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High-sensitivity troponin increase after exercise in patients with systemic right ventricle

Short title: High-sensitivity troponin increase after exercise in patients with SRV

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INTRODUCTION

Patients with systemic right ventricle (SRV) represent a unique subgroup of patients with congenital heart disease in whom the right ventricle supports the systemic circulation and is exposed to lifelong pressure overload. Recent studies using novel high-sensitivity troponin (hsTn) assays have shown that detectable hsTn levels are common in patients with SRV and are associated with SRV dysfunction and worse prognosis [1–3]. The exact pathophysiological process leading to this hsTn release is not yet known, but myocardial ischemia and injury are thought to play an important role. Higher myocardial demand, mechanical stress and hemodynamic overload associated with physical exercise could lead to a further increase in hsTn. Thus, we aimed to evaluate hsTn in patients with SRV both at rest and in response to maximal physical exercise.

MATERIAL AND METHODS

The study was a single-centre cohort study performed at the national referral centre for adult patients with congenital heart disease of the University medical centre Ljubljana, Slovenia. Patient enrolment took place from May 2019 to December 2021 and was delayed by the COVID

pandemic. All adult patients with SRV and either congenitally corrected transposition of the great arteries (CCTGA) or transposition of the great arteries after atrial switch (TGA-AS) were invited to participate. Patients with a single ventricle, acute or advanced chronic heart failure, uncontrolled arrhythmias or physical limitations precluding exercise testing were excluded. The study was approved by the Slovenian Medical Ethics Committee and patient informed consent was obtained. Every patient had a symptom-limited maximal cardiopulmonary exercise testing (CPET) performed on an upright cycle ergometer. Respiratory exchange ratio, peak oxygen consumption (pVO_2), percent of predicted peak VO_2 ($ppVO_2$) and ventilatory equivalent for carbon dioxide (VE/VCO_2) were measured. A venous blood sample for analysis of high-sensitivity troponin I (hsTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) was obtained right before and 180 minutes after CPET. A three-site sandwich hsTnI immunoassay (Siemens ADVIA Centaur — High-Sensitivity Troponin I Assay) with a quantification limit of 2.5 ng/l was used. Values above the 99th percentile of the upper reference limit (54 ng/l in males and 40 ng/l in females) were considered abnormal and a 20% increase after exercise was considered significant as previously described [4]. A chemiluminescence method was used for NT-proBNP analysis and values above 125.0 ng/l were considered abnormal. Demographic, clinical (history of arrhythmias or heart failure and New York Heart Association [NYHA] class) and imaging parameters were also collected. The SRV size was assessed by SRV basal diameter on echocardiography and SRV systolic and diastolic volumes on cardiac magnetic resonance imaging (CMR). Several parameters were used to assess SRV systolic function, including fractional area change (FAC) and global longitudinal strain (GLS) on echocardiography and SRV ejection fraction on CMR. Focal fibrosis of the SRV was assessed by the presence of late gadolinium enhancement on CMR.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, US). Categorical variables are presented as frequencies with percentages and continuous variables as mean (standard deviation [SD]) or median (interquartile range [IQR]). Comparisons were performed with Mann–Whitney, Wilcoxon signed ranks or Fischer’s exact test and correlations were assessed by Spearman’s rank test. A two-sided *P*-value of 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Forty-three adult patients with SRV were screened and of the 40 eligible patients 23 agreed to participate. One patient had incomplete biomarker data, therefore the final study group consisted of 22 (mean age 36.8 [9.7] years), predominantly male (77%) and paucisymptomatic (54% NYHA class 1, 46% class 2) SRV patients (15 with TGA-AS and 7 with CCTGA). Their exercise capacity was impaired, with a mean pVO_2 of 25.6 (6.9) ml/kg/min (mean $ppVO_2$ 69.3 [14.7]%). Echocardiography showed an SRV FAC of 31.1 (5.0)% and GLS of -14.7 (2.2)%. CMR was possible in 18 (82%) patients. Mean SRV ejection fraction was 48 (7.7)%, SRV dysfunction defined as ejection fraction <45% and late gadolinium enhancement were present in 7 (32%) patients.

At rest, 20 patients (91%) had hsTnI levels above the quantification limit, while two (9%) had abnormal hsTnI (220 and 107 ng/l, respectively). One was a TGA-AS patient with severe subpulmonary stenosis and cyanosis due to baffle leak and the second a CCTGA patient with reduced SRV dysfunction and heart failure. Median resting hsTnI was 6.0 (IQR 4.0–8.2) ng/l (**Figure 1**) and there was no difference between TGA-AS and CCTGA patients ($P = 0.89$). Resting hsTn values correlated with age ($r = 0.447$; $P = 0.04$), but not with NT-proBNP, echocardiographic, or CMR markers of SRV size, function and focal fibrosis. Resting NT-proBNP was associated with pVO_2 ($r = -0.447$; $P = 0.04$) and GLS ($r = -0.557$; $P = 0.007$).

After maximal effort CPET (mean respiratory exchange ratio 1.2 [0.1]) all patients had hsTnI above the quantification limit. The mean relative increase in hsTnI after exercise was 57.6 (82.0)% and a significant increase of >20% in hsTnI was observed in 14 (64%) patients, but none reached abnormal values. Median values of hsTnI ($P = 0.02$) and NT-proBNP ($P < 0.001$) after exercise were significantly higher compared to resting values (**Figure 1**). hsTnI values after exercise correlated with NT-proBNP before ($r = 0.441$; $P = 0.04$) and after exercise ($r = 0.439$; $P = 0.04$) and with SRV basal diameter assessed by echocardiography ($r = 0.529$; $P = 0.02$). There was a trend with age and FAC ($P = 0.07$ and 0.09 , respectively). NT-proBNP values after exercise correlated with hsTn values after exercise, pVO_2 ($r = -0.515$; $P = 0.01$) and GLS ($r = 0.513$; $P = 0.01$).

Our findings provide evidence that maximal physical exercise leads to a significant increase in hsTn levels in patients with SRV. Contrary, a previous study by Shafer et al. [5] found a non-significant increase in hsTn levels after exercise in 14 patients with SRV. This could be due to the

different exercise protocols used, as we obtained hsTn 3 hours after a maximal CPET, while they obtained hsTn 3 hours after a 60 minutes endurance test performed near ventilatory threshold. However, similar results to ours have been observed in patients with pulmonary arterial hypertension, in whom the right ventricle is also subjected to chronic pressure overload. In these patients, maximal exercise has been shown to significantly increase hsTn levels, which correlated with NT-proBNP and mean pulmonary artery pressure [6]. We also found a correlation between hsTn levels after exercise and NT-proBNP, which is a known predictor of adverse outcomes in patients with SRV [1]. Although there was also a correlation with SRV size assessed by echocardiography, there was no correlation between hsTn levels after exercise and echocardiographic or CMR markers of SRV size, function and focal fibrosis in our patients.

The exact mechanisms underlying the increase in hsTn levels after exercise in patients with SRV remain unknown. In patients with heart failure and reduced ejection fraction an increase in hsTn, NT-proBNP and norepinephrine after maximal exercise was observed, suggesting a link between hemodynamic overload, adrenergic activation, and myocardial injury [4]. The observed increase in NT-proBNP after exercise in our study indicates that maximal exercise is associated with a significant hemodynamic overload in patients with SRV. The mechanical stress and hemodynamic overload may also expose the supply-demand mismatch leading to myocardial ischemia and injury of the hypertrophied SRV. Both abnormal perfusion and impaired coronary flow reserve have been previously reported in patients with SRV [7, 8]. However, abnormal perfusion was not associated with resting hsTnI or NT-proBNP, while impaired coronary flow reserve was associated with BNP in patients with CCTGA.

It is important to note that our study has some limitations, including a small sample size and a lack of prospective follow-up. Additionally, direct comparison of hsTn values with available previous studies is not possible due to the use of different hsTn assays. We used hsTnI, which is considered to be more cardiac myocyte specific than hsTnT. The timing of blood sampling after exercise can also affect the results. In our study, samples were collected 3 hours after exercise, while in a study of patients with pulmonary arterial hypertension a significant increase in hsTn levels was observed only 5 hours after exercise [6].

In conclusion, our study demonstrated a significant increase in hsTnI levels after maximal physical exercise in adult patients with SRV. As hsTn is a promising new biomarker in patients with SRV,

further research is needed to investigate the pathophysiological mechanisms and prognostic implications of hsTn increase after exercise in these patients.

Article information

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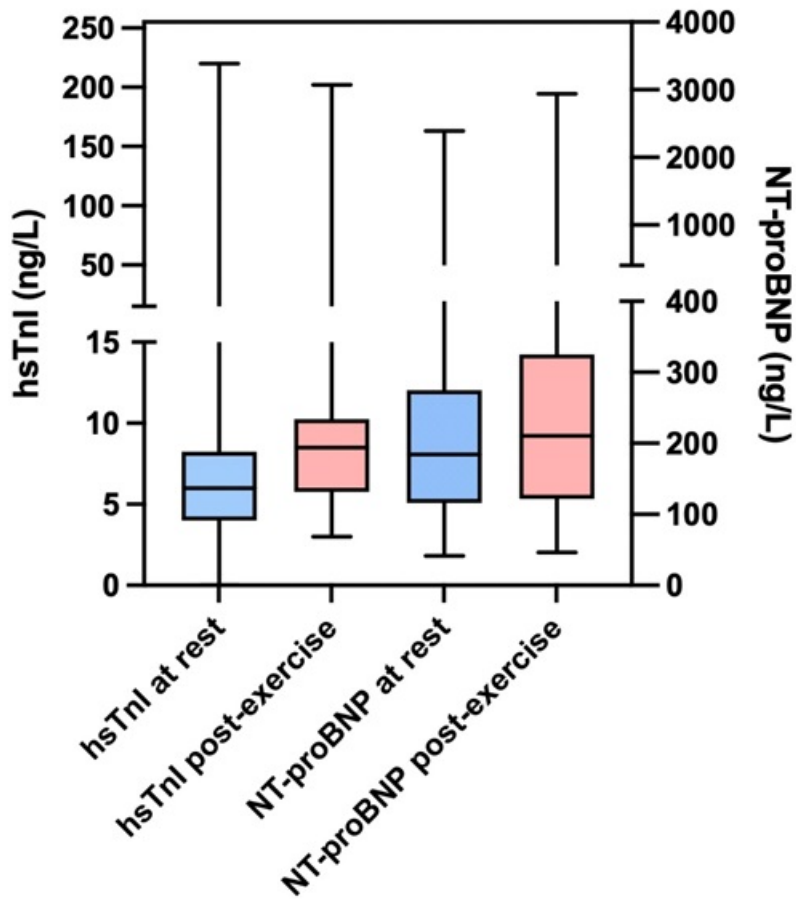


Figure 1. The box and whisker plot of hsTnI and NT-proBNP at rest and post-exercise in adult patients with SRV. Values of both hsTnI ($P = 0.02$) and NT-proBNP ($P < 0.001$) were significantly higher post-exercise compared to resting values

Abbreviations: hsTnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SRV, systemic right ventricle