## Scientific letter

### Highly sensitive troponin T dynamics and prognosis in asymptomatic severe aortic stenosis

### *Dinámica de troponina T de alta sensibilidad y pronóstico en pacientes con estenosis aórtica grave asintomática*

**To the Editor,**

Single measurements of cardiac biomarkers have shown predictive value in asymptomatic severe aortic stenosis (SAS). Our group has previously shown that a baseline level of highly sensitive troponin T (hsTnT) was associated with a 10-fold greater risk of events, and that incorporation of hsTnT into a model that included age, sex, aortic regurgitation $\geq 2+$, left atrial volume index, diastolic dysfunction of $\geq 2$, mean aortic gradient, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and longitudinal strain significantly increased discrimination and adequately reclassified 43% of patients[1]; nevertheless, dynamic changes of these biomarkers over time and their association with outcomes remain unknown.

To determine whether increases in biomarkers over time might improve event risk prediction in asymptomatic SAS, we examined the values of repeat NT-proBNP and hsTnT measurements at baseline and 6 months.

We prospectively studied 79 consecutive patients who were admitted to a heart valve clinic with asymptomatic SAS from January 2014 to June 2018. Two patient groups were established, based on whether they experienced events (n = 25) or no events (n = 54) within 1 year. Events were defined as the presence of cardiovascular death, SAS-related clinical symptoms, hospital admission due to cardiac causes, or an indication for aortic valve replacement.

The mean age was 74 ± 9 years; 30% had diabetes, 77% had dyslipidemia, 3 had clinically known ischemic heart disease, and only 1 had a history of myocardial infarction. However, on coronary angiography, 16 of the 45 patients examined had significant coronary stenosis (10 in 1 vessel, 4 in 2 vessels, 2 in 3 vessels, and 2 left main disease). Patients with severe aortic regurgitation were excluded. The mean ± standard deviation echocardiography values were as follows: maximum aortic velocity, 4.2 ± 0.28; aortic gradient, 48.2 ± 7.6 mmHg; aortic valve area, 0.78 ± 0.11 $cm^2$; left ventricular ejection fraction, 68 ± 5.6%; left atrial indexed volume, 40.3 ± 13.0 $mL/m^2$. Aortic regurgitation $\geq 2$ was present in 17% of patients. The median (Q1-Q3) baseline and 6-month NT-proBNP levels were 294 [139-656] and 350 [174-875] ng/L, respectively. The median (Q1-Q3) baseline and 6-month hsTnT levels were 13.0 [8.6-18.0] and 14.1 [8.9-23.2] ng/L, respectively.

The events occurring during the first year of follow-up were as follows: 16 patients developed symptoms (all had heart failure, 1 had angina and 2 had syncope, of whom 1 required hospital admission). Aortic replacement was indicated in 9 patients due to the results of the echocardiographic stress test, in 2 due to a drop in left ventricular ejection fraction, and based on symptoms in the remaining patients. Indications were never based on biomarker data. The clinician responsible for patient management and therapeutic decision-making was blinded to hsTnT values but not to NT-proBNP values.

On univariable analysis, several baseline echocardiographic data, baseline levels of both biomarkers and a > 20% change in hsTnT dynamics at 6 months ($\Delta$hsTnT > 20%) were significantly associated with the presence of events (table 1). We performed a multivariable binomial logistic regression analysis (backward stepwise conditional) to identify predictors for the risk of events at 1 year, including age, sex and variables with a value < 0.10 in the univariable analyses, and baseline maximum aortic velocity, considered clinically relevant for the addressed valvular disease. We found that a $\Delta$hsTnT > 20% from baseline to 6 months was an independent predictor of 1-year events (odds ratio, 8.23; 95% confidence interval [95%CI], 1.74-39.1; $P$ = .008), together with

**Table 1**
Univariable and multivariable (conditional backward stepwise) binomial logistic regression analysis for the risk of events at 1 year

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95%CI | *P* | OR | 95%CI | *P* |
| Age, y | 1.04 | 0.98-1.10 | .82 | – | – | – |
| Female sex | 0.55 | 0.20-13.7 | 1.48 | – | – | – |
| Delta in hsTnT > 20% | 3.91 | 1.29-11.9 | .02 | 8.23 | 1.74-39.1 | .008 |
| Delta in NT-proBNP > 30% | 2.34 | 0.89-6.17 | .08 | – | – | – |
| Delta in LVEF[a] | 0.97 | 0.92-1.02 | .20 | | | |
| Delta in maximum aortic velocity[a] | 1.06 | 0.96-1.16 | .59 | | | |
| LA indexed volume ($mL/m^2$) | 1.07 | 1.02-1.13 | .01 | – | – | – |
| ≥ 2+ aortic regurgitation | 5.33 | 1.66-17.1 | .005 | 5.73 | 1.24-26.6 | .03 |
| Baseline hsTnT[b] | 3.37 | 1.72-6.59 | < .001 | 4.68 | 1.79-12.3 | .002 |
| Baseline NT-proBNP[b] | 3.19 | 1.69-6.01 | < .001 | – | – | – |
| Baseline Simpson LVEF, per unit | 0.88 | 0.80-0.97 | .01 | – | – | – |
| Baseline maximum aortic velocity (m/s) | 3.47 | 0.69-17.5 | .13 | – | – | – |

95%CI, 95% confidence interval; hsTnT, highly sensitive troponin T; LA, left atrium; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio.
[a] Percentage of change.
[b] Log-transformed and per 1 standard deviation.

aortic regurgitation $\geq$ 2 + ($P$ = .03) and baseline hsTnT ($P$ = .002) (table 1). In a sensitivity analysis, only patients with clinical events were assessed and, in a multivariable binomial logistic regression analysis (backward stepwise conditional) including age, sex, and biomarker data (both baseline and dynamic changes) a ΔhsTnT $>$ 20% remained significantly associated with such events (hazard ratio, 5.31; 95%CI, 1.27-22.2; $P$ = .02). Thus, we recommend that measuring the hsTnT biomarker at predefined intervals of 6 months could improve asymptomatic SAS prediction and decision-making.

These findings are consistent with previous reports demonstrating that the progression of biomarker levels over time might anticipate events in patients with symptomatic SAS. Henry et al.[2] found that natriuretic peptide dynamics were valuable in this clinical setting, but did not measure other biomarkers. The present study highlights the value of a myocyte injury biomarker, namely hsTnT, and the limited value of a myocyte stress biomarker, namely NT-proBNP. Indeed, the significant association between ΔhsTnT $>$ 20% from baseline to 6 months and the occurrence of events was independent of classic variables with important predictive value in patients with asymptomatic SAS[3] (ie, the maximum aortic velocity, ejection fraction, and NT-proBNP changes), even after adjustment of the regression model with the baseline values of all these variables.

Further studies are needed to validate our finding that hsTnT dynamics could be used to indicate valve replacement before the occurrence of irreversible left ventricular changes. This biological approach is likely to be the next frontier in managing patients with severe SAS.[4,5]

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## CONFLICTS OF INTEREST

A. Bayés-Genís has received lecture honoraria from Roche Diagnostics. The rest of the authors declare no conflicts of interest.

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## Constrictive physiology due to epicardial fat

### *Fisiología constrictiva por grasa epicárdica*

**To the Editor,**

We present the case of a 73-year-old hypertensive, obese woman who presented with worsening functional class and dyspnea on minimal exertion. She had a history of permanent atrial fibrillation and numerous admissions for congestive heart failure with preserved left ventricular ejection fraction. Physical examination showed signs of congestion and a chest radiograph showed bilateral, predominantly right-sided, pleural effusion (figure 1A). The patient was admitted to the cardiology ward.

As this was the fifth time the patient had been admitted for pleural effusion with marked right-side predominance in the past year, it was decided to perform a thoracentesis, which showed transudative pleural fluid. A transthoracic echocardiogram (figure 1B,C) showed signs of pericardial constriction with a markedly dilated inferior vena cava that did not collapse with inspiration, apparent pericardial thickening with septal bounce (video 1 of the supplementary data), annulus reversus (lateral e' $<$ medial e') (figure 1D,E), and hepatic vein expiratory flow reversal (figure 1F). The patient also had severe tricuspid regurgitation with normal valvular and annulus morphology, allowing estimation of a pulmonary artery systolic pressure of 50 mmHg.

Based on these findings, it was decided to perform right heart catheterization, which demonstrated postcapillary pulmonary hypertension (mean pulmonary artery pressure of 40 mmHg and pulmonary capillary pressure of 27 mmHg) and a left ventricular dip and plateau pattern with elevation and equalization of end-diastolic pressures in both ventricles. These signs were all consistent with a diagnosis of constrictive pericarditis (figure 2A). The only relevant finding on a subsequent cardiac magnetic resonance imaging scan was abundant epicardial and mediastinal fat (without evident pericardial thickening) and signs of ventricular interdependence (figure 2B,C and video 2 of the supplementary data).

Given the striking constrictive physiology observed and the patient's history, it was decided to perform a pericardiectomy to remove fat. The outcome was favorable and the patient did not develop any complications and was discharged after 7 days. The postoperative echocardiogram showed moderate tricuspid regurgitation and decreased expression of findings indicative of elevated end-diastolic pressures in the right cavities (video 3 of the supplementary data). Follow-up outpatient radiographs showed minimal right-sided pleural effusion and no build-up of fluid since the surgery. The patient did not experience any new episodes or require hospitalization during 1 year of follow-up and remains in New York Heart Association class I.