.13, 1.78)	0.783 (0.732, 0.833)	1.36 (1.09, 1.70)	0.763 (0.709, 0.818)

HR refers to 1 SD increase. In this subsample, AUC for FRS covariates alone = 0.763 (0.710, 0.817) and for calculated FRS alone = 0.749 (0.694, 0.804). The FRS covariates includes: gender, age, BMI, total cholesterol, HDL-C, SBP, use of anti-hypertensive medication, diabetes status, and smoking status.
LAA, left atrial area; BSA, body surface area; CI, confidence interval; FRS, Framingham 10-year global CV risk score.

Table 5 Reclassification table: absolute number of participants classified in each risk strata of FRS covariates vs. adding information on LAA

Risk category	No event (n = 2335)				Events (n = 77)			
	FRS + LAA/height				FRS + LAA/height			
	<2.5%	2.5–4.9%	5.0–9.9%	≥10%	<2.5%	2.5–4.9%	5.0–9.9%	≥10%
FRS								
<2.5%	1339	81	5	0	13	4	0	0
2.5–4.9%	146	327	73	1	1	16	5	0
5.0–9.9%	2	75	157	30	0	4	11	2
≥10%	0	1	22	76	0	0	4	17
	FRS + LAA/BSA				FRS + LAA/BSA			
FRS								
<2.5%	1337	83	4	1	11	6	0	0
2.5–4.9%	138	336	72	1	1	17	4	0
5.0–9.9%	0	73	160	31	0	4	11	2
≥10%	0	1	17	81	0	0	4	17

LAA, left atrial area; BSA, body surface area; FRS, Framingham 10-year global CV risk score.

have not been rigorously evaluated in this age group.[1,18] We expected that LA size, as a validated predictor of CV events, would aid in risk stratification of young adults, particularly those with high risk burden that are underestimated by the FRS.[18]

LA size relates to left ventricular filling pressures and, therefore, diastolic dysfunction. The LA is likely to remodel early before clinical heart disease is established, since diastolic function is more likely to become impaired earlier during progression of cardiac dysfunction. In fact, LA size provides strong prognostic information in patients with established heart disease. Meris *et al.*[19] prospectively followed 610 post-MI patients from the VALIANT echocardiography study and showed that LA volume indexed by BSA was an independent predictor of all-cause mortality or HF hospitalization. Vazquez *et al.*[20] investigated ambulatory patients with chronic HF and showed that LA size was a strong predictor of all-cause death, pump-failure death, or sudden cardiac death.

Although the LA in many cases enlarges in a non-uniform 3D geometry, both M-mode and 2D echocardiography techniques have become established to estimate LA size.[5,21] It has been shown that 2D measurements as of LAA and particularly LA volume are more accurate to assess LA size, as they account for eccentric remodelling. M-mode LA anterior–posterior diameter is a highly precise measure, probably due to the simplicity of image acquisition and interpretation. However, more steps are required to compute 2D volumes, especially when assessing biplanar LA volume, which likely affects the measurement precision.

Tsang *et al.* assessed American Society of Echocardiography-based categories of indexed LA volume, LA four-chamber area, and indexed LAD in 317 patients (70 years in average) in sinus rhythm who were referred for a general medical consultation and followed them over a mean period of 3.5 $\pm$ 2.3 years for new events of AFib, stroke, TIA, MI, coronary revascularization, HF, and CV death. In this elderly population of outpatients, the authors show slightly better area under the curve for LA volume categories compared with area and diameter, but failed to report superior results for outcome prediction HRs.[22] Cameli *et al.* reported similar results after following 312 adults (71 years in average) in sinus rhythm over 3.1 $\pm$ 1.4 years. Although the assessment of LA function by speckle tracking echocardiography had the most robust results, sensitivity and specificity confidence intervals overlapped for LA volume, LAA, and LA diameter categories.[23]

The role of LA size predicting global CV events in early adulthood, however, is less well understood. We assessed a substantially large cohort of young healthy individuals over a 20-year follow-up period. In our study, both LAA and LAD measured in early adulthood are able to independently predict a combined endpoint of CV events. It is unlikely that LA eccentric remodelling would be significantly prevalent in our young and generally healthy population. Compared with LA volume, LAA and LAD are simpler measurements, which may reduce technical variation. Using both LAA and M-mode diameter, we acquired LA linear and 2D measurements, which we believe are adequate to the young and healthy CARDIA cohort. Moreover, the more recently recommended statistical evaluation that includes Cox regression models as well as discrimination, calibration, and reclassification[16] had not been assessed until now to establish the additional predictive value of LA size in CV risk stratification.

When added to the FRS CV risk factors, LA size improved modestly discrimination in our study, as assessed by the AUC. In fact, the FRS CV risk score alone already showed powerful CV event prediction ability. This FRS good performance in our young cohort may be the major factor related to the modest increases in discrimination found in our study.[24] This also may partially explain the inability to correctly reclassify risk by using NRI and IDI assessment. NRI performance for LA size may also be influenced by the lack of pathological remodelling in a young cohort of generally healthy individuals. LA size may be more useful improving risk classification in subgroups of young adults with risk factors, but the low number of events in our young population would affect the statistical power to investigate multiple subgroups of participants in CARDIA. A prospective study dedicated to a young population with comorbidities would be needed to answer this question.

The best way to index heart measures to body size is not totally clear, as indexing appears to affect the performance of cardiac parameters to predict CV events.[25,26] Height seems to be the most adequate indexing method for heart parameters in mathematical models.[25] Moreover, compared with BSA, indexing LA size by height was more robust to assess longitudinal changes in the CARDIA cohort.[8] Although no definitive difference was reported in our study, HRs consistently favoured indexing LA size by height and we found a statistical trend in the LAD AUC models in the same direction. Indexing LA by height in young adults may also be the most appropriate method to predict long-term events. Although the reports favour LA indexation by height in the CARDIA study, these findings should be further tested in other cohorts.

Our study also showed that LAA and LAD measured in young adulthood can independently predict CV events over a 20-year period and may lead to a modest increment in discrimination compared with risk factors alone. However, these measures did not improve reclassification of participants above conventional CV risk factors. Although no definitive conclusion regarding LA indexing can be driven from our study, HRs consistently favoured indexing LA size by height and a trend in discrimination also favoured LAD/height. Further research on the value of LA size in event prediction should focus on identifying subgroups of young adults (possibly with multiple risk factors) who may benefit of the use of LA size information to better stratify CV risk.

Limitations

In this study, we used LAA and LAD assessment that is practical, low cost, and validated, but may lack accuracy to completely account for LA eccentric remodelling. At the time that the CARDIA Year 5 was performed, the M-mode technique was the standard assessment of LA size and the only 2D LA assessment was four-chamber LAA, feasible in a limited number of participants. Attempts to reassess 2D images in Year 5 are challenged by image deterioration over time (images were originally recorded in video home system tapes).

The incident CV events affected 3.7% of the cohort, which is lower than other prospective studies. It may be explained by the low base risk of this young population of healthy individuals. The relatively low number of events affects the statistical power in subgroup

analyses. Therefore, we could not assess how LA size would perform in subgroups of participants with specific risk factors.

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Conflict of interest: The authors have no competing interests in this study.

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Objetivo Secundário

Testar a hipótese de que massa ventricular esquerda prediz desenvolvimento de disfunção ventricular esquerda em 20 anos de seguimento

Artigo 3 - Relation of Left Ventricular Mass at Age 23 to 35 Years to Global Left Ventricular Systolic Function 20 Years Later: from the Coronary Artery Risk Development in Young Adults Study

Relation of Left Ventricular Mass at Age 23 to 35 Years to Global Left Ventricular Systolic Function 20 Years Later (from the Coronary Artery Risk Development in Young Adults Study)

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Left ventricular (LV) mass and the LV ejection fraction (LVEF) are major independent predictors of future cardiovascular disease. The association of LV mass with the future LVEF in younger populations has not been studied. The aim of this study was to investigate the relation of LV mass index (LVMI) at ages 23 to 35 years to LV function after 20 years of follow-up in the Coronary Artery Risk Development in Young Adults (CARDIA) study. CARDIA is a longitudinal study that enrolled young adults in 1985 and 1986. In this study, participants with echocardiographic examinations at years 5 and 25 were included. LVMI and the LVEF were assessed using M-mode echocardiography at year 5 and using M-mode and 2-dimensional imaging at year 25. Statistical analytic models assessed the correlation between LVMI and LV functional parameters cross-sectionally and longitudinally. A total of 2,339 participants were included. The mean LVEF at year 25 was 62%. Although there was no cross-sectional correlation between LVMI and the LVEF at year 5, there was a small but statistically significant negative correlation between LVMI at year 5 and the LVEF 20 years later ($r = -0.10$, $p < 0.0001$); this inverse association persisted for LVMI in the multivariate model. High LVMI was an independent predictor of systolic dysfunction (LVEF <50%) 20 years later (odds ratio 1.46, $p = 0.0018$). In conclusion, LVMI in young adulthood in association with chronic risk exposure affects systolic function in middle age; the antecedents of heart failure may occur at younger ages than previously thought. **(Am J Cardiol 2014;113:377−383)**

Left ventricular (LV) mass and the LV ejection fraction (LVEF) are major independent predictors of future cardiovascular disease.[1−3] Quantification of LV function and geometry provides significant information for the evaluation and management of patients with heart disease.[4,5] In cross-sectional studies, LV mass has been associated with decreased regional systolic function.[6] Furthermore, in an elderly population, increased LV mass has shown predictive ability for a depressed LVEF over a 5-year follow-up period.[7] The Coronary Artery Risk Development in Young Adults (CARDIA) study prospectively assessed a young adult biracial cohort and reported a depressed LVEF as a strong predictor of incident heart failure in black participants over a 10-year follow-up period.[2] However, the association of LV mass with the future LVEF in younger populations has not been studied. Using the CARDIA cohort, we investigated the role of greater myocardial mass in young adults as a predictor of LV dysfunction over a 20-year follow-up period, evaluating the association between LV mass at the ages of 23 to 35 years with the LVEF 20 years later. We also explored the relations of LV mass with LV volumes. We hypothesized that LV mass and ejection capability are not necessarily strongly correlated early in life (when mass is generally normal and ejection power is at its peak) but that small echocardiographic differences in LV mass early in life predict the development of reduced ejection performance as early as middle adulthood.

Methods

CARDIA is a National Institutes of Health−sponsored multicenter study designed to investigate the development of coronary disease in young adults. Initially, 5,115 black and white men and women 18 to 30 years of age at the time of enrollment (1985 to 1986) were recruited and examined at 4 CARDIA field centers in Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Echocardiography was performed in the cohort at the follow-up year 5 and 25 examinations. The overall design and

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See page 382 for disclosure information.

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objectives of the CARDIA study have been presented elsewhere.[8] Of the 4,352 participants attending the year 5 examination, 4,243 participants underwent echocardiography. Of the 3,498 participants attending the year 25 examination, 3,474 underwent echocardiography. For this study, we evaluated 3,145 participants with echocardiographic assessments at CARDIA examinations for year 5 (baseline, from 1990 to 1991) and year 25 (2010 to 2011). Exclusion criteria were pregnancy at either exam (n = 38), year 5 LVEF <50% (n = 88), and absence of specific echocardiographic variables or other risk factors (n = 680). The remaining 2,339 patients were included in our analytic cohort.

CARDIA participants at year 5 underwent 2-dimensionally guided M-mode echocardiography to assess LV mass, as previously described.[9] LV functional parameters (LV end-diastolic volume [LVEDV], LV end-systolic volume [LVESV], and the LVEF) at the year 5 examination were assessed using M-mode echocardiography in a parasternal acoustic window, using the Teichholz technique.[10] CARDIA participants at the year 25 examination underwent 2-dimensinoally guided M-mode echocardiography in a parasternal window and 2-dimensional (2D) 4-chamber apical views following American Society of Echocardiography recommendations.[11] All studies were recorded in digital format using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Tokyo, Japan) and read at the Johns Hopkins University Echocardiography Reading Center in Baltimore, Maryland. Measurements were made by experienced analysts from digitized images using a standard software off-line image analysis system (Digisonics, Inc., Houston, Texas). LV mass index (LVMI) was acquired after dividing LV mass by body surface area at years 5 and 25.[10] The LVEF was assessed using the formula LVEF = [(LVEDV − LVESV)/LVEDV] × 100. At year 5, LVEDV and LVESV were assessed using the M-mode technique (Teichholz method). At year 25, LVEDV and LVESV were measured from apical 2D 4-chamber images. The LVEFs at year 25 between M-mode and 2D imaging were positively correlated ($r = 0.41$, $p < 0.0001$), and the mean difference was 8.2% (the M-mode LVEF was greater than the 2D LVEF; $p < 0.0001$). For the end point of LV volumes, LVEDV and LVESV were indexed to body surface area (LVEDV and LVESV).

Standardized protocols were used to measure height, weight, cholesterol, heart rate, blood pressure, smoking, educational level, and physical activity at baseline (year 5).[8] Gender and race were self-reported by the study participants. We used the average of the second and third of 3 blood pressure measurements after 5 minutes of rest; blood pressure was measured by random-zero sphygmomanometry at year 5 and using an Omron (Kyoto, Japan) device at year 25. Weight (in kilograms) and height (in meters) were measured in light clothing, and body mass index was calculated. Cigarette smoking was determined by self-report at each examination. Physical activity (in exercise units) was determined by a questionnaire.[12] Diabetes mellitus was determined as fasting glucose ≥126 mg/dl or the use of medication for diabetes. We used fasting glucose level at the year 0 examination as a year 5 variable because glucose was not measured at year 5. Total cholesterol, triglycerides, and high-density lipoprotein cholesterol were determined using an enzymatic assay; low-density lipoprotein cholesterol was calculated using the Friedewald equation.[13] Educational level was categorized into 2 groups: ≤12 years or equivalent and >12 years. History of heart disease at year 25 was determined using a questionnaire.

Descriptive statistics for the participants were summarized using means and SDs for continuous variables. Categorical variables are presented as numbers and percentages. Chi-square tests and F tests were used to compare the differences in the prevalence of various risk factors among the subgroups. Univariate linear regression analysis was conducted to assess the association of the LVEF at years 5 and 25. The correlations between LV mass and LV functional parameters (LVEDV, LVESV, and the LVEF) were assessed on a cross-sectional basis at years 5 and 25 to evaluate whether a longitudinal association between LV mass and LV functional parameters could be explained by a baseline cross-sectional relation between the 2 parameters. A longitudinal analysis explored the relations between year 5 LV mass and year 25 LV functional parameters. We created 3 multivariate linear regression analysis models to evaluate the association of year 5 LVMI with the year 25 LVEF. In model 1, we adjusted for the following year 5 variables: age, gender, and race. Model 2 was adjusted for model 1 plus educational level, systolic blood pressure, heart rate, body mass index, diabetes status, use of antihypertensive medications, smoking status (current smokers or former or nonsmokers), total physical activity score, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Model 3 was adjusted for model 2 plus the year 5 LVEF.

For a categorical approach, systolic dysfunction at year 25 was defined as an LVEF <50%.[14,15] We explored relations between LVMI at year 5 (per SD increase) and clinically relevant systolic dysfunction at year 25 using univariate and multivariate logistic regression analysis, reporting odds ratios and 95% confidence intervals. In multivariate logistic regression models, LVMI was adjusted for the same variables used in the multivariate linear regression analysis models. In additional analyses, the association between year 5 LVMI and year 25 LVEDV index or LVESV index was explored, because the LVEF is computed using measurements of LVEDV and LVESV. In model 1, we adjusted for the year 5 covariates age, gender, race, educational level, systolic blood pressure, heart rate, body mass index, diabetes status, use of antihypertensive medications, smoking status (current smokers or former or nonsmokers), physical activity score, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Model 2 was adjusted for model 1 plus year 5 LVEDV index or LVESV index, according to the dependent variable under investigation. Two-sided p values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using JMP version 10.0 for Windows (SAS Institute Inc., Cary, North Carolina) and Stata version 11.0 (Stata Corp LP, College Station, Texas).

Results

Demographic and risk factor data for the 2,339 CARDIA participants at baseline and echocardiographic parameters at years 5 and 25 are listed in Table 1. The study population was

Table 1
Participant characteristics at the year 5 examination

Variable	Systolic Dysfunction at Year 25 (n = 71)	Normal Systolic Function at Year 25 (n = 2,268)	p Value
Age (yrs)	30.2 ± 3.9	30.1 ± 3.6	0.8183
Men	45 (63.4%)	960 (42.3%)	0.0004
Black	42 (59.2%)	1,005 (44.3%)	0.0133
Educational level ≤12 yrs	24 (33.8%)	575 (25.4%)	0.1082
Body mass index (kg/m^2)	28.1 ± 6.2	25.3 ± 5.2	<0.0001
Body surface area (m^2)	1.96 ± 0.22	1.84 ± 0.21	<0.0001
Heart rate (beats/min)	68.4 ± 9.2	67.4 ± 9.7	0.3715
Systolic blood pressure (mm Hg)	111.1 ± 10.1	106.6 ± 10.8	0.0005
Diastolic blood pressure (mm Hg)	71.6 ± 9.4	68.3 ± 9.5	0.0044
Hypertension	4 (5.6%)	78 (3.4%)	0.3221
Diabetes mellitus	0 (0%)	38 (1.7%)	0.2715
Current smokers	22 (31.0%)	557 (24.6%)	0.2166
Using antihypertensive medications	1 (1.4%)	31 (1.4%)	0.9763
Physical activity score (exercise units)	401 ± 331	383 ± 294	0.6087
Total cholesterol (mg/dl)	187.2 ± 34.2	177.2 ± 33.3	0.0171
High-density lipoprotein cholesterol (mg/dl)	50.2 ± 13.8	54.1 ± 13.6	0.0239
Low-density lipoprotein cholesterol (mg/dl)	117.2 ± 33.1	108.0 ± 31.5	0.0223
Triglycerides (mg/dl)	96.5 ± 77.2	73.4 ± 46.7	0.0143
Echocardiographic variables			
LV mass (g)			
Year 5	173.9 ± 49.3	145.1 ± 41.9	<0.0001
Year 25	206.2 ± 78.1	165.0 ± 48.6	<0.0001
LVMI (g/m^2)			
Year 5	88.7 ± 22.3	78.3 ± 18.2	<0.0001
Year 25	99.5 ± 33.6	84.0 ± 20.2	<0.0001
LVEDV index (ml/m^2)			
Year 5	69.0 ± 11.8	63.4 ± 11.3	<0.0001
Year 25	66.4 ± 15.7	56.0 ± 11.6	<0.0001
LVESV index (ml/m^2)			
Year 5	26.6 ± 6.6	22.0 ± 6.2	<0.0001
Year 25	36.6 ± 10.5	21.4 ± 6.2	<0.0001
LVEF (%)			
Year 5	61.5 ± 6.4	65.4 ± 6.9	<0.0001
Year 25	45.2 ± 5.4	62.1 ± 6.3	<0.0001

Data are expressed as mean ± SD or number (percentage).

43.0% male and 44.8% black, with a mean age of 30.1 years. LVMI increased over the 20-year follow-up period, while LV volumes and the LVEF decreased in the same period. There were significant differences in all echocardiographic parameters between year 5 and year 25 ($p < 0.0001$). LVMI of the whole population was in the normal range. LVMI for those who developed LV systolic dysfunction was greater than for those who did not develop LV systolic dysfunction (88.7 vs 78.3 g/m^2, $p < 0.0001$). LVMI in young adults who developed LV systolic dysfunction was similar to the upper quartile of LVMI distribution in the full cohort at year 5. The cross-sectional correlations between LV mass and the LVEF were close to zero at year 5 ($r = -0.02$, $p = 0.91$) and at year 25 ($r = -0.002$, $p = 0.32$). When LV mass was indexed to body surface area, a modest but significant correlation was found with the LVEF at year 25 ($r = 0.07$, $p = 0.0005$), but no relation was found at year 5. In a longitudinal univariate analysis, LV mass and LVMI measured at baseline were significantly associated with the LVEF 20 years later (in both cases, $r = -0.1$, $p < 0.0001$). This significant relation remained after adjustment for anthropometrics, risk factors, and the LVEF at year 5 (Table 2). There were 71 (3.0%) participants with LVEFs <50% at year 25; of these, 83.1% did not self-report any history of heart disease. In a univariate analysis, each 1-SD increase in LVMI at baseline predicted an LVEF <50% after 20 years (odds ratio 1.59, 95% confidence interval 1.30 to 1.94, $p < 0.0001$). This association was consistent (odds ratio 1.46, 95% confidence interval 1.15 to 1.83, $p = 0.0018$) after adjustment for anthropometrics, risk factors, and the LVEF at year 5. There were negative correlations between LVEDV index and the LVEF at years 5 and 25 cross-sectionally (year 5: $r = -0.08$, $p < 0.0001$; year 25: $r = -0.26$, $p < 0.0001$) and between LVEDV index at baseline and the LVEF at year 25 ($r = -0.13$, $p < 0.0001$). LVMI at baseline had a direct positive correlation with LVEDV index ($r = 0.27$, $p < 0.0001$) and LVESV index ($r = 0.24$, $p < 0.0001$) at year 25. This association remained after adjustment for other risk factors and baseline echocardiographic parameters (Table 3).

Discussion

In this study, we assessed the relation between LVMI and LV function over a 20-year follow-up period in a large,

Table 2
Association between left ventricular mass index at the year 5 examination and the left ventricular ejection fraction at the year 25 examination (n = 2,339)

Year 5 Exam Variable	Model 1 ($R^2 = 0.02$)§		Model 2 ($R^2 = 0.02$)§		Model 3 ($R^2 = 0.04$)§	
	β Coefficient (Standardized)	95% CI	β Coefficient (Standardized)	95% CI	β Coefficient (Standardized)	95% CI
LVMI	−0.03 (−0.07)	(−0.04 to −0.01)‡	−0.03 (−0.07)	(−0.04 to −0.01)§	−0.03 (−0.08)	(−0.05 to −0.01)‡
Age	0.10 (0.05)	(0.02 to 0.18)*	0.10 (0.05)	(0.02 to 0.18)*	0.09 (0.05)	(0.01 to 0.16)*
Male gender	−0.64 (−0.09)	(−0.94 to −0.34)§	−0.70 (−0.10)	(−1.04 to −0.35)§	−0.49 (−0.07)	(−0.84 to −0.14)†
Black	0.04 (0.006)	(−0.24 to 0.32)	0.11 (0.02)	(−0.20 to 0.41)	0.12 (0.02)	(−0.19 to 0.42)
Educational level ≤12 yrs			−0.08 (−0.01)	(−0.42 to 0.26)	−0.06 (−0.007)	(−0.40 to 0.27)
Systolic blood pressure			−0.01 (−0.01)	(−0.04 to 0.02)	−0.02 (−0.03)	(−0.05 to 0.01)
Body mass index			−0.02 (−0.01)	(−0.08 to 0.04)	−0.02 (−0.02)	(−0.08 to 0.04)
Heart rate			−0.04 (−0.05)	(−0.07 to −0.01)*	−0.04 (−0.05)	(−0.07 to −0.01)*
Using hypertensive medications (vs none)			0.05 (0.002)	(−1.18 to 1.28)	−0.19 (−0.007)	(−1.41 to 1.03)
Diabetes mellitus			0.20 (0.008)	(−0.85 to 1.24)	0.27 (0.01)	(−0.77 to 1.30)
Current smoking (vs former/never)			0.12 (0.02)	(−0.21 to 0.46)	0.16 (0.02)	(−0.17 to 0.50)
Physical activity score			−0.002 (−0.01)	(−0.001 to 0.001)	−0.0003 (−0.001)	(−0.001 to 0.001)
High-density lipoprotein cholesterol			−0.01 (−0.02)	(−0.03 to 0.01)	−0.01 (−0.02)	(−0.03 to 0.01)
Low-density lipoprotein cholesterol			−0.002 (−0.008)	(−0.01 to 0.01)	−0.001 (−0.005)	(−0.01 to 0.01)
M-mode LVEF					0.16 (0.16)	(0.12 to 0.20)§

Model 1 adjusted for age, gender, and race at the year 5 examination. Model 2 adjusted for model 1 plus educational level, systolic blood pressure, body mass index, heart rate, use of antihypertensive medications, diabetes status, current smoking, intensity score, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol at the year 5 examination. Model 3 adjusted for model 2 plus the LVEF at the year 5 examination.

CI = confidence interval.

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.
§ $p < 0.0001$.

biracial cohort of young, generally healthy adults. Although LVMI and the LVEF were not related at baseline, higher LVMI was a strong predictor of a lower LVEF after 20 years. High LVMI was also related to high LV volumes 20 years later. Our results suggest that LVMI in young adulthood is an early marker of future impaired cardiac performance. When comparing those with LV systolic dysfunction and normal systolic function at year 25, there were significant difference for gender, race, body mass index, blood pressure, and LV structure and function at year 5, suggesting that chronic risk exposure and cardiac remodeling interact in producing future systolic dysfunction.

In cross-sectional analyses, LV mass and the LVEF were not related at either year 5 or year 25; there was a modest positive relation when LV mass was indexed to body surface area at year 25. Previous cross-sectional studies have shown an inverse relation between LV mass and systolic function in middle-aged to old populations.[6,16] Compared with the Strong Heart Study (SHS), fewer CARDIA participants had LVEFs <50% at years 5 and 25. Furthermore, LVMI was lower in our study than the SHS,[16] probably reflecting the younger, healthier profile of the CARDIA cohort.

A low LVEF is a major independent predictor of future heart failure.[2] A previous study reported that asymptomatic systolic dysfunction may be ≥2 times as common as symptomatic heart failure.[17] Redfield et al[14] reported that systolic dysfunction is frequently present in subjects without clinically recognized heart failure. Similarly, Wang et al[3] reported that asymptomatic LV systolic dysfunction predicts a two- to fourfold higher risk for heart failure and death compared with normal systolic function. In the Studies of Left Ventricular Dysfunction (SOLVD) trial, patients with low LVEFs had a higher cumulative rate of all-cause mortality than those with high LVEFs for 12 months; those with low LVEFs and high LV mass had the highest mortality rate.[18]

In cohort studies from populations older than the CARDIA cohort, LV mass contributed to incidence of heart failure.[2,19–21] In the Multi-Ethnic Study of Atherosclerosis (MESA), Cheng et al[22] reported that cardiac remodeling over middle to late adult life is characterized by a distinct pattern of increased LV mass/volume ratio and decreasing LV volumes by magnetic resonance imaging. This pattern was confirmed by analysis of echocardiographic measures in the Framingham Heart Study with increasing LV wall thickness and decreasing LV dimensions with advancing age.[23] Similarly, MESA reported that LVEDV as well as LV mass were predictors of incident heart failure.[24] LVESV has also been documented as a predictor of cardiovascular disease.[4] The Cardiovascular Health Study (CHS) investigators found that, in an elderly population, increased baseline LV mass was an independent risk factor for the development of a depressed LVEF 5 years latert.[7] Our data suggest that increased LV mass as a young adult may initiate the process at an earlier age than previously reported.

Our study findings indicate that exposure to cardiovascular risk factors at young age leads to early cardiac remodeling and LV systolic dysfunction. Advancing age and gender may also have an effect on myocardial remodeling and deformations.[23,25,26] These mechanisms may have an effect on the decreased LVEF.[23,25] Elevated heart rate at

Table 3
Association between left ventricular mass index at the year 5 examination and left ventricular end-systolic volume index or left ventricular end-systolic volume index at the year 25 examination (n = 2,339)

Year 5 Exam Variable	LVESV Index				LVESV Index			
	Model 1 ($R^2 = 0.15$)§		Model 2 ($R^2 = 0.18$)§		Model 1 ($R^2 = 0.11$)§		Model 2 ($R^2 = 0.16$)§	
	β Coefficient (Standardized)	95% CI	β Coefficient (Standardized)	95% CI	β Coefficient (Standardized)	95% CI	β Coefficient (Standardized)	95% CI
LVMI	0.10 (0.15)	(0.07 to 0.13)§	0.03 (0.05)	(0.003 to 0.06)*	0.05 (0.14)	(0.04 to 0.07)§	0.03 (0.08)	(0.01 to 0.05)§
Age	−.004 (−0.01)	(−0.17 to 0.08)	−0.03 (−0.009)	(−0.16 to 0.09)	−0.07 (−0.03)	(−0.14 to 0.01)	−0.05 (−0.03)	(−0.12 to 0.02)
Male gender	2.62 (0.22)	(2.06 to 3.18)§	2.59 (0.22)	(2.04 to 3.14)§	1.44 (0.21)	(1.11 to 1.77)§	1.21 (0.18)	(0.89 to 1.54)§
Black	−0.38 (−0.03)	(−0.88 to 0.11)	−0.06 (−0.005)	(−0.55 to 0.43)	−0.15 (−0.02)	(−0.44 to 0.14)	−0.03 (−0.005)	(−0.32 to 0.25)
Educational level ≤12 yrs	0.01 (0.0005)	(−0.54 to 0.55)	−0.07 (−0.005)	(−0.60 to 0.47)	0.09 (0.01)	(−0.23 to 0.41)	0.04 (0.005)	(−0.27 to 0.35)
Systolic blood pressure	0.09 (0.08)	(0.05 to 0.14)‡	0.10 (0.09)	(0.06 to 0.15)§	0.04 (0.07)	(0.02 to 0.07)†	0.05 (0.09)	(0.03 to 0.08)§
Body mass index	−0.06 (−0.03)	(−0.15 to 0.04)	−0.03 (−0.01)	(−0.12 to 0.07)	−0.002 (−0.002)	(−0.06 to 0.05)	0.01 (0.009)	(−0.04 to 0.07)
Heart rate	−0.11 (−0.09)	(−0.16 to −0.06)§	−0.10 (−0.08)	(−0.14 to −0.05)‡	−0.02 (−0.02)	(−0.05 to 0.01)	−0.01 (−0.02)	(−0.04 to 0.02)
Using hypertensive medications (vs none)	1.53 (0.03)	(−0.45 to 3.51)	1.22 (0.02)	(−0.73 to 3.16)	0.37 (0.01)	(−0.79 to 1.54)	0.53 (0.02)	(−0.61 to 1.66)
Diabetes mellitus	−1.33 (−0.03)	(−3.01 to 0.35)	−1.36 (−0.03)	(−3.01 to 0.29)	−0.68 (−0.03)	(−1.69 to 0.31)	−0.76 (−0.03)	(−1.72 to 0.21)
Current smoking (vs former/never)	0.22 (0.02)	(−0.32 to 0.76)	0.24 (0.02)	(−0.29 to 0.78)	0.04 (0.005)	(−0.28 to 0.36)	0.01 (0.002)	(−0.30 to 0.33)
Physical activity score	0.002 (0.05)	(0.0003 to 0.004)*	0.002 (0.04)	(0.0002 to 0.003)*	0.001 (0.005)	($-2.53e^{-5}$ to 0.002)	0.001 (0.04)	($2.32e^{-5}$ to 0.002)*
High-density lipoprotein cholesterol	0.01 (0.007)	(−0.03 to 0.04)	0.004 (0.004)	(−0.03 to 0.04)	0.01 (0.04)	(−0.01 to 0.03)	0.005 (0.01)	(−0.02 to 0.03)
Low-density lipoprotein cholesterol	−0.01 (−0.01)	(−0.02 to 0.01)	−0.02 (−0.005)	(−0.02 to 0.01)	−0.001 (−0.002)	(−0.01 to 0.01)	0.001 (0.03)	(−0.01 to 0.01)
LVEDV index			0.21 (0.2)	(0.17 to 0.26)§				
LVESV index							0.26 (0.23)	(0.22 to 0.30)§

Model 1 adjusted for age, gender, race, educational level, systolic blood pressure, body mass index, heart rate, use of antihypertensive medications, diabetes status, current smoking, intensity score, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol at the year 5 examination. Model 2 adjusted for model 1 plus LVEDV index or LVESV index at the year 5 examination.

CI = confidence interval.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.001$.

§ $p < 0.0001$.

rest is also associated with LV systolic dysfunction and is a prognostic indicator in cardiovascular mortality and morbidity.[27] Heart rate is a major determinant of cardiac energy metabolism, supporting a possible explanation for the prognostic role of heart rate.[27] Additionally, genetic factors may also be implicated in the cardiac remodeling pathway, starting early in life. The Framingham study suggested the association between sarcomere protein gene mutation in patients with unexplained increased LV wall thickness.[28] Our findings convey the need for a reliable assessment of clinically relevant cardiac remodeling in early life. Thus, our findings suggest that maintenance of cardiovascular risk factors in early life is clinically very important to prevent LV systolic dysfunction and possibly heart failure later in life.

Limitations include the use of different echocardiographic equipment and sonographers at the year 5 and 25 examinations, which may have affected the comparability of LV mass calculations, because in the later examinations, harmonic imaging was used. We used different techniques to compute the LVEF at years 5 and 25.[29] We also did not include an assessment of incident heart failure in our study, because of the small number of patients affected; future studies should address the role of LVMI in predicting incident heart failure in young adults.

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Disclosures

The authors have no conflicts of interest to disclose.

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Objetivo Secundário

Testar a hipótese de que disfunção diastólica prediz insuficiência cardíaca e fibrilação atrial em 8 anos de seguimento

Artigo 4 - Diastolic function assessed from tagged MRI predicts heart failure and atrial fibrillation over an 8-year follow-up period: the multi-ethnic study of atherosclerosis

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Diastolic function assessed from tagged MRI predicts heart failure and atrial fibrillation over an 8-year follow-up period: the multi-ethnic study of atherosclerosis

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Objectives The strain relaxation index (SRI), a novel diastolic functional parameter derived from tagged magnetic resonance imaging (MRI), is used to assess myocardial deformation during left ventricular relaxation. We investigated whether diastolic function indexed by SRI predicts heart failure (HF) and atrial fibrillation (AF) over an 8-year follow-up.

Methods As a part of the multi-ethnic study of atherosclerosis, 1544 participants free of known cardiovascular disease (CVD) underwent tagged MRI in 2000–02. Harmonic phase analysis was used to compute circumferential strain. Standard parameters, early diastolic strain rate (EDSR) and the peak torsion recoil rate were calculated. An SRI was calculated as difference between post-systolic and systolic times of the strain peaks, divided by the EDSR peak. It was normalized by the total interval of relaxation. Over an 8-year follow-up period, we defined AF ($n = 57$) or HF ($n = 36$) as combined ($n = 80$) end-points. Cox regression assessed the ability of SRI to predict events adjusted for risk factors and markers of subclinical disease. Integrated discrimination index (IDI) and net reclassification index (NRI) of SRI, compared with conventional indices, were also assessed.

Results The hazard ratio for SRI remained significant for the combined HF and AF end-points as well as for HF alone after adjustment. For the combined end-point, IDI was 1.5% ($P < 0.05$) and NRI was 11.4% ($P < 0.05$) for SRI. Finally, SRI was more robust than all other existing cardiovascular magnetic resonance diastolic functional parameters.

Conclusion SRI predicts HF and AF over an 8-year follow-up period in a large population free of known CVD, independent of established risk factors and markers of subclinical CVD.

Keywords Heart failure • Atrial • Fibrillation • Diastole • Magnetic resonance imaging

Introduction

Left ventricular diastolic dysfunction is a highly prevalent condition with strong associations with heart failure (HF) and atrial fibrillation (AF) established in previous cross-sectional studies. It has traditionally been thought that there is a similar pathophysiological mechanism underlying both diastolic HF and AF, secondary to abnormal diastolic function leading to elevated end-diastolic pressure; however, the specific role of abnormal myocardial diastolic deformation in this causation chain remains largely unclear[1–6].

Myocardial circumferential strain and strain rate using cardiovascular magnetic resonance (CMR)-tagged images have been shown to accurately and reproducibly quantify deformation of the left ventricle (LV) through systole and diastole.[7] Evaluation of diastolic function

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using CMR has, however, not been firmly established despite a number of prior efforts.[8–11] Early diastolic strain rate (EDSR) and torsion recoil rate have been used as diastolic parameters, but have not yet been shown to predict cardiovascular events.[8–10,12]

In this prospective study, strain relaxation index (SRI), a measure of diastolic function based on strain from tagged magnetic resonance imaging (MRI), is introduced. The ability of SRI to predict incident HF, AF, and the combination of HF with AF in a large asymptomatic multi-ethnic population over an 8-year follow-up period is tested, and compared with the predictive abilities of EDSR and the torsion recoil rate. The improvement in discrimination and reclassification of events with the addition of the different diastolic functional parameters over and above conventional risk factors and markers of subclinical cardiovascular diseases (CVDs) is investigated.

Methods

Theoretical framework of strain relaxation index

Figure 1 illustrates the deformation curves through the cardiac cycle. During the cardiac cycle, the circumferential strain reaches a minimum value (maximal shortening) at the peak systolic strain. In sequence, early left ventricular relaxation starts, followed shortly by the closure of the aortic valve (AVC). During the isovolumic relaxation time (IVRT), a positive peak can be observed in the circumferential strain rate curve following the AVC.[13] The post-systolic strain peak, a minimum in the strain curve, can be observed at the end of the IVRT. After the opening of the mitral valve, a positive peak can be observed in the strain rate curve, the peak early diastolic strain rate.[8]

The greater the difference between time to systolic and post-systolic strain peaks in the early stage of cardiac relaxation, the longer it takes to achieve the pressure drop required for diastolic filling. This is similar to the IVRT, which increases in the case of diastolic dysfunction.[14–16] Moreover, the early diastolic strain rate (EDSR) decreases with diastolic dysfunction, indicating stiffer tissue.[8] Therefore, the combination of early cardiac relaxation and tissue relaxation properties is proposed as an accurate indicator of diastolic LV function. SRI was calculated as follows:

$$\mathrm{SRI} = \frac{[(T_{\mathrm{pos}} - T_{\mathrm{sys}})/(\mathrm{RR}_{\mathrm{Interval}} - T_{\mathrm{sys}})]}{\mathrm{EDSR}}.$$

The SRI was calculated as the difference between post-systolic (T_{pos}) and systolic (T_{sys}) times of the strain peaks divided by the early diastolic strain rate (EDSR) peak. The time difference was normalized by the difference between the cardiac inter-beat interval and the time-to-peak

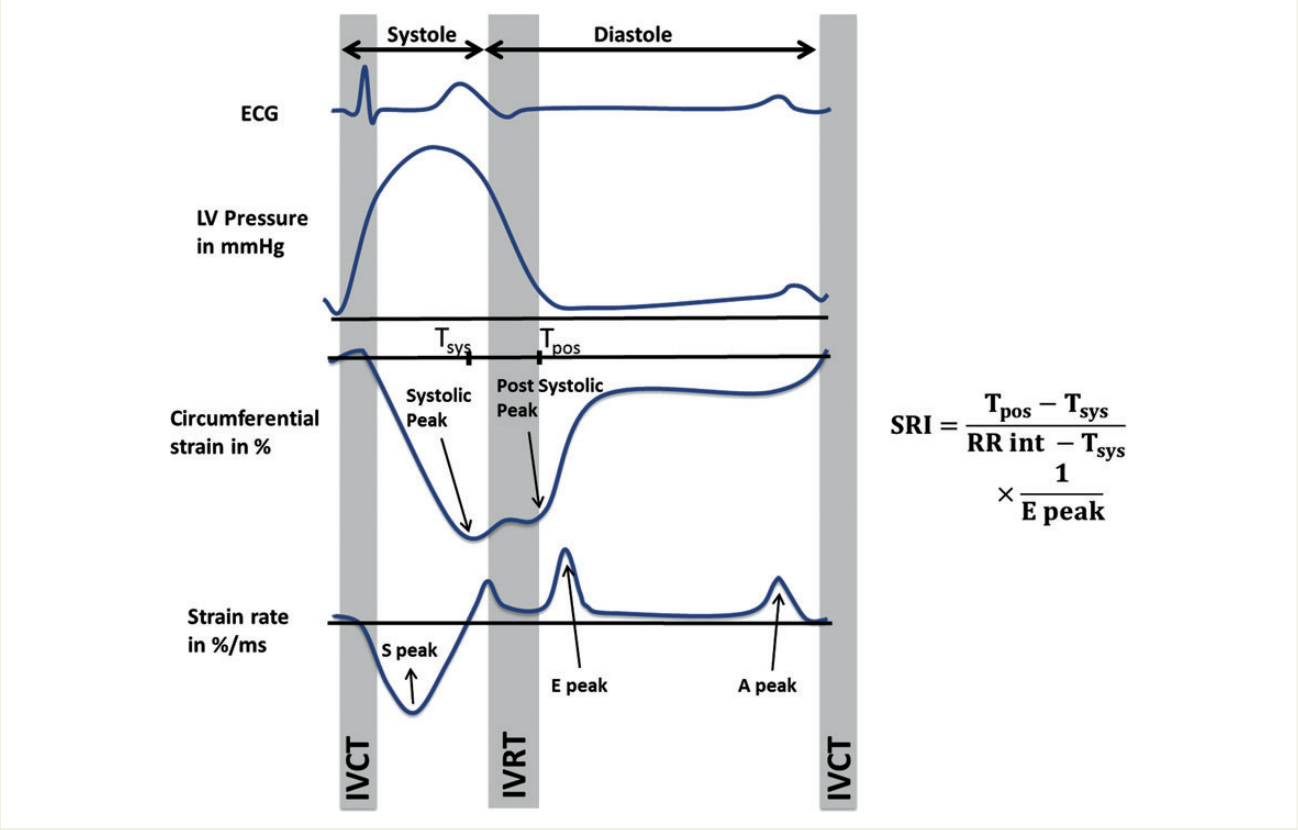

Figure 1 This figure illustrating the calculation of the proposed SRI from the circumferential strain and strain rate curves. More negative strain values indicate greater circumferential shortening. SRI is calculated as the ratio of the duration of very early relaxation to that of the diastolic interval, divided by the early diastolic strain rate peak. The myocardial relaxation as imagined with a hypothetical pressure curve and electrocardiograph for reference. SRI: strain relaxation index; RR int: RR interval; S peak: peak systolic strain rate; IVCT: isovolumic contraction time; IVRT: isovolumic relaxation time; E peak: peak early diastolic strain rate; A peak: peak atrial-diastolic strain rate; T_{sys}: time of occurrence of peak systolic strain; T_{pos}: time of occurrence of post-systolic strain peak.

systolic strain, representing the total interval of relaxation. SRI is presented in ms/%.

Study population

The design and population characteristics of the multi-ethnic study of atherosclerosis (MESA) have been described previously.[17,18] Briefly, MESA is a prospective, population-based observational cohort study of 6814 men and women representing four racial/ethnic groups (Caucasian, African-American, Hispanic, and Chinese-American), aged 45–84 years and free of clinical CVD at enrolment. As part of the baseline examination, between 2001 and 2002, a total of 5004 (73%) participants received comprehensive cardiac MRI studies at six field centres. The institutional review boards of all MESA field centres approved the study protocol, and all participants gave informed consent. Of the 5004 individuals who underwent cardiac MRI examination, 1617 with available clinical covariate data agreed to a slightly longer MRI examination to accommodate MRI tagging sequences. Of these participants, deformation data could not be analysed owing to data acquisition failure or insufficient quality for strain and strain rate determination in 73 participants. The remaining 1544 participants with complete circumferential strain, strain rate, and strain relaxation rate measurements were included in this analysis. Of these 1544 participants, 743 underwent a follow-up examination after an 8-year period, with MRI tagging as a part of the imaging protocol. Of these, 27 were excluded because of insufficient quality of determined strain or data acquisition failure. Tagged MR protocol and analysis methods remained the same in the baseline and follow-up visits.

Magnetic resonance imaging

Images were acquired in whole-body scanners using electrocardiogram triggered segmented k-space fast spoiled gradient-echo pulse sequences during breath holds. CMR myocardial horizontal and vertical tagging were performed on three LV short-axis slices (base, mid, and apex) by non-selective radiofrequency pulses separated by a spatial modulation of magnetization-encoding gradients. Parameters for imaging and analysis methods have been described previously.[18]

Short-axis-tagged slices were analysed by the harmonic phase method.[19] Systolic and post-systolic circumferential strain peaks were assessed from the mid-wall mid-ventricular circumferential strain (*Ecc*) and strain rates through the cardiac cycle. These were then used to compute SRI and EDSR. *Ecc* values are conventionally negative to express circumferential shortening. Torsion curves were computed as previously described.[20] The peak torsion recoil rate (deg/cm/ms) was calculated as the first minimum from the rate curve after peak torsion.

Follow-up and end-points

Events adjudicated as incident HF and AF as part of the MESA study were used as end-points. A telephone interviewer contacted each participant (or representative) every 6–9 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths.

Table 1 Baseline characteristics

Variable	Mean (SD)			
	Overall (n = 1544)	HF (n = 36)	AF (n = 57)	Combined (n = 80)
Age (years)	65 ± 9.7	70.2 ± 8.2	70.7 ± 9.1	70.3 ± 8.7
Body mass index (kg/m^2)	27.8 ± 4.7	28.9 ± 4.1	28.3 ± 4.1	28.6 ± 4.3
Systolic blood pressure (mmHg)	128 ± 20.7	134.8 ± 20.0	139.1 ± 22.5	136.9 ± 22.3
HDL cholesterol (mg/dL)	50.6 ± 14.5	49.1 ± 12.1	49 ± 14.1	48.8 ± 13.8
Total cholesterol (mg/dL)	194.2 ± 34.9	180.8 ± 26.9	183.9 ± 30.1	181.5 ± 28.8
EDSR (%/ms)	0.12 ± 0.06	0.10 ± 0.05	0.10 ± 0.05	0.10 ± 0.05
log(SRI) (ms/%)	0.78 ± 0.56	1.12 ± 0.45	1.01 ± 0.52	1.04 ± 0.51
Torsion recoil rate (deg/cm/ms)	−19 ± 11	−18 ± 13	−21 ± 13	−19 ± 13
Variable	**Proportion of participants (%)**			
	Overall (n = 1544)	HF (n = 36)	AF (n = 5)	Combined (n = 80)
Men	53	72.9	69.5	71.2
Race				
Caucasian	28.9	16.3	47.5	34.3
Chinese-American	14.6	10.8	11.9	10.9
African-American	27.8	27	16.9	21.9
Hispanic	28.7	45.9	23.7	32.9
Smokers				
Former	35.9	50	36.2	40.7
Current	11.3	11.1	12.1	11.1
Diabetes/ impaired fasting glucose	31.2	54	35.6	63
Use of hypertension medication	39.9	54.1	57.6	58.5

Shown are baseline characteristics of individuals who underwent tagged MRI at baseline and with information on conventional risk factors. For continuous variables, mean ± SD are given and for categorical variables, % are given.
SRI: strain relaxation index; EDSR: early diastolic strain rate; HF: heart failure; AF: atrial fibrillation; HDL: high-density lipoprotein.

Two physicians reviewed all records for independent end-point classification and assignment of event dates.[21]

Criteria for HF as end-point included symptomatic HF diagnosed by a physician and patient receiving medical treatment for HF and (i) pulmonary oedema/congestion by chest X-ray, and/or (ii) dilated ventricle or poor LV function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction. Participants who had a physician's diagnosis of HF were classified as having HF. Criteria for AF as end-point were if in-hospital AF was diagnosed according to ICD9 codes. The combined end-point was ascertained as the first-documented event of either HF or AF.

Conventional risk factor measures (age, race, gender; body mass index, smoking status, systolic blood pressure, use of hypertension medication, diabetes mellitus/impaired fasting glucose, low-density lipoprotein cholesterol, and total cholesterol),[21] serum concentration of n-terminal pro-brain natriuretic peptide (NT-proBNP),[22] and coronary calcium scores[23,24] were obtained as explained previously.

Statistical analysis

Probability distributions of all continuous variables were graphically examined and tested by the goodness-of-fit tests for normality. Summary statistics were presented as mean/SD for continuous variables and as percentages for categorical variables. Natural logarithmic transformation was applied to SRI, EDSR, and NT-proBNP, since these variables have skewed distributions. The mean differences in diastolic function between the follow-up and baseline exams were assessed by the two-sided *t*-test based on participants who had both baseline and the follow-up MRI exams. AHA recommendations for evaluating novel cardiovascular risk factors[25] were used for statistical analysis procedures.

Univariable Cox models were used to assess the prediction ability of diastolic function parameters separately on the time-to-event distribution of the combined end-point. Multivariable Cox models were used to assess the prediction ability of diastolic function parameters to the time-to-event distribution of the combined end-point with the addition of conventional risk factors. The hazard ratios (HRs) along with the corresponding 95% confidence intervals and *P*-values were used to make statistical inference on the covariate effects. The added value of diastolic function parameters to the existing model was calculated from the difference in the calculated Harrell's C-statistic and the significance of this difference.

A secondary analysis, also using multivariable Cox models, was performed to test the ability of diastolic function parameters to predict the time-to-event probabilities for HF and/or AF independent of other established risk factors. Since some participants have missing covariates, this analysis was performed on a subset of the full cohort. Because of the design of the study, the missing covariates can be reasonably assumed to be missing at random. Models considered were those with the progressive addition of established risk factors to conventional risk factors—coronary calcium score[24] (Model 1), LV mass index[26] (Model 2), LV ejection fraction (Model 3), and NT-proBNP[27] (Model 4). Calibration of the models was confirmed using the Gronnesby–Borgan tests to compare the expected and observed event rates across deciles for each model.

Integrated discrimination index (IDI) based on the Cox models was calculated to report the improvement in discrimination based on the survival probabilities with the addition of diastolic function parameters to the conventional risk factors.[28] Net reclassification index (NRI) based on the Cox models was used to quantify the number of individuals correctly and incorrectly reclassified with the addition of the new biomarker into low-, intermediate-, and high-risk categories within 8 years.[28] Risk categories of <5, 5–20, and $>20\%$ were used in the measurement of NRI for HF[27,29] and the combined end-points. For AF[29,30] as the end-point, categories were defined as <5, 5–15, and $>15\%$.

Two-tailed *P*-values were <0.05 used for significance testing. All statistical analysis was done using the STATA v11.0 (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics of the participants are provided in *Table 1*. HF was present in 2.6% ($n = 36$) of the population, whereas AF was incident in 3.9% ($n = 57$) over the 8-year follow-up period. Fourteen participants had both AF and HF, and 12 with AF preceding HF. The incidence of HF and AF were associated with increased age, male

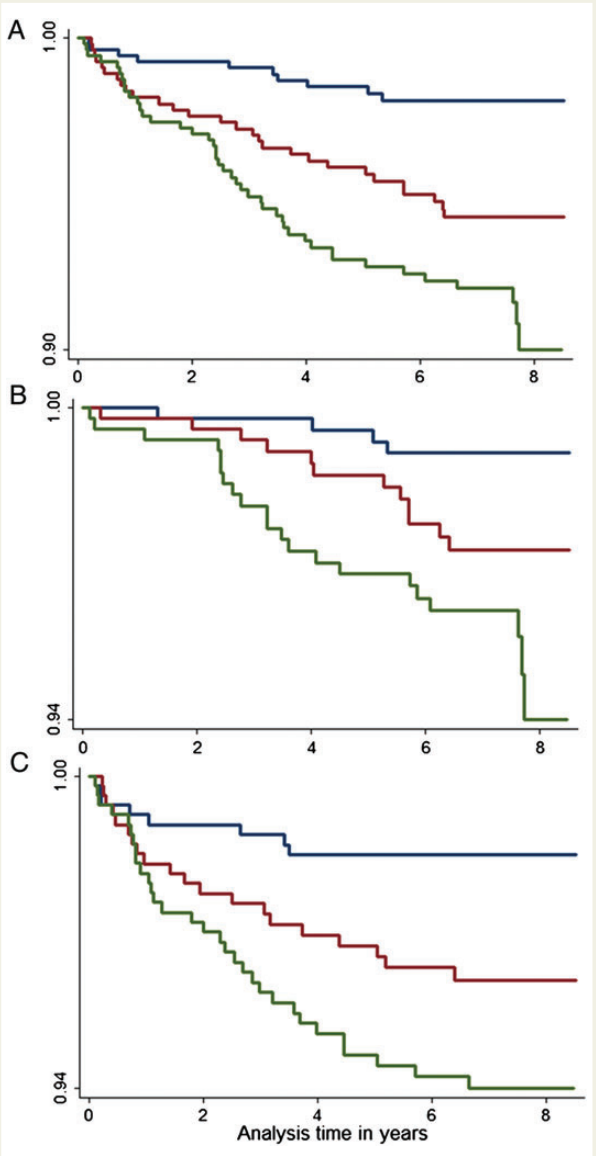

Figure 2 This figure show the Kaplan–Meier survival curves for combined (*A*), HF (*B*), and AF (*C*), end-points across tertiles of log(SRI). Individuals were free of AF or HF at baseline. log(SRI) expressed as median (minimum, maximum) across three tertiles were Q1: 0.119 (−0.2.239, 0.544), Q2: 0.805(0.544, 1.034), and Q3: 1.378(1.034, 3.471). $P < 0.001$ for all trends.

gender, higher body mass index, higher systolic blood pressure, decreased early diastolic strain rate, and increased SRI.

In the longitudinal follow-up, logSRI increased significantly ($P < 0.05$) from 0.74 ± 0.58 at baseline to 1 ± 0.58 at follow-up in the population free of clinical events ($n = 696$). In the same period and using the same population, early diastolic strain rate (EDSR) decreased from 0.12 ± 0.06 to 0.10 ± 0.04 ($P < 0.05$). The torsion recoil rate increased from -19.3 ± 11.2 at baseline to -22.7 ± 9.4 at follow-up ($P < 0.05$). In those with HF ($n = 7$), an increase in logSRI (0.97 ± 0.42–1.65 ± 0.41, $P < 0.05$), a decrease in EDSR (0.09 ± 0.03–0.06 ± 0.03, $P < 0.05$), and no significant change in the torsion recoil rate (-8.2 ± 7.9 to -14.7 ± 4.5, $P =$ NS) were seen from baseline to follow-up exams. In those with AF ($n = 14$), no significant changes were seen in logSRI (0.98 ± 0.93 to -0.76 ± 0.65, $P =$ NS), EDSR (0.10 ± 0.06 to -0.11 ± 0.05, $P =$ NS), and the torsion recoil rate (-9.6 ± 11.3 to -21.5 ± 10.3, $P =$ NS) from baseline to follow-up exams.

Prediction of a combined end-point of HF and AF as well as HF and AF

Using Kaplan–Meier survival curves, SRI showed robust prediction of HF, AF, and the combined end-points across tertiles (*Figure 2*). The HRs for SRI and EDSR alone were both significant for the combined end-point in the univariate analysis and after adjustment for conventional risk factors, with values favouring SRI. C-statistics showed better performance for SRI when compared with EDSR; with significant improvement in HF and a trend towards statistical significance for the combined end-point (*Table 2*). The torsion recoil rate did not predict HF, AF, or the combined end-point.

In a subset of the cohort ($n = 1255$; patients characteristics in *Tables 3* and *4*), SRI had consistent performance as an independent predictor of HF or AF after progressive adjustment to computed tomography-derived calcium score, LV mass index, LV ejection fraction, and serum NT-proBNP in addition to the conventional risk factors. In comparison, EDSR had significant predictive power independent of only calcium score, but not with the addition of LV mass index.

Discrimination and reclassification

For the combined end-point, there was a significant improvement in discrimination of risks for events and non-events as assessed by IDI with the addition of SRI to the conventional risk factor model of 1.5% ($P = 0.001$). The IDI for HF and AF as end-points were 1.1% ($P = 0.13$) and 1.0% ($P = 0.017$), respectively. The values for the combined end-point, HF, and AF using EDSR were 1.3% ($P = 0.006$), 0.9% ($P = 0.19$), and 0.7% ($P = 0.05$) respectively.

Risk category reclassification (NRI) was higher for the prediction of combined end-points when compared with only the conventional risk factors. NRI for the combined end-point using SRI and EDSR were 11.4% ($P = 0.007$) and 9.5% ($P = 0.044$), respectively. The improvement in the net reclassification was both a result of upward reclassification of events to higher risk categories and a downward reclassification of non-events. The NRI for HF and AF individually were not significant.

Discussion

In a large population free of known CVD at baseline, diastolic function from circumferential strain curves showed a powerful independent ability for the prediction of HF and AF over an 8-year follow-up period. The addition of diastolic function to conventional risk factors significantly improved discrimination and reclassification for the combined HF and AF end-point. SRI, a robust and sensitive SRI

Table 2 Prediction and discrimination assessment on the combined end-point of HF and/or AF for CMR-derived diastolic parameters ($n = 1544$)

	HR (95% CI)		Discrimination		
	Univariate	Multivariate	AUC	Difference	*P*
Combined ($n = 80$)					
log(EDSR)	0.32 (0.19–0.53)	0.51 (0.30–0.84)	0.763	0.005	0.556
log(SRI)	2.54 (1.76–3.66)	1.88 (1.29–2.74)	0.774	0.016	0.099
Torsion recoil rate	1.01 (0.99–1.03)	–	–	–	–
HF ($n = 36$)					
log(EDSR)	0.26 (0.12–0.55)	0.45 (0.21–0.97)	0.786	0.013	0.342
log(SRI)	3.22 (1.91–5.43)	2.25 (1.30–3.89)	0.803	0.030	0.039
Torsion recoil rate	1.02 (0.98–1.05)	–	–	–	–
AF ($n = 57$)					
log(EDSR)	0.39 (0.22–0.69)	0.57 (0.32–1.02)	0.774	0.003	0.612
log(SRI)	2.35 (1.52–3.62)	1.77 (1.13–2.76)	0.783	0.009	0.421
Torsion recoil rate	0.99 (0.97–1.02)	–	–	–	–

End-point is the participants who had atrial fibrillation and heart failure, whichever happened first. In multivariate analysis, adjustments were made for age, race, gender; body mass index, smoking status, systolic blood pressure, use of hypertension medication, diabetes mellitus/impaired fasting glucose, low-density lipoprotein (LDL) cholesterol, total cholesterol, and log(SRI).
SRI: strain relaxation index; EDSR: early diastolic strain rate; Combined, AF, or HF; HF: heart failure; AF: atrial fibrillation; AUC: area under the curve.

Table 3 Baseline characteristics for secondary analysis in the subpopulation

Variable	Mean (SD)			
	Overall (n = 1255)	HF (n = 28)	AF (n = 49)	Combined (n = 65)
Age (year)	65.3 ± 9.6	71.1 ± 7.5	70.9 ± 9.4	70.7 ± 8.6
Body mass index (kg/m^2)	27.6 ± 4.7	29.0 ± 4.2	28.1 ± 4.2	28.4 ± 4.3
Systolic blood pressure (mmHg)	128.2 ± 20.7	134.9 ± 19.8	140.4 ± 21.5	138.2 ± 21.6
HDL cholesterol (mg/dL)	50.6 ± 14.6	49.7 ± 12.7	49.8 ± 14.6	49.7 ± 14.3
Total cholesterol (mg/dL)	194 ± 34.9	181 ± 27.6	186.6 ± 30	183.9 ± 29.2
log(BNP) (pg/mL)	4 ± 1.19	5.51 ± 1.39	5.13 ± 1.29	5.14 ± 1.34
LV mass index (g/m$^{1.7}$)	61.3 ± 14.2	76.4 ± 21.4	69.5 ± 19.5	70.2 ± 18.6
LVEF (%)	69 ± 7.6	63.7 ± 11.6	67.9 ± 10.9	67.3 ± 10.6
EDSR (%/ms)	0.12 ± 0.06	0.10 ± 0.04	0.10 ± 0.04	0.10 ± 0.04
log(SRI) (ms/%)	0.76 ± 0.60	1.07 ± 0.42	1.01 ± 0.52	1.00 ± 0.49
Variable	**Proportion of participants (%)**			
	Overall (n = 1255)	HF (n = 28)	AF (n = 49)	Combined (n = 65)
Men	54.5	71.4	71.4	70.7
Race				
Caucasian	29.9	17.9	51.1	38.5
Chinese-American	16.2	10.7	10.2	10.8
African-American	23.9	21.4	14.2	16.9
Hispanic	30	50	24.5	33.8
Smokers				
Former	36.5	51.9	37.5	42.2
Current	10.8	11.1	12.5	10.9
Diabetes/impaired fasting glucose	31.9	60.7	36.7	46.2
Use of hypertension medication	39.5	50	55.1	55.4
Calcium score categories				
0	44.2	17.8	16.4	20.1
1–100	27.6	25	28.6	27.6
101–300	14.1	14.3	16.3	15.4
>300	14.1	42.9	48.7	36.9

Shown are baseline characteristics of individuals who underwent tagged MRI at baseline and with information on conventional risk factors. For continuous variables, mean ± SD are given and for categorical variables, % are given.
SRI: strain relaxation index; EDSR: early diastolic strain rate; BNP: brain natriuretic peptide.

Table 4 Prediction and discrimination assessment on the combined end-point of HF and/or AF for CMR-derived diastolic parameters (n = 1255, 65 events)

	log(EDSR)			log(SRI)		
	HR (95% CI)	AUC	Difference	HR (95% CI)	AUC	Difference
Model 1	0.53 (0.30–0.92)	0.784	0.007	1.81 (1.17–2.79)	0.791	0.014
Model 2	0.59 (0.34–1.05)	–	–	1.72 (1.11–2.67)	0.808	0.010
Model 3	0.60 (0.34–1.06)	–	–	1.72 (1.11–2.66)	0.808	0.010
Model 4	0.61 (0.34–1.09)	–	–	1.77 (1.13–2.76)	0.827	0.006

End-point is the participants who had atrial fibrillation or heart failure combined. In multivariate analysis, adjustments to different variables were made for each model. Model 1: age, race, gender; body mass index, smoking status, systolic blood pressure, diastolic blood pressure, use of hypertension medication, diabetes mellitus/impaired fasting glucose, LDL cholesterol, total cholesterol, categories of coronary calcium, and log(SRI); Model 2: Model 1 + LV mass index; Model 3: Model 2 + LV ejection fraction; Model 4: Model 3 + log(BNP).
SRI: strain relaxation index; EDSR: early diastolic strain rate; AUC: area under the curve.

to assess diastolic dysfunction by tagged CMR images, showed improved prediction, discrimination, and reclassification abilities in comparison with previously proposed CMR diastolic function parameters, such as EDSR and torsion recoil rate.

HF and AF are linked to a similar pathologic pathway, as both can be mediated by diastolic dysfunction secondary to similar cardiovascular risk factors. These risk factors have been associated with myocardial intracellular and extracellular, as well as electrophysiological changes that combine to create LV dysfunction, leading to both HF and AF.[1,31] In our study, both HF and AF had a similar association with CMR diastolic parameters, again suggesting that these two conditions likely share significant similar causal pathways.

Diastolic dysfunction is related to both diagnostic and prognostic aspects of HF and AF. In fact, diastolic function may be the earliest parameter to become altered in progressive LV dysfunction.[32] In this regard, clinical events of HF and AF have shown important relations to diastolic dysfunction as assessed by echocardiography, although such relationships have not been uniformly consistent in previous studies. Echocardiography has been used to predict HF and AF using parameters based on the diastolic phase (e.g. IVRT, deceleration time) and/or accounting for both early and late diastolic filling periods (E/A ratio).[3–6] CMR has proven to be the most accurate method to assess cardiac structure and systolic function. However, the assessment of diastolic dysfunction by CMR has not been established. Despite previous efforts, no CMR-derived diastolic parameter so far showed robust prediction ability for clinical events. In this study, we demonstrate that SRI is a robust predictor of clinical events known to be associated with impaired diastolic function, namely HF and AF.

The extent of post-systolic shortening, the local minimum found on the strain curve prior to the time of peak early diastolic strain rate, has been used to study the influence of ischaemia in segmental myocardial dysfunction.[33,34] However, in this study, we demonstrate that it is also a component of normal myocardial mechanical physiology.[35–38] The interval between the occurrence of the post-systolic peak and the peak systolic strain (analogous to the IVRT) is a measure of cardiac relaxation and is influenced by increased arterial impedance, intracellular calcium overload, and diastolic filling pressures.[15] The early-diastolic strain rate (EDSR), on the other hand, is mainly a measure of ventricular filling reflecting chamber stiffness due to fibrosis, myocyte loss, and changes in LV geometry. SRI, on the other hand, accounts for both the active (time difference between peaks) and passive processes (EDSR) of relaxation, possibly underlying its increased predictive power relative to other CMR-derived indices of diastolic impaired performance. Indeed, in this study, we show that SRI, as it combines diverse factors related to the very early relaxation period, has a better predictive ability when compared with the EDSR or torsion recoil rate. Multivariate analysis revealed that SRI was an independent predictor of HF or AF after adjustment for conventional risk factors, calcium score categories, CMR-derived LV mass index, LV ejection fraction, and NT-proBNP. Moreover, in comparison with baseline values, we demonstrate a temporal (after an 8-year follow-up) increase in SRI and a decrease in EDSR values, which are consistent with the diastolic functional decline associated with aging.

AF and HF with a preserved ejection fraction have emerged as cardiovascular epidemics. LV diastolic dysfunction measurement and grading by non-invasive means could be a crucial component as a complement to diagnosis in the clinical setting. The diagnostic relevance of imaging-based diastolic function indices and their application across different modalities is crucial. We have shown a diastolic function parameter that, in addition to providing robust prediction information and improved discrimination and reclassification, has the potential to be applied across different modalities. In addition to tagged MRI as shown here, other strain estimation methods, such as speckle tracking echocardiography, can potentially be used to derive SRI.

The limitations of the study include the small number of events as the MESA cohort includes only those without any CVD at baseline. A comparison of prediction powers of diastolic function from MRI with that from echocardiography could not be performed because echocardiographic data was not obtained at baseline. Tag fading can be a problem in measuring motion from harmonic phase in tagged MRI.[11] This is particularly true at mid-to-late diastole. In this study, the parameters measured were at very early and early diastole, when the effects of tag fading are minimal, if any. Of the 73 studies that were excluded, 32 (<2%) were excluded because of problems from tag fading affecting the acquisition.

In conclusion, we show that diastolic function assessed by SRI derived from tagged CMR studies provides robust predictive information for the future development of HF and AF over an 8-year follow-up period in a multi-ethnic asymptomatic population without CVD at baseline. SRI accounts for both myocardial relaxation and tissue compliance, and predicts HF and AF independent of established risk factors and conventional markers of subclinical CVD, such as coronary calcium score and left ventricular hypertrophy.

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Conflict of interest: none declared.

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Objetivo Secundário

Identificar fatores de risco para crescimento atrial ao longo de 20 anos de seguimento

Artigo 5 - Association of early adult modifiable cardiovascular risk factors with left atrial size over a 20-year follow-up period: the CARDIA study

BMJ Open

Association of early adult modifiable cardiovascular risk factors with left atrial size over a 20-year follow-up period: the CARDIA study

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ABSTRACT

Objectives: We investigate how early adult and 20-year changes in modifiable cardiovascular risk factors (MRF) predict left atrial dimension (LAD) at age 43–55 years.

Methods: The Coronary Artery Risk Development in Young Adults (CARDIA) study enrolled black and white adults (1985–1986). We included 2903 participants with echocardiography and MRF assessment in follow-up years 5 and 25. At years 5 and 25, LAD was assessed by M-mode echocardiography, then indexed to body surface area (BSA) or height. Blood pressure (BP), body mass index (BMI), heart rate (HR), smoking, alcohol use, diabetes and physical activity were defined as MRF. Associations of MRF with LAD were assessed using multivariable regression adjusted for age, ethnicity, gender and year-5 left atrial (LA) size.

Results: The participants were 30±4 years; 55% white; 44% men. LAD and LAD/height were modest but significantly higher over the follow-up period, but LAD/BSA decreased slightly. Increased baseline and 20-year changes in BP were related to enlargement of LAD and indices. Higher baseline and changes in BMI were also related to higher LAD and LAD/height, but the opposite direction was found for LAD/BSA. Increase in baseline HR was related to lower LAD but not LAD indices, when only baseline covariates were included in the model. However, baseline and 20-year changes in HR were significantly associated to LA size.

Conclusions: In a biracial cohort of young adults, the most robust predictors for LA enlargement over a 20-year follow-up period were higher BP and BMI. However, an inverse direction was found for the relationship between BMI and LAD/BSA. HR showed an inverse relation to LA size.

Strengths and limitations of this study

- We show the long-term effect of modifiable cardiovascular risk factors on left atrial size, over a 20-year follow-up period.
- This large cohort study helps understanding the role of risk factors on the left ventricular filling pressures over young adulthood.
- We used the left atrial diameter assessment by M-mode echocardiography, a practical, low cost and validated method. However, it may lack accuracy as it is based on the linear measurement of the anteriorposterior diameter and may not account for the left atrial eccentric remodelling.

INTRODUCTION

Left atrial (LA) remodelling is an important independent predictor of cardiovascular (CV) events in diverse populations. LA is structurally and functionally linked to the left ventricle, functioning as a reservoir during ventricular systole, a conduit during early diastole and contracting during late diastole to aid ventricular filling. Echocardiography is validated for the assessment of LA structure. M-mode echocardiography technique may evaluate the LA size by assessing the anteroposterior linear LA diameter (LAD), a widely used method in clinical practice and research.[1 2]

Similarly to other cardiac structures, LA scales with body size.[1 3] Several indexing methods have been proposed to adjust LA size for anthropometrics, but indexing by body surface area (BSA) is the most common and recommended.[1] Analyses of indexing left ventricular structure for body size indicate that BSA may over adjust for obesity-related increases in the left ventricular mass.[4] However, indexing cardiac structures to height theoretically reduces confounding effects and improves clinical management when compared with BSA.[5]

The National Heart, Lung and Blood Institute's Coronary Artery Risk Development in Young Adults (CARDIA) study investigates prospectively CV disease risk factors and

subclinical disease in a young population. In the CARDIA study, LAD has an association with subclinical atherosclerosis independent of other coronary artery disease risk factors.[6] There is no information on longitudinal determinants of LAD during the transition from young adulthood to middle age.

This study assesses how modifiable risk factors in young adulthood associate with LA size over a 20-year period. We investigate how early adult and 20-year changes in modifiable CV factors predict LAD at age 43–55 years. In addition, we explore how this prediction is affected by indexing LAD by BSA or height.

METHODS

Study design and sample

The CARDIA study is a prospective observational investigation that has completed 25 years of follow-up.[7] Between 1985 and 1986, 5115 African-American and white participants (aged 18–30 years) were enrolled in four field centres (Birmingham, Alabama; Oakland, California; Chicago, Illinois; and Minneapolis, Minnesota, USA). Then, the participants underwent follow-up examination in years 0, 2, 5, 7, 10, 15, 20 and 25, with echocardiograms performed in the entire cohort at years 5 and 25. We included participants who underwent echocardiography assessment and had data on LAD and modifiable CV risk factors at CARDIA examination years 5 and 25. From the 3240 participants who attended CARDIA examination year 5 (baseline in this study) and examination year-25, 24 participants did not have echocardiography performed at year 25 and 313 had incomplete data on covariates at CARDIA examination year 5 or 25. The final analytic cohort for this study included 2903 participants. All participants gave written informed consent.

Echocardiography

The CARDIA year 5 echocardiography standard protocol has been described.[8] Briefly, echocardiograms were performed in each field centre using an Acuson cardiac ultrasound machine (Siemens Healthcare; Erlangen, Germany), recorded in super-VHS tapes, and then interpreted following the American Society of Echocardiography (ASE) recommendations[9] at a single reading centre (University of California, Irvine, USA). In the field centres, parasternal long-axis two-dimensional views were used to guide the assessment of M-mode anteroposterior images from the aortic root and the left atrium. During the echocardiography interpretation, the LA linear dimension was measured from the leading edge of the posterior aortic wall to the leading edge of the posterior LA wall. CARDIA examination year 25 echocardiography used Artida cardiac ultrasound machines (Toshiba Medical Systems, Otawara, Japan), following acquisition and interpretation protocols similar to examination year 5. LADs from examination years 5 and 25 were indexed to BSA and height (in meters) from the corresponding examination year.

Risk factors assessment

We explored biological and lifestyle risk factors by assessing the association between modifiable risk factors and LA size. Although other factors may be related to LA size, modifiable risk factors were chosen among major CV risk factors known to be associated to LAD and that could be favourably modified by a healthy lifestyle, such as blood pressure (BP), use of medication for hypertension, body mass index (BMI), heart rate (HR), smoking status, alcohol use, physical activity score and diabetes status.

Assessment methods for risk factor variables have been described for the CARDIA study.[10] Briefly, use of medication, alcohol consumption (in milliliter of ethanol consumed per day) and smoking status (not smoking or current smoker) were assessed using questionnaires. After 5 min rest, the last two of a total of three measurements of BP were averaged for computing systolic (SBP) and diastolic BP (DBP) values; and HR was assessed in 30 s. A physical activity score was obtained from the CARDIA Physical Activity History, as previously described.[5] In the CARDIA study, the presence of diabetes was assessed at each examination based on a combination of history of medication use (every visit), fasting glucose $\geq$126 mg/dL (years 0, 7, 10, 15, 20 and 25), glucose tolerance test (years 10, 20 and 25; glucose $\geq$200 mg/dL) or glycated haemoglobin $\geq$6.5% (years 20 and 25). We defined presence of diabetes at baseline if any of these criteria was present at examination year 5. New cases of diabetes at examination year 25 were computed if the criteria for diabetes were established over the period between examination year 5 and the end of follow-up at examination year 25.

Data analysis

Continuous variables were described as mean±SD and categorical variables in per cents. For each participant, we compared all parameters assessed at CARDIA examination years 5 and 25. The differences between mean values were tested by paired t test and between proportions by McNemar's.

Cross-sectional relations between risk factors and LA size (both at year 5) were assessed by multivariate linear regression. The longitudinal relation between LA size at years 5 and 25 was also assessed. Multivariable regression models assessed the influence of examination year 5 modifiable risk factors on examination year 25 LAD, LAD/BSA and LAD/height. In sequence, multivariable regression models assessed the influence of modifiable risk factors at examination year 5 and their 20-year change on examination year 25 LAD, LAD/BSA and LAD/height. Ethnic-specific analysis for LAD/height was also performed for the fully adjusted model to explore ethnic particularities (for results see online supplementary material).

The association between LAD and BP was explored by including antihypertensive medication use with SBP or DBP as covariates in the regression models. The relation between diabetes and LAD was assessed using presence of diabetes at baseline and new cases of diabetes at

examination year 25. All multivariable regression models were adjusted for other known CV risk factors, here defined as non-modifiable by a healthy lifestyle: age, ethnicity, gender and examination year 5 LA size. Maximum education attained was tested, but did not show an association with LAD, and, therefore, was not included in the regression models (data not shown).

RESULTS

The participant characteristics at CARDIA examination years 5 and 25 are shown in table 1. Over 20 years (CARDIA examination 5–25), alcohol consumption, BMI and SBP increased significantly in the study cohort, while HR, tobacco use and the physical activity score decreased significantly. Although statistically significant, changes in mean alcohol consumption, heart rate and cigarette use over 20 years were not substantial. In the same period, the proportion of participants with hypertension and diabetes increased. LAD and LAD/height were modestly higher over the follow-up period, but LAD/BSA had a slight decrease.

In a cross sectional analysis at CARDIA examination year-5, BMI was directly related to LAD and LAD/height and an inverse relation was found for LAD/BSA. Being a current smoker and having higher resting HR were consistently related to higher LAD, LAD/BSA and LAD/height. Antihypertensive medication use, SBP and physical activity had significant direct relations to LAD, but no association was found after indexing LAD by height or BSA. Neither alcohol use nor presence of diabetes had cross-sectional association with LA size (table 2).

Table 3 shows the multivariable linear regression models for the influence of examination year 5 modifiable CV risk factors on LAD and its indices over a 20-year follow-up period, adjusted for age, race, gender and baseline LA size. Higher values of baseline SBP were significantly related to higher LAD and LAD/BSA over 20 years, with marginal significance for LAD/height. No significant relationship between LA size and DBP was found, when DBP was tested replacing SBP in the model. Higher BMI was related to higher CARDIA examination year 25 LAD and LAD/height. However, the opposite direction was found for baseline BMI in the regression model for LAD/BSA. Increase in baseline HR was related to lower values of LAD and LAD indices. Neither baseline smoking status, alcohol consumption nor physical activity score had significant prediction ability for LAD or LAD indices. The presence of diabetes at baseline was associated with enlarged LA size after a 20-year follow-up period.

In table 4, we show the results for multivariable regression models assessing simultaneously baseline (CARDIA examination year 5) and 20-year change covariates for the endpoints (measured at CARDIA examination year 25) of LAD, LAD/BSA and LAD/height. Lower baseline HR and HR 20-year changes showed a significant relationship to higher LAD and LAD indices at CARDIA examination year 25. Higher values of baseline SBP and SBP 20-year changes also related directly to LAD and LAD indices at year 25. Compared with SBP, DBP had a weaker relation to LA size when tested in the same models (see online supplementary table S1). Higher BMI and BMI changes were related to enlargement in LAD and LAD/height. However, again an inverse correlation was found for baseline BMI and changes when LAD/BSA was used as the endpoint. Neither smoking status, alcohol consumption nor physical activity score at baseline or over 20-year changes had significant

Table 1 Participant characteristics at examination year 5 and after a 20-year follow-up period (n=2903)

Variables	Examination year 5 Mean (SD)	Examination year 25 Mean (SD)	p Value
Age (years)	30 (4)	50 (4)	NA
BMI (kg/m^2)	26 (6)	30 (7)	<0.0001
SBP (mm Hg)	107 (11)	119 (16)	<0.0001
HR (bpm)	68 (10)	66 (10)	<0.0001
Alcohol use (mL/day)	11 (22)	12 (23)	0.006
Physical activity score (units)	378 (289)	339 (272)	<0.0001
Cigarettes (number/day)	3 (7)	2 (5)	<0.0001
LAD (cm)	35 (5)	37 (5)	<0.0001
LAD/BSA(cm/m^2)	1.9 (0.2)	1.8 (0.2)	<0.0001
LAD/height(cm/m)	2.1 (0.3)	2.2 (0.3)	<0.0001
	Proportion	**Proportion**	
White ethnicity	56%	NA	NA
Male gender	44%	NA	NA
Current smoker	26%	16%	<0.0001
Hypertension	4%	34%	<0.0001
Diabetes	1%	14%	0.0001

p Values for differences between mean values were tested by paired t test and between proportions by McNemar's test.
BMI, body mass index; BSA, body surface area; HR, heart rate; LAD, left atrial diameter assessed by M-mode echocardiography; NA, not applicable; SBP, systolic blood pressure.

Table 2 Multivariable linear regression for cross-sectional association of modifiable risk factors with left atrial size, both measured at examination year 5 (n=2903)

	Unindexed LAD (cm) (R^2=0.29)		LAD/BSA (cm/m^2) (R^2=0.08)		LAD/height (cm/m) (R^2=0.25)	
Variable	**Coefficient**	**p Value**	**Coefficient**	**p Value**	**Coefficient**	**p Value**
Presence of diabetes	−0.065	0.507	−0.028	0.626	−0.034	0.561
BMI (5 kg/m^2)	0.183	<0.0001	−0.025	<.0001	0.113	<0.0001
SBP (10 mm Hg)	0.021	0.005	0.004	0.374	0.007	0.125
HR (10 bpm)	−0.066	<0.0001	−0.033	<.0001	−0.037	<0.0001
Current smoker	0.070	<0.0001	0.041	<.0001	0.043	<0.0001
Using medication for HTN	0.174	0.005	0.062	0.0848	0.097	0.009
Alcohol consumption (20 mL/day)	0.010	0.159	0.007	0.0714	0.008	0.058
Physical activity score (300 u)	0.026	0.001	0.006	0.2091	0.009	0.049

Cross-sectional regression models adjusted for age, ethnicity and gender.
BMI, body mass index; BSA, body surface area; HR, heart rate; HTN, hypertension; LAD, left atrial dimension; SBP, systolic blood pressure.

prediction ability for LAD or LAD indices. Higher LAD was associated with baseline diabetes, but no statistical significance was found for the presence of diabetes at examination year 25. Caucasian and African-American participants showed similar results for the influence of risk factors on LA size (see online supplementary table S2).

DISCUSSION

In this study, we show how modifiable CV risk factors in a large cohort of young adults are associated with LAD over a 20-year period. During early adulthood, the most robust predictors for LA enlargement over a 20-year follow-up period were higher SBP, lower heart rate and higher BMI. In addition, the presence of diabetes at baseline showed a significant relation to high LA size at examination year 25. However, alcohol use, physical activity and smoking status did not show significant longitudinal influence.

Cardiac remodelling plays a central role in CV disease and may be characterised by heart chamber enlargement and dysfunction. The LA remodelling process strongly relates to increase in left ventricular filling pressures. Furthermore, LA structure and function show important associations to CV risk burden and clinical events prediction.[2 4 11] In a longitudinal assessment over 10 years in the CARDIA cohort, LAD assessed on 2724 participants at examination year 5 was associated with the presence of coronary calcium at CARDIA examination year 15 (2000–2001), independent of other risk factors such as age, sex, race, BMI, SBP, smoking and lipids.[6] The intensity of exposure to CV risk factors in youth correlates to early coronary disease.[12] However, there are limited data regarding how long-term risk factor exposure influences LA size.

LAD assessment by M-mode echocardiography is a practical, low cost and validated method.[9 13 14] It has high consistency, but may lack accuracy as it is based on the relationship between anteroposterior LAD and other spatial dimensions in the LA remodelling process.[1] Despite this intrinsic limitation, previous studies have shown the association between increased LAD by M-mode echocardiography and incident CV outcomes, particularly atrial fibrillation and cerebrovascular events.[15 16] Moreover, the LIFE Study followed with

Table 3 Multivariable linear regression for association of examination year 5 (baseline) modifiable risk factors with left atrial size over a 20-year follow-up period (n=2903)

	Unindexed LAD (cm) (R^2=0.29)		LAD/BSA (cm/m^2) (R^2=0.22)		LAD/height (cm/m) (R^2=0.26)	
Variable	**Coefficient**	**p Value**	**Coefficient**	**p Value**	**Coefficient**	**p Value**
Diabetes at baseline	0.231	0.029	0.119	0.030	0.142	0.024
BMI (5 kg/m^2)	0.108	<0.0001	−0.037	<0.0001	0.065	<0.0001
SBP (10 mm Hg)	0.020	0.011	0.010	0.016	0.009	0.061
HR (10 bpm)	−0.019	0.029	−0.005	0.257	−0.010	0.042
Current smoker	0.018	0.350	0.005	0.583	0.015	0.181
Using medication for HTN	−0.041	0.539	0.011	0.741	−0.024	0.549
Alcohol consumption (20 mL/day)	−0.010	0.188	0.004	0.319	−0.004	0.370
Physical activity score (300 u)	0.005	0.564	0.004	0.356	−0.001	0.846

Models adjusted for age at baseline, ethnicity, gender and left atrial size at baseline. Left atrial size at baseline refers to unindexed LAD, LAD/BSA or LAD/height, according to the endpoint in the regression model.
BMI, body-mass index; BSA, body surface area; HR, heart rate; HTN, hypertension; LAD, left atrial dimension; SBP, systolic blood pressure.

Table 4 Multivariable linear regression for influence of CARDIA examination year 5 (baseline) and 20-year change modifiable risk factors on left atrial size at CARDIA examination year 25 (n=2903)

	Unindexed LAD (cm) (R^2=0.35)		LAD/BSA (cm/m^2) (R^2=0.31)		LAD/height (cm/m) (R^2=0.33)	
Variable	**Coefficient**	**p Value**	**Coefficient**	**p Value**	**Coefficient**	**p Value**
Diabetes at baseline (year 5)	0.254	0.013	0.122	0.019	0.154	0.011
Diabetes at follow-up, but not baseline	0.017	0.480	−0.001	0.963	0.006	0.677
BMI at baseline (5 kg/m^2)	0.108	<0.0001	−0.040	<0.0001	0.065	<0.0001
BMI changes (5 kg/m^2)	0.126	<0.0001	−0.076	<0.0001	0.075	<0.0001
SBP at baseline (10 mm Hg)	0.034	<0.0001	0.014	0.002	0.018	<0.001
SBP changes (10 mm Hg)	0.025	<0.0001	0.012	<0.0001	0.017	<0.0001
HR at baseline (5 beats/30 s)	−0.048	<0.0001	−0.021	<0.0001	−0.028	<0.0001
HR changes (5 beats/30 s)	−0.049	<0.0001	−0.025	<0.0001	−0.030	<0.0001
Smoking status (vs never smoked)						
Not baseline, yes Y25	−0.057	0.295	−0.037	0.185	−0.036	0.264
Yes baseline, no Y25	0.007	0.771	−0.003	0.815	0.004	0.796
Yes baseline, yes Y25	0.010	0.680	0.010	0.381	0.013	0.325
Medication for HTN (vs never used)						
Not baseline, yes Y25	0.031	0.118	0.020	0.044	0.025	0.035
Yes baseline, no Y25	0.055	0.685	0.008	0.904	0.024	0.769
Yes baseline, yes Y25	−0.012	0.865	0.018	0.633	0.002	0.970
Alcohol consumption at baseline (20 mL/day)	−0.002	0.850	0.005	0.301	0.001	0.799
Alcohol consumption changes (20 mL/day)	0.006	0.423	0.006	0.128	0.004	0.322
Physical activity score at baseline (300 u)	0.013	0.217	0.003	0.574	0.004	0.541
Physical activity score changes (300 u)	0.008	0.402	0.004	0.383	0.005	0.399

Models adjusted for age at baseline, ethnicity, gender and left atrial size at baseline. Left atrial size at baseline refers to unindexed LAD, LAD/BSA or LAD/height, according to the endpoint in the regression model.
BMI, body mass index; BSA, body surface area; HR, heart rate; HTN, hypertension; LAD, left atrial dimension; SBP, systolic blood pressure; Y25, CARDIA study examination year 25.

echocardiograms 939 hypertensive patients for 4.8 years and found that enlarged baseline LAD increased risk for atrial fibrillation whereas reduction of LAD reduced the risk in models adjusted for age, LV mass, SBP and Framingham risk score.[17]

Similar to our study, cross-sectional relations between CV risk factors and LAD have been reported in the literature. Cuspidi *et al*[18] found significantly higher BMI and SBP with enlarged LAD in a population of 2500 uncomplicated patients with hypertension. Tsang *et al*[15] investigated 423 patients and also found cross-sectional relations of LAD with BMI and SBP. In a cross-sectional assessment of 4059 CARDIA participants at examination year 5, a low CV risk burden was associated with more favourable values for LA size. In this study, Gidding *et al*[19] showed that higher BMI, higher SBP, lower heart rate, tobacco use, higher serum glucose and higher self-reported physical activity were independently associated with enlarged LAD/height.

There are limited data on the longitudinal determinants of LA size. In this study, we assessed a generally healthy cohort examined at ages 23–35 and 43–55 years. BP, particularly SBP and BMI emerged as very robust risk factors associated with LAD and LAD change over 20 years. McManus *et al*[20] reported similar findings following an older population of 4403 Framingham Study participants over a 16-year follow-up period. BP and BMI were the major factors related to LAD enlargement. BP and obesity are known determinants of LV diastolic dysfunction and cardiac remodelling,[21 22] strongly associated with elevated filling pressures and LA enlargement. In fact, higher BP was a consistent determinant of LAD enlargement in our study. In our cohort of young participants, the association between BP and LA size was weaker in cross-sectional as compared with longitudinal regression models. This emphasises the importance of chronic exposure to high BP and subclinical cardiac endpoints, including LA size.

Obesity, as assessed by BMI, strongly relates to CV risk.[23] BMI was also consistently related to LA size in our study, but the relationship varied depending on the method used to index LAD. In this regard, indexing LAD by BSA may overadjust for deleterious effects of excess adiposity-producing values that underestimate risk in obese participants.[24 25] This is suggested by our results where the relationship between change in BMI and LAD/BSA was inverse despite the knowledge that BMI is strongly related to LAD in cross-sectional analyses, and BMI and LAD contribute to CVD risk. A cross-sectional study of 244 children found an independent association of LAD with body fat mass, body fat as a percentage of body mass, abdominal fat mass and body fat distribution.[26] Adjusting CV parameters for height alone appear to provide more stable longitudinal assessment.[3]

In our study, resting HR was associated to LAD and LAD/height but not to LAD/BSA at CARDIA examination year 25, when only year 5 variables were included in the regression models (table 2). Furthermore, lower

HR at baseline and its 20-year decrease emerged as significant determinants of LAD enlargement over the 20-year follow-up period (table 3). HR is inversely related to stroke volume at rest and a higher resting HR has shown an association with adverse events.[27–29] However, there may be a threshold effect for the adverse association of elevated HR. Values above 80 bpm may have a stronger association to CV risk in older populations, possibly related to the association of a higher oxygen consumption with higher prevalence of existing coronary disease and adverse cardiac function in this population.[30] These data suggest that some changes in LA size may be adaptive as opposed to adverse and are consistent with the cross-sectional inverse relationship between HR and LAD reported in the literature.[15 18 19]

Diabetes is a known risk factor for CV disease including heart failure. However, LA size had no cross-sectional association with diabetes in our study. Moreover, LA enlargement was related to baseline diabetes, but not its new development after 20 years. These findings suggest that the period of exposure to diabetes may play an important role in atrial remodelling.

LAD enlargement may be related to an adaptation process in exercise conditioning. Evidence of the association between physical activity and LAD have been reported in high-performance athletes,[31 32] and also in a cross-sectional analysis of CARDIA participants.[19] However, our study did not find a significant relationship between LAD and physical activity at baseline or with its 20-year changes. This is likely secondary to the small number of elite athletes in the cohort. Smoking is a major CV risk factor and is related to left ventricular fibrosis, mass and diastolic function. In fact, being a smoker had a cross-sectional relation with the higher LA size in our study. However, smoking status was not a significant longitudinal determinant of LA size in young adults over a 20-year follow-up period. Previous cross-sectional studies also failed to find significant relations regarding tobacco use and LA size.[15 18] Alcohol use also had no significant relation to LAD. Alcohol consumption has a controversial association to CV risk, probably influenced by the amount and type of the agent used.[33] In this regard, our study is limited by not accounting for the type of beverage used by the participants.

In a large biracial cohort of young adults, BP and BMI played a major role in LA enlargement over a 20-year period; resting HR and its 20-year changes were inversely related to LAD. In addition, diabetes at age 23–35 years, but not incident, was significantly related to a higher LAD size. Particularly interesting results were found regarding the LAD indexing process, with negative correlations between change in BMI and LAD/BSA values. Therefore, LAD indexed to BSA may not be the best indexing method for longitudinal assessment of LA size. Future studies directly comparing indexing methods in clinical event prediction are needed to establish the best method for indexing LA size.

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Association of early adult modifiable cardiovascular risk factors with left atrial size over a 20-year follow-up period: the CARDIA study

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Objetivo Terciário

Revisar a literatura sobre massa ventricular esquerda como preditora independente de eventos cardiovasculares e os efeitos da indexação sobre esse papel

Artigo 6 - LV mass assessed by echocardiography and CMR, cardiovascular outcomes, and medical practice

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CME

iREVIEWS

STATE-OF-THE-ART PAPER

LV Mass Assessed by Echocardiography and CMR, Cardiovascular Outcomes, and Medical Practice

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CME Objective for This Article: At the end of this activity the reader should be able to: 1) evaluate the role of LV mass to predict cardiovascular events in different populations; 2) understand the differences between assessment of LV mass by echocardiography and cardiac magnetic resonance; and 3) identify the role of indexing LV mass to body size, understanding limitations and strengths of height-derived and BSA-derived methods.

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LV Mass Assessed by Echocardiography and CMR, Cardiovascular Outcomes, and Medical Practice

The authors investigated 3 important areas related to the clinical use of left ventricular mass (LVM): accuracy of assessments by echocardiography and cardiac magnetic resonance (CMR), the ability to predict cardiovascular outcomes, and the comparative value of different indexing methods. The recommended formula for echocardiographic estimation of LVM uses linear measurements and is based on the assumption of the left ventricle (LV) as a prolate ellipsoid of revolution. CMR permits a modeling of the LV free of cardiac geometric assumptions or acoustic window dependency, showing better accuracy and reproducibility. However, echocardiography has lower cost, easier availability, and better tolerability. From the MEDLINE database, 26 longitudinal echocardiographic studies and 5 CMR studies investigating LVM or LV hypertrophy as predictors of death or major cardiovascular outcomes were identified. LVM and LV hypertrophy were reliable cardiovascular risk predictors using both modalities. However, no study directly compared the methods for the ability to predict events, agreement in hypertrophy classification, or performance in cardiovascular risk reclassification. Indexing LVM to body surface area was the earliest normalization process used, but it seems to underestimate the prevalence of hypertrophy in obese and overweight subjects. Dividing LVM by height to the allometric power of 1.7 or 2.7 is the most promising normalization method in terms of practicality and usefulness from a clinical and scientific standpoint for scaling myocardial mass to body size. The measurement of LVM, calculation of LVM index, and classification for LV hypertrophy should be standardized by scientific societies across measurement techniques and adopted by clinicians in risk stratification and therapeutic decision making. (J Am Coll Cardiol Img 2012;5:837–48)

Left ventricular mass (LVM) is an independent risk factor for prediction of cardiovascular events. However, the best way to incorporate LVM into clinical decision-making algorithms has not been established (1). Even in a range usually considered normal for healthy adults, LVM is positively related to systolic blood pressure, body mass index, and coronary calcium score by cardiac computed tomography (2,3). Elevation in myocardial mass may not be an inevitable consequence of aging, but better predicted by blood pressure, diabetes status, tobacco use, and body weight over time (4–8). Values of myocardial mass have also been shown to be associated with previous aneurysm of the abdominal aorta, subscapular skinfold thickness, left atrial size, resting heart rate, and physical activity (5,7,9–11). Increase in LVM, as related to cardiac remodeling, can be consequent to both an adaptive and a maladaptive process (12). The absence of an identifiable, pathological turning point for cardiac remodeling assessment from adaptive to maladaptive creates a challenge to the definition of normal LVM.

The distribution of LVM values is wide in a healthy population, with distinct patterns according to sex and ethnicity. Moreover, absolute values of myocardial mass are limited by not taking into account physiological variations related to body size. To adjust for these particularities, indexing LVM for anthropometry allows comparisons among different individuals. Several methods have been suggested for the normalization of LVM values—usually involving height, weight, or both. Indexing is also important because it affects who will be classified as having left ventricular hypertrophy (LVH) (1,13–19).

Echocardiography and cardiac magnetic resonance (CMR) are the best-documented imaging modalities used to assess myocardial mass. In both cases, scientific societies have elaborated guidelines discussing appropriate technical procedures, validation aspects, and clinical indications (20,21). Accurate quantification of cardiac dimensions is crucial for distinguishing disease states from normal variants (22). LVM is calculated using different algorithms for each modality and gives different average values for LVM with different degrees of accuracy (1).

Assessment of LVM in epidemiological studies has shown prognostic value (1). The importance of LVM and hypertrophy for clinical purposes is best evidenced for hypertensive populations. LVH is recognized by current guidelines as target-organ damage that influences the prognosis in hypertensive populations. However, recommendations for incorporation of LVM or LVH into hypertension treatment algorithms vary in different guidelines (23–25). This partly

explains why on a daily basis the clinical use of LVM measurements has not been firmly established—although extensively used as a surrogate endpoint in clinical trials (20,26).

In this review, we investigate 3 important points related to clinical use of LVM measurements: 1) comparison of LVM assessment by echocardiography and CMR; 2) outcomes prediction power of LVM; and 3) the different normalization methods used to index LVM. Our aim is to evaluate the strength of the evidence regarding the use of LVM measurements in clinical practice, as a predictor of events and as a therapeutic target.

LVM Assessment by Echocardiography and by CMR

Echocardiography. Although LVM may be assessed using 2-dimensional (2D) or 3-dimensional (3D) echocardiography, M-mode was the first noninvasive imaging technique developed and remains the recommended method (20,27). Whether using M-mode, 2D, or 3D measurements, LVM estimation by echocardiography is based on subtraction of the left ventricular (LV) cavity volume from the volume enclosed by the correspondent epicardium to obtain the myocardial volume, then multiplying by the myocardial density (taken to be 1.05 g/ml) (20). At the present time, the lack of long-term follow-up information using 2D or 3D echocardiography estimations of LVM as event predictors limits further discussion in this review.

In patients without major cardiac geometry distortions, the American Society of Echocardiography (ASE) recommends a formula to estimate LVM from linear dimensions based on the assumption of the LV as a prolate ellipsoid of revolution (Fig. 1). Linear measurements of interventricular septum wall thickness (IVST), as well as left ventricular internal diameter (LVID) and posterior wall thickness (PWT), should be done from the parasternal acoustic window in end-diastole at the level of the LV minor axis (mitral valve leaflet tips) using 2D-targeted M-mode or directly from 2D images (20). Although wall dimensions are used to assess LVM by echocardiography, regional increase in wall thickness seen in hypertrophic cardiomyopathy is a specific disease and will not be addressed in this review.

The first challenge to echocardiographic assessment of LVM is the correct identification of interfaces between the cardiac blood pool and the endocardium, as well as between the epicardium and pericardium. The correct M-mode reference beam orientation perpendicular to the septum can also be challenging. Poor acoustic windows and operator experience are also major concerns for echocardiography measurements. The LVM algorithm is performed cubing values of the primary linear measurements, which therefore magnifies measurement errors.

The need to calculate myocardial volume cubing linear dimensions—due to the geometric assumption of the prolate ellipsoid—is the major limitation for LVM estimated by M-mode echocardiography as related to accuracy and reproducibility (28–31). PRESERVE (Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement) assessed intrapatient reliability (interscan reproducibility) of echocardiographic LVM measurements, repeating echocardiograms in 183 hypertensive subjects with LVH. The intraclass correlation coefficient (ICC) for the linear measurements was 0.87 for LVID, 0.85 for IVST, and 0.83 for PWT (32). Bottini et al. (33) also assessed interscan reproducibility, repeating echocardiograms in 22 hypertensive subjects, and reported an average mean difference of 0.3 g between exams, with 95% limits of agreement from −96.3 g to 96.9 g. The same authors also had 2 readers independently assessing 24 echocardiography images, finding mean differences (95% limits of agreement) of 1.83 g (−48.8, 52.5) (33). Intrareader reproducibility for LVM by echocardiography was evaluated in 735 children of HIV-infected mothers in the prospective P(2)C(2) HIV study (34). Echocardiograms were analyzed in 10 clinical sites and then reassessed at a central facility. The internal LVID showed the highest agreement (ICC = 0.97), but lower correlation was found for PWT (ICC = 0.65) and IVST (ICC = 0.50) (34). Also for intrareader reproducibility, 21 subjects were assessed by Missouris et al. (29), showing a mean coefficient of variation (95% confidence interval [CI]) of 6.1% (3.9 to 8.3). Using 20 hypertensive male subjects, Spratt et al. (35) investigated echocardiography inter-reader reproducibility and found mean differences (95% limits of agreement) for LVM/body surface area (BSA) between 4.5 g/m^2 (−24.9, 33.9) and 6.4 g/m^2 (−23.0, 35.8) for harmonic imaging (HI) and fundamental imaging (FI), respectively.

The ASE-recommended algorithm is based on the formula first described by Devereux et al. in 1977, adding modifications (20,27,36,37). Due to the ability

ABBREVIATIONS AND ACRONYMS

BSA = body surface area
FI = fundamental imaging
GRE = gradient-echo
HI = harmonic imaging
ICC = intraclass correlation coefficient
IVST = interventricular septum thickness
LV = left ventricular/ventricle
LVH = left ventricular hypertrophy
LVID = left ventricular internal dimension
LVM = left ventricular mass
LVMi = left ventricular mass index
PWT = posterior wall thickness
SSFP = steady-state free precession

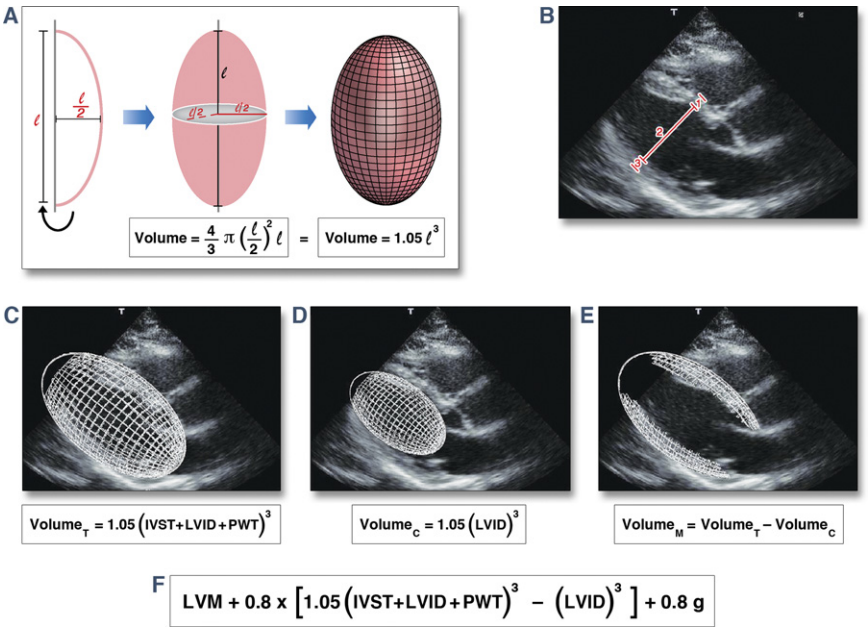

Figure 1. Principles for the Assessment of LVM by Echocardiography, as Recommended by the ASE

(A) A prolate ellipsoid of revolution, or prolate spheroid, is a 3-dimensional figure formed by revolving an ellipse about its major axes. The American Society of Echocardiography (ASE)-recommended formula assumes that the left ventricle has a prolate ellipsoid of revolution shape, with minor radii that are half the major radius. **(B)** Schematic representation of the linear measurements for the assessment of LVM by echocardiography (parasternal view), according to the ASE recommendations. 1 = interventricular septum thickness (IVST); 2 = left ventricular internal dimension (LVID); 3 = posterior wall thickness (PWT). **(C to E)** Images refer to a schematic representation of the steps for the estimation of left ventricular myocardial volume, as initially proposed by Devereux et al. (28). Left ventricular mass (LVM) is then calculated by multiplying the myocardial volume by the specific gravity of myocardium (1.05 g). **(C)** Calculation for the total left ventricular volume ($Volume_T$). **(D)** Calculation for the left ventricular internal cavity volume ($Volume_C$). **(E)** Calculation for the left ventricular myocardial volume ($Volume_M$). **(F)** The current ASE-recommended formula for the assessment of LVM. It is based on the initial concepts, but includes correction factors derived from regression analysis (20,35).

to improve definition of pericardial and endocardial borders, HI replaced FI in clinical practice. In the past, FI was limited to a fixed frequency for output and receiving (usually ~2.5 mHz), but the advent of HI allowed the emission of low-frequency ultrasound for good penetration and the reception of signal 2 octaves higher (38). When assessed by M-mode echocardiography, HI shows higher values for LVM compared with FI, but seems to correlate better to CMR measures (30,35,38,39).

Cardiac magnetic resonance. LVM evaluation by CMR permits a 3D high-resolution modeling of the LV free of cardiac geometric assumptions, contrast infusion, acoustic window dependency, or ionizing radiation. Both short-axis and long-axis techniques are highly accurate for quantification of LVM (40). The best-documented technique, however, uses a set of contiguous short-axis slices covering the entire LV from the atrioventricular ring down to the apex, acquired from a cine sequence. A combination of body matrix/torso radio frequency coils is used for the acquisition, using a 2D cardiac-gated pulse sequence. Ideally, images are acquired at resting lung volume. Myocardial volume is the area occupied between the endocardial and epicardial border multiplied by the interslice distance. By convention, LVM is measured at end-diastole. Similar to echocardiography, LVM is the product of this volume and the density of the myocardium (Fig. 2).

Early controversies were related to contour differences in LV quantification by CMR, with small studies favoring inclusion of papillary muscles in the calculation of myocardial mass (41–43). In fact, the measurement technique significantly influences the estimation of LVM (44). However, MESA (Multi-Ethnic Study of Atherosclerosis) enrolled the largest population with CMR assessment and showed better reproducibility when papillary muscles were excluded (45).

Technical developments in CMR image acquisition and post-processing influence LVM measurements. Black-blood techniques were previously used to assess LVM by CMR, moving to cine bright-blood techniques. More recently, steady-state free precession (SSFP) has replaced fast gradient-echo (GRE) se-

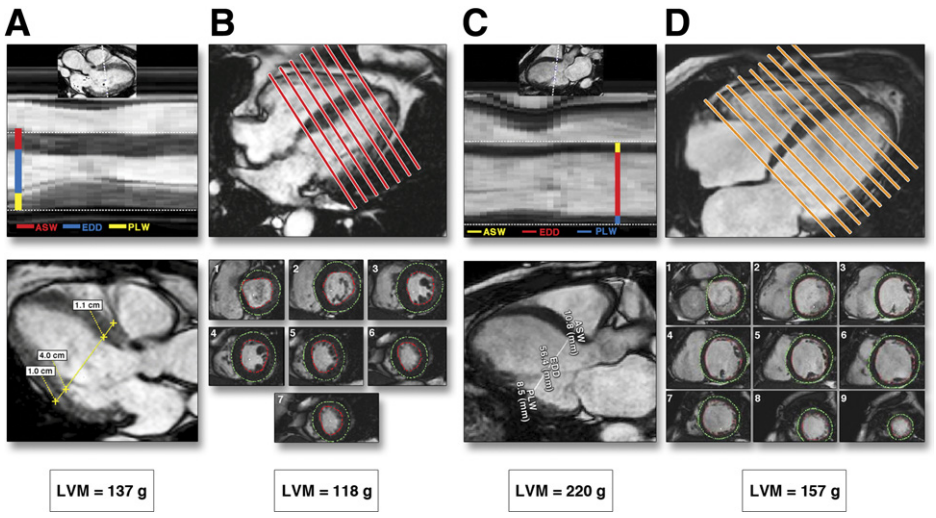

Figure 2. Images From CMR of 2 Patients With Chagas Cardiomyopathy

Case 1 has preserved cardiac geometry, but case 2 shows left ventricular remodeling. The usual assessment of LVM by cardiac magnetic resonance (CMR) does not require cardiac geometry assumptions, as opposed to linear measurements used in echocardiography. (Courtesy of Dr. Gustavo Volpe.) **(A and C)** CMR-derived images representing usual echocardiography views for linear measurements assessing LVM. The anterior septal wall (ASW) corresponds to the interventricular septal thickness; the end-diastolic dimension (EDD) corresponds to the left ventricular internal dimension; and the posterior lateral wall (PLW) corresponds to the posterior wall thickness. At the **bottom**, the ASE-recommended formula was used to calculate LVM (see Fig. 1 for a full description). **(B and D)** Usual CMR assessment for LVM, using contiguous short-axis slices covering the entire left ventricle from the atrioventricular ring to the apex (1 to 9). The estimated LVM is displayed at the bottom. Abbreviations as in Figure 1.

quences as the preferable CMR cine bright-blood technique. Compared with GRE techniques, SSFP sequences have substantially higher signal-to-noise and contrast-to-noise ratios and shorter acquisition times (46). SSFP sequences improve homogeneity of the blood pool signal and definition of the endocardial border throughout the cardiac cycle, improving the performance of automatic and manual delineation of contours for assessment of LVM (47). Studies comparing SSFP and GRE for calculation of LVM demonstrated a lower mass measured by the SSFP sequence, but both methods demonstrated good reproducibility (47,48).

In healthy participants, LVM assessed by CMR shows susceptibility to interobserver variation (49). Using 9 normal young volunteers, Missouris et al. (29) found CMR intrareader reproducibility between LVM estimations of 0.5% with 95% limits of agreement of ±11%. Bottini et al (33). assessed intrareader reproducibility in a population of 34 hypertensive subjects, finding mean differences (95% limits of agreement) of 0.32 g (−20.1, 21.7). Gandy et al. (50) showed that intrareader reproducibility of LVM measurements by CMR are dependent upon the clinical cardiac condition under investigation, with intraobserver coefficients of repeatability of 4.6 g for healthy volunteers, 6.7 g for post-myocardial infarct patients, 8.3 g in patients with congestive heart failure, and 9.8 g in patients with LVH. Moreover, Bellenger et al. (51) investigated 15 healthy adult volunteers and 15 patients with chronic stable heart failure that underwent 2 CMR scans 7 days apart, with correlation coefficient for the assessment of LVM of 0.99 and interscan average difference (95% limits of agreement) of 0.7 g (−6.3, 9.7) and 0.7 g (−11.9, 13.3) for normal and heart failure patients, respectively.

In fact, among the evaluations of LV volume, mass, and function by CMR, LVM appears to be the least reproducible and most variable parameter (44). This is because LVM is derived from the difference of 2 volumes (total LV volume and end-diastolic volume). Although gradually less significant over time, additional important limitations for wide clinical use of CMR include the following: elevated operational cost, time to acquire and analyze cine data, breath-hold dependency, hazards associated with ferromagnetic metal devices, and issues related to claustrophobia in susceptible patients.

Echocardiography versus CMR. Although CMR and echocardiographic LVM measurements show high correlation, absolute values of LVM differ between these techniques (Fig. 2) (29,30). The difference among estimates by echocardiography and CMR

indicates that the 2 methods cannot be used interchangeably in the assessment of LVM (33). Echocardiography is less expensive and has superior versatility, acceptability, and availability compared with CMR. These are practical issues that support clinical use of LVM assessed by echocardiography as an outcome predictor, as recommended by the most recent American Heart Association statement on cardiovascular risk assessment (52).

However, LVM determined by CMR is more accurate and precise than that provided by M-mode echocardiography (33). Interstudy reproducibility of CMR-derived parameters for LVM is also superior to 2D echocardiography for normal, dilated, and hypertrophic hearts (53). In fact, research studies using this method require substantially smaller sample sizes to assess outcome measures (51,53). The variability of echocardiography for evaluation of serial LVM changes has generated concerns (54). The previously reported probability of a true biological change in observed/predicted LVM over time was maximized for a single-reader difference >22% (55). Three-dimensional echocardiography improves accuracy and reproducibility compared with CMR, but is strongly dependent on equipment and technical conditions such as acoustic window quality (56–61).

LVM as a Predictor of Events

Longitudinal studies present in the MEDLINE database that investigated LVM, LVM index (LVMi), or LVH assessed by echocardiography or CMR as predictors of death or major cardiovascular outcomes were included in this analysis. The following criteria were applied to select articles: 1) echocardiographic studies using the ASE recommendations for chamber quantifications by M-mode technique (20,37); 2) survival analysis studies reporting hazard ratios and 95% CI; and 3) reports from multivariate analyses adjusted for at least 2 other traditional risk factors. In each study, analysis adjusted for the highest number of traditional cardiovascular risk factors was included. Analyses using covariates derived from other graphic/imaging diagnostic methods such as electrocardiography, ejection fraction, and LV volumes were excluded. Analyses that included pooled LVM data were excluded unless a classification of hypertrophy was clearly defined. For each study, we describe the mean follow-up time.

We included 26 longitudinal echocardiographic studies (Online Table 1) in our review. From those, 11 reported non-normalized LVM or LVMi as predictors of clinical outcomes (Online Fig. 1); 12 reported LVH (Online Fig. 2); and 8 reported serial changes in LVM or LVH status over time (Online Fig. 3). We included 5 studies for LVM assessed by CMR (Online Table 2). All CMR studies reported LVMi as outcome predictor; 2 also reported non-normalized LVM; and 1 additionally evaluated LVH. In the echocardiography group, a remarkable predominance of studies was oriented toward investigating hypertensive populations. For the CMR group, 4 of the 5 studies were based on participants from MESA, a population free from known cardiovascular disease at inclusion, using different outcomes and diverse methods for indexing LVM. Online Tables 1 and 2 also show the vast number of different LVH definitions used in these studies.

In Online Figure 4, the hazard ratios and 95% CI for the CMR group of studies are displayed according to the method used to index LVM, hypertrophy classification, and predicted outcomes. The 5 longitudinal CMR studies provide hazard ratios from 33 models. A direct comparison of events predictors is difficult due to the use of different clinical endpoints. Regardless of which method is used for normalization of LVM, however, most models demonstrated significant ability to predict events. For LVMi, the overall hazard ratio ranged from 1.0 (95% CI: 0.9 to 1.1) for prediction of coronary heart disease (62) to 2.2 (95% CI: 1.4 to 3.4) for prediction of a combined endpoint, including coronary heart disease or stroke (18).

Hazard ratios for the ability to predict events reported for LVM and LVMi in the echocardiography studies are shown in Online Figure 1, along with the mode of indexing and endpoint definitions. The 11 studies reported hazard ratios from 33 models. The hazard ratios ranged from 1.0 (95% CI: 0.99 to 1.02) for LVM indexed by BSA among subjects with diabetes—predicting a combined endpoint of cardiovascular death, ischemic heart disease, heart failure, end-stage renal disease, peripheral arterial disease, and stroke (63)—to 2.8 (95% CI: 1.6 to 4.7) for LVM predicting all-cause deaths among patients with heart failure (64).

The ability to predict events according to myocardial hypertrophy status by echocardiography is displayed in Online Figure 2. From the 10 included studies, 30 hazard ratios were reported. The hazard ratios ranged from 1.01 (95% CI: 1.0 to 1.02) for inappropriate LVM (>28% of excess, obtained by dividing LVM by predicted values based on a reference sample), predicting a composite endpoint (65) (see "composite 1" in the Online Fig. 2 legend for a full description) to 4.14 (95% CI: 1.8 to 9.7)

for LVH in patients without coronary artery disease, predicting all-cause mortality (66). Few studies are comparable, however, due to methodological differences. The majority of the studies report significant power to predict events for LVM, for LVMi, and for hypertrophy.

We assessed the ability to predict cardiovascular events by changes in LVMi or LVH classification over time using only echocardiography. Hazard ratios for serial changes in LVM or LVH status are displayed in Online Figure 3, with predicted outcome and mode of normalization. A total of 23 hazard ratios were reported in the 8 studies providing information on LVM and LVH status changes. In summary, the risk gradually increased according to LVM at baseline, with an increasing LVM or hypertrophy grading. When LV mass regressed after treatment, the hazard ratio was favorable, predicting an extensive composite endpoint (hazard ratio: 0.18, 95% CI: 0.05 to 0.7) (67) (see "composite 5" in the Online Fig. 3 legend for a full description). A maintained LVH status, however, significantly predicted a different composite endpoint (hazard ratio: 3.52, 95% CI: 2.5 to 4.6) (68) (see "composite 2" in the Online Fig. 3 legend for a full description).

Indexing Process

During the review process, we assessed several criteria used to normalize LVM. Online Figures 1, 3, and 4 display the wide variety of methods used to calculate LVMi. Heart size scales with the size of the body (22). Several different methods have been suggested for indexing LVM to anthropometric measures, usually based on height and/or weight, but the optimal way to normalize myocardial mass has not been established (20). Alternatively, procedures where measured LVM is indexed by dividing by expected LVM (based on a reference population free of major cardiovascular risk factors) have also been proposed, adding complexity to the calculation of LVMi. The most commonly used formula for computing BSA—the Dubois and Dubois regression ($BSA = 0.007184 \times \text{weight [Kg]}^{0.425} \times \text{height [cm]}^{0.725}$)—is based on an assessment of 9 cadaveric subjects reported in a 1916 publication, and its validity has been questioned (18,22,69).

Indexing LVM to BSA was the first normalization process used, but it seems to underestimate the prevalence of LVH in obese as well as in overweight hypertensive patients (17). Conversely, the prevalence of hypertrophy is higher in obese individuals for height-based indices that do not account for weight in overweight individuals (18). The purpose of indexing LVM for height with an allometric exponent is to attempt to approximate lean body mass and to possibly adjust for the impact of growth during childhood (70). Compared with LVM/BSA and LVM/height, indexation of LVM by height$^{2.7}$ appears to adjust better for the relations between height and LVM in hypertensive, obese individuals and to reduce the variability among normal subjects, providing a more sensitive cutoff for LVH (70,71). Comparing LVM indexed by BSA and height$^{2.7}$, LVM/height$^{2.7}$ has a better performance as a unique criteria to detect LVH prevalence in obese subjects (72). Also, in acromegaly, LVM indexed for height$^{2.7}$ appears to be the most appropriate method to identify LVH—particularly in patients who are also overweight (73).

Using a population of hypertensive subjects with low prevalence of obesity, de Simone et al. (74) (Online Table 1) compared indexing methods for LVM assessed by echocardiography as predictors of cardiovascular events. After adjustment for age and sex, indexing by height, height$^{2.7}$, or height$^{2.13}$ performed as well as BSA as outcome predictors (Online Fig. 1). de Simone also investigated American Indians free of cardiovascular disease, but with a high prevalence of obesity (Online Table 1) (75). Adjusted for age and sex, the presence of LVH identified by LVM normalized by height$^{2.7}$ and height$^{2.13}$ was associated with a higher proportion of outcomes than was LVH detected using LVM normalized by BSA (Online Fig. 1). In a cohort of patients undergoing dialysis (Online Table 1), more subjects were classified with LVH by LVM/height$^{2.7}$ compared with LVM/BSA (76). In this population, LVH classified either by normalization to BSA or height$^{2.7}$ predicted total and cardiovascular mortality. However, LVM/height$^{2.7}$ demonstrated better predictive ability compared with LVM/BSA (Online Fig. 1).

For LVM assessed by CMR, 2 studies used MESA (15) participants to compare indexing methods in their ability to predict clinical events (Online Table 2) (18,19). Chirinos et al. (19) initially included MESA CMR data and echocardiography data from the Asklepios Study (77) to compare LVM indexed by BSA, height, height$^{1.7}$, or height$^{2.7}$ in relation to the LVH classification. The authors conclude that indexation by height$^{1.7}$ would provide the best description of the relationship between LVM and body size in both echocardiography and CMR assessments. However, only

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the white and Chinese participants from MESA and white European subjects from the Asklepios Study were included in the analyses for the allometric exponent comparisons. In this study, survival analysis to establish the best indexation procedure was shown only for the MESA population. LVH defined by LVM/height$^{1.7}$ was reported to be related to all cardiovascular events, to hard cardiovascular events, and to all-cause mortality. Normalization by either height$^{2.7}$ or BSA, however, failed to predict all-cause mortality (Fig. 1) (19). Also using MESA participants, Brumback et al. (18) investigated LVM indexed by BSA, height^2, height$^{2.7}$, and 2 other allometric indices (percent-predicted LV mass based on height and sex; and percent-predicted LVM based on height, weight, and sex). The study found a higher prevalence of hypertrophy for indices that do not account for weight, but no significant difference was detected between indices for the outcomes prediction ability (18).

Gaps in Knowledge

An increase in LVM is the most important component of cardiac remodeling, resulting from an incompletely understood balance between cardiac stressors and compensatory mechanisms (12,28,78). However, the exact point when the increase of myocardial mass turns from an adaptive process to pathology is unknown. Obesity may be related to both adaptive and pathological increases in LVM. Future studies should address whether indexing methods can not only adjust for body size, but also account for adaptive changes in the obese and whether they influence clinical decision making.

The appropriate consideration of body size in the evaluation of cardiovascular structure affects recognition and treatment of cardiovascular disease states in pediatric and adult patients (22). The best approach seems to be normalization of LVM by height to some allometric power, specifying cutoff values of normality according to sex and ethnicity. When considering the definition of the appropriate height allometric exponent, the current literature still has important gaps in knowledge. Although height$^{1.7}$ seems to be promising to establish the best description for the relation between myocardial mass and body size, there are still strong limitations related to the cutoff definitions and to the limited longitudinal data available—especially for echocardiographic assessment of LVM. In this regard, most of the longitudinal scientific evidence is still related to normalization by height$^{2.7}$.

A reduction in intervertebral disk diameter occurs with aging, possibly accounting for artifactual individual changes over time in indexed parameters. Cumulative height loss from age 30 to 70 years may decrease approximately 3 cm of the original height for men and 5 cm for women (79). It affects the calculation of BSA, but should have higher impact on methods adjusted uniquely to height to an allometric power. However, the implications on LVMi of height changes related to aging are still unknown.

The majority of longitudinal studies assessing CMR-derived LVM predicting outcomes are from the MESA study (Online Table 2). Although addressing a large multiethnic population, the MESA results should be tested in other populations to assess how universal are these findings. There are also unclear aspects related to the assessment of LVM by CMR regarding the LV basal slices. Including or not including a more basal slice can be a major source of variability in the final LVM calculation, but this issue is not properly addressed in the literature. On the basis of the experience with the MESA study, a slice-by-slice analysis considering base when myocardium is present in more than 50% of the short-axis circumference appears to be appropriate. MESA also set the normality range for functional CMR and showed clinical event prediction for LVM assessed by resonance (15,19,62). However, these assessments were done with the GRE technique. The fact that GRE has been replaced by SSFP urges the necessity of new standard cutoff values for normality that account for technical differences.

Although CMR showed better performance than echocardiography for accuracy and precision in LVM evaluation (33), no direct comparison of the 2 methods has been performed for the ability to predict clinical events, the agreement for hypertrophy classification, or the cardiovascular risk reclassification. It is unknown how concordant CMR and echocardiography are regarding hypertrophy classification—especially when different indexing methods are considered. Additionally, there is a lack of knowledge regarding the risk reclassification for LVM when compared with traditional risk assessments (52,80).

Recommendations and Future Perspectives

We showed that LVM assessed by echocardiography has a good event prediction power, but has major limitations related to the need for cardiac geometric assumptions. Therefore, the ASE-recommended formula should be reported in all

echocardiograms performed in patients without major LV remodeling. To improve accuracy and reproducibility across laboratories, strict quality control recommendations should be enforced. In this regard, the Intersocietal Accreditation Commission for Echocardiography requires the measurement of IVST, PWT, and LVID by 2D or M-mode imaging, but has no special recommendation for LVM assessment (81). Laboratories should have technicians regularly perform intraobserver and interobserver reliability assessments to improve measurement accuracy.

The currently preferable method for LVM assessment by CMR is based in the scientific evidence collected by the MESA study, leading to the short-axis evaluation, with exclusion of papillary muscle. In addition, to include basal slides when myocardium is present in more than 50% of the short-axis circumference would be consistent with the MESA protocol. The Intersocietal Accreditation Commission for Magnetic Resonance has not made specific recommendations on LVM as criteria for quality control (82). Recommendations on standard reports and quality assessment should be consented by scientific societies.

For echocardiography, indexing LVM by height to the allometric power of 1.7 or 2.7 has shown the best relation to body size and events prediction. However, normal reference values have not been firmly established. Cutoff values endorsed by the ASE are based on FI technique and thus may not be applicable to the HI era. Values are not standardized for different ethnicities. For CMR, most of the longitudinal scientific evidence is based only on the MESA cohort of participants using GRE sequences. Standard recommendations for indexing and cut-points for hypertrophy across imaging modalities are needed to match current technologies used in daily practice.

The National Heart, Lung, and Blood Institute's Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (24) recognizes LVH as the most prominent clinical evidence of target-organ damage caused by hypertension in children and adolescents. The guidelines incorporate LVM measurement in the evaluation algorithm, recommending intensification of antihypertensive management if there is presence of LVH. However, the role of periodic echocardiographic determination of LVMi is restricted to patients who have established LVH (24). The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) is expected to be released in 2012 (83). The previous edition also lists LVH as target-organ damage for the heart and an independent risk factor. Aggressive blood pressure management is described as a strategy for LVH regression. However, echocardiography is not included among the routine or even in the optional tests and procedures (25). The European Society of Cardiology Guidelines for management of arterial hypertension uses LVH as criteria of subclinical organ damage influencing prognosis (23). In this context, echocardiography is recommended during diagnostic evaluation for more precise stratification of overall risk and for checking the status of organ damage during follow-up visits. In a therapeutic view, effects of different drugs on LVM and LVH are discussed. However, LVMi variation is not stated among therapeutic goals (23).

The way clinicians use LVM in their practice may not reflect the scientific recommendations from medical societies. An important issue related to LVM is its restricted clinical use in daily practice in contrast to the regular use of measurements of cardiac systolic function (20). In a multicenter survey performed in Italy, hypertension accounted for approximately 30% of echocardiographic examinations in outpatient hospitals or academic echocardiography labs (84). However, a large majority of echocardiographic examinations routinely performed on hypertensive patients did not report data on LVM, and if reported, the results were usually not indexed to anthropometric variables (84,85).

Conclusions

In the assessment of LVM, no superiority between echocardiography and CMR may be stated at this time, due to the absence of studies directly comparing the methods. Assessed by both echocardiography and CMR, LVM, and LVH are reliable cardiovascular event predictors. LVM assessed by echocardiography is more practical on a clinical basis. CMR would be preferable for research and specific clinical conditions requiring higher accuracy and reproducibility. Dividing LVM by height to some allometric power is the most promising indexing method for scaling myocardial mass to body size. The measurement of LVM and a definition of LVH based on outcomes should be agreed upon by scientific societies considering all available techniques.

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Key Words: cardiac magnetic resonance ■ cardiovascular events ■ echocardiography ■ LVH ■ LVM.

▶APPENDIX

For supplementary figures and tables, please see the online version of this paper.

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Objetivo Terciário

Identificar a acurácia da medida de massa ventricular esquerda por ecocardiografia e os efeitos da indexação na definição de hipertrofia ventricular

Artigo 7 - Left Ventricular Mass and Hypertrophy by Echocardiography and Cardiac Magnetic Resonance: The Multi-Ethnic Study of Atherosclerosis

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Left Ventricular Mass and Hypertrophy by Echocardiography and Cardiac Magnetic Resonance: The Multi-Ethnic Study of Atherosclerosis

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Background: Left ventricular mass (LVM) and hypertrophy (LVH) are important parameters, but their use is surrounded by controversies. We compare LVM by echocardiography and cardiac magnetic resonance (CMR), investigating reproducibility aspects and the effect of echocardiography image quality. We also compare indexing methods within and between imaging modalities for classification of LVH and cardiovascular risk. Methods: Multi-Ethnic Study of Atherosclerosis enrolled 880 participants in Baltimore city, 146 had echocardiograms and CMR on the same day. LVM was then assessed using standard techniques. Echocardiography image quality was rated (good/limited) according to the parasternal view. LVH was defined after indexing LVM to body surface area, height$^{1.7}$, height$^{2.7}$, or by the predicted LVM from a reference group. Participants were classified for cardiovascular risk according to Framingham score. Pearson's correlation, Bland–Altman plots, percent agreement, and kappa coefficient assessed agreement within and between modalities. Results: Left ventricular mass by echocardiography (140 ± 40 g) and by CMR were correlated ($r = 0.8$, $P < 0.001$) regardless of the echocardiography image quality. The reproducibility profile had strong correlations and agreement for both modalities. Image quality groups had similar characteristics; those with good images compared to CMR slightly superiorly. The prevalence of LVH tended to be higher with higher cardiovascular risk. The agreement for LVH between imaging modalities ranged from 77% to 98% and the kappa coefficient from 0.10 to 0.76. Conclusions: Echocardiography has a reliable performance for LVM assessment and classification of LVH, with limited influence of image quality. Echocardiography and CMR differ in the assessment of LVH, and additional differences rise from the indexing methods. (Echocardiography 2014;31:12-20)

Key words: left ventricular mass, left ventricular hypertrophy, echocardiography, image quality

Echocardiography and cardiac magnetic resonance (CMR) are the two most frequent imaging modalities used to assess left ventricular mass (LVM). Although CMR is considered the gold standard method for LVM evaluation, echocardiography is well validated, harmless, and widely available. In fact, echocardiography-derived LVM is usually performed in clinical practice and has shown prediction ability for cardiovascular outcomes.[1–3]

Anthropometric parameters have been used to normalize myocardial mass, minimizing the influence of body size in the population distribution. LVM is usually indexed (LVMi) by height to some allometric power, by body surface area (BSA), or by comparing it to a reference group of healthy subjects. Left ventricular hypertrophy (LVH)—defined by an LVMi greater than some specified cutoff value (often the 95th percentile value estimated from a healthy sample)—has an important role in clinical practice. The definition for LVH and its performance as a cardiovascular risk predictor is strongly related to the LVM indexing method.[4–9]

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Although LVMi and LVH are considered important markers for cardiovascular prognosis and therapeutic responses, the role of myocardial mass and hypertrophy in clinical practice has not been firmly established.[10] Echocardiography assessment has major limitations related to acoustic window quality, but how it affects the ability to assess LVM is unknown. Moreover, it is still unknown how concordant CMR and echocardiography are for the identification of hypertrophy. The controversies around echocardiography-derived LVM and LVH increase when different indexing methods and cutoff values are considered.[1,10]

Our study compares LVM acquired by echocardiography and CMR, investigating reproducibility aspects of both modalities. We also explore the effect of echocardiography image quality in the assessment of LVM. We compare indexing methods within and between imaging modalities for the classification of LVH and cardiovascular risk.

Methods:

Study Design and Population:

The National Heart, Lung, and Blood Institute's (NHLBI) Multi-Ethnic Study of Atherosclerosis (MESA) has been described in the literature.[11] In brief, between July 2000 and August 2002, 6,814 men and women who were free of clinically apparent cardiovascular disease were recruited from 6 U.S. communities: Baltimore city and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. The Baltimore city site included exclusively white and African-American participants. In the follow-up period between July 2005 and April 2007, a randomly selected subsample of participants from Baltimore city had echocardiography and CMR performed on the same day at the Johns Hopkins Hospital (Baltimore, MD). The institutional review boards at all centers approved the study, and all participants gave informed consent.

Echocardiography:

Echocardiograms were performed by an experienced sonographer using an Aplio scanner (Toshiba Medical Systems Corp, Tochigi, Japan) and were recorded onto digital media. At the same site, experienced readers analyzed the images using an offline system (Digiview 3.7.7.6, Digisonics Inc., Houston, TX, USA). As recommended by the American Society of Echocardiography (ASE), from a two-dimensional (2D) parasternal view, LVM was calculated using linear measurements of interventricular septal thickness, left ventricular (LV) internal dimensions, and LV posterior wall thickness at end-diastole (Fig. 1A).[2] Image quality was evaluated in the 2D parasternal view and rated according to the identification of the interfaces between cardiac blood pool and endocardium, and between the epicardium and pericardium. Images were rated as limited when at least one interface was not adequately assessed and as good when all interfaces were distinguished.

Cardiac Magnetic Resonance:

The method used to assess LVM by CMR in MESA has been described in the literature.[12] Briefly, images were acquired on a 1.5 T scanner (Avanto, Siemens, Malvern, PA, USA) using a 2D steady-state free precession (SSFP) acquisition in vertical long-axis, horizontal long-axis and short-axis orientations with the following parameters: TE 1.16 ms, TR 3.2 ms, flip angle 60°, receiver bandwidth ±1220 kHz, FOV 36 cm, slice thickness 8 mm, slice gap 2 mm, acquisition matrix 205 × 256, number of averages = 1, number of frames = 30. The endocardial and epicardial myocardial borders were contoured using a semi-automated 2D standard software (MASS 4.2, Medis, Leiden, The Netherlands). The difference between the epicardial and endocardial areas for all slices was multiplied by the slice thickness and section gap, and then multiplied by the specific gravity of the myocardium (1.05 g/ml) to determine the ventricular mass (Fig. 1B). Papillary

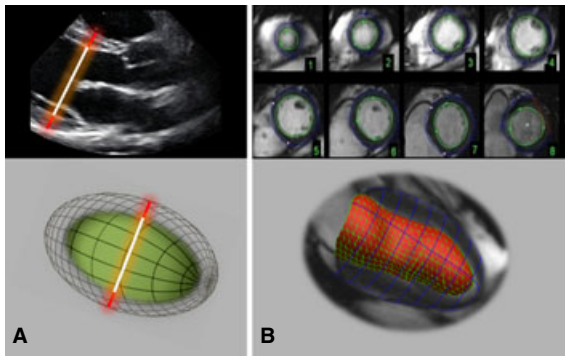

Figure 1. Illustrative representation of left ventricular mass (LVM) assessment by **A**. echocardiography and **B**. cardiac magnetic resonance (CMR). **A**. Linear measurements for interventricular septum thickness, left ventricular internal dimension, and posterior wall thickness using 2D echocardiography in a parasternal view. LVM is then calculated assuming that the left ventricle has the shape of a prolate ellipsoid of revolution (below). In this participant, LVM by echocardiography was 134 g; **B**. CMR using the Simpson method to assess LVM from short-axis views. CMR allows assessing cardiac geometry in its 3D shape (below). In this participant, LVM by CMR was 114 g.

muscle mass was included in the LV cavity and excluded from the LVM.[13]

Intra-Reader, Inter-Reader, and Inter-Scan Reproducibility:
Subsets of participants were randomly selected to have their echocardiography and CMR images reread by the same reader, and by different readers. A subset of participants was also randomly selected to have a second echocardiogram performed by the same sonographer within 1 week of the primary (initial) echocardiogram and read by the same reader. Efforts were made to blind the readers to the primary results. All readers had appropriate training and experience in large cohort studies (such as MESA, EDIC, and CARDIA) using the imaging modalities they performed.

Left Ventricular Mass Indices and Hypertrophy Definition:
LVM was indexed by four methods: (1) dividing by BSA, (2) dividing by height$^{1.7}$, (3) dividing by height$^{2.7}$, and (4) dividing by the predicted LVM based on a healthy sample. We used height to different allometric powers in #2 (height$^{1.7}$) and #3 (height$^{2.7}$), because these methods were found to perform differently for predicting CV outcomes in a previous MESA investigation.[6] Table I summarizes the indexing methods and cutoff values for LVH according to the imaging modality.

Statistical Analysis:
Continuous variables were reported in their mean values ± standard deviation (SD) and categorical variables in its proportions. Differences between mean values were evaluated with paired *t*-test and Fisher's exact test to assess differences in proportions. Linear regression and Pearson's correlation coefficient (r) were used to evaluate the relationship between LVM as determined by echocardiography and by CMR, as well as to assess correlations between LVM and blood pressure in this population. Bland–Altman plots were also used to describe differences between LVM as determined by echocardiography and by CMR, reporting the mean differences and 95% limits of agreement (95% LA). Inter- and intra-reader and inter-scan reproducibility performances were also evaluated in both modalities using intra-class correlation coefficients (ICC) and Bland–Altman plots.

Participants were divided into 3 cardiovascular risk groups by their Framingham 10-year cardiovascular risk score: low risk (<10%), intermediate risk (10%–20%), and high risk (>20%).[14] ANOVA was used to assess difference of the mean unindexed LVM and LVM indices among the cardiovascular risk groups (shown as supplemental material). Fisher's exact test was used to assess differences in proportions for hypertrophy classification according to cardiovascular risk. The proportion of participants whose classification for

TABLE I

Left Ventricular Mass Index (LVMi) and Definition of Left Ventricular Hypertrophy According to the LVMi Cutoff Value

Imaging Modality	Indexation	Calculation Method	LVMi Cutoff Value	Reference for Cutoff Value
Echo	BSA	LVMi = LVM/BSA	>115 g/m^2 for men; >95 g/m^2 for women	ASE Guidelines [2]
	Height$^{1.7}$	LVMi = LVM/height$^{1.7}$	≥81 g/m$^{1.7}$ for men; ≥60 g/m$^{1.7}$ for women	Asklepius Study[6]
	Height$^{2.7}$	LVMi = LVM/height$^{2.7}$	≥50 g/m$^{2.7}$ for men; ≥47 g/m$^{2.7}$ for women	de Simone[7]
	% Predicted	LVMi = 100 × LVM/Predicted LVM: Men: 16.6 × [weight (kg)]$^{0.51}$; women 13.9 × [weight (kg)]$^{0.51}$	>1.45	Cardiovascular Health Study[27]
CMR	BSA	LVMi = LVM/BSA	>106.2 g/m^2 for men; >84.6 g/m^2 for women	MESA[28]
	Height$^{1.7}$	LVMi = LVM/height$^{1.7}$	≥80 g/m$^{1.7}$ for men; ≥60 g/m$^{1.7}$ for women	MESA[6]
	Height$^{2.7}$	LVMi = LVM/height$^{2.7}$	>45.1 g/m$^{2.7}$ for men; >38 g/m$^{2.7}$ for women	MESA[28]
	% predicted	100 × LVM (g)/[a × height (m)$^{0.54}$ × weight (kg)$^{0.61}$], where a = 6.82 for women or 8.25 for men	>1.31	MESA[13]

CMR = cardiac magnetic resonance; Echo = echocardiography; LVMi = left ventricular mass index; BSA = body surface area; LVM = left ventricular mass; MESA = Multi-Ethnic Study of Atherosclerosis; % predicted = percent of predicted LVM.

hypertrophy (existence of hypertrophy or not) was concordant between indices was calculated, within and between imaging modalities. Cohen's kappa coefficient was also used to evaluate agreement.

Results:

A total of 880 subjects were enrolled in the site at Baltimore city; 155 were randomly selected to undergo echocardiography and CMR. From the total, 146 subjects had interpretable CMR and echocardiography on the same day and were included in the study; 100 (68%) of these had good quality echocardiography images. The mean value for LVM assessed by CMR was 128 $\pm$ 34 g and by echocardiography was 140 $\pm$ 40 g. Table II summarizes the clinical characteristics of all participants and the subsample with both interpretable echocardiography and CMR examinations.

The reproducibility profile had strong correlations and agreement for both CMR and echocardiography, with ICC ranging from 7.3 to 9.1 for inter-reader assessment by echocardiography and intra-reader assessment by CMR, respectively (Table III). With all the investigated indexing methods and images modalities, the mean LVMi value was higher with higher cardiovascular risk category (Table S1) and a strong relationship was found between LVM and blood pressure (Table S2). Statistically significant differences among means by cardiovascular risk category exist for all LVMi except for the percent-predicted LVMi by either echocardiography or standard CMR.

The mean value for echocardiography-derived LVM was 138 $\pm$ 38 g for participants with good-quality images and 142 $\pm$ 46 g for those with limited quality, without significant difference (P = 0.61). Similarly, no statistically signifi-

TABLE II

Characteristics of All Subjects Enrolled at the Site and the Sample for this Study

	All Participants (n = 880)		Included Participants (n = 146)	
Variable	Mean	SD	Mean	SD
Age (years)	68	9.7	66	8.8
Height (m)	1.7	0.1	1.7	0.1
Weight (kg)	83	18	82	18
Creatinine (mg/dL)	1.1	0.4	1.0	0.3
EF by CMR (%)	59	9.5	59	8.6
	Proportion		Proportion	
Male (gender)	47%		43%	
Diabetes/IFG*	38%		31%	
Hypertension†	59%		54%	
African Americans	49%		46%	

*Following 2003 ADA fasting criteria algorithm.
†Hypertension by JNC VI (1997) criteria.
SD = standard deviation; EF = ejection fraction by the two-dimensional Simpson method; CMR = cardiac magnetic resonance; LVM = left ventricular mass; IFG = impaired fasting glucose.

TABLE III

Reproducibility Assessment for CMR and Echocardiography

Reproducibility	n	ICC (P-value)	Mean Difference (95% Limits of Agreement)
CMR			
Intra-reader (EC)	15	0.91 (P < 0.001)	1.2 (−26.39, 28.81)
Inter-reader (EC vs. MN)	22	0.88 (P < 0.001)	12.35 (18.29, 43.00)
Echocardiography			
Intra-reader (AA)	15	0.84 (P < 0.001)	4.54 (−45.38, 54.46)
Inter-reader (AA vs. ES)	85	0.73 (P < 0.001)	11.85 (−39.86, 63.56)
Inter-scan (ES vs. ES)	15	0.85 (P < 0.001)	4.72 (−76.16, 85.63)

CMR = cardiac magnetic resonance; 2D = two-dimension; 3D = three-dimension; ICC = intra-class correlation coefficient.

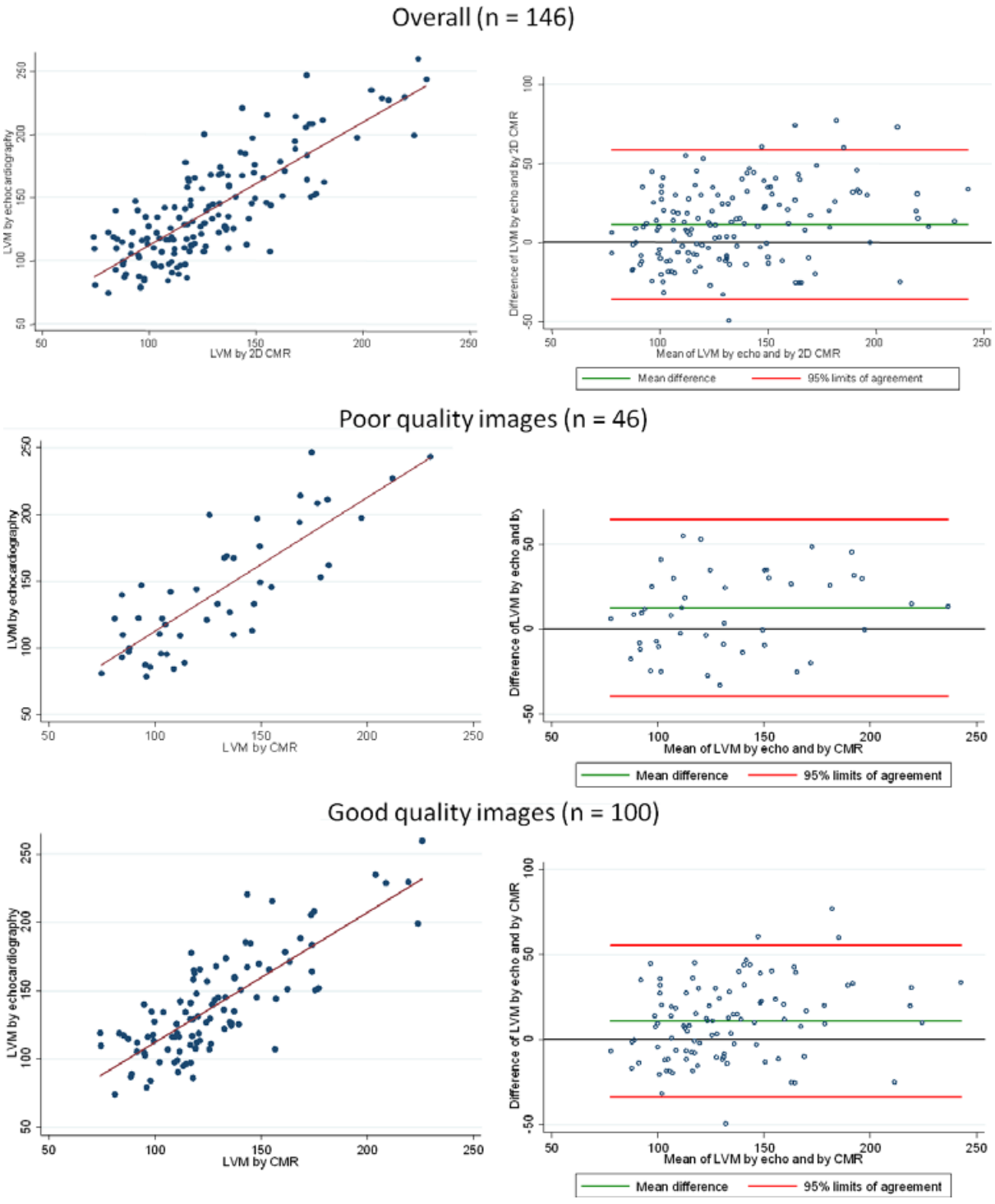

Figure 2. Scatter plots and Bland–Altman plots for LVM assessed by echocardiography and by CMR, overall and according to echocardiography image quality. LVM = left ventricular mass; echo = echocardiography; CMR = cardiac magnetic resonance.

cant difference was found for anthropometrics comparing the imaging quality groups. For participants with limited or good image quality scores, we found 56% and 57% of females, respectively; 49% of participants with limited image quality and 45% of those with good image quality were African Americans; and mean BMI of 30 $\pm$ 6 g/m^2 and 29 $\pm$ 5 g/m^2 for those

TABLE IV

Proportion of LVH for Diverse Indexing Methods and Imaging Modality in All Participants (n = 146), and by Framingham 10-year Cardiovascular Risk Score Category (n = 136)

Imaging Modality and Normalization Method	Hypertrophy (95% CI)	Hypertrophy Proportion (95% CI) According to CV Risk			P Value*
		Low (n = 48)	Intermediate (n = 42)	High (n = 46)	
LVH by Echocardiography					
BSA (%)	11.6 (6.4, 16.9)	6.2 (−0.7, 13.2)	9.5 (0.5, 18.6)	17.4 (6.2, 28.6)	0.2
Height$^{1.7}$ (%)	24.0 (17.0, 31.0)	22.9 (10.8, 35.0)	19.0 (6.9, 31.2)	26.1 (13.1, 39.0)	0.7
Height$^{2.7}$ (%)	7.5 (3.2, 12.0)	4.2 (−1.6, 9.9)	4.8 (−1.8, 11.3)	13.0 (3.1, 23.0)	0.3
% Predicted	3.4 (0.4, 6.4)	2.1 (−2.0, 6.2)	4.8 (−1.8, 11.3)	4.4 (−1.7, 10.4)	0.7
LVH by CMR					
BSA (%)	5.5 (1.7, 9.3)	4.2 (−1.6, 9.9)	4.8 (−1.8, 11.3)	4.4 (−1.7, 10.4)	1.0
Height$^{1.7}$ (%)	6.8 (2.7, 11.0)	4.2 (−1.6, 9.9)	7.1 (−0.8, 15.1)	8.7 (0.4, 17.0)	0.7
Height$^{2.7}$ (%)	6.2 (2.2, 10.1)	4.2 (−1.6, 9.9)	9.5 (0.5, 18.6)	6.5 (−1.0, 13.8)	0.6
% predicted	3.4 (0.4, 6.4)	2.1 (−2.0, 6.2)	4.8 (−1.8, 11.3)	4.4 (−1.7, 10.4)	0.7

*The P value refers to Fisher's exact test for difference in LVH classification according to cardiovascular risk group.
SD = standard deviation; CV = cardiovascular; CI = confidence interval; LVM = left ventricular mass; CMR = cardiac magnetic resonance; LVH = left ventricular hypertrophy; BSA = body surface area; % predicted - percent of the predicted LVM from a reference group of healthy subjects.

TABLE V

Proportion of Agreed Classification (Below Diagonal) and Cohen's Kappa Coefficient (Above Diagonal) for the Classification of Hypertrophy, According to the Different Image Modalities and Indices. In Gray, Results for Inter-Modality Agreement

Normalization Methodology		P_{LVH} (%)	2D CMR				Echocardiography			
			BSA	Height$^{1.7}$	Height$^{2.7}$	%Predicted	BSA	Height$^{1.7}$	Height$^{2.7}$	%Predicted
2D CMR	BSA	5.5	–	0.41*	0.44*	0.76*	0.37*	0.11‡	0.29*	0.44*
	Height$^{1.7}$	3.4	93%	–	0.61*	0.37*	0.23†	0.23*	0.23†	0.23†
	Height$^{2.7}$	6.8	94%	95%	–	0.55*	0.33*	0.14†	0.36*	0.25*
	% predicted	6.2	98%	94%	96%	–	0.42*	0.10‡	0.34*	0.59*
Echo	BSA	11.6	90%	87%	89%	92%	–	0.41*	0.53*	0.42*
	Height$^{1.7}$	24.0	77%	79%	77%	77%	82%	–	0.41*	0.20*
	height$^{2.7}$	7.5	92%	90%	92%	93%	92%	84%	–	0.34*
	% predicted	3.4	95%	92%	93%	97%	92%	79%	93%	–

*P < 0.001.
†P ≤ 0.01.
‡P < 0.05 for test of null hypothesis that kappa = 0.
CMR = cardiac magnetic resonance; BSA = body surface area; Echo = echocardiography; P_{LVH} = prevalence of left ventricular hypertrophy; % predicted = percent of the predicted LVM from a reference group of healthy subjects.

with limited and good quality images, respectively. The overall correlation between LVM by echocardiography and CMR was consistent (Fig. 2), regardless of echocardiography image quality scoring (r = 0.8; P < 0.001 for the overall relation, good quality images, and limited quality echocardiography images). Compared with CMR, LVM was higher when assessed by echocardiography in 10.8 g (95% LA = −33.8, 55.4) in participants with good image quality. In those with limited image quality, the difference between echocardiography and CMR was slightly higher: 12.6 g (95% LA = −39.7, 64.8).

For LVM assessment by CMR, the presence of hypertrophy ranged from 3.4% when indexed by predicted LVM to 6.8% when indexed by height$^{1.7}$. For echocardiography-derived LVH, the range was from 3.4% when indexed by the predicted LVM to 24.0% when indexed by height$^{1.7}$ (Table IV). The prevalence of hypertrophy did not differ significantly according to cardiovascular risk category for all 4 indexing methods in both imaging modalities.

The percent agreement for the classification of LVH according to the image modality and index method ranged from 77% to 98%. The highest value was related to CMR-derived measurements normalized by BSA compared to normalization by percent-predicted LVM. The lowest values were found for echocardiography-derived

LVM/height$^{1.7}$ compared to CMR-derived normalization by BSA, by height$^{2.7}$, or by the percent-predicted LVM. The Cohen's kappa coefficient ranged from 0.10—comparing the CMR-derived percent-predicted LVM with echocardiography LVM/height$^{1.7}$—to 0.76 for the comparison between CMR LVM/BSA with the CMR percent-predicted LVM (Table V).

Discussion:

Echocardiography is the most usual imaging method for assessing LVM in clinical practice, but CMR is well established as the gold standard modality.[1,3] Our study included echocardiograms and CMR scans performed on the same day in a representative biracial sample of MESA participants to explore controversial aspects regarding the comparison between these imaging modalities for the assessment of LVM and LVH. To the best of our knowledge, our study is the first to evaluate the agreement for LVH classification within and between imaging modalities across diverse LVM indexing methods. Moreover, aspects related to echocardiography image quality were also explored when compared with CMR.

Our results confirm studies which have shown that LVM by echocardiography linear measurements is higher on average compared to CMR measurements.[15–18] The PRESERVE study included echocardiography assessment of LVM to compare with CMR at baseline and after 1-year follow-up, and found a mean overestimation of myocardial mass by echocardiography of 27.6 $\pm$ 36.0 g and 37.1 $\pm$ 27.6 g, respectively.[19] In patients undergoing mitral valve replacement, the assessment by M-mode echocardiography overestimated LVM values compared to CMR (mean differences ranged from 70 to 108 g for post- and preoperative assessments, respectively), but both provided reliable information of myocardial mass regression.[16] We observed a mean difference of 11.3 g which is statistically significantly different from 0 (95% confidence interval for the mean difference: 9.4–13.2); however, this difference is likely too small to have an impact on clinical decisions. Moreover, the mean difference between LVM by echocardiography and CMR is similar in magnitude to the mean difference between readers of echocardiography or CMR (inter-reader echocardiography mean difference = 11.85; inter-reader CMR mean difference = 12.35, Table III).

As expected, the reproducibility of measurements by the same reader was better compared to the reproducibility of measurements by different readers, for both 2D CMR and echocardiography. Compared to our results (Table V), the literature has shown similar findings for echocardiography and CMR reproducibility. For inter-scan reproducibility, Bottini et al. repeated echocardiograms in 22 hypertensive subjects and found a mean difference (95% limits of agreement) of 0.3 g (−96.3, 96.9). The same authors also had two readers independently assessing 24 echocardiography images and 34 CMR images, finding mean differences (95% limits of agreement) of 1.83 g (−48.8, 52.5) and 0.32 g (−20.1, 21.7) for echocardiography and CMR, respectively.[15] Using 20 hypertensive male subjects, Spratt at el. investigated echocardiography inter-reader reproducibility and found mean differences (95% limits of agreement) for LVM/BSA between 4.5 g/m^2 (−24.9, 33.9) and 6.4 g/m^2 (−23.0, 35.8) for harmonic and fundamental imaging, respectively.[20] For echocardiography intra-observer reproducibility, 21 subjects were assessed by Missouris et al. showing a mean coefficient of variation (95% CI) of 6.1% (3.9, 8.3). Using 9 normal young volunteers, the same study found CMR intra-reader reproducibility between LVM estimations of 0.5% with 95% limits of agreement of $\pm$11%.[17]

Acoustic window and poor image quality are considered major limitations for the use of echocardiography in population studies and in clinical practice, but their real impact on the assessment of LVM is unclear. In our study, the ability to identify with confidence both blood/endocardium and epicardium/pericardium interfaces in a parasternal echocardiography window defined a good quality image. However, there is intrinsic subjectivity in this rating process, and more or less strict definitions for image quality may influence results. In our study, the echocardiography image quality did not appear to affect the correlation between LVM assessed by CMR and echocardiography.

Our study is the first using LVM assessed by echocardiography and by CMR on the same day to compare normalization by BSA, height$^{1.7}$, height$^{2.7}$, and as a proportion of the predicted LVM from a reference group of healthy subjects. The ASE recommends normalizing LVM by dividing it by BSA,[2] but standard recommendations are lacking for CMR.[3] Indexing to an allometrically scaled height has been suggested as a better indexing method for heart size parameters,[21] with promising results for LVM predicting clinical outcomes.[6] For 2D-CMR-derived LVM, all 4 indexing methods and cutoffs for hypertrophy classifications were previously described for the MESA population (Table I). For echocardiographic LVM, we used cutoffs for hypertrophy that reflect real practice and current echocardiography recommendations; however, the lack of cutoffs derived from the MESA sample could influence the agreement results.

Echocardiography seems to classify a larger number of participants with LVH, particularly when LVM is indexed to BSA; however, the long-term clinical implications of these differences are unknown. Although the prevalence of LVH was not statistically significant among risk categories in our study, the prevalence of LVH tended to be higher with the higher cardiovascular risk category. We also found that the mean LVM and LVM indices are higher with higher cardiovascular risk category. In fact, LVM and LVH have been shown to have a relationship with risk factors.[22] In the Northern Manhattan Study, the prevalence of LVH based on LVM indexed to BSA was 18%, 23%, and 35% for low, intermediate, and high-risk groups, respectively.[23]

The proportion of agreement and the kappa coefficient were generally better for comparisons between indices within imaging modality than between imaging modalies. The proportion agreement and kappa coefficient were each relatively similar for comparisons among indices except for comparisons with height$^{1.7}$, where they tended to be lower. Height$^{1.7}$ was first described by Chirinos et al. as the best description of the relationship between LVM determined by echocardiography and body size in European Caucasian subjects.[6] Further investigation of this index is needed.

Conclusions:

Left ventricular mass and hypertrophy are of high relevance in clinical and research settings,[24,25] but there are still important technical controversies.[26] Echocardiography has a reliable performance for LVM assessment and classification of LVH, with limited influence of image quality in our population. These findings support the use of LVM and LVH assessed by echocardiography in population studies and clinical practice. Compared to echocardiography, CMR seems to be appropriate for population studies aiming to find small differences in LVM or LVH using a lower number of examinations or for clinical conditions where small LVM changes over time are expected for a given patient. Echocardiography and CMR are not interchangeable techniques for the assessment of LVH and additional differences rise from the indexing methods. Direct comparisons between imaging modalities using long-term follow-up periods could clarify the clinical impact of these differences. In addition, efforts to standardize techniques and normalization methods are important to promote the use of LVM and LVH on a clinical basis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Left ventricular mass (LVM) and LVM indexes by imaging modality for all participants and by Framingham 10-year cardiovascular risk score category (n = 136).

Table S2. Correlations for blood pressure and LVM assessed by echocardiography and CMR (n = 136).

Objetivo Terciário

Identificar a reprodutibilidade das medidas de massa ventricular esquerda e dimensão atrial esquerda no estudo CARDIA

Artigo 8 - Quality Control and Reproducibility in M-mode, Two-dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year-25 Examination Experience

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Title: Quality Control and Reproducibility in M-mode, Two-dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year-25 Examination Experience

Article Type: Original Investigation

Keywords: Echocardiography; reproducibility; speckle tracking echocardiography; quality control

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Abstract: Introduction
Few large studies describe quality control procedures and reproducibility findings in cardiovascular ultra-sound, particularly in novel techniques such as Speckle Tracking (STE). We evaluate the echocardiography assessment performance in the CARDIA study Y25 examination (2010-2011) and report findings from a quality control and reproducibility program conducted to assess Field Center image acquisition and Reading Center (RC) accuracy.
Methods
The CARDIA Y25 examination had 3,475 echocardiograms performed in 4 US Field Centers and analyzed in a Reading Center, assessing standard echocardiography (LA dimension, aortic root, LV mass, LV end-diastolic volume [LVEDV], ejection fraction [LVEF]), and STE (2- and 4-chamber longitudinal, circumferential, and radial strains). Reproducibility was assessed using intra-class correlation coefficients (ICC), coefficients of variation (CV), and Bland-Altman plots.
Results
For standard echocardiography reproducibility, LV mass and LVEDV consistently had CV above 10% and aortic root below 6%. Intra-sonographer aortic root and LV mass had the most robust values of ICC in standard echocardiography. For STE, the number of properly tracking segments was above 80% in short-axis and 4-chamber and 58% in 2-chamber. Longitudinal strain parameters were the most robust and radial strain showed the highest variation. Comparing Field Centers with Echo RC STE readings, mean differences ranged from 0.4% to 4.1% and ICC from 0.37 to 0.66, with robust results for longitudinal strains.
Conclusion
Echocardiography image acquisition and reading processes in the CARDIA study were highly reproducible, including robust results for STE analysis. Consistent quality control may increase the reliability of echocardiography measurements in large cohort studies.

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***Letter of Submission**

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October 20th, 2013

Dear Dr. Pearlman,

Enclosed please find our manuscript **"Quality Control and Reproducibility in M-mode, Two-dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year-25 Examination Experience"** which we would like to be considered for publication in *JASE*. All authors have read and approved this version of the manuscript, which has not been published and is not being considered for publication elsewhere in whole or in part in any language. On behalf of all authors, there is no relevant disclosure related to this manuscript.

We look forward to hearing from you.

Sincerely yours,

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Title: Quality Control and Reproducibility in M-mode, Two-dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year-25 Examination Experience

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Abstract

Introduction

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The CARDIA Y25 examination had 3,475 echocardiograms performed in 4 US Field Centers and analyzed in a Reading Center, assessing standard echocardiography (LA dimension, aortic root, LV mass, LV end-diastolic volume [LVEDV], ejection fraction [LVEF]), and STE (2- and 4-chamber longitudinal, circumferential, and radial strains). Reproducibility was assessed using intra-class correlation coefficients (ICC), coefficients of variation (CV), and Bland-Altman plots.

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For standard echocardiography reproducibility, LV mass and LVEDV consistently had CV above 10% and aortic root below 6%. Intra-sonographer aortic root and LV mass had the most robust values of ICC in standard echocardiography. For STE, the number of properly tracking segments was above 80% in short-axis and 4-chamber and 58% in 2-chamber. Longitudinal strain parameters were the most robust and radial strain showed the highest variation. Comparing Field Centers with Echo RC STE readings, mean differences ranged from 0.4% to 4.1% and ICC from 0.37 to 0.66, with robust results for longitudinal strains.

Conclusion

Echocardiography image acquisition and reading processes in the CARDIA study were highly reproducible, including robust results for STE analysis. Consistent quality control may increase the reliability of echocardiography measurements in large cohort studies.

KEYWORDS

Echocardiography, reproducibility, speckle tracking echocardiography, quality control

Abbreviation List

2D - 2-dimensional

ASE - American Society of Echocardiography

BMI - body-mass index

CARDIA - Coronary Artery Risk Development in Young Adults

Echo RC - Echocardiography Reading Center

FC - Field Center

ICC - intra-class correlation coefficient

LA – left atrial

LV – left ventricular

LVEDV – LV end-diastolic volume

LVEF – LV ejection fraction

STE - speckle tracking echocardiography

Introduction

Observational cohort studies are often used to estimate the effects of long-term risk exposures on cardiac and organ injury in large populations. Cohort studies should measure random variation from many sources, including biological variation and variation from the acquisition and measurement of study variables. Reproducibility, or precision, assesses this random variation and is a major indicator of quality in observational studies and clinical-based imaging laboratories.[1-3] High standards of quality in large observational studies are critical to validity of interpretation but achieving these high standards is challenging. [4, 5]

Standardization of image acquisition and reading procedures may reduce measurement error.[6] The Coronary Artery Risk Development in Young Adults (CARDIA) study prospectively investigates risk factor development during young adulthood and includes echocardiography assessment in its protocol.[7] Between 2010 and 2011, for the CARDIA study examination Year-25 (Y25), a significant effort was exerted to develop a reproducible echocardiography protocol that included 2-dimensional (2D), M-mode, and speckle tracking echocardiography (STE) images. These standardization efforts were implemented by Field Center sonographers and analysts at the Echocardiography Reading Center (Echo RC).

For this study, a standardized protocol for image acquisition at Field Centers was developed and then taught to both in-field sonographers and readers at the Reading Center. We implemented a sophisticated quality control process to determine the intra-sonographer, inter-sonographer, intra-reader, and inter-reader variation in the interpretation of both standard echocardiographic measurements and speckle tracking echocardiography measurements. We report below the results of this quality control activity.

Methods

Study design and sample

The CARDIA study has been previously described.[7] Briefly, 5,116 African-American and White participants aged from 18 to 30 years were recruited from community-based target populations in 4 Field Centers (Birmingham, AL; Oakland, CA; Chicago, IL; and Minneapolis, MN) between 1985 and 1986. The contacts were stratified to achieve similar proportions according to race, age (< 25 and ≥ 25 years), gender, and education (with high school education or less than high school education).[7, 8] During the CARDIA Y25 exam (2010-2011), echocardiograms were performed at the 4 Field Centers and interpreted at the Echo RC (Johns Hopkins University, Baltimore, MD). A total of 3,499 participants attended the CARDIA Y25 examination between June 2010 and August 2011. From these, 3,475 (99.3%) underwent echocardiography exams; one participant withdrew his consent afterwards. Informed consent was obtained in all sites and the institutions committee on human research approved the study. The mean age was 50 ± 4 years, 43% were males, and 47% were African-American (participant clinical characteristics are shown in Supplement Table S2).

Echocardiography Scanning at Field Centers

The CARDIA Y25 echocardiography exam used the Artida™ cardiac ultrasound machine (Toshiba Medical Systems; Otawara, Japan) with a sector 30 BT transducer (fundamental frequency 2 - 5 MHz) to acquire and store in digital files M-mode, 2D, and STE images, among others. The full scanning protocol, developed by the Echo RC cardiologists and technologists, as well as members of the CARDIA Echo Committee, can be seen online at the CARDIA study website (http://cardia2.dopm.uab.edu/). The scanning protocol was designed to acquire the same echocardiographic views used in the Y5 CARDIA exam [9] and follow the most recent recommendations from the ASE.[6][9] STE was acquired from 4-chamber and 2-chamber apical views and also from a short axis view at the level of the papillary muscles. The STE initial pre-set included: frame rate = 46 fps (ensured > 40 fps); depth = 15cm; and scan

range = 83%. For each view, three consecutive cardiac cycles were recorded during quiet respiration. For intra- and inter-sonographer reproducibility and to assess biological variation, 46 participants from the 4 sites were re-scanned by the same sonographer and another 42 participants were re-scanned by a second sonographer.

Echo RC personnel and an equipment application specialist performed initial training for Field Center sonographers, consisting of a 2-day workshop at the Echo RC and 2 additional days at each Field Center. The Field Center sonographers underwent continued monitoring during the entire period of participant examinations, including regular electronic communication and monthly conference calls, relating to image quality and protocol adherence. A pre-planned conference call held on December 14th, 2010 specifically addressed re-training procedures for STE readings during the image acquisitions by the sonographers at the Field Centers.

Echocardiography Reading Center Interpretation Process

Images were electronically transferred from the Field Centers to the Echo RC immediately after acquisition and then randomly distributed to one of 4 experienced analysts. The reading protocol was designed by the analysts and experienced cardiologists. Image quality was scored as poor, fair, good, or excellent, according to a standard protocol (Supplement Table S1). Measurements for M-mode and 2D images were performed using Digiview^{TM} (Digisonics Systems; Houston, Texas) and followed the ASE recommendations.[10, 11] Using a validated software, Advanced Cardiology Package Wall Motion 2D Tracking^{TM} (Toshiba Medical Systems; Otawara, Japan), a semi-automatic assessment was performed by manual definition of endocardial border and wall thickness, followed by automatic border contours and myocardial tracking.

STE images were analyzed in a 16-segment basis for endocardial, mid-wall, and epicardial contours (6 segments for each view: 4-chamber,2-chamber, and short-axis). Longitudinal strain and strain rate curves were assessed from 4- and 2-chamber views. Circumferential and radial strain and

strain rates were assessed from the short-axis view. Segments with inadequate myocardial tracking by visual evaluation were excluded if unsuccessful attempt of manual correction. The STE image set (4-chamber, 2-chamber, or short-axis) was considered adequate for analysis if at least 3 segments were properly tracked. In image sets adequate for STE analysis, peak strain values were calculated using the average of segmental peaks for all properly tracked segments during LV systole.

Using randomly selected exams, group critiquing and peer review were performed in weekly meetings with cardiologists and analysts. The same group also performed adjudication procedures for abnormal measurements and outliers, indentified in periodic assessments.

Quality Control Assessment

The CARDIA Study has two primary focuses for quality control: (1) to assess errors and document the level of quality; and (2) to maintain and improve the quality of a subsequent collection of data.[7] A quarterly quality control assessment by the CARDIA Quality Control Committee evaluated the consistency of image acquisition and reading analysis.

To assess standard echocardiography reproducibility (inter-participant, intra-participant, inter-reader, and intra-reader), periodically, two 2D 4-chamber parameters (LV end-diastolic volume and ejection fraction) and three M-mode parameters (aorta root dimension, left atrial dimension, and LV mass) were evaluated. Additional intra- and inter-reader reproducibility was assessed for three left ventricular STE deformation parameters: (1) 4-chamber mid-wall global peak longitudinal strain; (2) 2-chamber mid-wall global peak longitudinal strain; (3) mid-wall global peak circumferential strain; and (4) total peak radial strain.

The Echo RC reader reproducibility was assessed for all four analysts. A subsample of images acquired in proportional numbers from each Field Center was randomly selected and blindly distributed to the analysts during regular readings. To assess inter-reader reproducibility in 2D and M-mode images, all 4 analysts read the same set of 200 images (total of 800 readings). The intra-reader reproducibility for

2D and M-mode images was assessed for all analysts by independently re-reading a set of 40 images (total of 160 readings). For intra-sonographer reproducibility, both sets of images from re-scanned participants were analyzed by the same reader at the Echo RC.

For STE analysis, values of strain parameters were compared according to the number of non-properly tracking segments. For the reproducibility evaluation in STE, a subset of 40 images was read by all 4 analysts for inter-reader reproducibility and independently re-analyzed by the same reader for intra-reader assessment. Additionally, we assessed the consistency of in-site STE measurement by Field Center sonographers. Just after acquisition, images were analyzed by Field Center sonographers with low experience in STE readings for peak longitudinal strain (total of 2832 participants; 1786 before sonographer re-training on STE) and peak circumferential strain (total of 2821 participants; 1788 before sonographer re-training on STE) immediately after image acquisition and compared to analysis at the Echo RC by experienced analysts.

Statistical Analysis

Continuous variables were described in mean values ± standard deviation (SD) and categorical variables in proportions. The distribution of the echocardiographic parameters was shown according to image quality. An additional analysis was performed if the variability in values was considered clinically meaningful. In this case, linear regression models were performed having the echocardiographic parameter as the dependent variable and image quality categories as the independent variable; adjusting for age, ethnicity, sex, body-mass index (BMI), and height as covariates.

Reproducibility was assessed computing intra-class correlation coefficient (ICC) and residual coefficient of variation (technical error) based on a linear mixed model. Bland-Altman plots and ICC compared STE measurements at the Field Center and at the Echo RC. The statistical analysis was performed using SAS 9.0 and STATA 11.0.

Results

Standard echocardiography

Of those that underwent echocardiography assessment in CARDIA Y25, the feasibility of standard measurements ranged from 90% for LV mass to 98% for aortic root, respectively. The majority of parameters had at least fair image quality. In opposition to LVEDV, LVEF, LA diameter, and aortic root measurements, LV mass had a mean value for poor quality images 31g (18%) above the overall value (Table 1). Adjusting for age, ethnicity, sex, BMI, and height, participants with fair and good quality images had statistically lower LV mass compared to those with poor quality (Supplement Table S3).

Table 2 shows the reproducibility assessment of re-scanned participants in the Field Centers (total of 88 subjects: 23 from Chicago; 25 from Birmingham; 25 from Oakland; and 15 from Minneapolis). For inter-sonographer reproducibility, the coefficient of variation ranged from 6% to 12% for LVEF and LV mass, respectively. The coefficient of variation for intra-sonographer reproducibility was from 5% for LVEF to 11% for LVEDV. The overall ICC ranged from 0.6 for 2D LV ejection fraction to 0.9 for M-mode LV mass.

Inter- and intra-reader reproducibility regarding standard 2D and M-mode echocardiography parameters were assessed for Echo RC analysts. For the inter-reader reproducibility, the coefficient of variation ranged from 5.6% for the M-mode assessment of the aortic root diameter to 11.3% for the M-mode LV mass. However, LV mass and end-diastolic volumes had the highest ICC values (both = 0.87) in inter-reader assessment. The intra-reader reproducibility analyses found coefficient of variation ranging from 4.1% for aortic root diameter to 11.5% for LV mass, with the highest ICC (0.86) for M-mode aortic root dimension (Table 3).

Speckle tracking echocardiography

STE tracings were attempted in all 3,474 echocardiography exams, but were not technically feasible in 106 participants (3%). From the remaining 3,369 interpretable cases, 724 participants (22%)

had all 18 segments interpretable. From the participants with interpretable STE images, the average of 5.1 segments per participant (85%) were considered properly tracking in the short-axis view; followed by 5.0 (83%) in the 4-chamber view and 3.5 (58%) for the 2-chamber view. The most frequent LV non-tracking segment in the short-axis view was the mid-anterior segment; apical-lateral in the 4-chamber view; and apical-anterior in the 2-chamber view (Figure 1). STE parameter standard deviation and coefficient of variation tended to increase as the number of excluded segments increased (Table 4).

Table 5 shows the reproducibility results for STE parameters. For inter-reader reproducibility, the coefficient of variation ranged from 10% for 4-chamber peak longitudinal strain to 15% for peak radial strain; while the ICC ranged from 0.6 for 4-chamber longitudinal strain to 0.8 for radial strain. In the intra-reader reproducibility assessment, the coefficient of variation ranged from 6% to 12% for 2-chamber longitudinal strain and radial strain, respectively. The intra-reader ICC ranged from 0.8 to 0.9 for 4-chamber longitudinal strain and radial strain, respectively.

When STE reading by sonographers at the Field Centers with limited experience in STE and compared to experienced readers' analysis at the Echo RC, peak longitudinal strain before re-training showed a mean difference of -0.35%, with 95% limits of agreement between -5.11% and 4.42%; and ICC = 0.60. After re-training, the mean difference was 0.08% (95% limits of agreement = -4.23, 4.38) and ICC was 0.66. For peak circumferential strain, the mean difference before re-training was -4.08% (95% limits of agreement = -12.53, 4.37) and ICC was 0.23; after re-training the mean difference was -2.58% (95% limits of agreement = -9.53, 4.38) and ICC was 0.37.

Discussion

This study describes quality control procedures and reproducibility findings for a large cohort of bi-racial adults undergoing a protocol of echocardiography that includes 2D, M-mode, and STE techniques. We report the quality control measures used in the echocardiography assessment and analysis in the CARDIA Y25 examination. A robust profile of echocardiography reproducibility was found

for 2D, M-mode, and STE techniques. The consistently low technical error of about 11% or less and the high values of ICC are thought to have been influenced by training and continued monitoring of the image acquisition process at the Field Centers and analysis at the Echo RC.

Standard echocardiography

LV mass assessment showed the highest intra-class correlation coefficient, showing a strong consistency as previously described in the literature.[12] In our study, however, the highest technical errors in standard 2D and M-mode parameters were found for M-mode-derived LV mass. The calculation of LV mass by M-mode requires geometric assumptions of the heart, calculating a 3D model based on linear measurements. This calculation requires cubing the values acquired from M-mode linear measurements, therefore magnifying the variation between readings.[10, 13]

In our study, LV mass had a higher variation compared to aortic root and LA diameter. The coefficients of variation values were consistent with previous CARDIA examinations. In the CARDIA Y5 exam, technical errors for components of variability for LV mass measurements were 10% for both intra- and inter-sonographer performance, 8% for intra-reader, and 14% for inter-reader.[9] In CARDIA Year-10, similar quality control measures granted coefficients of variation for measurement of LV mass of 10.6% for inter-reader, 9.5% for intra-reader, 13.5% for intra-sonographer, and 10% for inter-sonographer.[14] In the Cardiovascular Health Study, M-mode LV mass had 10% of variation between measurements (11% due to septal thickness, 4% LV dimension, and 8% posterior wall thickness) compared to 8% for LA dimension.[15] Values of technical errors in M-mode LV mass should be related to the inherent measurements challenges and the fact that the myocardial mass is derived from a formula that computes three different cubed measurements, increasing the source errors.[13] In contrast, aortic root and LA dimension derive from a single linear measurement, [10] with high reproducibility profile even in a small center with low volume of patients.[16] Low variation and high correlation has also been reported for measurements of carotid intima-media thickness, also assessed

by linear measurements, with ICC ranging from 0.79 to 0.98 and coefficient of variation ranging from 3.3% to 4.6%.[17]

Assessing LV ejection fraction is an important parameter of quality of care.[18] For the 2-dimensional echocardiography parameters, the coefficient of variation for LVEDV was higher in our study compared to LVEF. These results are similar to the literature. Himelman et al. assessed 3 normal subjects, producing 30 studies and 90 readings. The authors reported an inter-scan mean variability of 5% for LVEF and 10% for LVEDV; as well as inter-reader variability of 7% for LVEF and 19% for LVEDV.[19] Other studies reported inter-observer variation of 23% for LVEDV and 12% to 43% for LVEF.[20-22] However, ICC provides a more robust assessment of reproducibility, showing lower values for LVEF compared to LVEDV. This can be partially explained by the fact that, for computing LVEF, two volume measurements are needed (end-systolic and end-diastolic volumes), therefore increasing the possibility of measurement error.

Speckle tracking echocardiography

Cardiac deformation has long been assessed by magnetic resonance with high accuracy.[23, 24] STE is a novel method to assess cardiac deformation by ultra-sound, more sensitive and sophisticated to identify early abnormalities than traditional echocardiography parameters can.[25] As a relatively novel technique, a widely accepted standardization for normality values or technical assessment using STE still is lacking. In our study, averaging at least 3 LV segments seems adequate for STE parameters.

STE techniques have shown robust profile for accuracy and reproducibility in the literature.[26, 27] However, the reproducibility profile of STE in large cohort studies is not totally clear. The HUNT study enrolled 1,266 healthy European individuals to study the distribution of longitudinal systolic strain and strain rate. During the study, 10 European healthy volunteers were recruited to be scanned by two different echocardiographers; the images were analyzed twice for longitudinal deformation by both professionals. For global end-systolic global strain, the coefficient of repeatability was ± 2% strain for the

inter-reader analyses, and coefficients of variation were between 3% and 4%.[28] In our study, 40 images were read twice by all 4 readers to assess reproducibility (320 analyses) of longitudinal, radial, and circumferential deformation. Robust inter- and intra-reproducibility profiles were found for all STE parameters, favoring the measurement of longitudinal strain.

The consistency of STE measurement by multi-site sonographers in a large cohort was not been assessed before. Our results regarding FC sonographers indicate that STE readings, particularly longitudinal peak strain, can be reliably performed in the moment of image acquisition, after minimum STE-specific sonographer training. In fact, training and re-training appears to improve quality of measurements in the Field Centers. This is very useful information for large longitudinal studies aiming to use STE to accurately assess cardiac function and may influence for a wider use of STE in clinical settings.

We showed the quality control measures used in echocardiography acquisition and interpretation in the CARDIA Y25 examination. From the images acquired by Field Center sonographers, a robust inter-scan reproducibility of echocardiography measurements was found both within and between professionals. Moreover, robust reproducibility results were found for echocardiography analyzes in the CARDIA Core Imaging Laboratory, including 2D, M-mode, and STE imaging. We particularly show that STE can provide reliable information for large cohort studies. Consistent quality control may increase the reliability of echocardiography measurements in large cohort studies conducted over a long period of time. These results should give insights to implement strategies for increasing quality in echocardiography laboratories dedicated to clinical studies.

Acknowledgments / Disclosures

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Figure Legend

Figure 1. Number of properly tracking left ventricular segments during Speckle Tracking Echocardiography (STE) analysis in the CARDIA study, according to acoustic view (3,069 participants)

Tables

Table 1. Description of Echocardiography parameters in the Year-25 CARDIA examination, according to image quality

Image Quality	Number of Participants	Mean	SD
2D echo LVEDV (mL)			
Poor	76	110.24	35.37
Fair	1,186	111.79	29.81
Good	1,521	111.71	30.06
Excellent	439	113.67	32.27
Overall	3,222	111.97	30.40
2D echo LVEF (%)			
Poor	75	62.46	6.97
Fair	1,186	60.09	6.87
Good	1,521	61.51	7.16
Excellent	439	63.92	7.66
Overall	3,221	61.34	7.23
M-mode echo Aortic root (cm)			
Poor	309	3.26	0.47
Fair	1,023	3.11	0.41
Good	1,744	3.02	0.42
Excellent	340	3.03	0.38
Overall	3,416	3.07	0.42
M-mode echo LA diameter (cm)			
Poor	306	3.86	0.54
Fair	1,009	3.73	0.49
Good	1,721	3.67	0.50
Excellent	338	3.71	0.48
Overall	3,374	3.71	0.50
M-mode echo LV mass (g)			
Poor	87	198.63	60.22
Fair	958	168.62	54.57
Good	1,738	164.83	50.28
Excellent	339	175.09	52.66
Overall	3,122	168.05	52.51

Legend: LVEDV: 2D left ventricular end-diastolic volume (4-chamber view); LVEF: 2D left ventricular ejection fraction (4-chamber view); Ao Root: M-mode aorta root diameter; LA diameter: M-mode left atrial dimension; LV mass: M-mode left ventricular mass.

Table 2. Inter- and intra-sonographer reproducibility for M-mode and 2-D measurements in repeated echocardiography scans* in the CARDIA Y25 exam

	Reproducibility assessment				
	Inter-sonographer reproducibility (n = 42)				
	LVEDV	LVEF	Ao Root	LAD	LV mass
Coefficient of Variation, %	10.6	5.8	5.9	7.3	11.8
	Intra-sonographer reproducibility (n = 46)				
	LVEDV	LVEF	Ao Root	LAD	LV mass
Coefficient of Variation, %	11.2	5.1	5.3	6.0	10.3
	All-sonographer reproducibility (n = 88)				
	LVEDV	LVEF	Ao Root	LAD	LV mass
Intra-class correlation	0.80	0.58	0.81	0.73	0.91

Legend: LVEDV: 2D left ventricular end-diastolic volume; LVEF: 2D left ventricular ejection fraction; Ao Root: M-mode aorta root diameter; LAD: M-mode left atrial anterior-posterior diameter; LV mass: M-mode left ventricular mass.

*Mean interval between scans was 20 days.

Table 3. Inter- and intra-reader reproducibility in the re-assessment of the same M-mode and 2-D echocardiography images in the CARDIA Y25 exam

	Reproducibility assessment				
	Inter-reader reproducibility (n = 200)				
	LVEDV	LVEF	Ao Root	LAD	LV mass
Coefficient of Variation, %	9.8	7.7	5.6	6.4	11.3
Intra-class correlation	0.87	0.59	0.82	0.80	0.87
	Intra-reader reproducibility (n = 40)				
	LVEDV	LVEF	Ao Root	LAD	LV mass
Coefficient of Variation, %	8.9	6.1	4.1	5.9	11.5
Intra-class correlation	0.84	0.76	0.86	0.79	0.80

Legend: LVEDV: 2D left ventricular end-diastolic volume; LVEF: 2D left ventricular ejection fraction; Ao Root: M-mode aorta root diameter; LAD: M-mode left atrial anterior-posterior diameter; LV mass: M-mode left ventricular mass.

Table 4. Left ventricular speckle tracking echocardiography deformation parameters, according to acoustic view and number of properly tracking segments (n =3,069)

Acoustic view / Number of tracking segments	Number of Participants	Mean	SD	CV
4-chamber longitudinal strain (%)				
6	1,996	-14.36	2.31	-0.16
5	659	-14.53	2.54	-0.18
4	316	-14.90	3.22	-0.22
3	62	-14.72	3.60	-0.24
2-chamber longitudinal strain (%)				
6	1,236	-14.89	2.46	-0.16
5	579	-15.19	2.77	-0.18
4	354	-15.79	3.14	-0.20
3	62	-15.96	3.66	-0.23
Circumferential strain (%)				
6	2,115	-14.52	2.90	-0.20
5	582	-14.12	3.02	-0.21
4	337	-14.66	3.36	-0.23
3	57	-15.74	4.33	-0.27
Radial strain (%)				
6	2,115	36.22	12.16	0.34
5	582	34.10	13.62	0.40
4	337	32.87	13.44	0.41
3	57	34.55	17.92	0.52

Legend: SD – standard deviation; CV – coefficient of variation

Table 5. Inter- and intra-reader reproducibility in the re-assessment of the same Speckle Tracking Echocardiography images in the CARDIA Y25 exam

	Reproducibility assessment			
	Inter-reader reproducibility (n = 40)			
	4-ch Ell	2-ch Ell	Ecc	Err
Coefficient of variation, %	10.4	10.7	12.9	15.3
Intra-class correlation	0.55	0.71	0.67	0.84
	Intra-reader reproducibility (n = 160)			
	4-ch Ell	2-ch Ell	Ecc	Err
Coefficient of variation, %	6.6	5.5	6.8	12.1
Intra-class correlation	0.79	0.87	0.81	0.89

Legend:4-ch – 4-chamber; Ell– peak longitudinal strain; 2-ch – 2-chamber; Ecc – peak circumferential strain; Err – peak radial strain.

Figure

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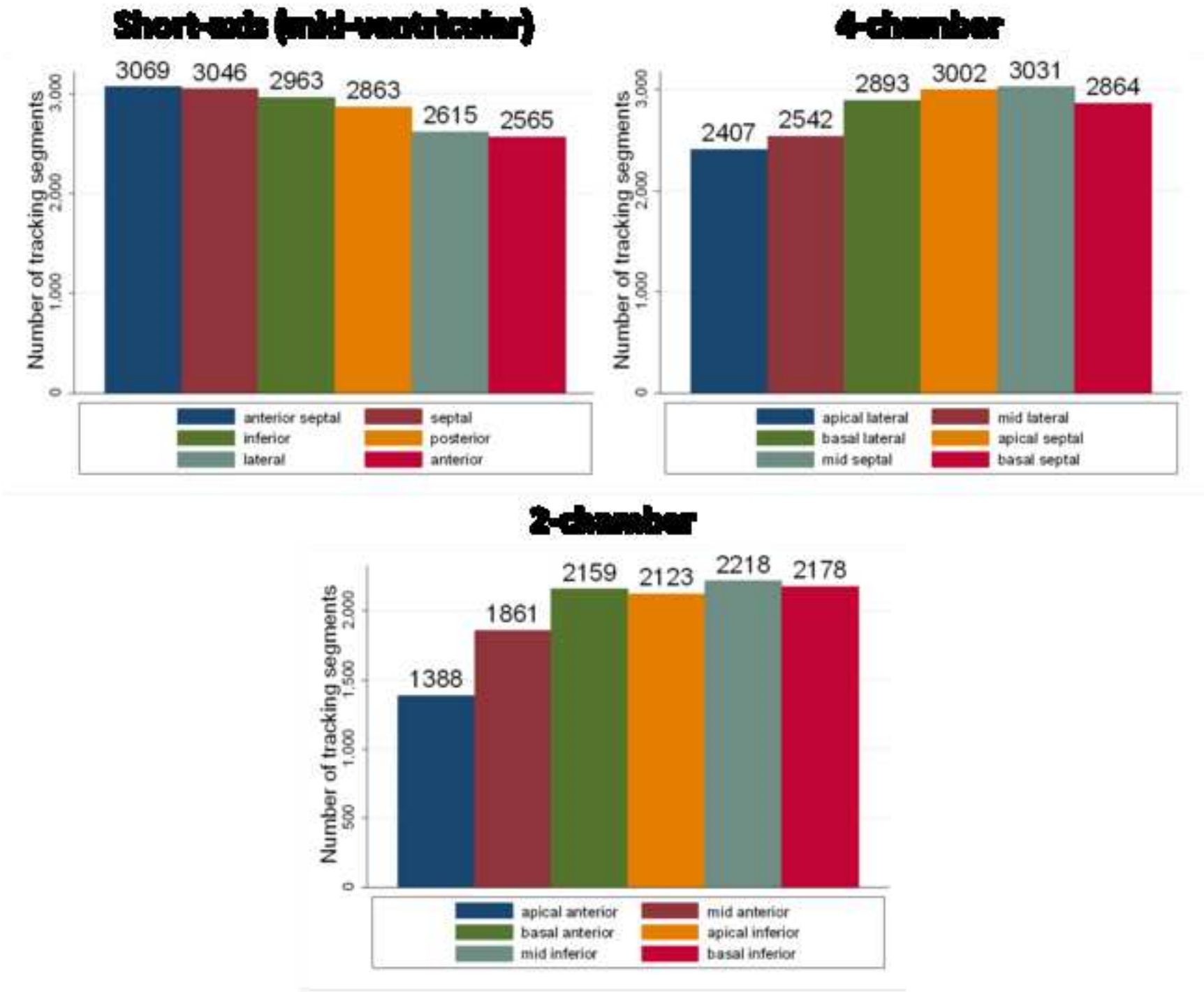

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6. Discussão

Nos anos recentes, um conjunto de publicações foi fruto das investigações científicas motivadas pelos objetivos dessa tese, contribuindo no desenvolvimento de um conhecimento amplo na relação tanto da hipertrofia ventricular esquerda como do remodelamento atrial esquerdo com risco cardiovascular em jovens adultos. Em resposta aos objetivos principais dessa tese, demonstramos o papel desses parâmetros como preditores de doença cardiovascular em adultos jovens. Apesar da ampla utilização desses parâmetros na prática clínica e em pesquisa nas últimas décadas, a ambos faltava uma avaliação metodológica rigorosa que pudesse contribuir para um posicionamento definitivo em algoritmos de estratificação de risco cardiovascular. Adicionalmente, investigamos os determinantes do remodelamento atrial esquerdo ao longo de 20 anos de seguimento, assim como reportamos a reprodutibilidade desses parâmetros a fim de estimar a precisão dos métodos de medida e investigamos o papel da indexação à dimensão corporal na relação com o risco cardiovascular. Os dados apresentados como resultado das investigações desta tese demonstraram-se de expressiva originalidade, denotando significativa contribuição ao conhecimento científico.

As taxas de morte por doenças cardiovasculares têm diminuído ao longo dos anos, mas ainda são importante causa de mortalidade no mundo. Baseando-se nas taxas de mortalidade de 2005, estimou-se que um norte-americano morra por doenças cardiovasculares a cada 37 segundos. Isso não se limita a pessoas de idade avançada. Apesar da expectativa de vida média de 78,7 anos nos EUA em 2010, cerca de 150.000 norte-americanos com idade inferior a 65 anos morreram por doenças cardiovasculares apenas no ano de 2010.[73] No Brasil, estima-se que houve 266.736 óbitos por causas cardiovasculares em 2003, correspondendo a 32,7% do total de óbitos no país nesse período. Já no ano de 2004, houve registro de 1.536.488 internações por doenças cardiovasculares no país, com taxa de óbito de 45,7%. No mesmo ano, estima-se um custo entre 8 bilhões e 11 bilhões de reais para o tratamento de formas graves de doenças cardiovasculares nos setores público e privado brasileiros.[74] Nas cidades brasileiras, as taxas de mortalidade em indivíduos entre 45 e 67 anos deu-se em valores tão ou mais elevados do que os da Europa ou EUA ao longo do período de 1984 a 1987. Comparada aos EUA e países da Europa, a cidade de Salvador (Bahia) figurou à frente de Itália, Espanha, Portugal, França e Japão nas taxas de mortalidade por doenças cardíacas entre homens. Quando as mulheres entre 45 e 67 anos foram

avaliadas, Salvador assume a quarta posição, à frente dos EUA e de todos os países europeus avaliados.[75]

As taxas de eventos cardiovasculares aumentam com a idade, sendo mais comuns acima dos 60 anos de vida.[73,74] No entanto, evidências científicas mostram que a aterosclerose se inicia na infância e segue ao longo do desenvolvimento do indivíduo até a idade adulta, tendo desde as mais tenra idade relação com os mesmos fatores de risco já bem definidos na vida adulta.[76] Com essa visão, estratégias de longo prazo para prevenção cardiovascular primária que envolvam avaliação de risco em idades precoces têm sido desenvolvidas e recomendadas.[77] Parece claro que a detecção de risco deve voltar-se aos jovens, a fim de detectarmos com acurácia indivíduos de maior risco ou possíveis alterações subclínicas. É conhecida a relação de custo-efetividade favorável a estratégias de prevenção cardiovascular primária comparada ao tratamento da doença estabelecida.[78] Para adultos assintomáticos, recomenda-se a avaliação de risco cardiovascular global a partir dos 20 anos de idade, tendo o Escore de Risco Cardiovascular de Framingham como referencial.[3] No entanto, são conhecidas as limitações do Escore de Risco Cardiovascular de Framingham global para estimar risco em uma população bi-racial de indivíduos jovens.[7]

Como esperado para jovens adultos saudáveis - como a população inicialmente incluída no estudo CARDIA - a taxa de eventos foi baixa, atingindo o total de 2,96% dos indivíduos nos 20 anos de seguimento. Apesar disso, o Escore de Risco Cardiovascular de Framingham global (ajustado pela idade como variável contínua) apresentou um bom desempenho para estratificação de risco na população do estudo CARDIA. Houve risco relativo em torno de 20, comparando os 1% classificados como em risco mais elevado pelo Escore de Risco Cardiovascular de Framingham com os classificados como risco menor que 2,5%.

Investigamos como massa ventricular esquerda e dimensão atrial esquerda, parâmetros ecocardiográficos amplamente disponíveis na prática clínica, podem agregar valor ao já conhecido Escore de Risco Cardiovascular de Framingham global. Com isso, esperamos melhorar o desempenho da estratificação de risco cardiovascular em adultos jovens. Para tanto, seguimos o que há de mais recente nas recomendações metodológicas para avaliação de marcadores de risco cardiovascular, rigorosamente avaliando poder preditor independente, calibração de modelos estatísticos, incremento em discriminação e poder de reclassificação de

massa ventricular esquerda e dimensão atrial esquerda quando comparados ao Escore de Risco Cardiovascular de Framingham global.[5]

Após ajuste para etnia, a medida da massa ventricular esquerda foi capaz de predizer doenças cardiovasculares independentemente do Escore de Risco Cardiovascular de Framingham global. A classificação para hipertrofia ventricular esquerda também mostrou-se preditora de eventos cardiovasculares nos 20 anos de seguimento, sugerindo que os valores de normalidade em jovens podem ser menores que os recomendados em fases mais avançadas da vida adulta. O acréscimo aos fatores de risco tradicionais de informação sobre a massa ventricular mostrou um modesto incremento na discriminação de indivíduos em diferentes níveis de risco, conforme demonstrado pela estatística-C. Também mostramos que adição de massa ventricular esquerda pode efetivamente reclassificar indivíduos quanto ao risco cardiovascular, quando comparado aos componentes do Escore de Risco Cardiovascular de Framingham global adicionado da etnia.

Nosso estudo mostrou que o remodelamento atrial esquerdo pode ser utilizado como preditor independente de risco cardiovascular global na prevenção primária de adultos jovens. Nesse sentido, a medida bidimensional da área atrial parece ser mais robusta que a simples medida linear anteroposterior, possivelmente por ser mais acurada na detecção do remodelamento atrial excêntrico. No entanto, o acréscimo aos fatores de risco tradicionais de informação sobre a dimensão atrial mostrou apenas um modesto incremento na discriminação de indivíduos em diferentes níveis de risco. Ademais, as medidas de remodelamento atrial esquerdo não foram capazes de reclassificar significativamente o risco cardiovascular dos indivíduos jovens investigados.

Nossos resultados mostraram que tanto hipertrofia do ventrículo esquerdo quanto as medidas de remodelamento do átrio esquerdo podem contribuir até certo ponto com a estratificação de risco cardiovascular de adultos jovens. Isso sugere que esses parâmetros podem vir a ser utilizados para complementar as informações das clarificações de risco tradicionalmente recomendadas, como o Escore de Risco Cardiovascular de Framingham global. No entanto, esses parâmetros talvez possam ser mais bem empregados em populações selecionadas de adultos jovens com múltiplos fatores de risco, grupo tipicamente com risco subestimado pelo Escore de Risco Cardiovascular de Framingham usado isoladamente.[7]

Disfunção clinicamente manifesta do ventrículo esquerdo está intimamente relacionada ao remodelamento cardíaco. A disfunção sistólica é usualmente medida na prática clínica pela fração de ejeção. Demonstramos que o aumento da massa ventricular esquerda em jovens correlaciona-se com a disfunção sistólica após 20 anos de seguimento. O átrio esquerdo aumentado – por suas funções na diástole ventricular de conduto, reservatório e sua contração ativa – costuma refletir aumento nas pressões de enchimento ventricular. Ademais, a hipertrofia ventricular esquerda provoca rigidez da parede miocárdica, com isso levando à diferentes graus de disfunção diastólica. Partindo dos princípios que relacionam a hipertrofia ventricular e o remodelamento atrial com a disfunção diastólica do ventrículo esquerdo, investigamos se esta também estaria relacionada com eventos cardiovasculares de longo prazo. Para tanto, utilizamos uma população do *Multi-Ethnic Study of Atherosclerosis* (estudo MESA), de idade mais avançada que a do estudo CARDIA e, portanto, mais afeita às consequências do remodelamento cardíaco. Com o desenvolvimento de um novo índice para o cálculo do relaxamento cardíaco a partir de mudanças sutis de deformação diastólica mensuradas por técnicas de ressonância magnética cardíaca, demonstramos que a disfunção diastólica em si também funciona como eficiente preditor de eventos cardiovasculares. Tal achado reforça a importância de desenvolvermos métodos práticos de mensurar alterações subclínicas de remodelamento cardíaco, tal como a massa ventricular e a dimensão atrial. Dessa forma, medidas de prevenção individualizadas podem vir a ser valiosas na prevenção da disfunção cardíaca clinicamente manifesta.

O tamanho do coração é proporcional às dimensões corporais.[79] Vários métodos de normalização têm sido adotados para indexar as medidas de massa ventricular e dimensão atrial ao tamanho corporal, normalmente derivados da altura, do peso corporal ou de ambos.[8] O maior volume de evidências investigando diferentes indexações é direcionado à medida da massa ventricular esquerda. No entanto, comparações na literatura entre diferentes métodos de indexação de massa ventricular esquerda como preditores de doenças cardiovasculares são escassas e controversas.[49,57,80] A indexação pela área de superfície corporal (ASC) foi a primeira a ser desenvolvida, mas evidências indicam que pode subestimar os valores de massa miocárdica em obesos e pessoas com sobrepeso.[81,82]

Apesar de nossa população manter-se – em média – acima do índice de massa corporal (IMC) considerado normal pela Organização Mundial de Saúde (IMC médio variou de 26±6 kg/m^2 no Ano-5 para 30±7 kg/m^2 no Ano-25),[83] encontramos resultados similares para predição de doenças cardiovasculares quando indexamos massa ventricular esquerda pela ASC ou altura^{2,7}. Nesse sentido, houve discreto efeito favorável à indexação pela ASC apenas quando o poder preditor independente foi avaliado pelos modelos de regressão de Cox. Isso pode ser influenciado pelo fato de que a indexação pela ASC leva em consideração tanto aumentos na massa ventricular esquerda de obesos decorrentes de processos adaptativos (portanto de baixo impacto no risco cardiovascular), quanto decorrentes de alterações patológicas (com impacto significativo no risco cardiovascular). Em relação a medidas da dimensão atrial, a indexação pela ASC e pela altura também foram similares na predição de eventos cardiovasculares de longo prazo. No entanto, a indexação pela altura mostra-se mais adequada na avaliação das mudanças nas dimensões atriais ao longo do tempo devido ao importante efeito da obesidade nas fases mais avançadas da vida adulta.

Pressão arterial sistólica elevada, baixa frequência cardíaca e alto IMC foram preditores robustos, mostrando consistência de resultado para maiores medidas de dimensão atrial esquerda. Conhecer a relação entre fatores de risco e os parâmetros ecocardiográficos ajuda na compreensão de como o progressivo remodelamento atrial esquerdo funciona como repositório de risco cardiovascular de longo prazo. Em nosso estudo, houve uma forte relação da pressão arterial e da obesidade com o remodelamento atrial esquerdo ao longo dos 20 anos de seguimento. De fato, pressão arterial e obesidade são conhecidos determinantes de disfunção diastólica e de remodelamento cardíaco,[15,84] ambos relacionados a aumento das pressões de enchimento do ventrículo esquerdo. Já os efeitos da diabetes sobre o remodelamento cardíaco parecem depender do tempo de exposição mais prolongado. Nossos resultados contribuem na formulação do conhecimento que embasa estratégias de prevenção de risco cardiovascular primário em adultos jovens.

Precisão e acurácia são parâmetros de extrema importância na consolidação de um marcador de risco cardiovascular. Apesar de tanto a massa ventricular esquerda quanto as medidas de dimensão atrial esquerda serem de uso corriqueiro na prática dos laboratórios de ecocardiografia, o perfil de reprodutibilidade dessas medidas em estudos populacionais de larga

escala é pouco conhecida. Além disso, a acurácia para classificação da hipertrofia ventricular esquerda e sua relação com as diversas formas de indexação também careciam de evidências científicas. Demonstramos em nosso artigo de reprodutibilidade das avaliações ecocardiográficas do estudo CARDIA que essas medidas podem ser feitas com elevado grau de precisão, particularmente com o emprego de treinamento continuado e controle de qualidade. Além disso, nosso estudo comparando medidas de hipertrofia ventricular por ecocardiografia e por ressonância magnética cardíaca no estudo MESA demonstraram um bom perfil de concordância entre os métodos. Considerando que a ressonância cardíaca é hoje o padrão ouro para medida da massa ventricular esquerda, demonstramos que medidas ecocardiográficas de hipertrofia ventricular possuem um bom perfil de acurácia.

7. Memorial: Descrição e Reflexões sobre O Processo de Doutorado e A Experiência no Hospital Johns Hopkins

Esta Tese de Doutorado inicia-se de uma inquietação acadêmico-científica. Como membro da Universidade Federal do Vale do São Francisco (UNIVASF; Petrolina, PE), surgiu a necessidade de que eu desenvolvesse conhecimento e treinamento em técnicas de imagem cardiovascular avançadas. Contando com a apresentação pelo meu atual orientador, fui aceito como *Fellow* de Imagem Cardiovascular do Hospital Johns Hopkins (Baltimore, Maryland, EUA), cujo setor é coordenado pelo Dr. João Lima. Minha proposta inicial era de treinamento em tomografia computadorizada cardíaca.

Antes de deixar o país rumo ao Hospital Johns Hopkins, tive a oportunidade de ser aprovado para matrícula no Programa de Doutorado em Medicina e Saúde Humana da Escola Bahiana de Medicina e Saúde Pública. Na ocasião, eu e meu orientador já dividíamos o interesse em estudar de forma mais rigorosa o valor incremental de marcadores de risco cardiovascular e no que tais marcadores poderiam realmente auxiliar o modelo de estratificação de risco tradicional. Como estava prestes a realizar o treinamento em tomografia computadorizada cardíaca, a primeira escolha natural pareceu-nos desenvolver estudo com o escore de cálcio coronariano. Dessa forma, já saí do país com o objetivo de treinar-me em tomografia mas também com uma perspectiva de desenvolver estudo de grande impacto no meu retorno.

A proposta inicial deu frutos maiores com a extensão do meu período de treinamento no Hospital Johns Hopkins, sob coordenação e orientação diretas do Dr. João Lima. Durante meu treinamento, foram utilizados cenários acadêmicos com vocação ora predominantemente clínica, ora predominantemente científica. Assim, consegui ir além da tomografia e desenvolvi novas habilidades também com ressonância magnética cardíaca, cintilografia cardíaca e novas técnicas de ecocardiografia. Dessa forma, nesse ambiente científico de extrema riqueza, fui exposto a grandes estudos como o CARDIA e o MESA, mas também o DCCT/EDIC, o CORE-64, o CORE-320, o TODAY, o PACE e o C-TRIP, para ficar nos mais marcantes.

Seja nos cenários eminentemente clínicos ou nos científicos, passei por um grande amadurecimento pessoal, profissional e científico a partir da convivência com múltiplos profissionais de diferentes formações. É imensurável a contribuição de reunir Cardiologistas,

Radiologistas, Médicos Nucleares, Ecocardiografistas, Técnicos em Imagem Cardiovascular, Engenheiros Biomédicos, profissionais de Tecnologia da Informação, Estatísticos, Epidemiologistas, enfim, inúmeros profissionais a contribuir agregando conhecimento. Também precisa ser ressaltado o amadurecimento resultante de administrar múltiplas fontes de contribuição tão ricas em diversidade, as quais convergem na produção do conhecimento muitas vezes sob intenso debate.

O processo de crescimento profissional no qual se insere esta Tese fez com que o objeto de estudo principal se modificasse, embora fosse mantida a temática do incremento proporcionado à avaliação de risco cardiovascular. O conhecimento adquirido no período em que estive em treinamento no Hospital Johns Hopkins foi fundamental para que pudesse prosseguir nas investigação ao retornar ao país e, também, às atividades cotidianas no Programa de Doutorado. Como fruto, temos este ano dois artigos focados nos objetivos principais da Tese e já aceitos para publicação neste ano. Além disso, outros artigos desenvolvidos ou em desenvolvimento nesse período também compõem nossos resultados.

As novas habilidades adquiridas ao longo deste caminho proporcionaram apresentações em vários cenários acadêmicos e assistenciais, bem como a honra de integrar as listas de finalistas de duas das mais prestigiosas premiações promovidas pela *American Heart Association:* o *Elizabeth Barrett-Connor Young Investigator Award in Cardiovascular Epidemiology* e o *Melvin Judkins Young Clinical Investigator Award in Cardiovascular Imaging/Radiology*. Por fim, o convite para compor como único brasileiro a lista de autores das diretrizes de medidas ecocardiográficas das câmaras cardíacas, em esforço conjunto da *American Society of Echocardiography* com a *European Association of Cardiovascular Imaging*, dá-nos a certeza da contribuição científica que surge fruto do conhecimento apresentado nesta Tese.

É nesse contexto que pretendo cada vez mais contribuir para o desenvolvimento científico da minha instituição de origem, a qual possui a árdua missão de desenvolver assistência médica e conhecimento científico de extrema qualidade na região do Sertão Nordestino; área tradicionalmente desprestigiada de projetos dessa natureza. O trabalho desenvolvido no qual resulta também esta Tese, dá-me a confiança de que serão vencidas as dificuldades que já surgem desde meu retorno, no caminho trilhado que visa ao desenvolvimento científico e da assistência médica de nossa região.

8. Perspectivas Futuras

Pretendemos desenvolver uma ferramenta de determinação de risco cardiovascular em jovens que utilize massa ventricular esquerda e os fatores de risco cardiovascular tradicionais. Baseando-se nos resultados encontrados no estudo CARDIA e apresentados nesta tese, um sistema de pontuação para escore ou aplicativo de estimativa de risco poderia ser útil à prática clínica ao possibilitar estimativa de risco cardiovascular mais precisa a um paciente jovem.

O baixo risco cardiovascular basal de adultos jovens saudáveis acarreta uma baixa incidência de eventos cardiovasculares em estudos de coorte prospectiva voltados a esses participantes, tal como o estudo CARDIA. No entanto, jovens com múltiplas comorbidades parecem mais expostos à possibilidade de eventos na meia idade. Estudos futuros especificamente voltados a esse grupo de maior risco podem vir a contribuir de forma adicional para a classificação de risco cardiovascular nessa população específica, possibilitando o planejamento de estratégias de prevenção mais individualizadas nos adultos jovens.

Para que as medidas ecocardiográficas se tornem mais amplamente utilizadas e reprodutíveis entre diferentes laboratórios, faz-se de extrema importância a padronização das técnicas de medida e o estabelecimento dos limites de normalidade. Nesse sentido a *American Society of Echocardiography* em esforço conjunto com a *European Association of Cardiovascular Imaging* decidiram pela revisão e atualização de suas diretrizes para medidas das câmaras cardíacas, a serem publicadas ainda em 2014 (Anexo I). As contribuições do estudo CARDIA às novas diretrizes contribuem na sedimentação das medidas ecocardiográficas de dimensão cardíaca.

9. Conclusões Específicas

1) Medidas de hipertrofia ventricular esquerda em adultos jovens mostram valor incremental ao modelo clínico tradicional na predição de risco cardiovascular. Medidas de remodelamento atrial esquerdo mostram valor preditor independente, mas não mostraram habilidade de reclassificar o risco cardiovascular dessa população.
2) O aumento da massa ventricular esquerda em jovens adultos correlaciona-se com a disfunção sistólica do ventrículo esquerdo após 20 anos.
3) Disfunção diastólica – como parâmetro intimamente relacionado ao remodelamento atrial e ventricular – demonstra valor preditor incremental para eventos cardiovasculares.
4) Pressão arterial e obesidade são os principais fatores de risco modificáveis associados ao remodelamento atrial esquerdo na vida adulta. A indexação pela altura parece mais adequada para avaliar o efeito da obesidade no remodelamento atrial.
5) Massa ventricular esquerda demonstrada valor preditivo independente para eventos cardiovasculares em diversas populações. Não há evidências suficientes que demonstrem superioridade entre os métodos de indexação.
6) A medida de massa ventricular esquerda pela ecocardiografia é acurada. O método de indexação empregado influencia na classificação de pacientes com hipertrofia ventricular.
7) As medidas de massa ventricular e dimensão atrial possuem bom perfil de reprodutibilidade e acurácia no estudo CARDIA.

10. Conclusão Geral

A utilização racional da medida ecocardiográfica de hipertrofia ventricular esquerda pode auxiliar na avaliação do risco cardiovascular primário de populações jovens, possibilitando estratificação de risco além do oferecido pelos métodos tradicionais. Já a medida da dimensão atrial esquerda é preditora independente para eventos cardiovasculares, mas não comprovou utilidade para reclassificar o risco cardiovascular em jovens.

As medidas ecocardiográficas de hipertrofia ventricular esquerda e de remodelamento atrial esquerdo são parâmetros validados e padronizados, cujas alterações podem estar presentes em fases subclínicas das doenças cardiovasculares.

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ANEXO

Anexo 1 – Diretrizes para medida ecocardiográfica das câmaras cardíacas

Artigo – (GUIDELINES) Recommendations for Cardiac Chamber Quantification by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Em revisão no Journal of the American Society of Echocardiography.*

Recommendations for Cardiac Chamber Quantification by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

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IV. AORTIC ANNULUS AND AORTIC ROOT

11. Aortic measurements
12. Identification of aortic root dilatation

V. INFERIOR VENA CAVA

Table LV_1. Recommendations for the echocardiographic assessment of left ventricular size

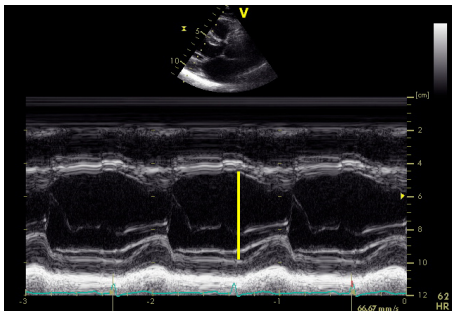
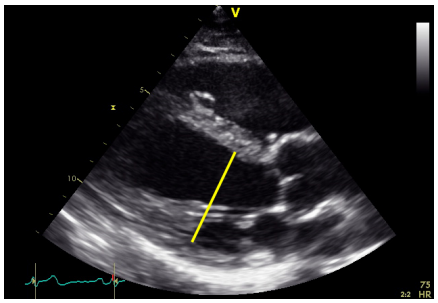
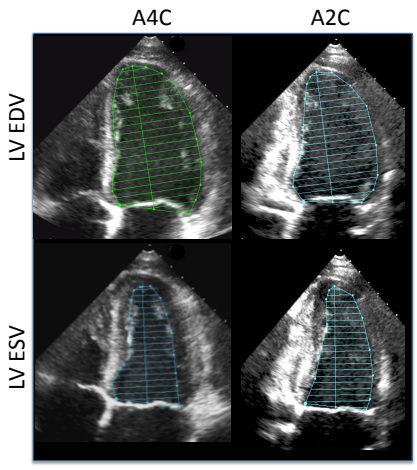
Parameters and method	Technique	Advantages	Limitations
Internal linear dimensions. Linear internal measurements of the LV should be acquired in the parasternal long axis view carefully obtained perpendicular to the LV long axis, and measured at the level of the mitral valve leaflet tips. Electronic calipers should be positioned on the interface between wall and cavity and the interface between wall and pericardium.	**M-mode tracing** 	• Reproducible • High temporal resolution • Wealth of published data	• Beam orientation frequently off axis • Single dimension, i.e. representative only in normally shaped ventricles
	2D-guided linear measurements 	• Facilitates orientation perpendicular to the ventricular long axis	• Lower frame rates than M-mode • Single dimension, i.e. representative only in normally shaped ventricles
End-diastolic and end-systolic volumes Volume measurements are usually based on tracings of the blood-tissue interface in the apical 4- and 2-chamber views. At the mitral valve level, the contour is closed by connecting the two opposite sections of the mitral ring with a straight line. LV length is defined as the distance between the middle of this line and the most distant point of the LV contour.	**Biplane disc's summation** 	• Corrects for shape distortions • Less geometrical assumptions compered to linear dimensions	• Apex frequently foreshortened • Endocardial dropout • Blind to shape distortions not visualized in the apical 2- and 4-chamber planes
	Area-length	• Partial correction for shape distortion	• Apex frequently foreshortened • Heavily based on geometrical assumptions

Table LV mass_1. Recommendations for the echocardiographic assessment of left ventricular mass

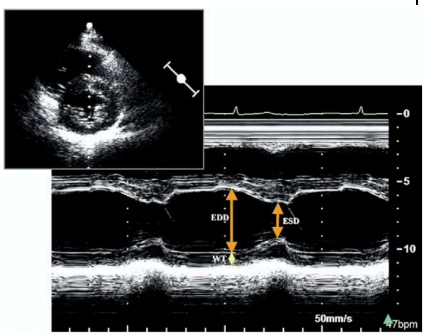
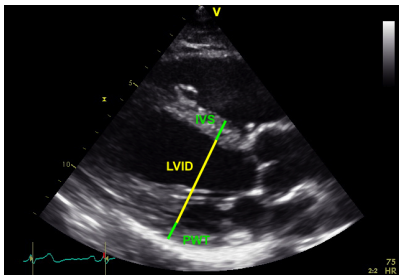
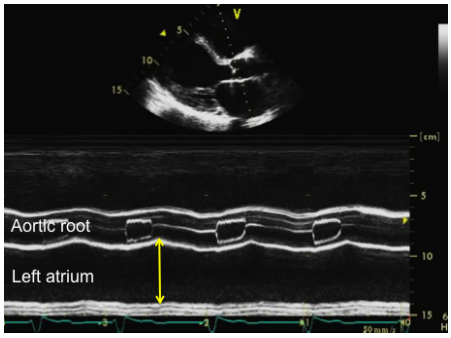
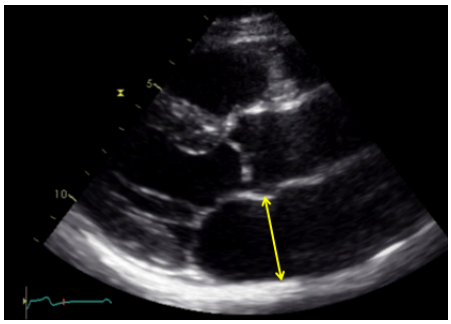
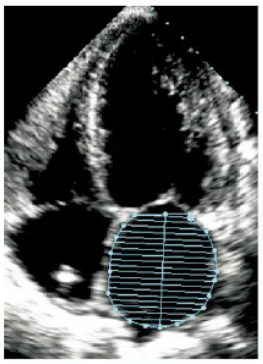
Parameters and method	Echo Imaging	Advantages	Limitations
Cube formula LV mass = 0.8 • 1.04 • [(IVS+LVID+PWT)^3 –LVID^3)+ 0.6 g Where IVS is inter-ventricular septum; LVID is LV internal diameter, and PWT is infero-lateral wall thickness. Linear internal measurements of the LV should be acquired from the parasternal approach and carefully obtained perpendicular to the LV long axis, and measured at the level of the mitral valve leaflet tips. M-mode measurements should be obtained from a targeted SAX view. All measurements should be performed at end-diastole.	**M-mode tracing** 	• Fast and widely used • Wealth of published data • Demonstrated prognostic value • Fairly accurate in normally shaped ventricles (i.e. systemic hypertension, aortic stenosis) • Simple for screening large populations	• Based on the assumption that the left ventricle is a prolate ellipsoid with a 2:1 long/short axis ratio and symmetric distribution of hypertrophy • Beam orientation frequently off axis • Since linear measurements are cubed, even small measurement errors in dimensions or thickness have an impact on accuracy • Overestimates LV mass • Inaccurate in the presence of asymmetric hypertrophy, dilated ventricles and other diseases with regional variations in wall thickness
	Two-dimensional 	Facilitates orientation perpendicular to the left ventricular long axis	• Based on the same geometrical assumptions as M-mode • Same limitations as M-mode in patients with abnormal LV geometry • Impact of harmonic imaging on the mass calculations and normal values remains to be defined • Normal values are less well established than for M-mode measurements

Table LA_1. Recommendations for the echocardiographic assessment of left atrial size

Parameters and method	Echo Imaging	Advantages	Limitations
Internal linear dimensions. The antero-posterior diameter of the left atrium can be measured in the parasternal long axis view perpendicular to the aortic root long axis, and measured at the level of the aortic sinuses by using the leading-edge to leading-edge convention.	**M-mode tracing** 	• Reproducible • High temporal resolution • Wealth of published data	• Single dimension not representative of actual left atrial size (particularly in dilated atria)
	2D-guided linear measurements 	Facilitates orientation perpendicular to left atrial posterior wall	• Lower frame rates than in M-mode • Single dimension only
Area Measured in 4-chamber apical view, at end-systole, on the frame just prior to mitral valve opening by tracing the LA inner border, excluding the area under the mitral valve annulus and the inlet of the pulmonary veins.	**Two-dimensional echocardiography** 	• More representative of actual left atrial size than antero-posterior diameter only	• Need for a dedicated view to avoid left atrial foreshortening • Assumes a symmetric shape of the atrium
Volume Two-dimensional volumetric measurements are based on tracings of the blood-tissue interface on apical 4- and 2-chamber views. At the mitral valve level, the contour is closed by connecting the two opposite	**Two-dimensional echocardiography**	• Enables accurate assessment of the asymmetric remodeling of the left atrium • More robust predictor of cardiovascular events than linear or area measurements	• Geometric assumptions about left atrial shape • Few accumulated data on normal population • Single plane volume calculations are inaccurate since they