UNIVERSIDADE DE SÃO PAULO
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Correlação Multimodal de Imagem e Biomarcadores na Estenose Aórtica de Baixo Fluxo e Baixo Gradiente e Fração de Ejeção Reduzida

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Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutora em Ciências.

Programa de Cardiologia

Orientador: Dr. Vitor Emer Egypto Rosa

Coorientador: Dr. Carlos Augusto Homem de Magalhães Campos

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Dedico a minha família, a minha mãe, a meu pai, a meus irmãos, as minhas cunhadas, a meus sogros e a meu marido, que apoiam incondicionalmente o meu crescimento profissional, e me inspiram na vida e na Medicina.

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“Há verdadeiramente duas coisas diferentes: saber e crer que se sabe. A ciência consiste em saber; em crer que se sabe reside a ignorância.”

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RESUMO

Lopes MAAAM. Correlação Multimodal de Imagem e Biomarcadores na Estenose Aórtica de Baixo Fluxo e Baixo Gradiente e Fração de Ejeção Reduzida [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2023.

Objetivos: O objetivo do presente estudo foi avaliar achados de imagem multimodal de acordo com biomarcadores sistêmicos, troponina I de alta sensibilidade (hsTnI) e níveis de peptídeo natriurético tipo B (BNP), na estenose aórtica de baixo fluxo e baixo gradiente (EAo*Gradb*), além de avaliar preditores de risco em pacientes submetidos à intervenção valvar. **Métodos:** Estudo prospectivo com pacientes EAo*Gradb* que realizaram hsTnI, BNP, angiografia coronária, ressonância magnética cardíaca (RMC) com mapeamento T1, ecocardiograma e ecocardiograma sob estresse com dobutamina (EcoS). Os pacientes foram divididos em 3 grupos de acordo com os níveis de BNP e hsTnI: Grupo 1 (n = 17) quando BNP e os níveis de hsTnI estavam abaixo da mediana [BNP < 1,98 vezes o limite superior de referência (URL) e hsTnI < 2,8 vezes URL]; Grupo 2 (n = 14) quando BNP ou hsTnI foram maiores que a mediana; e Grupo 3 (n = 18) quando ambos hsTnI e BNP estavam acima da mediana. Posteriormente, também foram avaliados 41 desses pacientes e divididos em 2 grupos: aqueles com gradiente entre o ventrículo esquerdo e a aorta menor ou igual a 25 mmHg ou maior que 25 mmHg, sendo avaliadas as taxas de mortalidade por todas as causas, e intraprocedimento, 30 dias e 1 ano. **Resultados**: Dos 49 pacientes incluídos nos 3 grupos, as características clínicas foram semelhantes entre os grupos. Os pacientes do grupo 3 tiveram menor impedância valvuloarterial (p = 0,03) e menor fração de ejeção do ventrículo esquerdo por meio do ecocardiograma (p = 0,02). A ressonância magnética cardíaca (RMC) identificou aumento progressivo dos ventrículos direito e esquerdo do Grupo 1 para o Grupo 3, e piora da fração de ejeção do ventrículo esquerdo (FEVE) (40 [31–47] *vs*. 32 [29–41] *vs*. 26 [19–33] %; p < 0,01) e da fração de ejeção do ventrículo direito (FEVD) (62 [53–69] *vs*. 51 [35–63] *vs*. 30 [24–46]%; p < 0,01). Além disso, foi demonstrado um aumento acentuado do Grupo 1 para o Grupo 3 na fibrose miocárdica avaliada pelo volume extracelular (ECV) (28,4 [24,8–30,7] *vs*. 28,2 [26,9–34,5] *vs*. 31,8 [28,9–35,5]%; p = 0,03) e ECV indexado (iECV) (28,7 [21,2–39,1] *vs*. 28,8 [25,4–39,9] *vs*. 44,2 [36,4– 51,2] ml/m^2, respectivamente; p < 0,01). Na análise dos resultados dos pacientes divididos pelos gradientes do ventrículo esquerdo e aorta (menor ou igual a 25 mmHg *vs.* maior que 25 mmHg), foi observada, na RMC, que a massa de realce tardio com gadolínio foi menor no grupo com gradiente transaórtico médio >25 mmHg (2,0 [0,0–8,9] *vs*. 8,5 [2,3– 15,0] gramas; p = 0,034), e o ECV do miocárdio e o ECV indexado foram semelhantes entre os grupos. As taxas de mortalidade em 30 dias e 1 ano foram de 14,6% e 43,8%, respectivamente. A mediana de seguimento foi de 4,1 (0,3–5,1) anos. Por análise multivariada ajustada para reserva contrátil (RC), apenas o gradiente transaórtico médio foi um preditor independente de mortalidade (taxa de risco: 0,923, intervalo de confiança de 95%: 0,864–0,986, p = 0,019). O gradiente transaórtico médio ≤ 25 mmHg foi associado à maior mortalidade por todas as causas taxas (log-rank p = 0,038), enquanto não houve diferença na mortalidade em relação à reserva contrátil (log-rank p = 0,114). **Conclusões:** Níveis mais elevados de BNP e hsTnI em pacientes EAo*Gradb* estão associados a piores parâmetros multimodais de remodelação cardíaca e fibrose. Além disso, o gradiente médio entre o ventrículo esquerdo e aorta foi o único preditor independente de mortalidade nesse subgrupo de

pacientes, especialmente se o gradiente entre o ventrículo esquerdo e a aorta fosse menor ou igual a 25 mmHg.

Palavras-chave: Estenose aórtica baixo fluxo baixo gradiente. Biomarcadores. BNP. Troponina. Ressonância magnética cardíaca.

ABSTRACT

Lopes MAAAM. Multimodality Imaging Methods in Biomarkers in Classical Low- Flow Low- Gradient Aortic Stenosis [tese]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2023.

Objectives: The aim of the present study was to evaluate multimodal imaging findings according to systemic biomarkers, high-sensitivity troponin I (hsTnI) and type B natriuretic peptide (BNP) levels, in low flow, low gradient aortic stenosis (LFLG-AS), in addition to assessing risk predictors in patients undergoing valve intervention. **Methods**: Prospective study with LFLG-AS patients submitted to hsTnI, BNP, coronary angiography, cardiac magnetic resonance (CMR) with T1 mapping, echocardiography and dobutamine stress echocardiography. Patients were divided into 3 groups according to BNP and hsTnI levels: Group 1 (n = 17) when BNP and hsTnI levels were below the median [BNP < 1.98 times the upper reference limit (URL) and hsTnI < 2.8 times URL]; Group 2 (n = 14) when BNP or hsTnI were greater than the median; and Group 3 (n = 18) when both hsTnI and BNP were above the median. Subsequently, 41 of these patients were also evaluated and divided into 2 groups: those with a mean transaortic gradient less than or equal to 25 mmHg *vs.* greater than 25 mmHg, with assessment of mortality rates from all causes, intraprocedural, 30-day and 1-year. **Results:** Regarding the 49 patients included in 3 groups, clinical features (including risk scores) were similar between groups. Patients in group 3 had lower valvular-arterial impedance (P = 0.03) and lower left ventricular ejection fraction (P = 0.02) on echocardiography. CMR imaging identified progressive enlargement of right and left ventricles from Group 1 to Group 3, and worsening of left ventricular ejection fraction (LVEF) (40 [31–47] *vs*. 32 [29–41] *vs.* 26 [19–33]%; p<0.01) and right ventricular ejection fraction (RVEF) (62 [53–69] *vs*. 51 [35–63] *vs*. 30 [24–46] %; p < 0.01). In addition, a marked increase in myocardial fibrosis assessed by extracellular volume (ECV) was demonstrated (28.4 [24.8–30.7] *vs*. 28.2 [26.9–34.5] *vs*. 31.8 [28.9–35.5]%; p =0.03) and indexed ECV (iECV) (28.7 [21.2–39.1] *vs*. 28.8 [25.4–39.9] *vs*. 44.2 [36.4–51.2] ml/m^2, respectively; p < 0.01) from Group 1 to Group 3. In the analysis of the results regarding left ventricular and aorta gradients (less than or equal to 25 mmHg *vs.* greater than 25 mmHg) it was observed on CMR that the late gadolinium enhancement mass was smaller in the group with mean transaortic gradient >25 mmHg (2.0 [0.0–8.9] *vs*. 8.5 [2.3–15.0] grams; p = 0.034), and myocardial ECV and indexed ECV were similar between groups. The 30-day and 1-year mortality rates were 14.6% and 43.8%, respectively. The median follow-up was 4.1 (0.3–5.1) years. By multivariate analysis adjusted for flow reserve, only mean transaortic gradient was an independent predictor of mortality (hazard ratio: 0.923, 95% confidence interval: 0.864–0.986, p=0.019). The mean transaortic gradient ≤ 25 mmHg was associated with higher all-cause mortality rates (log-rank p = 0.038), while there was no difference in mortality regarding flow reserve (log-rank p=0.114). **Conclusions**: Higher levels of BNP and hsTnI in LFLG-AS patients are associated with worse multimodal parameters of cardiac remodeling and fibrosis. Furthermore, the mean gradient between left ventricle and aorta was the only independent predictor of mortality in this subgroup of patients, especially if the mean transaortic gradient was less than or equal to 25 mmHg.

Keywords: Low flow low gradient aortic stenosis. Biomarkers. BNP. Troponin. Cardiac magnetic resonance.

LISTA DE FIGURAS

LISTA DE SIGLAS E ABREVIATURAS

2D	Bidimensional
3D	Tridimensional
ACC/AHA	*American College of Cardiology/American Heart Association*
AVA	Área Valvar Aórtica
BNP	Peptídeo Natriurético Cerebral
EAo	Estenose Aórtica
EAo*Gradb*	Estenose Aórtica com Gradiente Baixo e Fração de Ejeção Reduzida
EcoS	Ecocardiograma com Estresse com Dobutamina
ECV	Volume de Distribuição Extracelular do Contraste
ESC/EACTS	*European Society of Cardiology/European Association for Cardiology*
EuroSCORE II	Escore de Risco EuroSCORE II
FEVD	Fração de Ejeção do Ventrículo Direito
FEVE	Fração de Ejeção do Ventrículo Esquerdo
iECV	Índice de Volume de Distribuição Extracelular do Contraste
iECV	Volume de Distribuição Extracelular do Contraste Indexado
iVDFVD	Índice de Volume Diastólico Final do Ventrículo Direito
iVDFVE	Índice de Volume Diastólico Final de Ventrículo Esquerdo
iVSFVD	Índice de Volume Sistólico Final do Ventrículo Direito
iVSFVE	Índice de Volume Sistólico Final do Ventrículo Esquerdo
NYHA	*New York Heart Association*
PCR	Proteína C Reativa
RC	Reserva Contrátil
RMC	Ressonância Magnética Cardíaca
ROC	*Receiver Operating Characteristic*
STS	*Society of Toracic Surgeons*
TAVR	Implante Valvar Aórtico Percutâneo
TnI-Ultr	Troponina Ultrassensível

LISTA DE SÍMBOLOS

%	Porcentagem
≤	Menor ou igual
<	Menor
≥	Maior ou igual
>	Maior
mmHg	Milímetros de mercúrio
cm^2	Centímetro quadrado
cm^2/m^2	Centímetro quadrado por metro quadrado
µg/kg/min	Micrograma por quilo por minuto
±	Mais ou menos
mm	Milímetro
cm/s	Centímetro por segundo
mmol/kg	Milimol por quilo
mg/dl	Miligrama por decilitro
$ml/m^2.s$	Mililitro por metro quadrado vezes segundos
ng/dl	Nanograma por decilitro
pg/dl	Picograma por decilitro
m/s	Metros por segundo
ml/m^2	Mililitro por metro quadrado
$mmHg/ml/m^2$	Milímetros de mercúrio por mililitro por metro quadrado
g	Grama

SUMÁRIO

1 INTRODUÇÃO

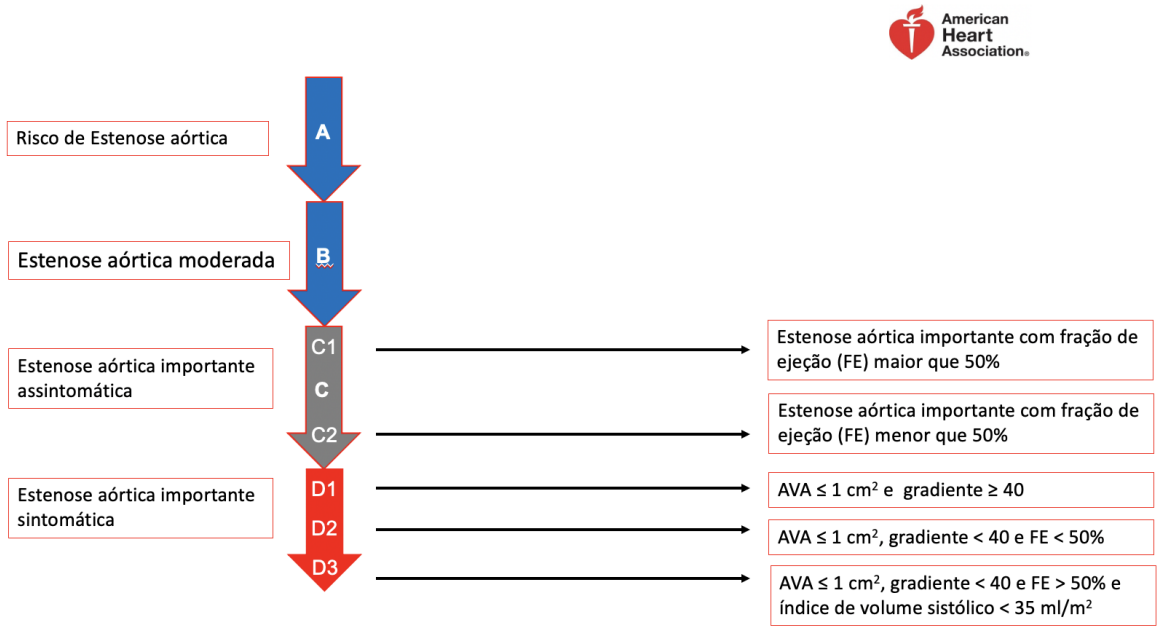
1 INTRODUÇÃO

1.1 ESTADO ATUAL DO CONHECIMENTO

A estenose aórtica (EAo) apresenta prevalência crescente na atualidade em razão do aumento da expectativa de vida e do consequente envelhecimento da população. Atualmente, a causa mais comum de EAo é a calcificação aórtica, que acomete, principalmente, pacientes idosos[1, 2]. Países subdesenvolvidos ainda têm como etiologia mais prevalente a doença reumática e a endocardite infecciosa[3]. No Brasil, devido a sua pirâmide etária transicional, típica de países em desenvolvimento, encontramos um pico bimodal de prevalência de EAo, ou seja, encontramos pacientes de todas as etiologias nas diferentes faixas etárias[4]. A EAo importante é definida ecocardiograficamente com área valvar aórtica (AVA) ≤ 1,0 cm² e/ou AVA indexada ≤ 0,6 cm²/m² na presença de gradiente médio entre o ventrículo esquerdo e aorta ≥ 40 mmHg e/ou velocidade máxima do jato aórtico ≥ 4,0 m/s[4]. Sabe-se que o tempo de sobrevida esperado para portadores de EAo importante associado à insuficiência cardíaca é cerca de dois anos[5].

A EAo "*low flow low gradient*" ou EAo com baixo fluxo, baixo gradiente e fração de ejeção reduzida (EAo*Gradb*) é o termo utilizado para identificar os casos que apresentam área valvar ≤ 1,0cm² associados à gradiente transvalvar aórtico baixo (< 40mmHg) e disfunção ventricular esquerda (fração de ejeção do ventrículo esquerdo [FEVE] < 50%). Esta apresentação, definida como estágio D2 na evolução da EAo pela *American College of Cardiology/American Heart Association* (ACC/AHA) (Figura 1)[6], ocorre em cerca de 5 a 10% dos pacientes com EAo e é um dos maiores desafios diagnósticos em pacientes com doenças valvares[7, 8]. Esta situação decorre da dificuldade em diferenciar os pacientes que apresentam EAo *verdadeiramente-importante*, em que a disfunção ventricular decorre de desajuste de pós-carga (*afterload mismatch)* excessivo e o ventrículo não consegue gerar um gradiente sistólico, daqueles com EAo *pseudo-importante*, ou seja, a EAo é moderada e o fator predominante é a doença do miocárdio, sendo a gravidade da EAo superestimada devido à abertura incompleta da válvula[9].

Figura 1 – Classificação da estenose aórtica pela American *College of Cardiology/American Heart Association* (ACC/AHA)



Estágios de classificação da estenose aórtica, sendo A pacientes que têm fatores de risco para ter estenose aórtica (valva aórtica bicúspide, esclerose valvar aórtica); o estágio B engloba pacientes com estenose aórtica progressiva (moderada); o estágio C se divide em 2, sendo C1 pacientes com estenose aórtica importante assintomática e C2 aqueles estenose aórtica importante assintomática e disfunção do ventrículo esquerdo. Já o estágio 3 se divide em 3 grupos, sendo D1 pacientes com estenose aórtica importante sintomática; D2, pacientes com estenose aórtica importante com baixo-fluxo e baixo-gradiente e fração de ejeção reduzida e D3, pacientes com estenose aórtica importante de baixo-gradiente e fração de ejeção normal sintomáticos. AVA, área valvar aórtica; EAo, estenose aórtica; FE, fração de ejeção.
Fonte: Adaptado de ACC/AHA[6]

O único tratamento realmente efetivo, capaz de promover aumento de anos de vida e alívio dos sintomas do paciente com EAo*Gradb*, é a intervenção valvar[10]. Esta intervenção, seja por via cirúrgica ou percutânea, reduz a barreira imposta ao ventrículo esquerdo, podendo melhorar ou até, em certos casos, normalizar a função ventricular[11, 12]. Além de idade avançada, a sintomatologia (classe funcional pela *New York Heart Association*), coexistência com doença arterial coronária e disfunção ventricular sistólica são os principais fatores prognósticos tanto antes quanto após a intervenção nos pacientes com EAo importante[13]. O registro TOPAS-TAVI também mostrou, como fatores independentes de mortalidade após o implante transcateter percutâneo aórtico (TAVR), a presença de anemia e doença pulmonar obstrutiva crônica[12]. Dessa maneira, os pacientes com gradiente baixo apresentam pior prognóstico e morbimortalidade perioperatória maior quando comparados aos casos de EAo com gradiente elevado (> 40mmHg)[14].

1.2 EXAMES DE IMAGEM: DIAGNÓSTICO E PROGNÓSTICO

O ecocardiograma transtorácico com Doppler é a ferramenta diagnóstica habitual para a avaliação inicial de EAo[15]. Além de prover parâmetros hemodinâmicos e funcionais relacionados ao grau de estenose, o exame também permite determinação da calcificação valvar. A gravidade da EAo pode ser avaliada pelo gradiente de pressão transvalvar e pela área do orifício de fluxo aórtico (AVA)[16-18]. Entretanto, nesse subgrupo de pacientes com discordância entre a AVA e o gradiente transvalvar médio, o exame padrão-ouro para definição da gravidade anatômica é o ecocardiograma com estresse com dobutamina (EcoS)[19-23].

Com baixas doses do fármaco (até 20 µg/kg/min), avaliamos, inicialmente, a presença de reserva contrátil (RC), definida como um aumento de 20% no volume ejetado (*stroke volume*) e/ou aumento de 10 mmHg do gradiente médio transaórtico após 20 mcg/kg/min ou a dose máxima tolerada de dobutamina. Aqueles com RC que têm aumento da AVA e manutenção do gradiente médio são definidos como EAo *pseudo-importante*, enquanto aqueles que apresentam redução ou manutenção da AVA e aumento do gradiente médio são definidos como EAo *verdadeiramente importante*[24]. Entretanto, aproximadamente, 1/3 dos pacientes têm diagnóstico inconclusivo nesse teste pela incapacidade de responder à dobutamina e aumentar a contratilidade ventricular. Tais pacientes são descritos como sem RC e a realização de escore de cálcio valvar com tomografia computadorizada é impreterível para diagnóstico (Figura 2)[2, 4].

Figura 2 – Avaliação de estenose aórtica verdadeiramente importante versus estenose aórtica pseudo-importante

Fluxograma demonstrando a avaliação de pacientes com estenose aórtica baixo fluxo baixo gradiente e fração de ejeção reduzida. Para ajudar na diferenciação entre estenose aórtica moderada (*pseudo-importante*) e verdadeiramente importante, utilizamos a infusão de dobutamina e avaliamos inicialmente o volume sistólico ejetado e gradiente transaórtico médio. Se houver elevação do volume ejetado em 20% ou do gradiente médio em 10 mmHg, estamos diante de um paciente que respondeu bem à medicação inotrópica e chamamos isso de reserva contrátil positiva. Em seguida, avaliaremos se a área valvar aumenta, sendo esses pacientes classificados como estenose aórtica modera e disfunção de ventrículo esquerdo por outro motivo, ou se a área valvar aórtica se mantém ou diminui, sendo classificado com estenose aórtica importante, com baixo fluxo, baixo gradiente e com reserva, estágio D2; se estenose moderada, trata-se de estágio B concomitante a outra miocardiopatia. No entanto, alguns pacientes não respondem à infusão de dobutamina e são considerados sem reserva contrátil. Nesse caso, o exame foi ineficaz, devendo usar o escore de cálcio da valva aórtica pela tomografia e, se encontramos valores elevados (maior que 2000UA para homens e 1300UA para mulheres), estamos diante de uma estenose verdadeiramente importante, estágio D2, mas sem reserva contrátil. AVA, área valvar aórtica; EAo, estenose aórtica.
Fonte: Adaptado da Diretriz Brasileira de Valvopatia, 2020[4].

Dessa maneira, a confirmação da gravidade anatômica da EAo*Gradb* por meio do EcoS nem sempre é possível. Ou seja, muitas vezes, outros métodos complementares são necessários para melhorar a acurácia diagnóstica. Além disso, evidências atuais demonstram que a presença de RC no EcoS tem valor prognóstico discutível e tal exame deve apenas ser utilizado para avaliação da gravidade anatômica valvar[25, 26].

Adicionalmente, avanços tecnológicos como o ecocardiograma tridimensional (3D) tem demonstrado ser promissor em relação ao método convencional na avaliação de pacientes com doença valvar em diversos aspectos: 1) melhora na mensuração de volumes e funções cavitárias; 2) avaliação anatômica mais acurada;

e 3) melhor avaliação da gravidade de algumas valvopatias[27]. Essa modalidade diminuiu as variações inter-avaliadores com melhor acurácia do método. Metodologias automatizadas foram apresentadas para extrair a morfologia da AVA em várias fases cardíacas[28]. Cortes multiplanares obtidos com transdutor 3D, analisados por técnicas derivadas do Doppler tecidual (*Strain* e *Tissue-Tracking*) e pelo *Strain* Bidimensional (*speckle tracking*), permitem avaliação da contratilidade segmentar, utilizando-se com quantificação do pico sistólico de cada segmento miocárdico do ventrículo esquerdo. A importância do *strain* está ainda mais relacionada ao prognóstico do paciente, sendo um fator adicional na indicação de intervenção[29].

A ressonância magnética cardíaca (RMC) é o método padrão-ouro para medir a espessura da parede do ventrículo esquerdo (VE), massa, volumes e fração de ejeção. Além disso, é capaz de detectar alterações estruturais no miocárdio do VE, incluindo avaliação da fibrose cicatricial com a técnica do realce tardio com gadolínio e intersticial com Mapeamento T1[30]. Em relação à RMC, foi observada um pior prognóstico em pacientes com presença de fibrose focal e remodelamento inapropriado (hipertrofia concêntrica) do VE associados a EAo importante[31]. Sabe-se que a fibrose miocárdica interfere com o processo difusional, dificulta o aporte de oxigênio e de nutrientes à molécula por redução do leito vascular, com piora da capacidade contrátil das fibras miocárdicas remanescentes. Assim, pode impedir seu deslizamento e diminuir a complacência miocárdica, comprometendo a função diastólica. Compreende-se, então, que o componente fibrótico da remodelação ventricular, devido ao aumento do contingente de fibroblastos do interstício miocárdico, contribuiria para piora da função ventricular[31]. Em um estudo com 166 pacientes com EAo importante e 37 voluntários saudáveis, os pacientes com EAo tiveram um aumento difuso da fibrose do miocárdio, com o índice de volume de distribuição extracelular do contraste (iECV) fornecendo a melhor discriminação comparado aos casos- controle[30]. Além disso, o estudo publicado por Rosa VE et al. [32] demonstrou que pacientes com EAo*Gradb* apresentaram, aproximadamente, 2 vezes mais fibrose pelo volume de distribuição extracelular do contraste (ECV) e iECV que os pacientes com gradiente alto[25, 26]. É importante ressaltar que a fibrose difusa pode regredir após alívio da sobrecarga de pressão na intervenção valvar da valva aórtica[33].

1.3 BIOMARCADORES SÉRICOS

Diante da dificuldade de avaliação isolada por métodos de imagem, marcadores séricos vêm sendo utilizados para melhorar a estratificação de risco. Em 2002, Nunes JP et al.[34] demonstraram a correlação entre os níveis de troponina elevados com grau de hipertrofia do ventrículo esquerdo e aumento da pressão sistólica pulmonar em pacientes com EAo comparada com população controle (pacientes sem doença cardiovascular estabelecida). Outro estudo que correlacionou biomarcadores e prognóstico, em pacientes com EAo importante submetidos à cirurgia de troca valvar ou mantidos de forma conservadora, demonstrou que a combinação de BNP, troponina ultrassensível (TnI-Ultr) e proteína C reativa (PCR) em pacientes com EAo importante em tratamento clínico teve valor prognóstico e correlação com mortalidade[1]. Dahou et al[35] avaliaram o impacto prognóstico da troponina e BNP combinados em 65 pacientes com EAo*Gradb* e 33 pacientes com EA paradoxal. Foi demonstrado que a elevação dos biomarcadores (BNP ≥ 550 pg/ml e troponina T cardíaca de alta sensibilidade ≥ 15 ng/l) teve impacto prognóstico. Além disso, BNP sozinho foi correlacionado com parâmetros de função do VE e troponina correlacionada com parâmetros de geometria e função do VE. Outro estudo bastante relevante no subgrupo de pacientes é o subestudo do TOPAS que evidenciou o aumento do BNP associado à relação inversa com a AVA, fluxo transvalvar e volume sistólico, e relação direta com resistência valvar, além de demonstrar nesse estudo ser um fator preditor de todas as causas de mortalidade[36].

1.4 INTERVENÇÃO NA ESTENOSE AÓRTICA DE BAIXO FLUXO E BAIXO GRADIENTE

A decisão de intervenção na EAo*Gradb* deve ser individualizada considerando elementos como comorbidades associadas, grau de calcificação valvular, extensão da doença coronária e possibilidade de revascularização. Habitualmente, a relação entre risco e benefício na intervenção desse subgrupo de pacientes é favorável devido à melhora dos sintomas e à menor mortalidade no longo prazo[37]. Há uma escassez de informações sobre o prognóstico atual de pacientes com EAo*Gradb* submetidos à cirurgia e a falta de uma ferramenta de avaliação de risco cirúrgico nesse subgrupo de pacientes com EAo. A TAVR é uma opção excelente, sendo

menos invasivo, associado a bons desfechos em EAo*Gradb,* porém ainda apresenta uma alta mortalidade em 2 anos. Existem poucos estudos prospectivos comparando TAVR e cirurgia nesse subgrupo de paciente[38].

Outro fato importante a ser mencionado é sobre a RC. Durante muitos anos, a EAo*Gradb* ficou dividida de acordo com a presença ou ausência de RC no EcoS. Rosa VE et al. [25] demonstraram, em um estudo com RMC, que os pacientes sem RC não apresentam mais LGE, ECV ou iECV quando comparados àqueles com RC, sugerindo que a RC não deva ser relacionada à fibrose focal ou difusa[39]. Também corroborando com tais achados, o registro TOPAS-TAVI demonstrou que a recuperação da FEVE nesse grupo de pacientes não é influenciada pela presença ou ausência de RC[12]. Dessa maneira, a RC aparenta influenciar apenas no diagnóstico da gravidade anatômica em pacientes com EAo*Gradb,* não contraindicando a intervenção valvar.

Diante do exposto, o objetivo deste estudo é avaliar a correlação de biomarcadores (BNP e TnI-Ultr) com alterações estruturais cardíacas identificadas por exames de imagem (RMC e o ecocardiograma 3D com strain) em portadores de EAo*Gradb*. Além disso, avaliaremos os fatores de pior prognóstico nos pacientes desse subgrupo que foram submetidos à troca valvar aórtica.

2 OBJETIVOS

2 OBJETIVOS

2.1 OBJETIVO PRIMÁRIO

O objetivo deste trabalho será o de correlacionar biomarcadores (TnI-Ultr e BNP) com a avaliação multimodal de exames de imagens (ecocardiograma tridimensional e a ressonância magnética cardíaca com mapa T1) em pacientes com EAo*Gradb*.

2.2 OBJETIVOS SECUNDÁRIOS

Avaliação de preditores de prognóstico tardio:

- Óbito por todas as causas;
- Reintervenção;
- Implante de marca-passo;
- Infarto agudo do miocárdio;
- Acidente vascular cerebral;
- Insuficiência Renal Aguda.

3 MÉTODOS

3 MÉTODOS

Estudo retrospectivo com 49 pacientes com EAo*Gradb* definida pelo ecodopplercardiograma como AVA ≤ 1,0cm² associada a baixo gradiente transaórtico médio (< 40mmHg) e à fração de ejeção do ventrículo esquerdo reduzida (FEVE < 50%)[40]. Foram selecionados indivíduos que se encontraram em acompanhamento no Ambulatório da Unidade Clínica de Valvopatias (Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, InCor HC FMUSP) no período de abril de 2013 a abril de 2015.

Todos os pacientes foram submetidos à avaliação clínica e laboratorial, além dos três métodos diagnósticos: ecocardiograma 3D, RMC com mapa T1 e EcoS, sendo esse último o padrão-ouro para definir a presença de RC e o diagnóstico da gravidade anatômica.

Dados clínicos descritos incluíram idade, sexo, superfície corpórea, sintomas, uso de medicações, além de diagnósticos documentados de fatores de risco cardiovascular, como hipertensão arterial, diabetes, fibrilação atrial e doença arterial coronária.

Nos pacientes com EAo sem RC, foi necessária a realização do escore de cálcio valvar pela tomografia computadorizada de tórax (≥ 1300 AU no sexo feminino e ≥ 2000 AU no sexo masculino definem EAo importante)[4, 40].

Todos os pacientes com EAo*Gradb* foram submetidos a EcoS, ecocardiograma transtorácico bidimensional e 3D, RMC com realce tardio de gadolínio e mapeamento T1 e exames laboratoriais, incluindo TnI-Ultra (ADVIA Centaur TnI-Ultra; *Siemens Healthcare Diagnostics*, Tarrytown, NY; valor de referência: 0,015 ng/ml) e peptídeo natriurético tipo B (BNP) (ADVIA Centaur; *Siemens Medical Solutions Diagnostic*, Los Angeles, CA, valor de referência: 200 pg/ml). Os pacientes foram divididos em 3 grupos de acordo com os níveis de BNP e/ou TnI-Ultra:

a) Grupo 1 (grupo Biomarcadores Baixos): Pacientes com BNP e TnI-Ultra abaixo do valor mediano (BNP < 395 pg/ml [1,98 vez o valor de referência] e TnI-Ultra < 0,042 ng/ml [2,8 vezes o valor de referência]);
b) Grupo 2 (grupo Biomarcadores Intermediários): Pacientes com BNP ou TnI-Ultra maior ou igual ao valor mediano (BNP ≥ 395pg/ml [≥ 1,98 vezes] ou TnI-Ultra ≥ 0,042 ng/ml [≥ 2,8 vezes]);

c) Grupo 3 (grupo Biomarcadores Altos): Pacientes com BNP e TnI-Ultra maior ou igual ao valor mediano (BNP ≥ 395 pg/ml [≥ 1,98 vezes] e TnI-Ultra ≥ 0,042 ng/ml [≥ 2,8 vezes]).

Os pacientes que apresentaram confirmação diagnóstica de EAo importante com condições satisfatórias para cirurgia foram encaminhados para tratamento cirúrgico convencional pela equipe assistencial ambulatorial. Na presença de contraindicação ao procedimento, foi analisada a possibilidade de tratamento percutâneo, caso contrário, indicado tratamento clínico. Uma vez identificados os pacientes com indicação de tratamento cirúrgico da valva aórtica, estes seguiram a rotina de pré-operatório da equipe de Valvopatias do InCor HC FMUSP. Tais pacientes foram submetidos à cineangiocoronariografia e a presença de doença arterial coronária foi definida pela presença de estenose luminal maior que 70% nas artérias epicárdicas principais. A escolha do tipo de prótese a ser implantada foi individualizada, respeitando a escolha do paciente.

Para análise de desfechos secundários, os pacientes foram divididos em grupos de acordo com o valor da mediana do gradiente transaórtico médio (≤25 e >25 mmHg) e analisadas as taxas de mortalidade por todas as causas, intraprocedimento, em 30 dias e em 1 ano.

Esse estudo é uma subanálise de estudo já previamente aprovado pelo Comitê de Ética em Pesquisa (CAPPesq, SDC 3858/12/114; CAAE 10216613.4.0000.0068). Não foram realizadas coletas laboratoriais nem realizados procedimentos adicionais no presente estudo. Previamente, foi realizada uma avaliação sobre a contribuição da ressonância magnética cardíaca e do ecocardiograma tridimensional para avaliação da RC em pacientes com EAo importante com gradiente baixo e fração de ejeção reduzida [25] .

3.1 CRITÉRIOS DE INCLUSÃO

Presença de EAo*Gradb*, definida como AVA ≤ 1,0 cm² ou ≤ 0,6 cm²/m² se indexada pela superfície corpórea, com baixo gradiente transaórtico (gradiente médio < 40 mmHg), e FEVE < 50%, em classe funcional de I a IV pela *New York Heart Association* (NYHA).

3.2 CRITÉRIOS DE EXCLUSÃO

Foram excluídos pacientes com outra valvopatia primária anatomicamente importante concomitante (como doença valvar mitral primária importante e insuficiência aórtica importante); pacientes submetidos à cirurgia valvar prévia; portadores de marca-passo definitivo com contraindicação à realização da RMC; miocardiopatia não isquêmica; e aqueles com EAo *pseudo-importante* após a realização do EcoS. Também foram excluídos das análises aqueles que não puderam realizar todos os exames do protocolo após a inclusão.

3.3 AVALIAÇÃO ECOCARDIOGRÁFICA

A análise ecocardiográfica foi conduzida pelo mesmo examinador, sendo realizada no período pré-operatório e após 6 a 8 meses da intervenção. O exame foi realizado com o paciente em decúbito lateral esquerdo e utilizado equipamento comercialmente disponível, apresentando transdutor setorial eletrônico multifrequencial, com recurso de Doppler pulsado, Doppler contínuo, Doppler tecidual e mapeamento de fluxo em cores. Os exames foram realizados de acordo com as recomendações da Sociedade Americana de Ecocardiografia[41-44]. Foram obtidas, pelo menos, três medidas de cada variável, sendo utilizada a média dos valores de cada uma.

As variáveis ecocardiográficas avaliadas foram:

1) Espessura do septo e da parede posterior do ventrículo esquerdo no final da diástole, para cálculo do índice de massa ventricular esquerda (de acordo com formulação de Devereux);
2) Função sistólica ventricular esquerda, por meio do cálculo da FEVE de acordo com a regra de Simpson (medida bidimensional);
3) AVA, pela equação de continuidade;
4) Função diastólica ventricular esquerda.

O EcoS farmacológico incluiu a análise ecocardiográfica em repouso completa, além monitorização dos batimentos cardíacos, saturação de oxigênio e eletrocardiograma, segundo os protocolos internacionais[45]. A infusão de dobutamina foi iniciada na dose de 5 μg/kg/min, sendo acrescentados outros 5 μg/kg/min a cada 3 minutos até alcançar a dose total de até 20 μg/kg/min, ou a dose

máxima tolerada pelo paciente[46]. A RC foi definida como um aumento de 20% no volume ejetado (*stroke volume*) ou aumento no gradiente médio (≥ 10 mmHg) após a dose máxima do fármaco tolerada. Nos pacientes com RC, a presença de AVA ≤ 1,0 cm² definiu o mesmo com EAo verdadeiramente importante. Nos casos de AVA > 1,0 cm² com aumento de pelo menos 0,3 cm², a EAo foi considerada EAo pseudo-importante e estes pacientes foram excluídos das análises. Naqueles em que não houve aumento no volume de ejeção em, pelo menos, 20% ou no gradiente médio em mais de 10 mmHg, a gravidade da EAo não pode ser estabelecida e o paciente teve o diagnóstico de EAo sem RC [24]. Pacientes em uso de betabloqueadores e/ou digitálicos tiveram essas medicações suspensas ou reduzidas à mínima dose tolerável. O diâmetro da via de saída do ventrículo esquerdo foi considerado constante nos diferentes estados de fluxo e os valores basais foram utilizados para o cálculo do volume ejetado. Em pacientes com fibrilação atrial, todos os parâmetros relacionados à RC foram medidos em uma média de 10 batimentos cardíacos consecutivos[44, 47].

Os critérios de interrupção da administração do fármaco foram:

a) angina progressiva;

b) depressão maior que 2 mm do segmento ST no eletrocardiograma de controle;

c) aparecimento de alteração da contratilidade segmentar ao ecocardiograma;

d) arritmia importante;

e) efeitos colaterais intoleráveis;

f) nível de 85% da frequência cardíaca máxima; ou

g) infusão da dose máxima do fármaco.

A análise ecocardiográfica 3D foi conduzida pelo mesmo examinador, o qual não teve acesso ao resultado do EcoS. A avaliação foi realizada com o paciente em decúbito lateral esquerdo, com equipamento comercialmente disponível (Epic, *Philips Ultrasound*, Andover, MA, USA com transdutor de 5-MHz). Foram analisados:

a) Ventrículo esquerdo:
   - a.i) Volume diastólico final do ventrículo esquerdo,
   - a.ii) Volume sistólico final do ventrículo esquerdo,
   - a.iii) FEVE,
   - a.iv) Índice de volume diastólico 3D do ventrículo esquerdo,
   - a.v) Índice do volume sistólico 3D do ventrículo esquerdo,

a.vi) Massa 3D,

a.vii) Índice de massa 3D,

a.viii) Impedância valvuloarterial.

b) Valva Aórtica:

b.i) AVA/Grau de gravidade da estenose por planimetria 3D,

b.ii) Caracterização da valva aórtica.

Avaliação da contratilidade segmentar foi realizada utilizando-se cortes multiplanares obtidos com transdutor 3D, analisados por técnicas derivadas do Doppler tecidual (*Strain* e *Tissue-Tracking*) e pelo *Strain* Bidimensional (*speckle tracking*) com quantificação do pico sistólico de cada segmento miocárdico do ventrículo esquerdo.

3.4 AVALIAÇÃO PELA RESSONÂNCIA MAGNÉTICA CARDÍACA

A RMC com a técnica do Mapa T1 foi realizada em aparelho Phillips 1,5 Tesla (Achieva, Philips, Best, The Netherlands), com bobina cardiovascular, no período pré-operatório. Inicialmente, foram realizadas as aquisições habituais com *steady state free precession*, formando a imagem em cine, durante um período de apneia e as análises foram realizadas com o *software* CVi42 (Circle CVi, Calgary, Canada). As dimensões do ventrículo esquerdo, massa miocárdica (indexada pela área de superfície corpórea), índices de volumes do ventrículo esquerdo e FEVE foram aferidas a partir de cortes do eixo curto nos momentos de volume sistólico final e volume diastólico final. A imagem de realce tardio foi realizada 20 minutos após a infusão de bolus de gadolínio-DTPA na dose de 0,1 mmol/kg com a utilização de bomba injetora, por meio de acesso venoso periférico. As sequências de pulsos foram sincronizadas ao eletrocardiograma, visando a aumentar as taxas de sinal-ruído e melhorar a qualidade das imagens.

As medidas de T1 foram realizadas antes da injeção de contraste e 5, 10, 15, 20 e 30 minutos após injeção do contraste paramagnético, utilizando protocolo de sequência de inversão *Look Locker* modificada (da sigla, em Inglês, MOLLI) sincronizada ao eletrocardiograma, previamente descrita[48]. Como alguns pacientes apresentavam áreas de realce tardio, realizamos análises incluindo e excluindo todas as áreas de fibrose focal. Delineações endocárdicas e epicárdicas foram traçadas manualmente em todas as imagens dos 3 segmentos no eixo curto. Na primeira

análise, calculamos o valor do T1 em cada segmento, o que resultou um T1 global do miocárdio (pré e pós-gadolínio). Na segunda análise, utilizamos regiões de interesse em áreas sem realce tardio e o T1 do miocárdio foi calculado excluindo as áreas de fibrose focal. Em ambas as análises, colocamos uma região de interesse na cavidade cardíaca para o cálculo do T1 do sangue. Em pacientes com fibrilação atrial, as aquisições de imagem do mapa T1 foram repetidas e uma média dos valores do T1 foi calculada nas sequências pré e pós-gadolíneo[49]. Além disso, todos pacientes apresentavam frequência cardíaca controlada (entre 60 e 90 bpm) no momento da realização do exame.

A partir da aferição dos respectivos T1, foi calculada a fração de volume extracelular (ECV). O ECV representa a parcela de tecido extracelular e, portanto, de fibrose miocárdica difusa. Esta variável é dada em forma de porcentagem de área. O ECV foi calculado a partir das medidas do mapa T1 do sangue e miocárdio do pré e pós-injeção do gadolínio, e ajustado pelo hematócrito do paciente (coletado no mesmo dia do exame), com a fórmula que segue: ECV = (1-hematócrito) x ΔR1mioc/ΔR1sangue (onde ΔR1 é [1/T1 pré-contraste – 1/T1 pós-contraste]). Já o iECV, variável que representa a carga total de fibrose do ventrículo esquerdo, foi calculado por meio da fórmula: iECV = ECV (%) x volume miocárdico diastólico final diastólico do ventrículo esquerdo indexado pela superfície corporal[50].

Os seguintes itens também foram avaliados:

1) dimensões, análise segmentar e função de ventrículo esquerdo;
2) grau e caracterização de fibrose miocárdica;
3) AVA, gradiente transvalvar aórtico, fluxo aórtico, fluxo regurgitante aórtico e fração regurgitante aórtica;
4) investigação de comprometimento de demais valvas.

A aquisição e as análises das imagens de ressonância magnética foram realizadas pela equipe médica especializada em ressonância cardiovascular do InCor HC FMUSP, estando esses “cegos” em relação aos dados clínicos dos pacientes.

3.5 AVALIAÇÃO LABORATORIAL

Todos os pacientes foram submetidos à coleta dos seguintes exames: hemograma completo, função renal, dosagem de eletrólitos, coagulograma, BNP

(ADVIA Centaur®, *Siemens Medical Solutions Diagnostic*, Los Angeles, CA, USA), PCR e troponina I (ADVIA Centaur® TnI-Ultra, *Siemens Healthcare Diagnostics*, Tarrytown, NY, USA).

4 ANÁLISE ESTATÍSTICA

4 ANÁLISE ESTATÍSTICA

As variáveis contínuas foram apresentadas como média ± desvio padrão ou mediana (intervalo interquartil) e o teste de Shapiro-Wilk foi utilizado para testar a normalidade das variáveis. As variáveis categóricas foram apresentadas como porcentagens. A transformação logarítmica foi aplicada para normalizar a distribuição de dados. Aplicou-se o teste de Mann-Whitney U-test, Kruskall-Wallis ou ANOVA para variáveis contínuas; e o teste qui-quadrado e o exato de Fisher para variáveis categóricas, conforme apropriado. A análise *post hoc* foi realizada com o teste de Tukey. Coeficientes de correlação de Spearman foram usados para avaliar a correlação dos dados. A curva ROC foi aplicada para BNP e TnI-Ultra para discriminar o aumento de ECV, iECV, índice de volume sistólico final de ventrículo esquerdo (i*VS*FVE), índice de volume diastólico final de ventrículo esquerdo (iVFDVE), índice de volume sistólico final de ventrículo direito (iVFSVD), índice de volume diastólico final do ventrículo (iVFDVD), fração de ejeção do ventrículo direito (FEVD) e fração de ejeção do ventrículo esquerdo (FEVE), utilizando valores de corte estabelecidos na literatura (ECV > 28%; iECV > 22,5 ml/m²; iVSFVE ≥ 29 ml/m² para mulheres e ≥ 36 ml/m² para homens; iVDFVE ≥ 74 ml/m² para mulheres e ≥ 85 ml/m² para homens; i*VS*FVD ≥ 33 ml/m² para mulheres e ≥ 43 ml/m² para homens; iVDFVD ≥ 77 ml/m² para mulheres e ≥ 93 ml/m² para homens; FEVD < 55%; e FEVE < 55% [6, 21, 22]. Os pacientes também foram divididos em grupos de acordo com a mediana gradiente transaórtico médio: ≤25 ou >25 mmHg. Para obter dois grupos com número equilibrado de pacientes, esse ponto de corte foi determinado a partir do valor mediano do gradiente transaórtico médio. A avaliação de preditores de mortalidade foi realizada utilizando-se o teste de Regressão de Cox, sendo que variáveis com p<0,10 na análise univariada foram incluídas na análise multivariada. Todos os testes foram 2 caudais, e um P <0,05 foi usado para indicar estatística Todas as análises foram realizadas no pacote estatístico SPSS, versão 23 (IBM, Armonk, NY).

5 RESULTADOS

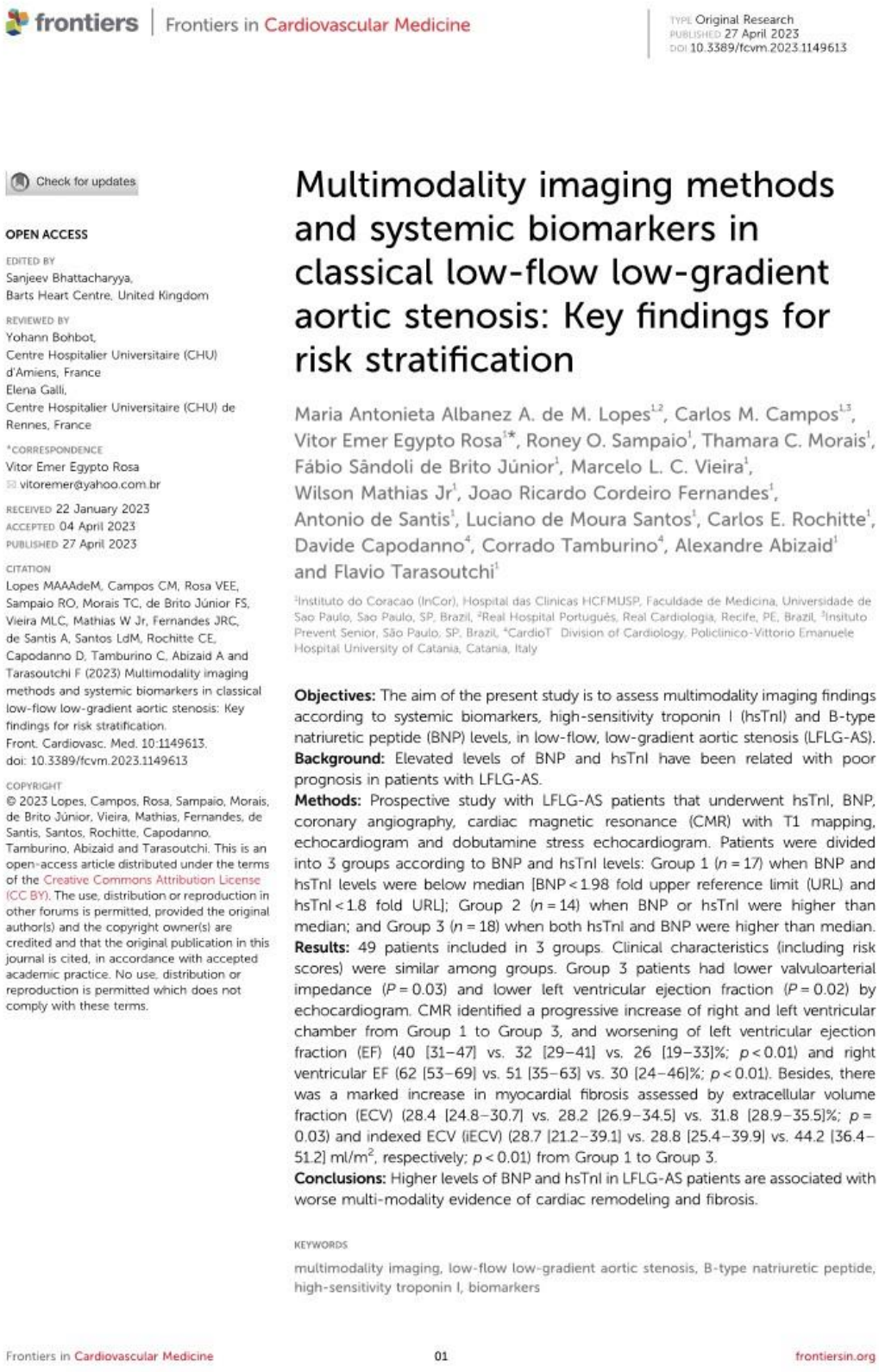
5 RESULTADOS

5.1 ARTIGO 1

Lopes MAAAM, Campos CM, Rosa VEE, Sampaio RO, Morais TC, de Brito Júnior FS, Vieira MLC, Mathias W Jr, Fernandes JRC, de Santis A, Santos LM, Rochitte CE, Capodanno D, Tamburino C, Abizaid A, Tarasoutchi F. **Multimodality imaging methods and systemic biomarkers in classical low-flow low-gradient aortic stenosis: Key findings for risk stratification.** Front Cardiovasc Med. 2023 Apr 27;10:1149613. doi: 10.3389/fcvm.2023.1149613. PMID: 37180790; PMCID: PMC10174252. (Anexo A)

Nesse artigo, de acordo com o objetivo principal desta tese, foram analisados 49 pacientes com EAo*Gradb* divididos em 3 grupos em relação ao nível de BNP e troponina I ultrassensível (hsTnI): Grupo 1 (n=17) quando BNP e os níveis de hsTnI estavam abaixo da mediana (BNP<1,98 vezes o limite superior de referência [URL] e hsTnI<2,8 vezes o URL); Grupo 2 (n=14) quando BNP ou hsTnI foram maiores que mediana; e Grupo 3 (n=18) quando tanto o hsTnI quanto ao BNP foram maiores que a mediana. A RMC identificou um aumento progressivo dos ventrículos direito e esquerdo do Grupo 1 para o Grupo 3, além de piora progressiva da FEVE. Também foi evidenciado um aumento acentuado na fibrose miocárdica avaliada pelo ECV e iECV do Grupo 1 para o Grupo 3. Não houve associação da progressão dos grupos com os parâmetros de RC do VE.

Figura 3 – Artigo1: Multimodality imaging methods and systemic biomarkers in classical low-flow low-gradient aortic stenosis: Key findings for risk stratification



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Multimodality imaging methods and systemic biomarkers in classical low-flow low-gradient aortic stenosis: Key findings for risk stratification

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Objectives: The aim of the present study is to assess multimodality imaging findings according to systemic biomarkers, high-sensitivity troponin I (hsTnI) and B-type natriuretic peptide (BNP) levels, in low-flow, low-gradient aortic stenosis (LFLG-AS).
Background: Elevated levels of BNP and hsTnI have been related with poor prognosis in patients with LFLG-AS.
Methods: Prospective study with LFLG-AS patients that underwent hsTnI, BNP, coronary angiography, cardiac magnetic resonance (CMR) with T1 mapping, echocardiogram and dobutamine stress echocardiogram. Patients were divided into 3 groups according to BNP and hsTnI levels: Group 1 ($n = 17$) when BNP and hsTnI levels were below median [BNP < 1.98 fold upper reference limit (URL) and hsTnI < 1.8 fold URL]; Group 2 ($n = 14$) when BNP or hsTnI were higher than median; and Group 3 ($n = 18$) when both hsTnI and BNP were higher than median.
Results: 49 patients included in 3 groups. Clinical characteristics (including risk scores) were similar among groups. Group 3 patients had lower valvuloarterial impedance ($P = 0.03$) and lower left ventricular ejection fraction ($P = 0.02$) by echocardiogram. CMR identified a progressive increase of right and left ventricular chamber from Group 1 to Group 3, and worsening of left ventricular ejection fraction (EF) (40 [31–47] vs. 32 [29–41] vs. 26 [19–33]%; $p < 0.01$) and right ventricular EF (62 [53–69] vs. 51 [35–63] vs. 30 [24–46]%; $p < 0.01$). Besides, there was a marked increase in myocardial fibrosis assessed by extracellular volume fraction (ECV) (28.4 [24.8–30.7] vs. 28.2 [26.9–34.5] vs. 31.8 [28.9–35.5]%; $p = 0.03$) and indexed ECV (iECV) (28.7 [21.2–39.1] vs. 28.8 [25.4–39.9] vs. 44.2 [36.4–51.2] ml/m^2, respectively; $p < 0.01$) from Group 1 to Group 3.
Conclusions: Higher levels of BNP and hsTnI in LFLG-AS patients are associated with worse multi-modality evidence of cardiac remodeling and fibrosis.

KEYWORDS
multimodality imaging, low-flow low-gradient aortic stenosis, B-type natriuretic peptide, high-sensitivity troponin I, biomarkers

Introduction

Low-flow, low-gradient aortic stenosis (LFLG-AS) with reduced ejection fraction is the term used to identify patients with aortic valve area (AVA) ≤ 1.0 cm^2 associated with low mean transaortic gradient (<40 mmHg) and reduced left ventricular ejection fraction (LVEF < 50%) (1). This entity is described in up to 10% of the aortic stenosis population (1, 2). It has been shown that classical LFLG-AS patients have poor outcomes with conservative management but are also considered being at high risk of events for both transcatheter and surgical aortic valve replacement (3).

Imaging methods have fundamental role in the diagnosis and management of valvular heart disease. Cardiac magnetic resonance (CMR) can provide detailed information about the myocardial disease. CMR assesses the impact of high afterload pressures on myocardial function and can quantify extracellular volume expansion (ECV) using T1 mapping (4).

Circulating biomarkers are commonly used in clinical decision making for diagnosing, risk stratification and management of various cardiovascular diseases (5). Several studies have showed strong relationships between the B-type natriuretic peptide (BNP) level and symptom development, left ventricular (LV) hypertrophy, LV function, severity of aortic stenosis and mortality (6). Although high-sensitivity troponin I (hsTnI) plasma levels are not mentioned in current guideline recommendations, combined measure of BNP and hsTnI have been recognized as predictors of adverse outcomes in LFLG-AS patients (7–9).

Although both biomarkers and imaging methods have shown prognostic implications, literature remains scarce on the relationship between them in LFLG-AS patients. Therefore, the aim of the present study was to assess the relationship between multimodality imaging methods and cardiac biomarkers (BNP and hsTnI) to help clarify the diagnosis and prognosis of patients with LFLG-AS.

Methods

Study population

Patients with symptomatic LFLG-AS defined as mean gradient < 40 mmHg and indexed AVA ≤ 0.6 cm^2/m^2, with reduced LVEF (< 50%) were enrolled ($n = 49$; **Figure 1**). Exclusion criteria were: (I) previous valve surgery, (II) severe aortic regurgitation, (III) CMR incompatible devices or contraindications to gadolinium, (IV) severe primary mitral valve disease, (V) nonischemic cardiomyopathies, or (VI) diagnosis of pseudo-severe aortic stenosis on dobutamine stress echocardiogram. The study protocol was reviewed and approved by the local institutional ethics committee. All patients provided written informed consent.

Study protocol

All of the patients with LFLG-AS underwent dobutamine stress echocardiogram, transthoracic echocardiography, T1 mapping and late gadolinium enhancement (LGE) CMR, and laboratory tests, including hsTnI (ADVIA Centaur TnI-Ultra; Siemens Healthcare Diagnostics, Tarrytown, NY; reference value: 0.015 ng/ml) and

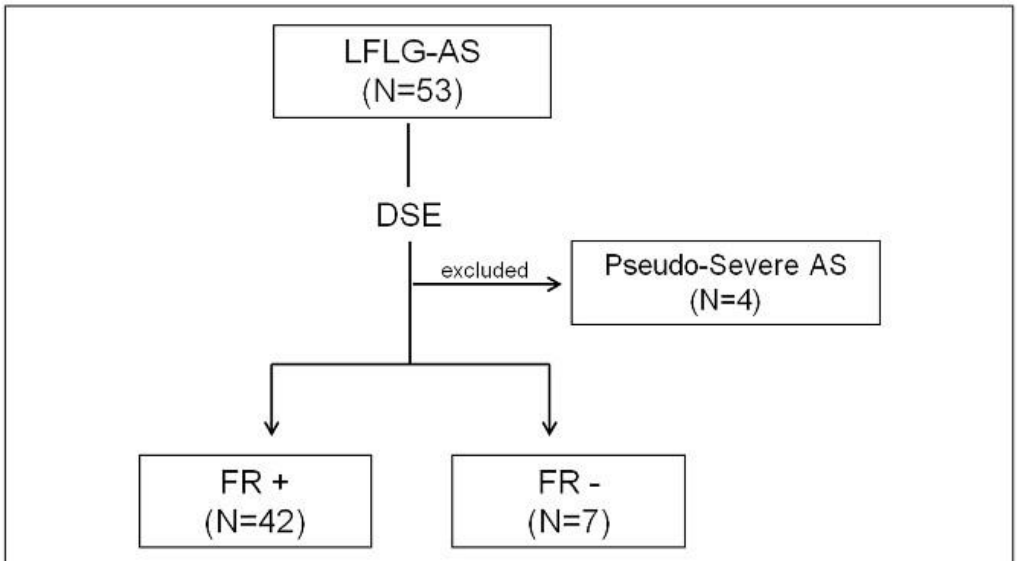

FIGURE 1
Study flowchart. Selection of the study population. AS, aortic stenosis; DSE, dobutamine stress echocardiography; FR, flow reserve; and LFLG, low-flow, low-gradient.

BNP (ADVIA Centaur; Siemens Medical Solutions Diagnostic, Los Angeles, CA, reference value: 200 pg/ml). Patients were divided in 3 groups according to BNP and hsTnI levels:

- Group 1 (low biomarkers group): Patients with both BNP *and* hsTnI below the median value (BNP < 395 pg/ml [< 1.98 folds upper reference value] *and* hsTnI < 0.042 ng/ml [<2.8 folds]);
- Group 2 (intermediate biomarkers group): Patients with either BNP *or* hsTnI higher or equal than the median value (BNP ≥ 395 pg/ml [≥1.98 folds upper reference value] or hsTnI ≥ 0.042 ng/ml [≥2.8 folds upper reference value]);
- Group 3 (high biomarkers group): Patients with *both* BNP and hsTnI higher or equal than the median value (BNP ≥ 395 pg/ml [≥1.98 folds upper reference value] and hsTnI ≥ 0.042 ng/ml [≥2.8 folds upper reference value]).

Coronary angiography

All patients underwent coronary angiography, and coronary artery disease was defined as the presence of >50% luminal stenosis on major epicardial coronary arteries.

Echocardiography

All transthoracic Doppler-echocardiographic exams were analyzed in a central echocardiography laboratory at our Institution. All echocardiographic parameters measured using the methods recommended by the American Society of Echocardiography (10, 11). Dobutamine stress echocardiogram was performed as previously described using a commercially available ultrasound system (Vivid 9; GE Healthcare, Milwaukee, WI) (12). Briefly, the dobutamine infusion protocol consisted of 5-min increments of 2.5 to 5 μg/kg per minute up to a maximum dosage of 20 μg/kg per minute. A minimum of 3 consecutive cycles were recorded. In patients with flow reserve (defined as the percentage increase in stroke volume index ≥20%), the presence of true-severe aortic stenosis was defined by a mean transaortic gradient ≥ 40 mmHg with an AVA ≤1.0 cm^2 during dobutamine stress (12). In patients without flow reserve, aortic valve calcium score on computed tomography was used to confirm aortic stenosis severity (≥1,300 AU in women and ≥2000AU in men) (12–14). All flow reserve echocardiographic

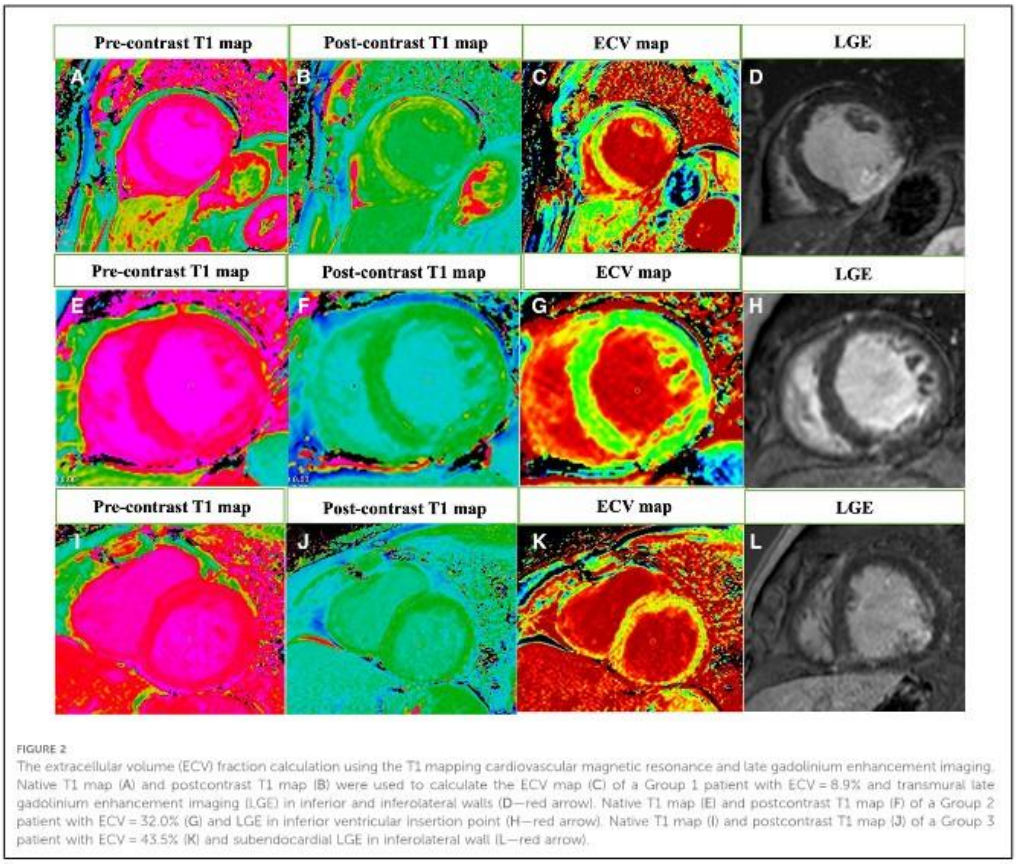

FIGURE 2
The extracellular volume (ECV) fraction calculation using the T1 mapping cardiovascular magnetic resonance and late gadolinium enhancement imaging. Native T1 map (A) and postcontrast T1 map (B) were used to calculate the ECV map (C) of a Group 1 patient with ECV = 8.9% and transmural late gadolinium enhancement imaging (LGE) in inferior and inferolateral walls (D—red arrow). Native T1 map (E) and postcontrast T1 map (F) of a Group 2 patient with ECV = 32.0% (G) and LGE in inferior ventricular insertion point (H—red arrow). Native T1 map (I) and postcontrast T1 map (J) of a Group 3 patient with ECV = 43.5% (K) and subendocardial LGE in inferolateral wall (L—red arrow).

parameters were measured in a mean of 10 consecutive heart beats in patients with atrial fibrillation (11). Valvulararterial impedance was calculated using the following formula: (systolic arterial pressure + mean transaortic gradient)/stroke volume index. Left ventricular global longitudinal strain was measured by speckle tracking with dedicated commercial software (EchoPAC V 110.0.x; GE Healthcare, Milwaukee, WI) as previously reported (15). Global longitudinal strain data were expressed in absolute value (|%|) and were defined as the mean of longitudinal strain of the 2-chamber, 3-chamber, and 4-chamber apical view.

CMR protocol

All patients underwent CMR using a clinical 1.5-T CMR scanner (Achieva; Philips, Best, the Netherlands), and the analyses were performed by 2 investigators in a central CMR core laboratory at our Institution, blinded to clinical and echocardiographic parameters, as previously described (12). LGE images were acquired using a phase-sensitive inversion recovery sequence and the inversion time was individually determined to null the normal myocardial signal. LGE quantification was obtained with thresholding technique by 3 standard deviations above remote myocardium. T1 mapping MOLLI images were acquired pre and 15 min after gadolinium injection in 3 short-axis images (basal, mid-ventricular, and apical levels). T1 mapping analysis were performed including and excluding areas of LGE. Endocardial and epicardial delineations, including LGE areas, were manually traced in all 3 short-axis images, for global myocardial T1 calculation (pre- and post-gadolinium images). Subendocardial and transmural LGE areas were manually excluded using a region of interest (ROI) delimitation tool, for non-enhanced myocardium T1 calculation

TABLE 1 Baseline clinical and laboratory data of the study population.

	Group 1 Low biomarkers ($n = 17$)	Group 2 Intermediate biomarkers ($n = 14$)	Group 3 High Biomarkers ($n = 18$)	P value*
Age, years	66.65 ± 6.6	71.07 ± 9.6	65.44 ± 8.5	0.16
Body surface area, m^2	1.82 ± 0.16	1.77 ± 0.12	1.82 ± 0.17	0.42
Female gender	6 (35.3)	3 (21.4)	2 (11.1)	0.22
Diabetes Mellitus	7 (41.2)	6 (42.9)	5 (27.8)	0.61
Hypertension	14 (82.4)	10 (71.4)	10 (55.6)	0.22
Atrial fibrillation	4 (23.5)	3 (21.4)	5 (27.8)	0.91
NYHA III/IV	7 (14.3)	9 (18.4)	12 (24.5)	0.26
Angina	2 (11.8)	6 (42.9)	4 (22.2)	0.36
Coronary artery disease	6 (35.3)	5 (35.7)	7 (38.9)	0.97
One vessel	2 (11.8)	2 (14.3)	0 (0)	0.39
Two vessels	1 (5.9)	2 (14.3)	2 (11.1)	0.39
Three vessels	3 (17.6)	1 (7.1)	5 (37.8)	0.39
Previous CABG	3 (17.6)	1 (7.1)	3 (16.7)	0.66
EuroSCORE II, %	2.82 ± 2.5	3.36 ± 1.8	4.03 ± 3.3	0.31
STS, %	2.87 ± 2.1	3.76 ± 2.1	3.16 ± 1.9	0.26
Medications				
ACE inhibitor or ARB	16 (94.1)	10 (71.4)	9 (50)	<0.01[‡]
Beta blockers	12 (70.6)	4 (28.6)	10 (55.6)	0.06
Antiplatelets	13 (76.5)	10 (71.4)	8 (44.4)	0.11
Diuretics	14 (82.4)	12 (85.7)	17 (94.4)	0.50
Statins	16 (94.1)	9 (64.3)	11 (61.1)	0.03
Digital	2 (11.8)	3 (21.4)	4 (22.2)	0.68
Oral anticoagulation	4 (23.5)	2 (14.3)	6 (33.3)	0.45
Electrocardiogram				
Left Bundle Branch Block	5 (29.4)	5 (35.7)	3 (16.7)	0.44
Right Bundle Branch Block	0 (0)	2 (14.3)	1 (5.6)	0.19
Laboratory data				
Hematocrit, %	39.4 ± 10.3	40.6 ± 5.0	41.6 ± 6.6	0.70
C reactive protein, pg/ml	3.16 (1.14–3.12)	9.54 (2.43–11.47)	13.04 (1.41–14.02)	0.12
eGFR, ml/min	67.7 ± 22.7	47.0 ± 17.0	50.7 ± 22.5	0.01[†]
CKD (eGFR <60 ml/min)	3 (17.6)	6 (42.9)	9 (50)	0.12
High-sensitivity troponin I, ng/ml	0.01 (0.0085–0.02)	0.12 (0.03–0.17)	0.16 (0.05–0.16)	<0.01[*†]
B-type natriuretic peptide, pg/ml	148.87 (66–200)	498.35 (109.25–679.5)	1,245.94 (583.75–1,608)	<0.01[‡§]

Values are mean ± standard deviation, median (interquartile range), or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

*Overall P value among groups: group 1, group 2 and group 3.

[†]Significant difference ($P < 0.05$) between group 1 vs. group 2.

[‡]Significant difference ($P < 0.05$) between group 1 vs. group 3.

[§]Significant difference ($P < 0.05$) between group 2 vs. group 3.

(pre- and post-gadolinium images). An additional ROI was placed at the center of the LV cavity, for blood pool T1 calculation. In patients with atrial fibrillation, T1 mapping image acquisition was repeated, and an average of T1 values was calculated in both pre- and post-gadolinium sequences. Besides, all these patients had controlled heart rate (60–90 bpm) at the time of CMR (16).The extracellular volume fraction (ECV) (for global and for non-enhanced myocardium) was calculated using a correction for blood hematocrit (collected on the same day of CMR acquisition), as follows: ECV = (1−hematocrit) * (ΔR1 myocardium/ΔR1blood pool). Where ΔR1 = (1/T1post-gadolinium − 1/T1pre-gadolinium). We also calculated the indexed ECV (iECV) of non-enhanced myocardium using the following formula: ECV × indexed LV end-diastolic myocardial volume, as previously described (4) (**Figure 2**).

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range) and Shapiro-Wilk test was used to test the normality of variables. Categorical variables were presented as percentages. Log transformation was applied to normalize data distribution. Kruskall-Wallis, or ANOVA test was applied for continuous variables, and chi-square test and Fisher exact test was applied for categorical variables, as appropriate. The *post hoc* analysis was performed with Tukey test. Spearman correlation coefficients were used to evaluate data correlation. ROC curve was applied for BNP and hsTnI to discriminate increase in ECV, iECV, left ventricle end-systolic volume index (LVESVi), left ventricle end-diastolic volume index (LVEDVi), right ventricle end-systolic volume index (RVESVi), right ventricle end-diastolic volume index (RVEDVi), right ventricle ejection fraction (RVEF), and left ventricle ejection fraction (LVEF), using cutoff values established in the literature (ECV > 28% (17); iECV > 22.5 ml/m^2; LVESVi ≥ 29 ml/m^2 for women and ≥36 ml/m^2 for men; LVEDVi ≥ 74 ml/m^2 for women and ≥85 ml/m^2 for men; RVESVi ≥ 33 ml/m^2 for women and ≥43 ml/m^2 for men; RVEDVi ≥ 77 ml/m^2 for women and ≥93 ml/m^2 for men; RVEF < 55%; and LVEF < 55% (4, 18). All tests were 2 tailed, and a $P < 0.05$ was used to indicate statistical significance. All analyses were conducted using the statistical package SPSS, version 23 (IBM, Armonk, NY).

Results

Baseline patients data

The main clinical and laboratory data are shown in **Table 1**. Among the 49 patients included in the present study, the mean age was 67.4 ± 8.4 years, 38 patients (77%)

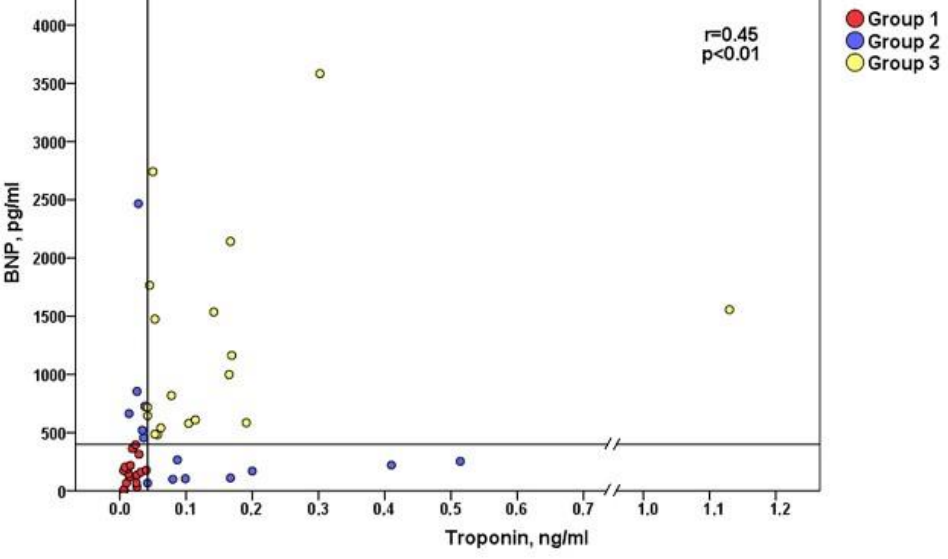

FIGURE 3
Correlation between B-type natriuretic peptide (BNP) and troponin I (hs-TnI). Groups were divided according to biomarkers median levels: Group1 patients (red dots) with BNP and hs-TnI below median; Group 2 patients (blue dots) with BNP or hs-TnI above median; and Group 3 patients (yellow dots) with both BNP and hs-TnI above median. *r = Spearman correlation coefficient.

were male, 34 (69%) had hypertension, 18 (37%) had diabetes, and 18 (37%) had coronary artery disease. The mean STS score was 3.24 ± 2.08% and the mean EuroSCORE II was 3.39 ± 2.66%.

Seventeen patients were in the low biomarkers group (Group 1), 14 in the intermediate (Group 2) and 18 in the high biomarkers group (Group 3). Overall, the baseline clinical characteristics among groups are in Table 1. The baseline characteristics are similar among 3 groups. One exception is the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blocker and statin. Also, estimated glomerular filtration rate was also different between groups (67.7 ± 22.7 vs. 47.0 ± 17.0 vs. 50.7 ± 22.5 ml/min, respectively; $p = 0.01$) with significant difference between groups 1 and 2 ($p = 0.02$ for *post hoc* test). As shown in Figure 3, hsTnI and BNP had positive correlation ($r = 0.450$, $p < 0.01$). Baseline characteristics according isolated BNP and hsTnI tertiles are shown in Supplementary Tables S1, S2, respectively.

Baseline echocardiography and echocardiographic stress data

Table 2 depicts echocardiographic findings at baseline. Overall, the median LVEF was 34% [28–41], the median AVA was 0.88 [0.70–0.96] cm^2, and the mean transaortic gradient was 25 ± 7 mmHg. At baseline echocardiogram, we found LVEF (37.0 [32.5–43.5] vs. 35.5 [28.0–40.8] vs. 28.0 [22.0–37.5]%, respectively; $p = 0.02$), lower in group 3 compared to group 1 ($p = 0.01$ for *post hoc* analysis), and valvuloarterial impedance (5.2 [4.8–5.5] vs. 5.7 [5.0–6.6] vs. 4.8 [4.4–5.3] mmHg/ml/m^2, respectively; $p = 0.03$), with significant difference between groups 2 and 3 ($p = 0.02$ for *post hoc* analysis). Interestingly, there were no significant difference regarding the presence of flow reserve between the groups (76.5% vs. 100.0% vs. 88.2%, respectively; $p = 0.07$). Baseline echocardiography and echocardiographic stress data according isolated BNP and hsTnI tertiles are shown in Supplementary Tables S3, S4, respectively. Among patients with no FR, the

TABLE 2 Baseline echocardiography and dobutamine stress echocardiography data.

	Group 1 Low biomarkers ($n = 17$)	Group 2 Intermediate biomarkers ($n = 14$)	Group 3 High biomarkers ($n = 18$)	*P* value*
Baseline Echocardiography				
Aortic root, mm	33.0 (29.0–37.0)	31.5 (30.0–34.25)	32.0 (30.0–35.5)	0.92
Left atrium, mm	45.0 ± 5.9	46.0 ± 5.5	50.0 ± 6.8	0.06
Interventricular septum, mm	11.0 ± 1.9	11.2 ± 2.9	11.1 ± 1.7	0.98
Posterior wall, mm	10.0 (9.0–11.0)	11.0 (9.75–12.0)	10.0 (9.5–11.0)	0.55
LVEDV, mm	56.82 ± 5.60	58.42 ± 7.10	60.66 ± 7.60	0.26
LVESV, mm	44.82 ± 6.50	45.71 ± 6.50	49.88 ± 8.90	0.13
LVEF, %	37.0 (32.5–43.5)	35.5 (28.0–40.8)	28.0 (22.0–37.5)	0.02†
LV mass, g	136.90 ± 26.30	148.78± 28.40	167.72± 65.90	0.14
Stroke volume index, ml/m^2	33.5 (31.0–44.8)	31.5 (27.8–39.3)	37.0 (29.0–42.9)	0.50
Aortic valve area, cm^2	0.87 (0.80–1.00)	0.81 (0.65–0.95)	0.82 (0.70–0.95)	0.37
Aortic valve area index, cm^2/m	0.48 ± 0.10	0.45 ± 0.00	0.44 ± 0.00	0.51
Peak transaortic gradient, mmHg	41.76 ± 13.60	45.92 ± 12.30	42.66 ± 13.10	0.66
Mean transaortic gradient, mmHg	24.29 ± 8.90	27.14 ± 6.50	25.00 ± 8.00	0.60
Moderate/severe functional mitral regurgitation	6.0 (35.3)	5.0 (35.7)	6.0 (33.3)	0.98
Moderate/severe functional tricuspid regurgitation,	3.0 (17.6)	2.0 (14.3)	2.0 (11.1)	0.85
Systolic pulmonary artery pressure, mmHg	41.4 ± 12.0	46.0 ± 11.0	43.8 ± 9.9	0.70
Valvuloarterial impedance, mmHg/ml/m^2	5.2 (4.8–5.5)	5.7 (5.0–6.6)	4.8 (4.4–5.3)	0.03‡
Global longitudinal strain, [−]%	10.29 ± 2.40	10.43 ± 3.20	8.98 ± 2.20	0.25
Dobutamine Stress Echocardiography				
Basal aortic valve area, cm^2	0.90 (0.78–1.05)	0.80 (0.75–0.89)	0.90 (0.60–1.00)	0.21
Peak stress aortic valve area, cm^2	0.98 (0.79–1.40)	0.86 (0.80–1.00)	0.84 (0.67–1.00)	0.89
Basal mean transaortic gradient, mmHg	25.69 ± 8.10	28.31 ± 8.60	26.00 ± 8.90	0.68
Peak stress mean gradient, mmHg	37.37 ± 11.50	38.77 ± 9.70	44.00 ± 21.60	0.63
Basal stroke volume index, ml/m^2	34.84 ± 6.60	30.67 ± 9.40	35.02 ± 21.40	0.77
Peak stress stroke volume index, ml/m^2	41.47 ± 7.10	40.36 ± 15.10	36.63 ± 7.80	0.56
Presence of flow reserve	13 (76.5)	14 (100.0)	15 (88.2)	0.07

Values are mean ± standard deviation, median (interquartile range), or n (%). LV means left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; and LVESV, left ventricular end-systolic volume.
*Overall *P* value among groups: group 1, group 2 and group 3.
†Significant difference ($P < 0.05$) between group 1 vs. group 3.
‡Significant difference ($P < 0.05$) between group 2 vs. group 3.

severity of AS was assessed by computed tomography in all patients, and the median valve calcium score was 1,885 (1,291–5,875) AU.

Cardiac magnetic resonance imaging

The CMR at baseline demonstrated various differences according to biomarkers levels groups (Table 3, Figures 4, 5). There was an increase in right and LV (systolic and diastolic) volumes from Group 1 to Group 3 (Figures 5A–D). Consequently, there was a deterioration of ejection fraction of both right and LV as biomarkers pattern worsened (Figures 4C, D). There were also differences in the groups regarding iECV (28.7 [21.2–39.1] vs. 28.8 [25.4–39.9] vs. 44.2 [36.4–51.2] ml/m^2, respectively; overall $p < 0.01$; with *post hoc* $p < 0.01$ between groups 1 and 3 and *post hoc* $p = 0.04$ between groups 2 and 3) (Figure 4A) and ECV including delayed-enhancement images (28.4 [24.8–30.7] vs. 28.2 [26.9–34.5] vs. 31.8 [28.9–35.5]%, respectively; overall $p = 0.03$; with *post hoc* $p = 0.02$ between groups 1 and 3) (Figure 4B). Baseline CMR imaging data according isolated BNP and hsTnI tertiles are shown in Supplementary Tables S5, S6, respectively.

Accuracy of BNP and hsTnI in the assessment of cardiac repercussion

Both isolated BNP and hsTnI demonstrated excellent accuracy capacity to detect increase in iECV, LVESVi and LVEF (Figures 6B,C,H, respectively), and moderate capacity to detect increase in ECV, LVEDVi and RVEF (Figures 6A,D,G, respectively). BNP also had excellent discriminative capacity to detect increase in RVESVi and RVEDVi, however, hsTnI had only moderate capacity (Figures 6E,F, respectively).

Discussion

The main findings of the present study can be summarized as follows: (1) In LFLG-AS patients, group classification according to BNP and hsTnI levels was associated with progressive worsening of imaging parameters of bi-ventricular remodeling and LV fibrosis by CMR; (2) the elevation of BNP and hsTnI was also associated with worse echocardiographic LVEF despite reduction on valvuloarterial impedance; (3) both BNP and hsTnI demonstrated good discriminative capacity to detect increase in LV parameters of function and fibrosis; (4) higher levels of BNP and hsTnI were not associated with flow reserve parameters.

Patients with LFLG-AS correspond to 5%–10% of patients with AS (1). They also represent a more challenging subgroup of AS patients both from a diagnostic and prognostic point of view. Previous series have shown high surgical mortality with an even worse prognosis with conservative therapy (19–22). Transcatheter aortic valve replacement (TAVR) is an attractive alternative due to its less invasive profile. It is associated with good short-term outcomes in LFLG-AS patients, however with a high 2-year mortality (23). There is a lack of prospective studies comparing surgical and TAVR in LFLG-AS, hindering prognostic stratification and risk assessment.

TABLE 3 Baseline cardiac magnetic resonance data.

	Group 1 Low biomarkers ($n = 17$)	Group 2 Intermediate biomarkers ($n = 14$)	Group 3 High biomarkers ($n = 18$)	*P* value*
RVEDV index, ml/m^2	58.8 (48.2–65.6)	59.0 (50.6–82.5)	81.0 (59.3–100.8)	0.03†
RVESV index, ml/m^2	24.7 (14.5–31.0)	32.0 (20.5–38.8)	48.1 (34.6–73.8)	<0.01†
RV ejection fraction, %	62.0 (53.0–69.0)	51.0 (35.2–63.0)	30.3 (24.0–46.3)	<0.01†
LVEDV index, ml/m^2	108.7 (77.0–139.4)	103.0 (87.0–136.7)	132.3 (116.3- 167.1)	0.01†‡
LVESV index, ml/m^2	65.0 (43.0–80.7)	74.0 (57.1–93.5)	99.0 (78.3–131.0)	0.01†
LVEF, %	40.0 (31.5–47.0)	32.0 (29.0–41.5)	26.2 (19.1–33.0)	<0.01†
Aortic valve area, cm^2	0.84 ± 0.23	0.79 ± 0.22	0.89 ± 0.40	0.68
Positive transmural delayed-enhancement images	6.00 (35.30)	1.00 (7.70)	9.00 (56.30)	0.02‡
Positive mesocardial delayed-enhancement images	1.00 (5.90)	5.00 (38.50)	5.00 (31.30)	0.06
LV mass, g	187.70 ± 52.43	201.46 ± 41.58	211.55 ± 60.76	0.44
Late gadolinium enhancement mass, g	10.05 ± 13.04	8.30 ± 11.45	11.81 ± 11.91	0.52
ECV including delayed-enhancement images, %	28.4 (24.8–30.7)	28.2 (26.9–34.5)	31.8 (28.9–35.5)	0.03†
ECV without delayed-enhancement images, %	26.8 (26.2–29.3)	28.7 (26.2–32)	30.4 (28.2–33.7)	0.06
iECV, ml/m^2	28.7 (21.2–39.1)	28.8 (25.4–39.9)	44.2 (36.4–51.2)	<0.01†‡

Values are mean ± standard deviation, median (interquartile range), or *n* (%). ECV indicates extracellular volume; iECV, indexed extracellular volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; and RVESV, right ventricular end-systolic volume.

*Overall *P* value among groups: group 1, group 2 and group 3.

†Significant difference ($P < 0.05$) between group 1 vs. group 3.

‡Significant difference ($P < 0.05$) between group 2 vs. group 3.

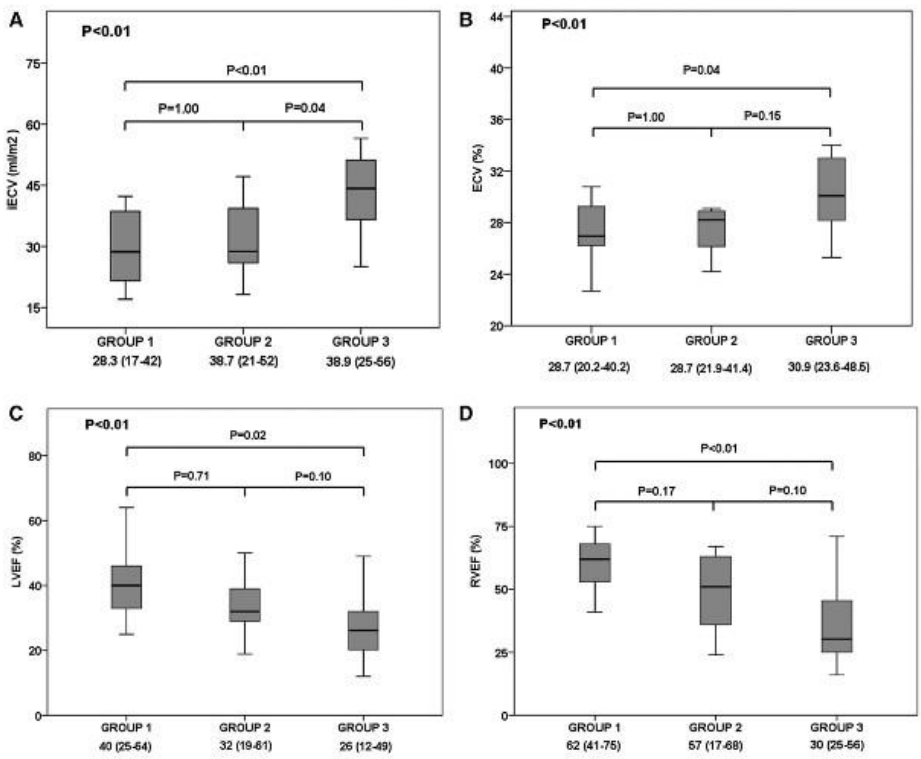

FIGURE 4
Cardiac magnetic resonance imaging's findings according to troponin I and B-type natriuretic peptide groups: Group 1 (low biomarkers group); Group 2 (intermediate biomarkers group; Group 3 (high biomarkers group). Comparison of (A) indexed extracellular volume fraction (iECV), (B) extracellular volume fraction (ECV), (C) left ventricular ejection fraction (LVEF), and (D) right ventricular ejection fraction (RVEF) between patients of group 1, 2 and 3. Solid horizontal line indicates mean value; gray box, 1SD; and vertical line, high and lowest mean values.

CMR is a novel tool in the prognostic assessment of AS patients. Focal fibrosis demonstrated by LGE has been shown to be a powerful mortality predictor (4, 24, 25). Besides, ECV and iECV are validated parameters to estimate diffuse histological fibrosis, and their association with LGE can also predict development of LV decompensation (4, 26). Compared to high-gradient AS, LFLG-AS have significantly higher ECV, iECV and LGE mass (12). Furthermore, CMR predicts mortality in LFLG-AS patients according to the number of impaired LV components as follows: presence of LGE, worsening of LV global longitudinal strain (>−11%), and increased ECV (>28%) (17). The greater the number of impaired components, the worse the outcomes, demonstrating the importance of LV functional and structural assessment in patients with LFLG-AS (17).

In this context, isolated troponin and BNP proved to be LV remodeling markers and mortality predictors, both in high-gradient AS and LFLG-AS (27–30). This predictive ability is an important issue, as assessment with biomarkers is easier and less expensive than by CMR. Thus, studies comparing both methodologies are increasingly necessary. However, data on combined LFLG-AS assessment of troponin, a marker of myocyte cell death, and BNP, a hormone released because of increased intracavitary cardiac pressure, are lacking. Dahou et al., in a recent study, evaluated the prognostic impact of combined troponin and BNP in 65 LFLG-AS patients and 33 paradoxical AS patients. It was demonstrated that the elevation of biomarkers had a prognostic impact. Furthermore, BNP alone was correlated with parameters of LV function and troponin correlated with parameters of LV geometry and function. Besides, this was an echocardiographic study that used predefined parameters of normality of biomarkers (BNP ≥ 550 pg/ml and high-sensitivity cardiac troponin T ≥ 15 ng/l) (30).

The present study is the first to evaluate the classification according to BNP and hsTnI levels as surrogated markers of progressive worsening of imaging parameters of bi-ventricular remodeling and LV fibrosis by CMR and echocardiography in a LFLG-AS cohort. As troponin assays may differ between centers,

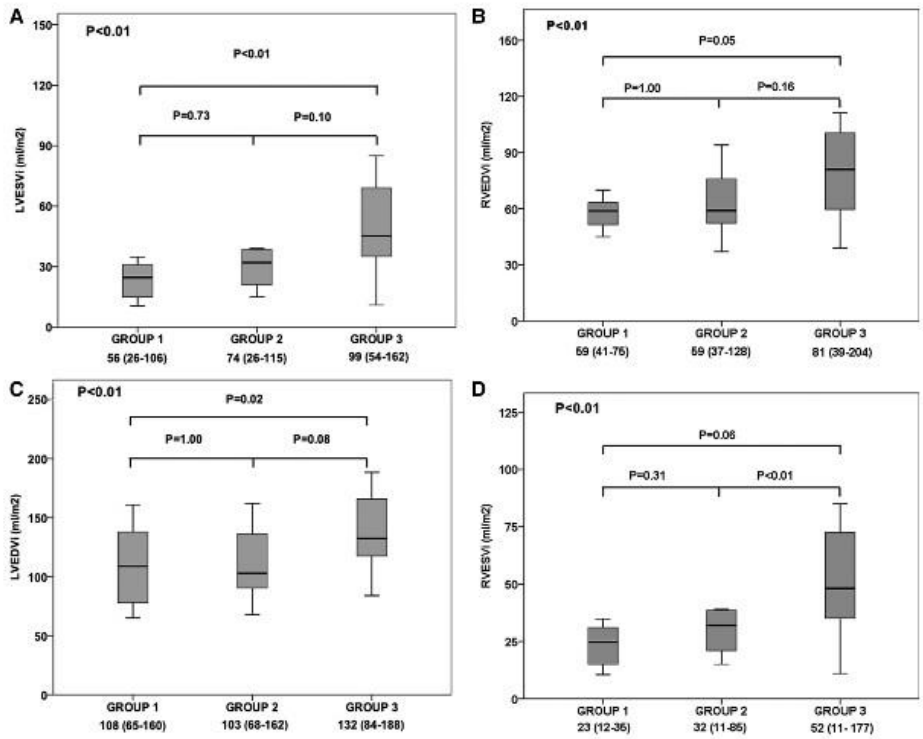

FIGURE 5
Cardiac magnetic resonance imaging's findings according to troponin I and B-type natriuretic peptide groups: Group 1 (low biomarkers group); Group 2 (intermediate biomarkers group; Group 3 (high biomarkers group). Comparison of (A) indexed left ventricular end-systolic volume (LVESVI), (B) indexed right ventricular end-diastolic volume (RVEDVI), (C) indexed left ventricular end-diastolic volume (LVEDVI), and (D) indexed right ventricular end-systolic volume (LVEDVI), between patients of group 1, 2 and 3. Solid horizontal line indicates mean value; gray box, 1SD; and vertical line, high and lowest mean values.

we chose to use folds of increase to define raises in these biomarkers (BNP above ~2 folds and hsTnI above~3 folds of reference values). Interestingly, Group 3 patients (increased BNP and hsTnI) had lower valvuloarterial impedance values and this finding can be explained by the reduction in ventricular function with a consequent tendency to reduce the mean transaortic gradient compared to the other groups.

As CMR is the gold standard for cardiac cavity and function measurements, the proposed group definition demonstrated that the progression of the groups was associated with worsening of parameters of cavity measurement and function by CMR, including interstitial fibrosis (31). ECV and iECV progression according to the groups reaffirms that the use of biomarkers correlates with marked cardiac prognostic changes, and the group definition can be used as a surrogate of structural heart disease. Indeed, isolated BNP and hsTnI had adequate capacity to detect increase in ECV and iECV, and reduced LVEF and RVEF. Therefore, as expected, the association of both elevated biomarkers defines a group with increased cardiac chambers and diffuse fibrosis, and possibly worse prognosis. Besides, T1 mapping CMR has an important role in the evaluation of differential diagnoses of cardiomyopathy, as cardiac amyloidosis. Thus, the patients included in the present study had a median ECV value of ≈30%, different of the 46.9% cutoff value used to rule out cardiac amyloidosis in Martinez-Naharro et al. study (32). These results confirm that, in our cohort, cardiac amyloidosis did not justify LFLG-AS phenotype. Also, despite similar echocardiographic pulmonary artery systolic pressure between the groups, such findings reinforce the hypothesis that RV dysfunction was a consequence of the AS excessive afterload mismatch, and not as a result of another cardiac disease.

Other important fact to mention is about flow reserve. LFLG-AS traditionally has been further divided according to the presence or absence of flow reserve on dobutamine stress echocardiography. Earlier series described poor prognosis in patients without flow reserve, suggesting that the absence of flow reserve was related to a more damaged LV (19–22). However, recent studies contradict these findings, demonstrating that such patients without flow

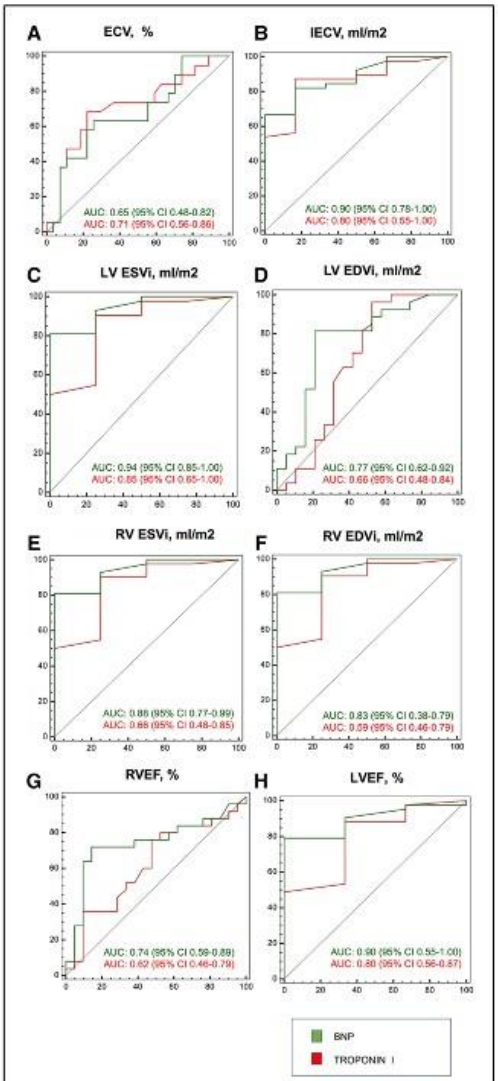

FIGURE 6
ROC curve of BNP and troponin I for cardiac magnetic resonance imaging findings. Biomarkers were tested for: (A) ECV > 28%; (B) IECV > 22.5 ml/m^2; (C) LVESVi≥29 ml/m^2 for women and ≥36 ml/m^2 for men; (D) LVEDVi ≥ 74 ml/m^2 for women and ≥85 ml/m^2 for men; (E) RVESVi ≥ 33 ml/m^2 for women and ≥43 ml/m^2 for men; (F) RVEDVi ≥ 77 ml/m^2 for women and ≥93 ml/m^2 for men; (G) RVEF < 55%; and (H) LVEF < 55% (4, 18).

reserve do not have more diffuse fibrosis compared to those with flow reserve, in addition to showing similar recovery of LVEF after valve intervention (12, 33). In agreement with such studies, there was no difference according to the group definition regarding the absence of flow reserve. Flow reserve characterization increasingly appears to be related only with AS severity confirmation and not for prognostic information.

Limitations

This is an observational single-center study, with a relatively small number of patients, albeit large for this clinical entity. The effect of interventions in these patients, serial changes in biomarkers and imaging could not be tested. Besides, cutoff values were defined according to the median biomarkers values found in our population. However, despite small sample size, there were no differences in the groups regarding comorbidities and coronary artery disease, and this classification demonstrated good discriminative capacity to detect increase in LV parameters of function and fibrosis, and the use of folds of increase can help with external validation. However, there were differences between groups regarding the use of angiotensin-converting enzyme and angiotensin receptor blocker. Despite being a confounding factor, this limitation can be explained by the fact that Group 3 patients had lower bi-ventricular ejection fraction values and, with the presence of a fix afterload generated by severe AS, they had lower tolerance to use of vasodilator drugs. Besides, although there is no evidence of prognostic improvement with guideline directed medical therapy in patients with severe AS and ventricular dysfunction, all patients were on these drugs, at maximum tolerated doses, while awaiting interventional treatment. Another limitation is that BNP and hsTnI are not specific to AS. Also, atrial fibrillation may jeopardize T1-mapping measurements. Nevertheless, incidence of atrial fibrillation was similar between the group and we carefully repeated and averaged T1-mapping measurements, in addition to performing adequate heart rate control, in order to decrease the deleterious effects of atrial fibrillation on these data (16). Although this was a prospective cohort with multimodality evaluation, future studies with a larger number of patients are still warranted to further evaluate the impact of biomarkers in cardiac remodeling in LFLG-AS patients.

Conclusions

In LFLG-AS patients, group classification according to BNP and hsTnI levels was associated with progressive worsening of imaging parameters of bi-ventricular remodeling and LV fibrosis by CMR, and worse echocardiographic LVEF despite reduction on valvuloarterial impedance. Besides, higher levels of BNP and hsTnI were not associated with flow reserve parameters.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Author contributions

ML, CC, and VR contributed to database, design of study and wrote the manuscript. LS, RS, FB, JF, AS, AA, FT wrote sectios of the manuscript. DC and CT conception of the study. TM, MV, WM, CR contributed to the images sections, and wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1149613/full#supplementary-material.

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Fonte: Lopes et al. (2023).

5.2 ARTIGO 2

Tessari FC*, Lopes MAAAM*, Campos CM, Rosa VEE, Sampaio RO, Soares FJMM, Lopes RRS, Nazzetta DC, de Brito FS Jr, Ribeiro HB, Vieira MLC, Mathias W Jr, Fernandes JRC, Lopes MP, Rochitte CE, Pomerantzeff PMA, Abizaid A, Tarasoutchi F. **Risk prediction in patients with classical low-flow, low-gradient aortic stenosis undergoing surgical intervention.** Front Cardiovasc Med. 2023 Jun 12;10:1197408. doi: 10.3389/fcvm.2023.1197408. PMID: 37378406; PMCID: PMC10291604. (Anexo B)

* Autoras compartilharam a autoria do paper.

Nesse estudo relacionado ao desfecho secundário da tese, avaliamos 41 pacientes com EAo*Gradb.* Estes foram divididos em 2 grupos em relação ao gradiente transvalvar aórtico ecocardiográfico basal (repouso): ≤ 25 mmHg (n=20) e >25 mmHg (n=21). Os principais achados foram que o gradiente transaórtico médio foi o único preditor independente de mortalidade em um seguimento mediano de 4 anos. Além disso, a RC do VE não foi preditora de eventos. Esses achados corroboram que a RC deve ser utilizada apenas na avaliação diagnóstica dos pacientes com EAo*Gradb*, e não prognóstica.

Figura 4 – Artigo 2: Risk prediction in patients with classical low-flow, low-gradient aortic stenosis undergoing surgical intervention

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Risk prediction in patients with classical low-flow, low-gradient aortic stenosis undergoing surgical intervention

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Introduction: Classical low-flow, low-gradient aortic stenosis (LFLG-AS) is an advanced stage of aortic stenosis, which has a poor prognosis with medical treatment and a high operative mortality after surgical aortic valve replacement (SAVR). There is currently a paucity of information regarding the current prognosis of classical LFLG-AS patients undergoing SAVR and the lack of a reliable risk assessment tool for this particular subset of AS patients. The present study aims to assess mortality predictors in a population of classical LFLG-AS patients undergoing SAVR.

Methods: This is a prospective study including 41 consecutive classical LFLG-AS patients (aortic valve area ≤1.0 cm^2, mean transaortic gradient <40 mmHg, left ventricular ejection fraction <50%). All patients underwent dobutamine stress echocardiography (DSE), 3D echocardiography, and T1 mapping cardiac magnetic resonance (CMR). Patients with pseudo-severe aortic stenosis were excluded. Patients were divided into groups according to the median value of the mean transaortic gradient (≤25 and >25 mmHg). All-cause, intraprocedural, 30-day, and 1-year mortality rates were evaluated.

Results: All of the patients had degenerative aortic stenosis, with a median age of 66 (60–73) years; most of the patients were men (83%). The median EuroSCORE II was 2.19% (1.5%–4.78%), and the median STS was 2.19% (1.6%–3.99%). On DSE, 73.2% had flow reserve (FR), i.e., an increase in stroke volume ≥20% during DSE, with no significant differences between groups. On CMR, late gadolinium enhancement mass was lower in the group with mean transaortic gradient >25 mmHg [2.0 (0.0–8.9) g vs. 8.5 (2.3–15.0) g; $p = 0.034$), and myocardium extracellular volume (ECV) and indexed ECV were similar between groups. The 30-day and 1-year mortality rates were 14.6% and 43.8%, respectively. The median follow-up was 4.1 (0.3–5.1) years. By multivariate analysis adjusted for FR, only the mean transaortic gradient was an independent predictor of mortality (hazard ratio: 0.923, 95% confidence interval: 0.864–0.986, $p = 0.019$). A mean transaortic gradient ≤25 mmHg was associated with higher all-cause mortality rates (log-rank $p = 0.038$), while there was no difference in mortality regarding FR status (log-rank $p = 0.114$).

Conclusions: In patients with classical LFLG-AS undergoing SAVR, the mean transaortic gradient was the only independent mortality predictor in patients with LFLG-AS, especially if ≤25 mmHg. The absence of left ventricular FR had no prognostic impact on long-term outcomes.

KEYWORDS

aortic stenosis, risk prediction, valve surgery, echocardiography, cardiac magnetic resonance

Introduction

Classical low-flow and low-gradient aortic stenosis (LFLG-AS) is a challenging clinical entity that has garnered increased recognition in recent years. It is characterized by a mismatch between a reduced aortic valve area (AVA) and a nonsevere transaortic mean gradient in patients with reduced left ventricular ejection fraction (LVEF). Recent studies report that classical LFLG-AS accounts for 5%–10% of patients with severe aortic stenosis (AS) (1, 2).

Although aortic valve replacement (AVR) is a well-established management strategy for classical LFLG-AS, studies on interventional risk prediction are largely noncontemporary and have primarily focused on transcatheter AVR (TAVR) (3–8). For instance, once considered a survival marker, left ventricular flow reserve (FR) has recently come under scrutiny for its prognostic relevance (2, 3, 7). Furthermore, earlier studies have examined a heterogeneous population of low-gradient AS, and their findings may not be entirely generalizable to classical LFLG-AS patients (5, 6, 9).

Therefore, there is currently a paucity of information regarding the current prognosis of classical LFLG-AS patients undergoing surgical AVR (SAVR) and the lack of a reliable risk assessment tool for this particular subset of AS patients. The present study aims to assess mortality predictors in a population of classical LFLG-AS patients undergoing SAVR.

Methods

Study population and protocol

This study included a prospective cohort comprising 41 consecutive patients with classical LFLG-AS (i.e., AVA ≤1.0 cm^2, mean transaortic gradient <40 mmHg, and LVEF <50%) and SAVR indication. Exclusion criteria were (I) severe primary mitral or aortic regurgitation, (II) moderate-to-severe mitral stenosis, (III) cardiac magnetic resonance (CMR)-incompatible devices or contraindications to gadolinium-enhanced CMR, (IV) previous valve surgery, (V) nonischemic cardiomyopathies, and/or (VI) diagnosis of pseudo-severe AS on dobutamine stress echocardiography (DSE) ($n = 4$) (**Figure 1**). A dedicated electronic case report form was designed to collect baseline characteristics, procedure details, and clinical follow-up data. All patients underwent DSE, 2D and 3D transthoracic echocardiography, CMR with T1 mapping and late gadolinium enhancement (LGE) evaluation, and laboratory examination. Coronary angiography was performed in each patient, and coronary artery disease was considered in the presence of >50% luminal stenosis on the major epicardial coronary artery.

Patients were divided into groups according to the mean transaortic gradient ≤25 or >25 mmHg. In order to obtain two groups with a balanced number of patients, this cutoff was determined from the median value of the mean transaortic gradient. All-cause mortality, intraprocedural mortality, 30-day mortality, 1-year mortality, stroke, myocardial infarction, pacemaker implantation, pericardial effusion, postprocedural atrial fibrillation, and reintervention were evaluated. Written informed consent was provided from all the patients, and the study protocol was reviewed and approved by the local institutional ethics committee.

Echocardiography

All transthoracic echocardiographs were analyzed in a central echocardiography laboratory. DSE was performed as previously described (2, 10) using a commercially available ultrasound system (Vivid 9; GE Healthcare, Milwaukee, WI, United States), as rest 2D echocardiography. The presence of FR was defined as an increase in stroke volume ≥20% during DSE. True-severe AS was defined by the presence of a mean transaortic gradient ≥40 mmHg with an AVA ≤1.0 cm^2 during DSE, and pseudo-severe AS was defined by a mean transaortic gradient <40 mmHg and an AVA >1.0 cm^2. In the absence of FR, AS severity was confirmed by the computed tomography aortic valve calcium score and considered severe if ≥1,300 AU in women and ≥2,000 AU in men (11, 12). Echocardiographic parameters were measured using the methods recommended by the American Society of Echocardiography (13). Left ventricular global longitudinal strain was measured by speckle tracking with dedicated commercial software (EchoPAC V 110.0.x; GE Healthcare, Milwaukee, WI, United States), as previously reported (14). Three-dimensional echocardiography was performed using a commercially available ultrasound system (EPIQ Ultrasound, with a 5 MHz transducer; Philips, Andover, MA, United

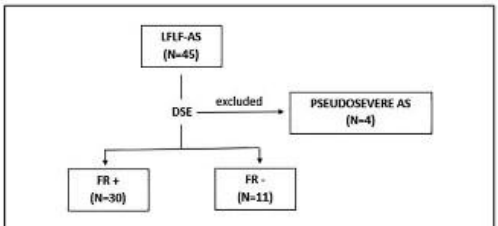

FIGURE 1
Study flowchart. Selection of the study population. All patients without flow reserve on dobutamine stress echocardiography underwent an aortic valve calcium score on computed tomography. AS, aortic stenosis; DSE, dobutamine stress echocardiography; FR, flow reserve; LFLG, low-flow, low-gradient.

States), and the parameters were analyzed according to standard recommendations (15).

CMR protocol

All CMR exams were performed using a clinical 1.5-T CMR scanner (Achieva; Philips, Best, the Netherlands), and the analyses were performed by two experienced investigators in a central CMR core laboratory at our institution. The analyses were performed using CVi42 (Circle CVi; Calgary, Canada) software, and images were acquired and coupled to the electrocardiograph during breath-hold. LGE imaging for myocardial fibrosis was performed 10 min after a bolus (0.2 mmol/kg body weight) of gadolinium-based contrast. Native T1 mapping and T1 postcontrast mapping were calculated before and 15–20 min after the intravenous injection of 0.2 mmol/kg gadolinium-based contrast, respectively, using the modified look-locker inversion-recovery sequence, performed in expiratory apnea, into three segments of the left ventricle short axis (base, mid, and apex). The T1 value was calculated as a global myocardial T1 (pre- and postgadolinium) value and excluded subendocardial and transmural fibrosis areas (segments with mid-wall LGE were included). Atrial fibrillation patients had controlled heart rates (60–90 bpm) during the exam, and T1 mapping image acquisition was repeated, taking into account the average of T1 values in both pre- and postgadolinium sequences. The extracellular volume (ECV) was calculated using the following formula: $ECV_{myo} = (1 - \text{hematocrit}) \times \Delta R1_{myo} / \Delta R1_{blood}$, where $\Delta R1 = (1/T1\ \text{precontrast} - 1/T1\ \text{postcontrast})$ (16). To calculate the indexed ECV (iECV), the following formula was used: ECV (excluding areas of focal fibrosis) × indexed left ventricular end-diastolic myocardial volume (17).

Data analysis

Continuous variables were presented as median (25th–75th percentile). Categorical variables were presented as percentages. The Mann–Whitney *U*-test was applied for continuous variables, and the Fisher exact test or χ^2 test was applied for categorical variables, as appropriate. Cox regression analysis was used to evaluate the predictors of all-cause mortality. Variables with a $p < 0.05$ in univariate analyses were entered in the multivariable model and adjusted for FR. Survival curves were estimated using the Kaplan–Meier method and compared between patient groups with the log-rank test. All tests were two-tailed, and a $p > 0.05$ was used to indicate statistical significance. All analyses were conducted using statistical package SPSS, version 20 (IBM, Armonk, NY, United States).

Results

Patient characteristics

Clinical characteristics and laboratory data are summarized in Table 1. A total of 41 patients with severe degenerative LFLG-AS were enrolled. The median age was 66 (60.0–73.5) years, with a male predominance (82.9%). Functional class III or IV by NYHA classification was present in 51.2%, 26.8% had angina, and only 3% had syncope. There was a high prevalence of comorbidities such as hypertension (68.3%), diabetes (39%), chronic kidney disease (39%), and atrial fibrillation (26.8%), and 36.6% had concomitant coronary artery disease. Almost one-third of the patients had left bundle branch block (29.3%) on the baseline electrocardiogram. The median EuroSCORE II was 2.19% (1.5%–4.78%), and the median STS was 2.19% (1.6%–3.99%). Patients were compared regarding the two-dimensional echocardiographic mean transaortic gradient. Twenty patients had a mean transaortic gradient ≤25 mmHg, and 21 patients had a mean transaortic gradient >25 mmHg. There were no differences in clinical and laboratory data regarding group definition (Table 1).

Echocardiography data

Baseline transthoracic and DSE data are summarized in Table 2. There were no differences between the groups regarding two- and three-dimensional echocardiography in terms of morphological and functional characteristics, except that patients in the mean transaortic gradient >25 mmHg group had, as expected, a higher mean transaortic gradient [33 (30–36) vs. 21 (19–23) mmHg; $p < 0.001$], peak transaortic gradient [53 (49–61) vs. 36 (30–39) mmHg; $p < 0.001$], and peak aortic valve velocity [3.64 (3.5–3.9) vs. 2.99 (2.70–3.11) m/s; $p < 0.001$]. The median stroke volume index was 34 (30–40) ml/m^2, the global longitudinal strain was 10% (8.7%–12%) [–], and the valvuloarterial impedance was 5.2 (4.7–5.7) mmHg/ml/m^2, with no difference between groups. Regarding three-dimensional echocardiography, data between groups were also similar, with a median LVEF of 31 (24–39)%, AVA of 0.83 (0.66–0.90) cm^2, and AVA index of 0.43 (0.37–0.47) cm^2/m^2.

On DSE, FR was present in most of the patients (73.2%), with no significant differences between the groups. Peak stress parameters did not differ significantly between the groups, except for the peak stress mean transaortic gradient, which was higher in the mean transaortic gradient ≤25 mmHg group [42 (33–49) vs. 32 (22–45) mmHg; $p = 0.030$]. In contrast to the 2D echocardiography evaluation, the median stroke volume index was higher in the mean transaortic gradient >25 mmHg group [32.2 (27.0–45.7) vs. 25.5 (20.2–31.2) ml/m^2, $p = 0.012$]. However, this difference was no longer observed after dobutamine infusion [39 (35–45) vs. 30.6 (28.0–38.7) ml/m^2, $p = 0.063$].

CMR data

CMR data are shown in Table 3 and were similar between the groups, except for LGE mass, which was lower in the mean transaortic gradient >25 mmHg group [2.0 (0.0–8.9) vs. 8.5 (2.3–15.0) g; $p = 0.034$]. Delayed-enhancement images showed a transmural pattern in 29.3% and a mesocardial pattern in 26.8%. Interstitial fibrosis analyses were also similar

TABLE 1 Baseline clinical and laboratory data of the study population.

Variable	Total ($n = 41$)	Mean transaortic gradient ≤25 ($n = 20$)	Mean transaortic gradient >25 ($n = 21$)	p-value
Clinical data				
Age, years	66 (60.0–73.5)	69 (61.7–73.7)	65 (57.5–73.5)	0.290
Body surface area, m^2	1.80 (1.71–1.92)	1.79 (1.72–1.92)	1.81 (1.67–1.95)	0.917
Male sex	34 (82.9)	18 (90.0)	16 (76.2)	0.410
Diabetes	16 (39.0)	9 (45.0)	7 (33.3)	0.656
Hypertension	28 (68.3)	14 (70.0)	14 (66.7)	1.000
Atrial fibrillation	11 (26.8)	7 (35.0)	4 (19.0)	0.424
Coronary artery disease	15 (36.6)	10 (50.0)	5 (23.8)	0.157
One vessel	3 (7.3)	1 (5.0)	2 (9.5)	
Two vessels	5 (12.2)	2 (9.5)	3 (15.0)	
Three vessels	7 (17.1)	1 (4.8)	6 (30.0)	
Previous CABG	6 (14.6)	4 (20.0)	2 (9.5)	0.410
EuroSCORE II, %	2.19 (1.50–4.78)	3.32 (1.72–5.25)	1.79 (1.13–3.90)	0.101
STS, %	2.19 (1.60–3.99)	3.14 (1.68–3.83)	1.90 (1.40–4.44)	0.351
Symptoms				
NYHA III/IV	21 (51.2)	11 (55.0)	10 (47.6)	0.873
Angina	11 (26.8)	6 (28.6)	5 (25.0)	1.000
Syncope	3 (7.3)	1 (5.0)	2 (9.5)	1.000
Medications				
ACE inhibitors or ARB	29 (70.7)	14 (70.0)	15 (71.4)	1.000
Beta blockers	21 (51.2)	12 (60.0)	9 (42.9)	0.432
Antiplatelets	23 (56.1)	12 (60.0)	11 (52.4)	0.860
Diuretics	35 (85.4)	15 (75.0)	20 (95.2)	0.093
Statins	29 (70.7)	12 (60.0)	17 (81.0)	0.258
Digoxin	9 (22.0)	5 (25.0)	4 (19.0)	0.719
Oral anticoagulation	11 (26.8)	7 (35.0)	4 (19.0)	0.424
ECG				
Left bundle branch block	12 (29.3)	6 (30.0)	6 (28.6)	1.000
Right bundle branch block	2 (4.9)	–	2 (9.5)	0.488
Laboratory data				
Hemoglobin, mg/dl	13.5 (12.7–14.3)	13.3 (12.5–14.3)	13.7 (12.7–14.6)	0.309
Hematocrit, %	41 (39–44)	40 (38–43)	41 (39–45)	0.160
eGFR, ml/min	55 (46–64)	48 (36–61)	59 (45–72)	0.130
CKD (eGFR < 60 ml/min)	16 (39.0)	11 (55.0)	5 (23.8)	0.084
Troponin I, ng/ml	0.043 (0.025–0.102)	0.043 (0.020–0.102)	0.045 (0.026–0.105)	0.758
B-type natriuretic peptide, pg/ml	378 (138–659)	259 (138–630)	469 (131–710)	0.739
C-reactive protein, mg/dl	2.9 (1.5–6.8)	2.6 (1.5–6.1)	3.4 (1.5–8.0)	0.771

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.
Values are median (25th–75th percentile) or n (%).
Bold values denote statistical significance.

between groups: overall ECVs including and excluding positive delayed-enhancement were 28.9% (26.8%–33.2%) and 28.7% (26.3%–31.9%), respectively, and iECV was 34.9 (24.9–40.8) ml/m^2.

Procedural data and outcomes

Procedural data and postprocedural outcomes are summarized in Table 4. The occurrence of postprocedural complications was evaluated and compared between the groups, with no statistical difference. Infection was the most frequent complication, followed by atrial fibrillation (43.9% and 19.5%, respectively). A definitive pacemaker was implanted in three (7.3%) patients; stroke and pericardial effusion both occurred in only one (2.4%) patient. Concomitant coronary artery bypass graft was performed in three patients from each group, with no statistical difference between groups. There was no ascending aortic procedure nor mitral valve intervention. Cardiopulmonary bypass time was the only variable with a difference between the groups and was lower in the patients with mean transaortic gradient >25 mmHg [60 (52–73) vs. 77 (60–100) min; $p = 0.023$]. Both 30-day and 1-year mortality rates were also similar, and there was no intraprocedural mortality.

All-cause mortality was evaluated with a median follow-up of 4.1 (0.3–5.1) years. In the univariate analysis of predictors of all-cause mortality (Table 5 and Supplementary Table S1), three variables were associated with the outcome: STS [hazard ratio

TABLE 2 Baseline two- and three-dimensional echocardiography and dobutamine stress echocardiography data.

Variable	Total ($n = 41$)	Mean transaortic gradient ≤25 ($n = 20$)	Mean transaortic gradient >25 ($n = 21$)	p-value
Baseline 2D echocardiography				
LVEF, %	35 (28–43)	34 (26–41)	38 (28–43)	0.461
LVEDD, mm	58 (55–63)	57 (53–64)	58 (55–63)	0.824
LVESD, mm	46 (40–52)	47 (38–52)	46 (40–52)	0.989
LVEDV, ml	190 (171–243)	184 (156–243)	207 (178–245)	0.289
LVESV, ml	128 (102–163)	135 (102–169)	124 (102–163)	0.968
LV mass, g/m^2	142 (128–170)	138 (129–160)	146 (119–182)	0.321
Mean transaortic gradient, mmHg	26 (21–33)	21 (19–23)	33 (30–36)	**<0.001**
Peak transaortic gradient, mmHg	41 (36–53)	36 (30–39)	53 (49–61)	**<0.001**
Peak aortic valve velocity, m/s	3.2 (2.99–3.64)	2.99 (2.70–3.11)	3.64 (3.5–3.9)	**<0.001**
PASP, mmHg	43 (34–50)	44 (32–51)	43 (35–50)	0.799
Aortic diameter, cm	33 (30–35.75)	33 (30–36.75)	32 (30–35)	0.989
Left atrium diameter, cm	48 (42.5–50)	48 (43.25–49.75)	46 (41–51)	0.927
Septum, cm	11 (9–13)	11.5 (9–13)	11 (9.5–12.5)	0.906
Posterior wall, cm	10 (9.5–12.0)	10.5 (9.0–11.7)	10 (10–12)	0.661
Aortic valve area, cm^2	0.85 (0.66–0.95)	0.88 (0.80–0.95)	0.82 (0.62–0.96)	0.758
Aortic valve area index, cm^2/m^2	0.47 (0.36–0.51)	0.47 (0.38–0.52)	0.46 (0.34–0.50)	0.383
Stroke volume index, ml/m^2	34 (30–40)	35 (31–42)	33 (30–40)	0.901
Valvuloarterial impedance, mmHg/ml/m^2	5.2 (4.7–5.7)	5.0 (4.6–5.6)	5.3 (4.8–5.8)	0.512
Global longitudinal strain ([−] %)	10 (8.7–12)	10 (9–12)	10 (6.8–12)	0.620
Moderate/severe functional mitral regurgitation	13 (31.7)	6 (30.0)	7 (33.3)	1.000
Moderate/severe functional tricuspid regurgitation	5 (12.2)	3 (15.0)	2 (9.5)	0.663
Segmental dysfunction	9 (22.0)	5 (25.0)	4 (19.0)	0.719
Diastolic dysfunction				0.502
Grade 1	8 (29.6)	5 (33.3)	3 (25.0)	
Grade 2	11 (40.7)	6 (40.0)	5 (41.7)	
Grade 3	4 (14.8)	3 (20.0)	1 (8.3)	
Baseline 3D echocardiography				
LVEF, %	31 (24–39)	31 (24–38)	35 (24–39)	0.718
LVEDV, ml	173 (150–212)	159 (148–206)	185 (166–218)	0.183
LVESV, ml	115 (87–145)	111 (84–138)	123 (90–155)	0.445
Aortic valve area, cm^2	0.83 (0.66–0.90)	0.85 (0.70–0.91)	0.70 (0.61–0.90)	0.327
Aortic valve area index, cm^2/m^2	0.43 (0.37–0.47)	0.46 (0.41–0.49)	0.41 (0.36–0.45)	0.134
Dobutamine stress echocardiography				
Flow reserve	30 (73.2)	14 (70.0)	16 (76.2)	0.925
Basal aortic valve area, cm^2	0.80 (0.72–0.96)	0.84 (0.69–0.98)	0.80 (0.73–0.95)	1.000
Peak stress aortic valve area, cm^2	0.85 (0.70–0.97)	0.89 (0.63–1.00)	0.80 (0.71–0.90)	0.443
Basal mean transaortic gradient, mmHg	29 (22–32)	22 (18–30)	31 (27–34)	**0.002**
Peak stress mean transaortic gradient, mmHg	35 (29–47)	32 (22–45)	42 (33–49)	**0.030**
Basal stroke volume index, ml/m^2	29.7 (24.6–37.7)	25.5 (20.2–31.2)	32.2 (27.0–45.7)	**0.012**
Peak stress stroke volume index, ml/m^2	36.5 (29.4–42.0)	30.6 (28.0–38.7)	39 (35–45)	0.063
Basal indexed flow rate, ml/m^2 s	101 (85–126)	94 (73–121)	118 (88–145)	0.190
Peak indexed flow rate, ml/m^2 s	137 (106–162)	106 (95–139)	143 (126–164)	0.037

DSE, dobutamine stress echocardiography; Gm, mean transaortic gradient; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PASP, pulmonary arterial systolic pressure.
Values are median (25th–75th percentile) or n (%).
Bold values denote statistical significance.

(HR): 1.253, 95% confidence interval (CI): 1.019–1.541, $p = 0.032$], 2D echocardiographic mean transaortic gradient (HR: 0.932, 95% CI: 0.882–0.984, $p = 0.011$), and C-reactive protein (HR: 1.033, 95% CI: 1.008–1.059, $p = 0.011$). However, in the multivariate analysis adjusted for FR, only 2D echocardiographic mean transaortic gradient was an independent predictor of mortality (HR: 0.908, 95% CI: 0.837–0.984, $p = 0.019$). As demonstrated in Figure 2, patients with transaortic mean gradient >25 mmHg had a lower rate of all-cause mortality during the follow-up (log-rank $p = 0.038$), while the presence of FR (Figure 3) had no impact on mortality (log-rank $p = 0.239$).

Discussion

The main findings of the present study, including patients with classical LFLG-AS undergoing SAVR, can be summarized as follows: (1) the rest transaortic mean gradient was the only independent

TABLE 3 Cardiac magnetic resonance data.

Variable	Total ($n = 41$)	Mean transaortic gradient ≤25 ($n = 20$)	Mean transaortic gradient >25 ($n = 21$)	p-value
RVEDV index, ml/m^2	60.2 (54.3–85.5)	63.5 (52.3–90.5)	59.4 (56.5–75.0)	0.629
RVESV index, ml/m^2	32.4 (20.5–44.6)	31 (18.7–49.2)	32.4 (22.3–41.9)	0.764
RV ejection fraction, %	47 (30–63)	56 (30–66)	45 (31–58)	0.206
LVEDV index, ml/m^2	115 (87–137)	111 (87–138)	120 (87–137)	0.958
LVESV index, ml/m^2	78 (56–98)	79 (49–101)	78 (57–98)	0.979
LVEF, %	32 (25–43)	34 (23–46)	31 (28–43)	0.865
Aortic valve area, cm^2	0.8 (0.6–0.9)	0.8 (0.7–0.9)	0.7 (0.6–0.9)	0.235
Peak transaortic gradient, mmHg	36 (28–63)	33 (25–50)	40 (34–81)	0.134
Mean transaortic gradient, mmHg	9 (5–13)	8 (5–11)	11 (6–17)	0.174
Positive mesocardial delayed-enhancement images	11 (26.8)	6 (30)	5 (23.8)	0.925
Positive transmural delayed-enhancement images	12 (29.3)	7 (35.0)	5 (23.8)	0.657
LV mass, g	199 (168–247)	200 (151–255)	199 (174–231)	0.927
LGE mass, g	4.9 (0.0–12.7)	8.5 (2.3–15.0)	2.0 (0.0–8.9)	0.034
ECV including positive delayed-enhancement images, %	28.9 (26.8–33.2)	29.6 (26.9–33.8)	28.7 (26.5–32.0)	0.341
ECV excluding positive delayed-enhancement images, %	28.7 (26.3–31.9)	28.9 (26.7–33.0)	27.1 (25.8–30.0)	0.291
iECV, ml/m^2	34.9 (24.9–40.8)	37.1 (26.9–41.5)	34.1 (24.8–38.7)	0.404

ECV, extracellular volume; Gm, mean transaortic gradient; iECV, indexed extracellular volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume.
Values are median (25th–75th percentile) or n (%).

TABLE 4 Procedure data and post-procedure outcomes.

Variable	Total ($n = 41$)	Mean transaortic gradient ≤25 ($n = 20$)	Mean transaortic gradient >25 ($n = 21$)	p-value
Cardiopulmonary bypass time, min	69 (55–92)	77 (60–100)	60 (52–73)	**0.023**
Cross-clamp time, min	51 (40–68)	60 (42–83)	44 (39–60)	0.099
Concomitant CABG	6 (14.6)	3 (15.0)	3 (14.3)	1.000
30-day mortality	6 (14.6)	2 (10.0)	4 (19.0)	0.663
1-year mortality	14 (43.8)	9 (45.0)	5 (41.7)	1.000
Stroke	1 (2.4)	1 (5.0)	—	0.488
Definitive pacemaker	3 (7.3)	1 (5.0)	2 (9.5)	1.000
Pericardial effusion	1 (2.4)	—	1 (4.8)	1.000
Infection	18 (43.9)	10 (50.0)	8 (38.1)	0.536
Atrial fibrillation	8 (19.5)	5 (25.0)	3 (14.3)	0.454
Reintervention	2 (4.9)	—	2 (9.5)	0.488

CABG, coronary artery bypass graft.
Values are median (25th–75th percentile) or n (%).
Bold values denote statistical significance.

TABLE 5 Univariate and multivariate analyses of predictors of all-cause mortality adjusted for flow reserve.

	HR	Univariate analysis		p-value	HR	Multivariate analysis		p-value
		95.0% CI				95.0% CI		
		Lower limit	Upper limit			Lower limit	Upper limit	
STS, %	1.253	1.019	1.541	0.032	1.157	0.927	1.444	0.197
2D echocardiographic mean transaortic gradient, mmHg	0.932	0.882	0.984	0.011	0.908	0.837	0.984	0.019
C-reactive protein, mg/dl	1.033	1.008	1.059	0.011	1.026	1.000	1.053	0.050
Flow reserve	2.594	0.759	8.866	0.129	3.103	0.728	13.217	0.126

CI, confidence interval; HR, hazard ratio.

predictor of mortality; and (2) the absence of left ventricular FR was not associated with worse outcomes in a median of 4-year follow-up.

Classical LFLG-AS affects only 5%–10% of the population with AS and represents an advanced stage of the disease, as the impaired left ventricle is unable to generate a rest high transaortic gradient. This entity is related to poor clinical outcomes, and conservative treatment has been associated with mortality rates as high as 60% in 2 years (8, 18). However, despite an increased risk for adverse outcomes even with surgical or transcatheter AVR, robust data show that aortic intervention is still beneficial

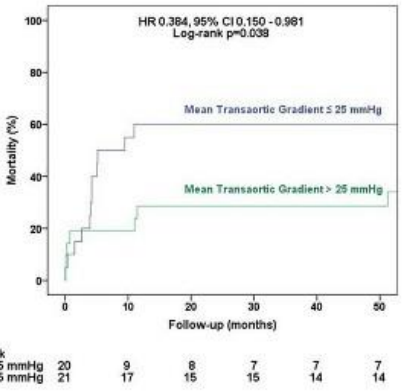

FIGURE 2
All-cause mortality according to the mean transaortic gradient. Survival curves according to the mean transaortic gradient ≤25 and >25 mmHg at rest echocardiography.

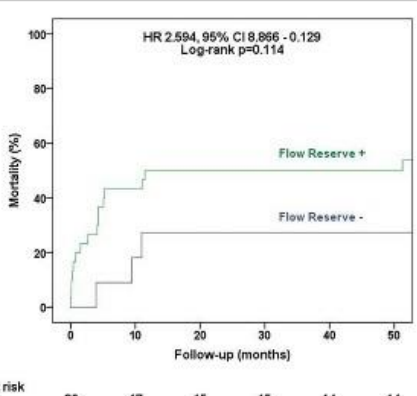

FIGURE 3
All-cause mortality according to the flow reserve status. Survival curves according to the presence or absence of flow reserve at dobutamine stress echocardiography.

compared to the traditional approach (9, 19–21). Thus, it is imperative to recognize the patients with classical LFLG-AS who will benefit from SAVR, and studies on this topic are scarce.

The absence of FR on DSE has been described for a long time as a predictor of higher mortality in patients undergoing SAVR, with an operative mortality rate of about 30% vs. 5%–7% in the presence of FR (8). However, several recent studies have tried to refute such a theory. First, a prospective study including patients with classical LFLG-AS evaluated by CMR demonstrated that the absence of FR is not related to the amount of diffuse interstitial fibrosis assessed by ECV and iECV, refuting the previous idea that patients without FR could have larger amounts of fibrosis and therefore an increased operative risk (2). Second, the TOPAS-TAVI registry demonstrated that the absence of FR was neither associated with higher mortality rates nor with lower LVEF recovery after TAVR (7). This is in line with Buchanan et al. (3), who showed that FR did not predict all-cause mortality at 30 days or 1 year after TAVR, and Sato et al. (20), who also demonstrated that FR was not a predictor of better survival (3, 20). However, Sato et al. (20) were the only ones who evaluated SAVR patients, but still, the analysis did not differentiate those who underwent TAVR procedures (20). Thus, the results of these studies may not necessarily extend to patients undergoing SAVR exclusively, as those included in the present study.

The multicentric TOPAS registry evaluated predictors of poor outcomes in patients with low-gradient AS undergoing SAVR, TAVR, or a medical approach (5, 7, 9). The TOPAS-TAVI registry demonstrated that lower hemoglobin levels, chronic obstructive pulmonary disease, and moderate-to-severe residual aortic regurgitation were predictors of poor outcomes in a 2-year follow-up after TAVR (7). Another substudy demonstrated a prognostic value of both brain natriuretic peptide (BNP) and high-sensitivity troponin T levels in patients with classical and paradoxical LFLG-AS. Moreover, when occurring simultaneously, values ≥550 pg/ml and ≥15 ng/L, respectively, were independent predictors of 2-year mortality, with higher mortality compared to the elevation of none or only one biomarker (5). A third study on patients undergoing CMR demonstrated that impaired ventricular global longitudinal strain (< −11%), higher ECV (>28%) and LGE presence were predictors of worse outcomes, with a cumulative effect on survival analysis curves (9). However, in these last two studies, the pooled data included not only classical LFLG-AS but also paradoxical AS and normal-flow low-gradient AS (5, 9). It is important to note that AS subtypes have different pathophysiologies since classical LFLG-AS is similar to heart failure with reduced ejection fraction, while the paradoxical AS has similar characteristics to heart failure with preserved ejection fraction. Thus, it is possible that mortality predictors may be different for such pathologies, and they should be studied separately.

Studies including only classical LFLG-AS patients undergoing SAVR are scarce and noncontemporary, revealing high surgical mortality but even worse outcomes with conservative medical treatment (4, 6, 8, 10, 18). Such data corroborate the indication of intervention in patients with classical LFLG-AS and the need for new risk prediction strategies. In line with previous studies, we demonstrated that a lower transaortic mean gradient was associated with worse outcomes, especially if ≤25 mmHg (6, 8). It is noteworthy that, despite there being no difference in LVEF between groups, these patients with lower gradients also presented lower cardiac output at rest and a trend to lower cardiac output at stress, as demonstrated by the basal and peak stroke volume index on DSE, which could indicate a more advanced stage of the disease and, hence, a poor prognosis.

The median value of the mean transaortic gradient (≤25 mmHg) was arbitrarily chosen as the cutoff to divide the population into two groups to obtain two groups with a comparable number of patients. Baseline characteristics were similar between them, except for LGE mass, which was higher among patients with a mean transaortic gradient ≤25 mmHg. Interestingly, different from the present study, LGE was also one of the mortality predictors described by Fukui et al.

(9), and this discrepancy could be explained by the higher LGE prevalence demonstrated by that study (67% vs. 53.7% in the present study). In addition, the different populations included in their study (i.e., paradoxical LFLG and normal-flow low-gradient AS, besides classical LFLG-AS) may also impact the results (9). Patients with a mean transaortic gradient of ≤25 mmHg had longer cardiopulmonary bypass time. However, no surgical technical issues could account for this observation, as the rates of coronary artery bypass graft procedures were similar between the groups, and patients did not undergo any other concomitant interventions. Moreover, although longer cardiopulmonary bypass time may influence prognosis and introduce potential bias in the present study, it was not deemed significant as a predictor of mortality in the analysis.

Due to its less invasive nature, TAVR appears to have a higher survival benefit than SAVR (19). The present study demonstrated that classical LFLG-AS patients undergoing SAVR had a higher 30-day mortality rate (14.6%) than that predicted by EuroSCORE II [2.19% (1.50%–4.78%)] and the STS score [2.19% (1.60%–3.99%)]. Meanwhile, the TOPAS registry demonstrated a different scenario in those patients undergoing TAVR, with a 30-day mortality rate of 3.8%, which was lower than the mortality risk predicted by the STS score and EuroSCORE II [7.7% (5.3%–12.0%) and 10.5% (5.5%–17.3%), respectively] (7). However, currently available surgical risk scores may not adequately assess the operative risk, and further studies are needed to obtain better prediction tools for this specific high-risk population.

Study limitations

This is a single-center study with a heterogeneous population and a relatively small number of patients, although large for this entity. The small number of events may have impacted the mortality prediction, despite being enough to fit the developed model (22). In this cohort, different from the former studies, only patients with classical LFLG-AS undergoing SAVR were included. Moreover, further randomized studies are needed to compare treatment strategies in classical LGLF-AS patients (TAVR vs. SAVR).

Conclusion

In patients with classical LFLG-AS undergoing SAVR, the echocardiographic rest transaortic mean gradient was the only independent predictor of mortality. In addition, the absence of left ventricular FR was not associated with worse outcomes, confirming the diagnostic rather than the prognostic value of FR.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Comite de Etica e Pesquisa do Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo—HCFMUSP (55605922.9.0000.0068). Written informed consent for participation was not required for this study in accordance with national legislation and institutional requirements.

Author contributions

FCT, FT, MAAL, and VEER contributed to the conception and design of the study. FCT, VEER, MLCV, FSdBJ, RRSL, and DCN organized the database. VEER and CMC performed the statistical analysis. FCT and VEER wrote the first draft of the manuscript. FCT, VEER, and CMC wrote sections of the manuscript. FJMMS, HBR, WM, JRCF, CER, PMAP, AA, and RRSL contributed to the interpretation of data for the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1197408/full#supplementary-material

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Fonte: Tessari et al. (2023).

6 ANÁLISE CRÍTICA

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Pacientes com EAo*Gradb* fazem parte de um subgrupo de pacientes com EAo bastante complexos e que merecem uma atenção especial tanto em relação ao diagnóstico como prognóstico. No primeiro dos presentes estudos, avaliamos pacientes EAo*Gradb,* dividindo-os em grupos de acordo com os níveis de BNP e hsTnI e comparando-os com a progressão de alterações em exames de imagem multimodal. Foram analisados 49 pacientes incluídos em 3 grupos em relação ao nível de BNP e troponina I ultrassensível (hsTnI): Grupo 1 (n=17) quando BNP e os níveis de hsTnI estavam abaixo da mediana (BNP<1,98 vezes o limite superior de referência [URL] e hsTnI<2,8 vezes o URL); Grupo 2 (n=14) quando BNP ou hsTnI foram maiores que mediana; e Grupo 3 (n=18) quando tanto o hsTnI quanto ao BNP foram maiores que a mediana. A progressão dos grupos foi associada com piora dos parâmetros de imagem de remodelamento e fibrose do ventrículo esquerdo pela RMC. A elevação do BNP e hsTnI também foi associada à pior FEVE pelo ecocardiograma. Ambos BNP e hsTnI demonstraram boa capacidade discriminativa para detectar aumento nos parâmetros de função e fibrose do ventrículo esquerdo. A progressão de ECV e iECV de acordo com os grupos reafirma que o uso de biomarcadores se correlaciona com alterações prognósticas cardíacas marcantes, e a definição de grupo pode ser usada como um substituto em relação à doença estrutural.

O segundo estudo demonstrou que o gradiente transaórtico médio, principalmente se ≤ 25 mmHg, foi o único preditor de mortalidade após intervenção em uma coorte de pacientes com EAo*Gradb* submetidos à cirurgia de troca valvar aórtica em um seguimento com mediana de 4 anos. Apesar de não haver diferença na FEVE entre os grupos (gradiente médio ≤ 25 mmHg versus > 25 mmHg), o grupo com menor gradiente médio também apresentou menor débito cardíaco em repouso e uma tendência a menor débito cardíaco no estresse, como demonstrado pelo índice de volume sistólico basal e de pico no EcoS, podendo indicar um estágio mais avançado da doença e, portanto, um mau prognóstico. Importante ressaltar que estudos incluindo apenas pacientes com EAo*Gradb* clássico submetidos à cirurgia de troca valvar são escassos e não contemporâneos, revelando elevada mortalidade, mas resultados ainda piores ocorreram com tratamento médico conservador[40].

A taxa de mortalidade de 30 dias, em nosso estudo, foi de 14,6%, maior do que a prevista pelo EuroSCORE II (2,19 [1,50-4,78]%) e STS (2,19 [1,60-3,99]%). No

entanto, os escores de risco cirúrgico atualmente disponíveis podem não avaliar adequadamente o risco operatório nesse cenário, e mais estudos são necessários para obter melhores ferramentas de previsão para esta população específica de alto risco. O registro TOPAS demonstrou um cenário diferente naqueles pacientes submetidos a TAVR, com taxa de mortalidade em 30 dias de 3,8%, menor do que o risco de mortalidade previsto pelo escore STS e EuroSCORE II (7,7 [5,3–12,0]% e 10,5 [5,5–17,3]%, respectivamente)[12]. Assim, devido à sua natureza menos invasiva, o TAVR parece ter maior benefício de sobrevivência do que cirúrgico[51].

Outro fato importante a ser mencionado é sobre a RC. EAo*Gradb*, tradicionalmente, tem sido dividido de acordo com a presença ou ausência de RC no EcoS. Estudos da primeira década dos anos 2000 descreviam um pior prognóstico em pacientes sem RC, sugerindo que a ausência de RC estava relacionada a um VE mais danificado[39, 46, 52, 53]. Além da evolução das técnicas cirúrgicas, estudos recentes não corroboram tais achados. Rosa VE et al. [25] demonstraram, em um estudo com RMC, que os pacientes sem RC não apresentam mais LGE, ECV ou iECV quando comparados àqueles com RC, sugerindo que a RC não deva ser relacionada à fibrose focal ou difusa [39]. Confirmando tais achados, o registro TOPAS-TAVI demonstrou que a recuperação da FEVE nesse grupo de pacientes não é influenciada pela presença ou ausência de RC[12]. Assim, de acordo com tais achados, nosso primeiro estudo evidenciou que a RC não se correlacionou com a progressão dos grupos de acordo com os níveis de BNP e hsTnI, enquanto no segundo estudo a RC não foi preditora de mortalidade após a intervenção valvar cirúrgica. Desta forma, a RC, cada vez mais, parece estar relacionada apenas com confirmação da gravidade EAo e não como marcador prognóstico.

7 CONCLUSÕES

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Níveis mais elevados de BNP e hsTnI em pacientes EAo*Gradb* estão associados à remodelamento cardíaco e fibrose. Além disso, o gradiente transaórtico médio foi o único preditor independente de mortalidade nesse subgrupo de pacientes, especialmente se o gradiente transaórtico médio fosse menor ou igual a 25 mmHg.

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ANEXOS

ANEXO A – Tabelas suplementares referente ao Artigo 1

Supplemental Table 1: Baseline Clinical and Laboratory Data of the Study Population According BNP Tertiles

	Low BNP (n=16)	Intermediate BNP (n=17)	High BNP (n=16)	P value*
Clinical Data				
Age, years	66.9 ± 7.0	66.5 ± 9.6	69.1 ± 8.9	0.66
Body surface area, m²	1.81 ± 0.15	1.80 ± 0.17	1.81 ± 0.14	1.00
Female gender	6 (37.5)	3 (17.6)	2 (12.5)	0.21
Diabetes Mellitus	8 (50)	5 (29.4)	5 (31.3)	0.40
Hypertension	13 (81.3)	13 (76.5)	8 (50)	0.12
Atrial fibrillation	4 (25)	5 (29.4)	3 (18.8)	0.77
Angina	5 (31.3)	4 (23.5)	3 (18.8)	0.71
Previous CABG	3 (18.8)	1 (5.9)	3 (18.8)	0.43
EuroSCORE II, %	2.95 ± 2.41	2.71 ± 1.77	4.63 ± 3.40	0.11
STS, %	3.08 ± 1.93	2.89 ± 2.10	3.81 ± 2.27	0.47
Medications				
ACE inhibitor or ARB	14 (87.5)	13 (76.5)	12 (50)	0.05
Beta blockers	9 (56.3)	7 (41.2)	10 (62.5)	0.45
Antiplatelets	12 (75)	9 (52.9)	10 (62.5)	0.42
Diuretics	14 (87.5)	14 (82.4)	15 (93.8)	0.60
Statins	15 (93.8)	10 (58.8)	11 (68.8)	0.04
Digital	3 (18.8)	4 (23.5)	2 (12.5)	0.71
Oral anticoagulation	4 (25)	5 (29.4)	3 (18.8)	0.77
Electrocardiogram				
Left Bundle Branch Block	5 (31.3)	5 (29.4)	3 (18.8)	0.68
Right Bundle Branch Block	0 (0)	1 (5.9)	2 (12.5)	0.23
Laboratory data				
Hematocrit, %	41.4 ± 1.1	40.6 ± 3.3	41.2 ± 1.2	0.89
C reactive protein, pg/ml	3.31 ± 3.44	9.26 ± 16.58	13.62 ± 18.63	0.14
CKD (eGFR <60 mL/min)	6 (37.5)	3 (17.6)	9 (56.3)	0.07
High-sensitivity troponin I, ng/ml	0.05 ± 0.02	0.12 ± 0.04	0.15 ± 0.08	0.26
B-type natriuretic peptide, pg/ml	107.5 (4-177)	408.5 (191-610)	1319 (645-2741)	<0.01†‡§

Values are mean±standard deviation, median (interquartile range), or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
*Overall *P* value among groups: group 1, group 2 and group 3.
†Significant difference (*P*<0.05) between group 1 vs group 2.
‡Significant difference (*P*<0.05) between group 1 vs group 3.
§Significant difference (*P*<0.05) between group 2 vs group 3.

Supplemental Table 2: Baseline Clinical and Laboratory Data of the Study Population According to Troponin I Tertiles

	Low Troponin I (n=16)	Intermediate Troponin I (n=17)	High Troponin I (n=16)	P value*
Clinical Data				
Age, years	67.19 ± 7.83	69.41 ± 10.01	65.69 ± 7.28	0.45
Body surface area, m²	1.82 ± 0.17	1.84 ± 0.13	1.76 ± 0.16	0.29
Female gender	5 (31.3)	2 (11.8)	4 (25)	0.37
Diabetes Mellitus	7 (43.8)	6 (35.3)	5 (31.3)	0.76
Hypertension	13 (81.3)	10 (58.8)	11 (68.8)	0.37
Atrial fibrillation	3 (18.8)	6 (35.3)	3 (18.8)	0.45
Angina	2 (12.5)	2 (11.8)	8 (50)	**0.02**
Previous CABG	2 (12.5)	3 (17.6)	2 (12.5)	0.89
EuroSCORE II, %	2.4 ± 1.7	4.1 ± 3.6	3.8 ± 2.3	0.17
STS, %	2.7 ± 1.8	3.5 ± 2.5	3.6 ± 1.9	0.41
Medications				
ACE inhibitor or ARB	15 (93.8)	10 (58.8)	10 (62.5)	0.03
Beta blockers	13 (81.3)	6 (35.3)	7 (43.8)	0.02
Antiplatelets	11 (68.8)	12 (70.6)	8 (50)	0.40
Diuretics	13 (81.3)	16 (94.1)	14 (87.5)	0.52
Statins	14 (87.5)	11 (64.7)	11 (68.8)	0.26
Digital	2 (12.5)	3 (17.6)	4 (25)	0.66
Oral anticoagulation	3 (18.8)	5 (29.4)	4 (25)	0.77
Electrocardiogram				
Left Bundle Branch Block	6 (37.5)	1 (5.9)	6 (37.5)	0.03
Right Bundle Branch Block	1 (6.3)	2 (11.8)	0 (0)	0.25
Laboratory data				
Hematocrit, %	39.6 ± 10.7	42.0 ± 5.5	41.7 ± 5.3	0.77
C reactive protein, pg/ml	6.4 ± 11.3	9.8 ± 14.0	9.8 ± 18.9	0.77
CKD (eGFR <60 mL/min)	2 (12.5)	8 (47.1)	8 (50)	0.05
High-sensitivity troponin I, ng/ml	0.015 (0.01-0.03)	0.04 (0.03-0.08)	0.17 (0.08-0.51)	<0.01†‡§
B-type natriuretic peptide, pg/ml	160 (4-854)	541 (66-2741)	580 (100-3583)	0.03†‡

Values are mean±standard deviation, median (interquartile range), or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
*Overall *P* value among groups: group 1, group 2 and group 3.
†Significant difference (*P*<0.05) between group 1 vs group 2.
‡Significant difference (*P*<0.05) between group 1 vs group 3.
§Significant difference (*P*<0.05) between group 2 vs group 3.

Supplemental Table 3: Baseline Echocardiography and Dobutamine Stress Echocardiography Data According BNP Tertiles

	Low BNP (n=16)	Intermediate BNP (n=17)	High BNP (n=16)	P Value*
Baseline Echocardiography				
Aortic root, mm	32 ± 3.4	32.8 ± 5.3	33.1 ± 5.5	0.81
Left atrium, mm	41 (38-57)	44.5 (42-47)	49.0 (39-57)	0.04‡
Interventricular septum, mm	11.3 ± 2.1	11.2 ± 2.3	10.9 ± 2.4	0.84
Posterior wall, mm	10.8 ± 1.4	10.5 ± 1.7	9.9 ± 1.9	0.32
LVEDV, mm	57.8 ± 6.3	58.1 ± 6.4	60.2 ± 8.1	0.58
LVESV, mm	45.7 ± 5.5	45.9 ± 7.6	49.2 ± 9.5	0.37
LVEF, %	38 (26-35)	35 (20-47)	28 (19-45)	0.02‡
LV mass, g	146.6 ± 27.2	153.9 ± 51.7	154.3 ± 57.5	0.87
Stroke volume index, ml/m²	36.0 ± 10.3	36.0 ± 9.4	35.4 ± 8.1	0.98
Aortic valve area, cm²	0.88 ± 0.2	0.78 ± 0.2	0.85 ± 0.2	0.23
Aortic valve area index, cm²/m	0.49 ± 0.1	0.43 ± 0.1	0.46 ± 0.1	0.22
Peak transaortic gradient, mmHg	42.4 ± 14.5	43.9 ± 11.4	43.4 ± 13.6	0.95
Mean transaortic gradient, mmHg	24.9 ± 8.5	26.2 ± 7.9	25.0 ± 7.8	0.88
Moderate/severe functional mitral regurgitation	5 (31.3)	6 (35.3)	6 (37.5)	0.72
Moderate/severe functional tricuspid regurgitation	2 (12.5)	3 (17.6)	2 (12.5)	0.89
Systolic pulmonary artery pressure, mmHg	42 ± 10.7	43.4 ± 13.5	45.4 ± 10.0	0.78
Valvuloarterial impedance, mmHg/ml/m²	5.4 ± 0.8	5.4 ± 1.0	4.8 ± 0.9	0.15
Global longitudinal strain, [−]%	10.6 ± 3.1	10.2 ± 2.5	8.7 ± 2.2	0.14
Dobutamine Stress Echocardiography				
Basal aortic valve area, cm²	0.88 ± 0.2	0.86 ± 0.2	0.81 ± 0.2	0.60
Peak stress aortic valve area, cm²	0.98 ± 0.2	0.85 ± 0.3	0.88 ± 0.2	0.32
Basal mean transaortic gradient, mmHg	27 ± 9.9	26.3 ± 8.9	26.2 ± 6.8	0.96
Peak stress mean gradient, mmHg	38.4 ± 10.2	40.2 ± 18.1	42.8 ± 19.1	0.85
Basal stroke volume index, ml/m²	35.2 ± 8.6	29.4 ± 7.2	35.7 ± 22.0	0.58
Peak stress stroke volume index, ml/m²	39.6 ± 9.4	43.5 ± 11.2	35.8 ± 8.4	0.29
Presence of flow reserve	12 (75)	14 (82.4)	9 (56.3)	0.24

Values are mean±standard deviation, median (interquartile range), or n (%). LV means left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; and LVESV, left ventricular end-systolic volume.
*Overall P value among groups: group 1, group 2 and group 3.
†Significant difference (P<0.05) between group 1 vs group 2.
‡Significant difference (P<0.05) between group 1 vs group 3.
§Significant difference (P<0.05) between group 2 vs group 3.

Supplemental Table 4: Baseline Echocardiography and Dobutamine Stress Echocardiography Data According Troponin I Tertiles

	Low Troponin I (n=16)	Intermediate Troponin I (n=17)	High Troponin I (n=16)	**P Value***
Baseline Echocardiography				
Aortic root, mm	31.8 ± 5.2	33.3 ± 5.2	32.9 ± 3.9	0.68
Left atrium, mm	44.9 ± 5.4	49.5 ± 5.5	46.9 ± 7.9	0.12
Interventricular septum, mm	10.6 ± 2.1	11.8 ± 2.3	11.1 ± 2.0	0.29
Posterior wall, mm	10.1 ± 1.8	10.9 ± 1.9	10.1 ± 1.3	0.25
LVEDV, mm	57.6 ± 5.8	58.2 ± 7.0	60.3 ± 8.6	0.51
LVESV, mm	45.6 ± 5.6	45.7 ± 8.7	49.4 ± 8.2	0.56
LVEF, %	36 ± 6.9	33.4 ± 8.6	32.7 ± 8.6	0.28
LV mass, g	132.8 ± 23.6	160.5 ± 52.2	161.1 ± 53.9	0.14
Stroke volume index, ml/m²	36.7 ± 9.5	37.2 ± 6.4	33.2 ± 11.2	0.43
Aortic valve area, cm²	0.87 ± 0.2	0.86 ± 0.2	0.78 ± 0.1	0.35
Aortic valve area index, cm²/m	0.48 ± 0.1	0.46 ± 0.1	0.44 ± 0.1	0.53
Peak transaortic gradient, mmHg	41.8 ± 13.8	43.0 ± 13.9	45.1 ± 11.5	0.78
Mean transaortic gradient, mmHg	24.1 ± 2.2	26.3 ± 2.1	25.7 ± 1.6	0.72
Moderate/severe functional mitral regurgitation	6 (37.5)	4 (23.5)	7 (43.8)	0.46
Moderate/severe functional tricuspid regurgitation,	3 (18.8)	0 (0)	4 (25)	0.03
Systolic pulmonary artery pressure, mmHg	40.9 ± 12.3	40.8 ± 8.6	48.3 ± 10.7	0.19
Valvuloarterial impedance, mmHg/ml/m²	5.15 (4.2-6.2)	5.00 (2.2-6.4)	5.3 (4.4-7.8)	0.05
Global longitudinal strain, [−]%	10.0 ± 1.9	10.2 ± 2.7	9.4 ± 3.5	0.71
Dobutamine Stress Echocardiography				
Basal aortic valve area, cm²	0.88 ± 0.2	0.85 ± 0.2	0.83 ± 0.2	0.76
Peak stress aortic valve area, cm²	1.00 ± 0.3	0.88 ± 0.2	0.84 ± 0.2	0.27
Basal mean transaortic gradient, mmHg	25.9 ± 8.3	27.2 ± 7.2	26.3 ± 10.2	0.91
Peak stress mean gradient, mmHg	37.4 ± 9.8	41.9 ± 15.0	40.5 ± 19.5	0.88
Basal stroke volume index, ml/m²	33.4 ± 7.8	31.0 ± 10.8	36.5 ± 21.8	0.67
Peak stress stroke volume index, ml/m²	40.1 ± 7.8	39.2 ± 8.4	38.5 ± 12.8	0.96
Presence of flow reserve	11 (68.8)	13 (76.5)	11 (68.8)	0.85

Values are mean±standard deviation, median (interquartile range), or n (%). LV means left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; and LVESV, left ventricular end-systolic volume.
*Overall P value among groups: group 1, group 2 and group 3.
†Significant difference (P<0.05) between group 1 vs group 2.
‡Significant difference (P<0.05) between group 1 vs group 3.
§Significant difference (P<0.05) between group 2 vs group 3.

Supplemental Table 5: Baseline Cardiac Magnetic Resonance Data According BNP Tertiles

	Low BNP (n=16)	Intermediate BNP (n=17)	High BNP (n=16)	P Value*
RVEDV index, mL/m²	58.9 (37-76)	59.4 (30-111)	92 (39-204)	0.04‡
RVESV index, mL/m²	22.5 (12-34)	31 (11-79)	65 (11-177)	<0.01‡
RV ejection fraction, %	61 (41-75)	57 (27-68)	29 (16-71)	<0.01‡
LVEDV index, mL/m²	102 (65-158)	131 (70-169)	125 (84-188)	0.02‡†
LVESV index, mL/m²	63 (26-106)	80 (48-131)	88 (54-162)	<0.01‡
LVEF, %	40 (26-64)	30 (18-45)	28 (12-49)	<0.01‡
Aortic valve area, cm²	0.80 ± 0.06	0.90 ± 0.07	0.87 ± 0.12	0.54
Positive transmural delayed-enhancement images	0.36 ± 0.13	0.33 ± 0.13	0.42 ± 0.15	0.61
Positive mesocardial delayed-enhancement images	0.14 ± 0.10	0.33 ± 0.13	0.25 ± 0.13	0.32
LV mass, g	177 ± 11	204 (16)	216 (15)	0.10
Late gadolinium enhancement mass, g	11.2 ± 3.3	9.3 ± 3.2	8.9 ± 2.3	0.79
ECV including delayed-enhancement images, %	29.5 ± 1.5	30.3 ± 1.2	31.5 ± 1.6	0.19
ECV without delayed-enhancement images, %,	29.0 ± 1.4	30.1 ± 1.1	30.8 ± 1.8	0.50
iECV, ml/m²	28.5 (17-42)	38.8 (21.6-51.2)	38.8 (25.0-56.5)	**0.01**†‡

Values are mean±standard deviation, median (interquartile range), or n (%). ECV indicates extracellular volume; iECV, indexed extracellular volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; and RVESV, right ventricular end-systolic volume.
*Overall P value among groups: group 1, group 2 and group 3.
†Significant difference (P<0.05) between group 1 vs group 2.
‡Significant difference (P<0.05) between group 1 vs group 3.
§Significant difference (P<0.05) between group 2 vs group 3.

Supplemental Table 6: Baseline Cardiac Magnetic Resonance Data According Troponin I Tertiles

	Low Troponin I (n=16)	Intermediate Troponin I (n=17)	High Troponin I (n=16)	P Value *
RVEDV index, mL/m²	58.1 ± 16.8	71.9 ± 23.5	79.1 ± 43.1	0.15
RVESV index, mL/m²	24.5 ± 14.5	42.1 ± 23.7	49.7 ± 42.0	0.06
RV ejection fraction, %	64 (28-75)	45 (17-71)	40 (16-67)	0.01†‡
LVEDV index, mL/m²	99 (65-161)	123 (91-188)	137 (78-184)	0.03‡
LVESV index, mL/m²	61 (26-120)	80 (54-162)	92 (39-162)	0.03‡
LVEF, %	40 (25-64)	33 (14-49)	29 (12-50)	0.03‡
Aortic valve area, cm²	0.80 ± 0.2	0.96 ± 0.3	0.77 ± 0.3	0.17
Positive transmural delayed-enhancement images	0.27 ± 0.46	0.35 ± 0.49	0.43 ± 0.51	0.67
Positive mesocardial delayed-enhancement images	0.07 ± 0.25	0.29 ± 0.47	0.36 ± 0.50	0.16
LV mass, g	184.4 ± 54.7	199.4 ± 50.2	217.2 ± 51.8	0.25
Late gadolinium enhancement mass, g	7.96 ± 2.2	11.10 ± 13.3	11.82 ± 11.0	0.66
ECV including delayed-enhancement images, %	28.7 ± 5.9	31.0 ± 6.4	31.9 ± 6.7	0.28
ECV without delayed-enhancement images, %	28.5 ± 6.0	30.1 ± 5.4	30.5 ± 3.4	0.56
iECV, ml/m²	27.4 (17-42)	38.6 (26-57)	40.4 (25-54)	0.01‡

Values are mean±standard deviation, median (interquartile range), or n (%). ECV indicates extracellular volume; iECV, indexed extracellular volume; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; and RVESV, right ventricular end-systolic volume.
*Overall P value among groups: group 1, group 2 and group 3.
†Significant difference (P<0.05) between group 1 vs group 2.
‡Significant difference (P<0.05) between group 1 vs group 3.
§Significant difference (P<0.05) between group 2 vs group 3.

ANEXO B – Tabelas suplementares referente ao Artigo 2

Supplemental Table 1: Univariated analysis of predictors of all-cause mortality

continua

	HR	95.0% CI		*P* value
		Lower limit	Upper limit	
Clinical data				
Age, years	1.020	0.962	1.541	0.511
Body surface area, m^2	2.054	0.107	39.574	0.633
Female sex	1.210	0.404	3.628	0.734
Diabetes	1.321	0.546	3.193	0.537
Hypertension	3.135	0.915	10.737	0.069
Atrial fibrillation	1.723	0.686	4.332	0.247
Coronary artery disease	1.938	0.794	4.728	0.146
One vessel	0.000	0.000		0.982
Two vessels	2.125	0.588	7.676	0.250
Three vessels	3.726	1.312	10.581	0.014
Previous CABG	1.101	0.322	3.766	0.878
EuroSCORE II, %	1.054	0.907	1.223	0.494
STS, %	1.253	1.019	1.541	**0.032**
Symptoms				
NYHA III/IV	0.787	0.325	1.903	0.595
Angina	0.627	0.209	1.876	0.403
Syncope	0.043	0.000	31.360	0.349
ECG				
Left bundle branch block	1.255	0.500	3.151	0.629
Right bundle branch block	0.044	0.000	90.108	0.422
Laboratory data				
Hemoglobin, mg/dl	0.793	0.571	1.101	0.166
Hematocrit, %	0.910	0.814	1.018	0.101
eGFR, mL/min	0.990	0.968	1.014	0.411
CKD (eGFR < 60 mL/min)				
Troponin I, ng/mL	6.532	0.419	101.902	0.181
B-type natriuretic peptide, pg/mL	1.001	1.000	1.001	0.133
C-reactive protein, mg/dL	1.033	1.008	1.059	**0.011**
Baseline 2D echocardiography				
LVEF, %	0.987	0.936	1.040	0.617
LVEDD, mm	0.997	0.935	1.063	0.920
LVESD, mm	1.014	0.956	1.075	0.648
LVEDV, mL	0.997	0.987	1.006	0.469
LVESV, mL	1.000	0.989	1.011	0.996
LV mass, g/m^2	0.995	0.984	1.005	0.327
Mean transaortic gradient, mmHg	0.932	0.882	0.984	**0.011**

continuação

Supplemental Table 1: Univariated analysis of predictors of all-cause mortality

	HR	95.0% CI		*P* value
		Lower limit	Upper limit	
Baseline 2D echocardiography				
PASP, mmHg	1.008	0.963	1.055	0.733
Septum, cm	1.038	0.862	1.249	0.695
Posterior wall, cm	1.012	0.784	1.305	0.930
Aortic valve area, cm^2	1.623	0.124	21.300	0.712
Aortic valve area index, cm^2/m^2	1.292	0.009	176.471	0.919
Stroke volume index, mL/m^2	1.003	0.951	1.057	0.916
Valvuloarterial impedance, $mmHg/mL/m^2$	0.775	0.480	1.251	0.296
Global longitudinal strain ([−] %)	1.033	0.894	1.195	0.657
Moderate/severe functional mitral regurgitation	0.702	0.255	1.934	0.494
Moderate/severe functional tricuspid regurgitation	2.594	0.855	7.869	0.092
Diastolic dysfunction				
Grade 1	0.819	0.149	4.505	0.819
Grade 2	0.988	0.199	4.911	0.989
Grade 3	0.866	0.121	6.168	0.885
Baseline 3D echocardiography				
LVEF, %	0.986	0.936	1.039	0.603
LVEDV, mL	0.995	0.985	1.006	0.374
LVESV, mL	0.999	0.987	1.011	0.863
Aortic valve area, cm^2	2.202	0.131	37.046	0.584
Aortic valve area index, cm^2/m^2	1.845	0.008	447.236	0.827
Dobutamine stress echocardiography				
Flow reserve	2.594	0.759	8.866	0.129
Basal aortic valve area, cm^2	0.147	0.010	2.176	0.163
Peak stress aortic valve area, cm^2	0.548	0.035	8.657	0.669
Basal mean transaortic gradient, mmHg	0.955	0.902	1.012	0.117
Peak stress mean transaortic gradient, mmHg	1.005	0.970	1.041	0.778
Basal stroke volume index, mL/m^2	1.008	0.964	1.054	0.735
Peak stress stroke volume index, mL/m^2	0.999	0.935	1.069	0.988
Basal indexed flow rate, $mL/m^2 \cdot s$	1.001	0.983	1.020	0.893
Peak indexed flow rate, $mL/m^2 \cdot s$	1.007	0.990	1.025	0.407
Cardiac Magnetic Resonance				
RVEDV index, mL/m^2	1.002	0.989	1.015	0.742
RVESV index, mL/m^2	1.000	0.987	1.014	0.968
RV ejection fraction, %	0.996	0.971	1.021	0.734
LVEDV index, mL/m^2	1.006	0.992	1.020	0.400
LVESV index, mL/m^2	1.009	0.995	1.023	0.208
LVEF, %	0.985	0.946	1.026	0.472
Positive mesocardial delayed-enhancement images	1.675	0.668	4.202	0.272

Supplemental Table 1: Univariated analysis of predictors of all-cause mortality

conclusão

	HR	95.0% CI		*P* value
		Lower limit	Upper limit	
Cardiac Magnetic Resonance				
Positive transmural delayed-enhancement images	1.068	0.410	2.784	0.893
LV mass, g	0.998	0.989	1.007	0.683
LGE mass, g	1.030	0.986	1.075	0.183
ECV including positive delayed-enhancement images, %	1.023	0.936	1.117	0.621
ECV excluding positive delayed-enhancement images, %	1.030	0.945	1.123	0.499
iECV, mL/m^2	1.021	0.981	1.064	0.303
Procedure data				
Cardiopulmonary bypass time, min	1.008	0.995	1.022	0.220
Cross-clamp time, min	0.998	0.981	1.015	0.808

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1, 2 and 3.