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ORIGINAL ARTICLE

Timing of Dynamic NT-proBNP and hs-cTnT Response to Exercise Challenge in Asymptomatic Children with Moderate Aortic Valve Regurgitation or Moderate Aortic Valve Stenosis

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Abstract Patients with congenital aortic valve stenosis (AVS) can remain asymptomatic but may develop progressive and often underestimated exercise intolerance. The risk of increased left ventricular (LV) wall stress, irreversible myocardial fibrosis and sudden death in untreated patients warrants earlier intervention. The timing for curative therapy for severe AVS is clear, but optimal timing for moderate stenosis (modAS) is unknown. AVS often coexists with aortic regurgitation, which adds a volume overload to an already pressure-overloaded LV, adding an additional challenge to the estimation of disease severity. We investigated the possible value of N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) upon treadmill exercise challenge in children with asymptomatic modAS versus moderate regurgitation (modAR). The aim was to determine optimal timing of peak biochemical response. Blood samples were obtained at rest, and then at 20, 40 and 60 min after peak exercise comparing modAS and modAR to healthy controls. Exercise performance was equivalent in all groups, with no difference for biomarker levels at rest. The increase in NT-proBNP was significant in modAR at 40 min (99.2 ± 48.6 ng/L; $p = 0.04$) and 60 min into recovery (100.0 ± 53.7 ng/L; $p = 0.01$), but not in modAS. The increase in hs-cTnT was significant only at 60 min into recovery for modAS and modAR. NT-proBNP and hs-cTnT following exercise challenge are possible discriminant biomarkers of modAR from modAS and controls at 60 min into recovery despite comparable exercise performance. This offers a promising avenue for future stratification of aortic valve disease and optimal timing of intervention.

Keywords Aortic regurgitation · Aortic stenosis · Aortic valve disease · Biomarker · NT-proBNP · High-sensitivity cardiac troponin T · hs-cTnT · Treadmill testing

Introduction

Usually asymptomatic at rest, congenital aortic valve stenosis (AVS) is likely to progress to exercise intolerance, increased left ventricular wall stress and sudden cardiac death. This is typically a slow process to which children reduce their physical activity as to limit their symptoms despite progression of AVS, ongoing myocardial injury and maladaptive remodeling. Compared to the general population, there is an increased mortality in moderate AVS in the adult, with myocardial fibrosis, which does not regress after valve replacement [14, 18, 20]. Accordingly, there is a trend toward earlier intervention [1, 26], but optimal timing remains unknown. Given these premises, true disease severity and risk of sudden death are underestimated based on symptomatology alone [20]. Whereas current recommendations are clear for severe and mild AVS, they basically rely on gradient progression or onset of symptoms for patients with moderate stenosis (modAS) [4]. Several markers of progression have been identified in an adult population. However, these studies never addressed modAS exclusively and are often retrospective in nature [14]. The

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same controversy exists with regard to aortic regurgitation, with surgical triggers being clinical symptoms of congestive heart failure or decreasing LV function. Earlier surgical intervention is a source of ongoing debate. Often, both regurgitant and stenotic valve disease coexist, making the assessment of the predominant lesion challenging.

From a pathophysiological standpoint, aortic stenosis increases afterload and wall stress of the LV at rest, and to a higher degree during exercise. We therefore hypothesized that exercise increases myocardial demand, which creates a state of relative mismatch between myocardial perfusion and demand. Although higher brain natriuretic peptide (BNP) levels have been correlated with progression of AVS in the adult [15], response to exercise remains unknown. In modAR, the LV suffers a volume overload, which increases stroke volume, until dysfunction develops. Resting BNP levels have been shown to be a stronger independent prognostic marker in severe AR with normal LV function [21]. The natriuretic response to exercise has not been reported to our knowledge. In the present study, we sought to describe the response pattern of N-terminal proBNP (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) in children with modAS or modAR following an exercise challenge test. The specific aim of this study was to determine timing at which the maximal values of these biomarkers would occur after exercise.

Study Design

The research protocol was approved by our Institutional Scientific and Ethic Boards. Parental or legal guardian written informed consent was obtained prior to enrollment. Patient's assent was also obtained. This is a prospective study comparing children with modAS to modAR and healthy controls (CTL). ModAS was defined by a mean Doppler pressure gradient of 20–39 mmHg [17] with normal left ventricular function, no reported symptoms and no more than mild AR if any. Normal LV function was defined as LVEF greater than 55 %. ModAR group included subjects with moderate valve regurgitation defined by a retrograde to anterograde velocity time integral ratio of 20–40 % at the level of the thoracic aorta [3] with absent or mild Doppler pressure gradient (mean gradient <25 mmHg). CTL subjects were of similar age and sex distribution to modAS. CTL subjects were asymptomatic children with physiological murmur. Inclusion and exclusion criteria of modAS and modAR are summarized in Table 1.

Materials and Methods

In all subjects, exercise stress testing must have been considered as a safe test by the treating cardiologist. The presence of symptoms was assessed by charts review and a standardized questionnaire at the time of enrollment. Exercise testing consisted of a modified Bruce protocol.

Echocardiography was obtained for all subjects at rest and 2–3 min after peak exercise. A complete 2D, color, pulsed and continuous-wave Doppler echocardiogram was performed according to standard techniques [10]. Two-dimensional speckle tracking analyses were performed on grayscale images of the left ventricle obtained in the apical two-, three- and four-chamber views, and short-axis mid-ventricular views. Left ventricular circumferential strain was determined from the mid-LV views, and global longitudinal strain was determined in the three apical views using EchoPAC software (GE Healthcare, Mississauga, ON, Canada). The endocardial border and the width of the region of interest were traced at end-systole and adjusted to include the entire myocardium. Values were compared to published age-specific normal values [12].

Biomarkers were obtained at rest, and then at 20, 40 and 60 min after peak exercise. NT-proBNP was obtained with the Elecsys system (Roche, Mannheim, Germany). NT-proBNP was chosen instead of BNP for its longer half-life and better stability in vitro [6, 25]. The hs-cTnT measurement was taken by electro-chemiluminescence, which is based on the detection of cardiac troponin T with a mixture of highly specific biotinylated and ruthenium-labeled cardiac troponin T antibodies (Roche, Mannheim, Germany).

Statistical Analysis

Results are expressed as mean ± standard deviation (SD). Statistical analyses were performed using SigmaStat version 3.5 (Dundas Software, Germany). Student *t* test (or the *U* Mann–Whitney nonparametric test in case of non-normal distribution) was used to compare continuous variables between groups, and a paired Student *t* test was used to compare after exercise biomarkers' serum levels to baseline levels. Analysis of variance with pairwise comparison was used for group comparison, using the Student–Newman–Keuls method. A p value under 0.05 was considered statistically significant.

Results

There were 11 modAS, 9 modAR and 10 CTL patients, none of whom reported cardiac symptoms (Table 2). There was no difference in basic echocardiographic variables, at rest or after peak exercise in either group (Table 3). Only 1 modAS patient and 2 modAR had elevated septal and lateral E/e′ after exercise testing, but without statistical significance ($p = 0.07$).

Table 1 Inclusion and exclusion criteria

Inclusion criteria

1. Ability to perform treadmill exercise testing
2. Exercise testing deemed not risky by the attending cardiologist
3. Asymptomatic upon chart review and questionnaire
4. Patients with mild or trivial mitral, tricuspid or pulmonary valvular regurgitation
5. Native or previously dilated isolated AVS
6. Moderate AVS with mean LV-Ao gradient 20–39 mmHg with no more than mild AR (for modAS group)
7. Moderate AR with no more than mild AVS (for modAR group)

Exclusion criteria

1. Refusal to consent or to assent to the study
2. Self-reported symptoms at rest or during exertion
3. Cases or controls with severe regurgitation of aortic, mitral, pulmonary or tricuspid valve
4. Patients with mitral, pulmonary or tricuspid stenosis
5. Children who are unable to perform treadmill testing (e.g., age < 5 years, physical limitation to perform a treadmill stress test)
6. Patients with the following conditions which could potentially affect NT-proBNP levels: receiving chemotherapy or who had received known cardiotoxic chemotherapy, systemic hypertension, pulmonary hypertension, renal failure, hypertrophic or dilated cardiomyopathy, associated significant or complex congenital heart defects, other heart defects with dilatation of cardiac chambers, patients with chronic recurrent inflammatory diseases (e.g., juvenile rheumatoid arthritis, inflammatory bowel disease). Subjects with known chronic inflammatory, autoimmune diseases (e.g., juvenile rheumatoid arthritis, lupus, inflammatory bowel disease)

Table 2 Group characteristics

Group	modAS ($n = 11$)	modAR ($n = 9$)	CTL ($n = 10$)
Age (years)	14 ± 2	13 ± 4	11 ± 3
M/F	7:4	6:3	4:6
BSA (m^2)	1.52 ± 0.3	1.47 ± 0.4	1.21 ± 0.4
ΔLV-Ao peak (mmHg)	45 ± 21	34 ± 15	4 ± 4
ΔLV-Ao mean (mmHg)	25 ± 12	22 ± 7	2 ± 2
Aortic valve anatomy	9 bicuspid	5 bicuspid	Tricuspid 10/10
	1 unicuspid	1 unicuspid	
	1 quadricuspid	3 tricuspid	
Previous intervention	3/11 balloon dilatation	2/9 balloon dilatation	none

p value nonsignificant for all parameters

All subjects completed treadmill testing with comparable duration, percentage of maximal heart rate and METS (Table 4). All patients were asymptomatic during treadmill testing. In one female modAS patient, treadmill testing was interrupted because of ST-segment depression at 10 min into exercise and 87 % of expected maximal heart rate (HR). No arrhythmias occurred, and she recovered quickly. Blood pressure (BP) response to exercise was normal (>20 mmHg increase) [19] for most subjects in modAS although systolic BP response was at the lower end of normal for one patient (+21 mmHg) and insufficient for three others (+17, +3 and +13 mmHg). In modAR, only one subject had an abnormal rise in systolic BP responses (+10 mmHg). One patient in modAR had isolated, monomorphic and asymptomatic PVCs during exercise testing at 7 min 30 s into exercise with no other anomalies. Holter recordings following treadmill test yielded an asymptomatic non-sustained ventricular run in one male modAS subject. There were no other arrhythmic events.

Exercise-induced biochemical response was completed in all subjects. At rest, NT-proBNP was significantly higher in modAR (93.2 ± 49.3 ng/L) compared to modAS (55.8 ± 46.8 ng/L; $p = 0.037$), with comparable trend compared to CTL (56.4 ± 23.0 ng/L; $p = 0.06$); however, the difference was not statistically significant between modAS and CTL ($p = 0.972$). Following treadmill exercise (Fig. 1), NT-proBNP increased significantly in modAR to 99.2 ± 48.6 ng/L at 40 min into recovery ($p = 0.04$) and remained elevated at 60 min (100.0 ± 53.7 ng/L; $p = 0.01$). In modAS, those levels did not vary significantly after exercise challenge from rest and did not differ from control subjects either. On the other hand, hs-cTnT was significantly higher at rest in both

Table 3 Echocardiography parameters at rest and post-exercise

	modAS			modAR			CTL		
	Rest	Post-ex	*p*	Rest	Post-ex	*p*	Rest	Post-ex	*p*
ΔLV-Ao peak (mmHg)	45 ± 21	43 ± 20	0.55	34 ± 15	32 ± 19	0.65	4 ± 4	5 ± 4	0.17
ΔLV-Ao mean (mmHg)	25 ± 12	23 ± 11	0.28	22 ± 7	20 ± 11	0.25	2 ± 2	3 ± 2	0.24
EF (%)	69 ± 8	63 ± 11	0.56	63 ± 11	63 ± 9	0.33	57 ± 4	60 ± 10	0.55
SF (%)	49 ± 14	44 ± 7	0.26	39 ± 11	37 ± 6	0.85	36 ± 10	36 ± 3	0.93
E/A mitral	2.1 ± 0.7	2 ± 0.6	0.54	2 ± 0.7	1.6 ± 0.4	0.11	2.1 ± 0.3	1.9 ± 0.4	0.21
E/e′ sept	7.2 ± 2	7.4 ± 2	0.43	8.9 ± 3	9.5 ± 2	0.58	6.6 ± 2	7.1 ± 2	0.16
E/e′ lat	7.7 ± 3	7.5 ± 3	0.78	8.8 ± 4	7.8 ± 3	0.29	6.2 ± 3	6.2 ± 1	0.95
LV MPI	0.25 ± 0.07	0.30 ± 0.1	0.13	0.26 ± 0.1	0.25 ± 0.1	0.66	0.32 ± 0.09	0.33 ± 0.07	0.68

Table 4 Treadmill testing data

Treadmill test	modAS	modAR	CTL
Symptoms	0	0	0
Premature ventricular contractions	0	2	0
Non-sustained ventricular tachycardia	0	0	0
Sustained ventricular tachycardia	0	0	0
ST depression	1	0	0
Duration (min)	18 ± 4	18 ± 4	19 ± 6
METS	12 ± 4	12 ± 3	11 ± 4
% Of max HR (%)	87 ± 8	85 ± 8	81 ± 14
Abnormal BP drop	0	0	0
Systolic BP increase >20 mmHg	8	8	10
Systolic BP increase <20 mmHg	3	1	0

Nonsignificant statistics ($p > 0.05$) between groups for all parameters

disease groups (3.6 ± 5.0 ng/L in modAS and 3.8 ± 5.2 ng/L in modAR) compared to CTL (0.0 ± 0.0 ng/L), where there were no detectible levels in any (Fig. 2). Exercise challenge, however, yielded similar levels at 20 and 40 min into recovery (p = NS). Nevertheless, those levels remained significantly elevated in modAR ($p = 0.046$) with a nonsignificant trend in modAS ($p = 0.083$), compared to CTL. The drop in hs-cTnT between 40 min into recovery and 60 min into recovery was, however, nonsignificant in modAS ($p = 0.099$) and modAR ($p = 0.056$) despite an apparent trend compared to CTL.

From the myocardial dynamic perspective, left ventricular strain (Table 5) was altered on global longitudinal assessment in modAS and modAR compared to CTL at rest (−19.5 ± 3.0 % and −19.3 ± 2.0 % vs −22.3 ± 1.3 %, respectively; $p = 0.002$ and 0.02) and following treadmill challenge (−19.3 ± 3.2 % and −18.8 ± 2.2 % vs −22.6 ± 2.0 %; $p = 0.01$ and 0.002) (Table 5). Circumferential strain was lower in modAR compared to CTL at rest (−21.3 ± 1.7 % vs −23.2 ± 0.95; $p = 0.02$) but not after exercise challenge (−19.7 ± 2.5 vs −21.8 ± 2.0; $p = 0.1$). The same trend was observed in modAS at rest but did not reach statistical significance (−21.5 ± 2.4 vs 23.2 ± 0.95; $p = 0.09$). No statistically significant difference was noted within groups before and after exercise challenge. There were no significant differences for global longitudinal or circumferential strain between modAS and modAR. There were subjects in modAR and modAS whose GLS and CS were below age-specific normals at rest and after exercise testing (Table 6). CTL all had normal strain values for age.

Discussion

This study shows NT-proBNP response to exercise to be a possible discriminant test in modAR compared to modAS and healthy subjects. Despite a small sample size, we were able to detect a statistically significant rise of NT-proBNP between 40 and 60 min after peak exercise. This observation seems to be supported by LV strain analysis showing reduced global longitudinal strain in modAR and modAS at rest and after exercise challenge and reduced circumferential strain in modAR at rest compared to modAS and CTL. Similarly, hs-cTnT yielded a sustained increase following exercise up to 60 min into recovery compared to healthy controls. In addition, hs-cTnT appears to be discriminative at rest compared to healthy subjects, but not among the disease groups.

The increase in BNP and NT-proBNP is typically secondary to an increase in ventricular wall stress, due to volume or pressure overload [5, 7, 8, 11, 13, 16, 27]. The NT-proBNP response in our study could be explained by a higher LV wall stress in modAR patients at rest and after exercise challenge as compared to modAS and CTL. Cutoff values for NT-proBNP with predictive prognostic value have been identified for severe asymptomatic AR and AS

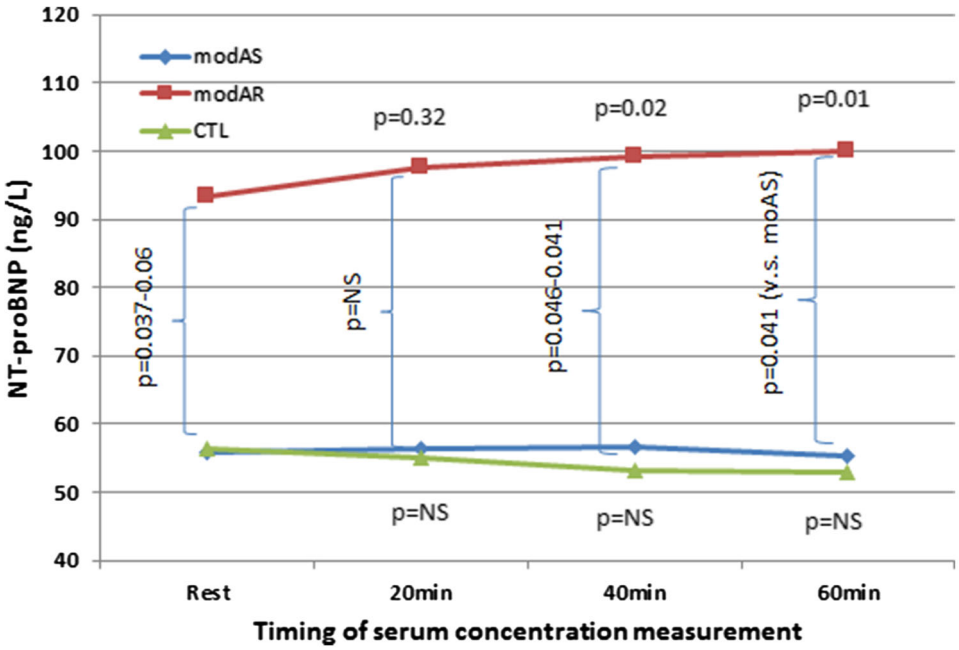

Fig. 1 NT-proBNP response to exercise testing. Significant *p* values represent *t* test within group compared to baseline. *Vertical p* values compare modAR to modAS and CTL at each stage. *Horizontal p* values compare recovery serum levels to resting serum level within each group

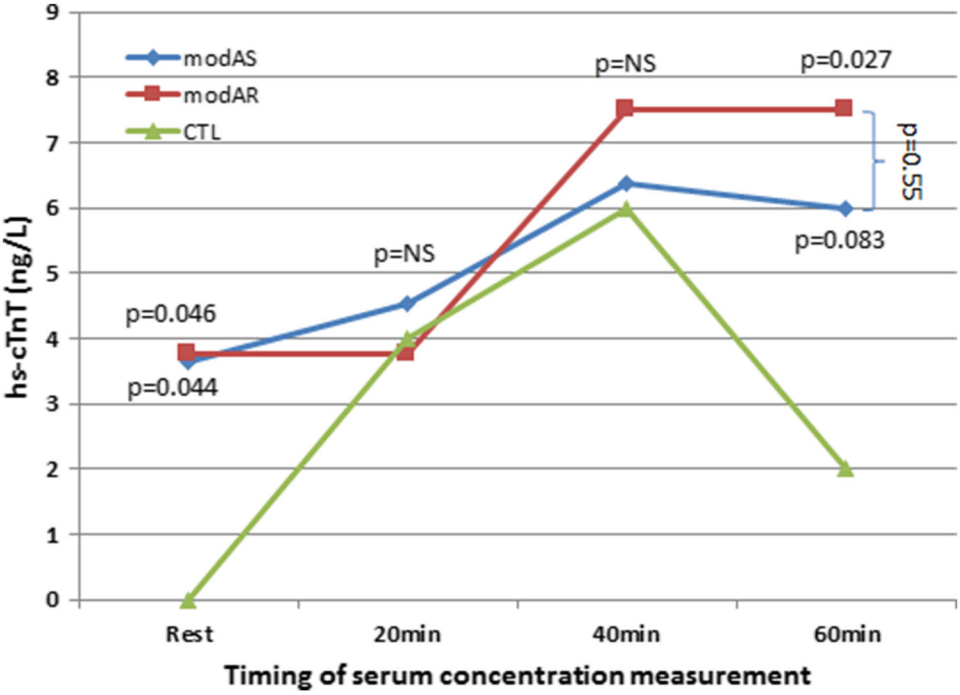

Fig. 2 hs-cTnT response to exercise testing. Significant *p* values represent pairwise *t* test between study subjects (modAS or modAR) and controls (CTL)

Table 5 Left ventricular strain analysis at rest and post-exercise

	modAS		modAR		CTL	
	Rest	Post-ex	Rest	Post-ex	Rest	Post-ex
GLS (%)	−19.5 ± 3.1*	−19.3 ± 3.2*	−19.3 ± 2.0*	−18.8 ± 2.1*	−22.3 ± 1.3	−22.6 ± 2.0
CS (%)	−21.5 ± 2.3	−21.5 ± 3.3	−21.2 ± 1.7*	−19.7 ± 2.4	−23.2 ± 1.0	−21.8 ± 2.0

* Lower strain values ($p < 0.05$) versus CTL at similar stage

GLS global longitudinal strain; *CS* circumferential strain

Table 6 Proportion of abnormally low GLS and CS for age

	modAS		modAR		CTL	
	Rest	Post-ex	Rest	Post-ex	Rest	Post-ex
Abnormally low GLS (count)	5/11	6/11	4/9	1/9	0/10	0/10
Abnormally low CS (count)	3/11	4/11	1/9	1/9	0/10	0/10

X^2 analysis

$p = 0.04$ for GLS modAS versus modAR versus CTL at rest, and $p = 0.008$ post-exercise

$p = 0.11$ for CS modAS versus modAR versus CTL at rest, and $p = 0.072$ post-exercise

$p =$ NS at rest versus post-exercise in all groups

in adult populations [2]. The response to exercise testing has not been studied. The dynamic assessment of NT-proBNP could be a novel way to assess mixed aortic valve disease.

In adult-reported series, elevated resting BNP is associated with faster progression of modAS [14, 15]. Very recently, such elevation was recorded in a series of asymptomatic elderly adults with severe aortic valve stenosis [5]. In this series, patients in the upper second and third tertiles of exercise-induced BNP were more likely to reach the study endpoint of either death or valve replacement. Noticeably, exercise-induced BNP correlated linearly with resting BNP concentration, which raises the question of whether an exercise challenge was really necessary in this group of patients. In contrast, our modAS subjects had similar NT-proBNP levels to controls at rest, levels which did not vary after exercise. This may be due to longer half-life of NT-proBNP compared to BNP, which was found to be more sensitive to subtle changes such as in Kawasaki disease [7]. However, the exercise-related variation has not been studied in children in general, or in patients with less than severe aortic stenosis in particular.

Although the mechanisms of activation are independent, the release of the cardiac natriuretic peptide appears concomitantly with that of cardiac troponin in the setting of acute coronary syndrome [9, 23]. Recently, emphasis on hs-cTnT detecting subtle elevation of troponin breakdown was shown to play a role in the risk stratification of future heart failure, congestive failure and related mortality [23]. Very recently, hs-cTnT was tested in a series of adult patients with AVS [22]. Accordingly, all subjects had detectible levels of hs-cTnT, with significant survival prediction according to the intensity of hs-cTnT release. It was also studied in strenuous exercise following marathon competition, reflecting non-necrotic phenomenon in the myocardium under strenuous exercise [24]. In our current series, hs-cTnT response was not significantly different in any of the study groups early into recovery from treadmill testing, but seems promising at 60 min following peak exercise. The hypothesis by which a subendocardial ischemia might occur during exercise remains to be validated in a larger cohort, with higher degree of stenosis.

Our results suggest a novel way to assess aortic valve disease severity using exercise challenge and biochemical markers. The exercise-induced pathophysiological changes, primarily secretion of NT-proBNP, seem to discriminate modAR from modAS and healthy CTL. We believe that biomarker response to exercise will further discriminate between groups of rapidly progressive aortic valve disease. A larger, prospective study is needed to validate these results and to lead to more generalizable conclusions.

Conclusion

In this study, we have shown that NT-proBNP is higher at rest and increases in modAR after exercise challenge. This difference becomes significant from 40 min after peak exercise onward. The same increase was not observed in modAS or CTL subjects. In contrast, higher resting hs-cTnT becomes non-discriminative upon recovery in this pilot study. Biochemical response to exercise testing could be a novel way for future stratification of aortic valve disease, reflecting the physiological consequence of the disease as it increases LV wall stress. With a larger, prospective cohort, with varying combinations of aortic valve disease, possible cutoff values could be identified to better predict the optimal timing of intervention.

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Compliance with Ethical Standards

Conflict of interest Authors have no conflicts of interest to declare.

Ethical standard This work was completed according to local and international ethics standards for human research. Institutional ethics approval complying with regulations granting proper respect of human rights was granted.

Informed consent Consent was obtained from all participants' parent/legal.

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