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Subpulmonary ventricular function and inflammation are related to clinical heart failure in patients with a systemic right ventricle

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ABSTRACT

Background: Timely diagnosis of heart failure (HF) in patients with a systemic right ventricle (sRV) is difficult but important since clinical deterioration is fast once HF develops. We aimed to compare echocardiography and biomarker profile between sRV patients with and without HF and patients with a systemic left ventricle diagnosed with HF (sLV-HF).

Methods and results: Eighty-seven sRV patients and 30 sLV-HF patients underwent echocardiographic evaluation and blood sampling. Compared to sRV patients without HF, sRV-HF patients had more remodeling of the subpulmonary LV (spLV) (internal diameter 3.9 cm [3.3–5.7] vs 3.4 cm [2.9–3.9], P = 0.03, posterior wall 0.93 cm [0.76–1.20] vs 0.71 cm [0.59–0.91], P = 0.006) and lower spLV systolic function: ejection fraction (59 % ± 14 vs 70 % ± 10, P = 0.011), mitral annular plane systolic excursion (1.7 cm ± 0.5 vs 2.1 cm ± 0.4, P = 0.003), fractional area change (47 % [38–58] vs 59 % [51–70], P = 0.002) and lateral strain rate (−1.2/s ± 0.46 vs −1.5/s ± 0.39, P = 0.016). Inflammatory biomarkers were higher in sRV-HF patients compared to those without HF: red cell distribution width (13.3 fL [12.8–14.1] vs 12.6 fL [12.3–13.1], P < 0.001), neutrophil lymphocyte ratio (NLR, 3.7 [2.2–4.9] vs 2.4 [1.9–3.0], P = 0.015), C-reactive protein (CRP, 2.5 mg/dL [1.0–4.2] vs 1.2 mg/dL [0.0–2.0], P = 0.005) and compared to sLV-HF patients (NLR (3.7 [2.2–4.9] vs 2.5 [1.7–3.3], P = 0.044) and CRP (2.5 mg/dL [1.0–4.2] vs 0.85 mg/dL [0.6–2.0], P = 0.006).

Conclusion: Biventricular echocardiographic evaluation with a focus on the subpulmonary LV together with assessing inflammatory status in sRV patients could help in an earlier detection of HF.

1. Introduction

Patients with complete transposition of the great arteries (TGA) who have undergone atrial switch repair (either a Mustard or Senning operation) and patients with congenitally corrected transposition of the great arteries (ccTGA) have a biventricular circulation with a systemic right ventricle (sRV). Although the sRV initially adapts to the increased pressure load [1,2], sRV dysfunction, tricuspid regurgitation and heart failure (HF) become increasingly prevalent over time [3]. For sRV patients, HF is the leading cause of death [4]. Making a HF diagnosis in sRV patients is challenging given the paucity of HF-related symptoms [5], the lack of echocardiographic reference values for sRV (dys)function and the absence of an universal definition for adults with congenital heart disease (ACHD) and HF [6]. Nevertheless, a timely HF diagnosis is crucial because clinical deterioration occurs rapidly as soon as clinical HF develops [3].

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Therefore, there is a need to better understand which echocardiographic and biochemical markers are associated with HF in sRV patients and how these differ from patients with a systemic left ventricle in a biventricular circulation diagnosed with HF. This study aimed at evaluating biventricular function with echocardiography and biochemical markers of inflammation in sRV patients with and without HF and sLV-HF patients.

2. Materials and methods

2.1. Patient population

This study was reviewed and approved by the Ethical Committee of UZ/KU Leuven under study number S63490. Written informed consent to participate in the study was obtained prior to enrollment. Patients with a systemic right ventricle (TGA or ccTGA) were prospectively enrolled during their routine follow-up at the congenital heart disease clinic at the University Hospitals of Leuven. Every patient underwent a comprehensive echocardiographic examination and venous blood sampling. sRV patients were stratified into two groups based on the presence or absence of clinical heart failure (sRV-HF and sRV-no HF respectively). An additional cohort of patients with sLV diagnosed with HF (sLV-HF) without a congenital heart anomaly was included during their routine follow-up at the heart failure clinic at the University Hospitals of Leuven.

sRV-HF definition: signs and symptoms of HF requiring medical therapy with at least one of the following: I) impaired ventricular function with elevated intracardiac pressures on echocardiography or during cardiac catheterization, II) elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) and/or III) peak oxygen consumption in lowest quartile according to the published norms for patients with a sRV [7].

sLV-HF definition: signs and symptoms of HF with reduced (EF $\leq$ 40 %) or mid-range EF (EF = 41–49 %) according to ESC guidelines [8].

Exclusion criteria were age of <18 years, CRP >10 mg/dL, current pregnancy, presence of an auto-immune disease, and use of immunosuppressive drugs or nonsteroidal anti-inflammatory drugs within the 2 weeks.

2.2. Data collection

2.2.1. Echocardiography

Images were acquired using a Vivid 9 ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway) and analyzed offline using GE EchoPAC software (version 204, GE Vingmed Ultrasound, Horten, Norway).

2.2.1.1. Standard grayscale, Doppler, and myocardial velocity echocardiographic variables. At least two consecutive heartbeats were analyzed with values represented as mean values. In an apical 4-chamber view, RV/LV area at end diastole and end systole, LV/RV fractional are change (FAC), annular plane systolic excursion (APSE) of the mitral and tricuspid annulus from M-mode recordings and RV/LV ejection fraction using Simpson's biplane method were obtained. Mitral and tricuspid valve insufficiency was evaluated based on visual inspection and graded from 1 (none) to 4 (severe). Peak lateral mitral and tricuspid annular systolic velocity (S′) were measured. In sRV patients the size of the LV posterior wall (LVPW), LV internal diameter (LVID) and the thickness of the interventricular septum (IVS) was measured.

2.2.1.2. 2D speckle tracking. In an apical 4-chamber view, longitudinal strain and strain rate were analyzed using the 2D speckle tracking technique. For consistency between sRV and sLV patients, the interventricular septum was included with the systemic ventricle. Peak systolic values were calculated as peak negative strain and strain rate between semilunar valve opening and closure. All measurements were averaged over 3 consecutive beats. Timing information was measured from semilunar and atrioventricular valve Doppler traces during the same examination with a similar R-R interval.

2.2.2. Invasive haemodynamic assessment

From a subset of patients with heart failure (12/29, 41 %) invasive haemodynamic pressure measurements are available. Right atrial pressure, pulmonary capillary wedge pressure, end-diastolic and systolic pressures of the systemic RV and subpulmonary RV are shown in Table S1. In addition, we report mean pulmonary artery pressures, pulmonary vascular resistance (PVR) and cardiac index (CI) (Table S1).

2.2.3. Biochemistry

On the day of inclusion, peripheral venous blood sampling was sent to and analyzed by the clinical laboratory of UZ Leuven. Absolute and relative numbers of neutrophil and lymphocytes, red cell distribution width (RDW), C-reactive protein (CRP), sodium, serum creatinine, high-sensitive troponin T (hs-troponin T), NT-proBNP and ferritin were analyzed. Neutrophil-lymphocyte ratio (NLR) was calculated by dividing the absolute counts of neutrophils and lymphocytes from differential counts.

2.3. Statistical analysis

All statistical tests were performed using IBM SPSS Statistics for Windows (version 28.0.0.0, SPSS, Chicago) and data figures were made with Rstudio (version 2023.06.1 + 524). Normality was tested using the Kolmogorov-Smirnov test or Shapiro-Wilk test as appropriate. Descriptive data for continuous variables are reported as means ± standard deviation or as median with interquartile ranges as appropriate based on normality. Descriptive data for discrete variables are presented as frequencies or percentages. For comparison of continuous data among the different groups, one-way ANOVA or Kruskal-Wallis tests with post-hoc Dunn's tests were performed and proportions across the different groups were analyzed with Chi-square or Fisher-exact test as appropriate. For all correlations and univariate analyses, the Spearman rho correlation coefficient is reported. All tests were two-sided and considered statistically significant if the P-value was below 0.05.

3. Results

In total 87 sRV patients (71 % male, 28 % ccTGA) and 30 sLV-HF patients (70 % male) were included. The median age of the sRV group was 38 (33–45) years and the mean age of the sLV patients was 68 ± 13 years (Table S1). Twenty-nine (33 %) sRV patients had HF, of which 10 (35 %) were patients with ccTGA. A schematic of the inclusion process can be found in the supplemental materials (Fig. S1).

3.1. Comparisons between sRV patients with and without HF

When sRV-HF patients were compared to those without HF, sRV-HF patients were older (44 years vs 35 years, P < 0.001), more symptomatic (57 % vs 18 % were in NYHA class $\geq$ II, P < 0.001) and received more HF therapy (Table S1). sRV-HF patients had higher inflammatory markers: RDW (13.3 fL (12.8–14.1) vs 12.6 fL (12.3–13.1), P < 0.001), CRP (2.5 mg/dL (1.0–4.3) vs 1.2 mg/dL (0.0–2.0), P = 0.005) and NLR (3.7 (2.2–4.9) vs 2.4 (1.9–3.0), P = 0.015) (Table 1). Additionally, sRV-HF patients had higher natriuretic peptide levels (NT-proBNP 921 (365–1452) vs 208 (114–322) ng/L, P < 0.001). The regurgitation of the systemic atrioventricular (AV) valve was more severe in sRV-HF patients (22 % vs. 16 % patients had a systemic AV regurgitation >2/4, P = 0.034). Myocardial longitudinal deformation was lower in the systemic (right) ventricle of the HF patients (Table 2): septal strain (-10.6 % ± 2.7 vs −12.4 % ± 2.8, P = 0.026), lateral strain (−11.5 % ± 4.1 vs −13.2 % ± 4.0, P = 0.046), GLS (−11.2 % ± 2.6 vs −12.6 % ± 2.8, P = 0.047)

Table 1
Laboratory parameters.

	All sRV patients n = 87	sRV no HF n = 58	sRV-HF n = 29	sLV-HF n = 30	P-value$_1$	P-value$_2$	P-value$_3$	P-value$_4$
Parameter, *n (%)*								
PMN (%), *sRV 82 (94), sLV 30 (100)*	64.1 ± 8.7	63.1 ± 8.7	66.3 ± 8.5	63.0 ± 9.0	0.287	0.143	0.879	0.185
Lymphocytes (%), *sRV 92 (94), sLV 30 (100)*	24.9 ± 7.7	26.5 ± 7.2	19.0 ± 7.6	25.0 ± 8.1	**0.024**	**0.006**	0.508	0.090
RDW (%), *sRV 87 (100), sLV 30 (100)*	12.8 (12.4–13.2)	12.6 (12.3–13.1)	13.3 (12.8–14.1)	13.8 (13.0–14.2)	**<0.001**	**<0.001**	**<0.001**	0.261
NLR, *sRV 82 (94), sLV 30 (100)*	2.6 (2.0–3.7)	2.4 (1.9–3.0)	3.7 (2.2–4.9)	2.5 (1.7–3.3)	**0.041**	**0.015**	0.971	**0.044**
CRP (mg/dL), *sRV 87 (100), sLV 30 (100)*	1.4 (0.6–3.0)	1.2 (0.0–2.0)	2.5 (1.0–4.2)	0.85 (0.6–2.0)	**0.008**	**0.005**	0.700	**0.006**
Creatinine (mg/dl), *sRV 87 (100), sLV 30 (100)*	0.87 (0.77–1.01)	0.85 (0.75–0.92)	1.02 (0.81–1.14)	1.28 (0.89–1.68)	**<0.001**	**0.002**	**<0.001**	**0.015**
Sodium (mmol/L), *sRV 87 (100), sLV 30 (100)*	140 (139–141)	140 (139–141)	140 (139–140)	139 (137–141)	0.147	0.291	0.124	0.514
Hs-troponin T (ng/L), *sRV 87 (100), sLV 30 (100)*	7.5 (5.0–11.0)	5.9 (4.2–8.8)	12.0 (7.2–18.0)	18.0 (11.0–33.0)	**<0.001**	**<0.001**	**<0.001**	**0.017**
NT-proBNP (ng/L), *sRV 87 (100), sLV 30 (100)*	275 (140–703)	208 (114–322)	921 (365–1452)	675 (369–1404)	**<0.001**	**<0.001**	**<0.001**	0.505
Ferritin (mcg/L), *sRV 80 (92), sLV 30 (100)*	187 (107–270)	197 (132–263)	142 (93–323)	225 (85–395)	0.631	0.424	0.646	0.388

PMN = polymorphonuclear neutrophils; RDW = red blood cell distribution width; NLR = neutrophil-lymphocyte ratio; CRP = C-reactive protein; hs-troponin = high-sensitivity troponin, NT-proBNP = N-terminal pro-brain natriuretic peptide; P-value$_1$ = sRV no HF vs sRV-HF vs sLV-HF, P-value$_2$ = sRV no HF vs sRV-HF, P-value$_3$ = RV no HF vs sLV-HF, P-value$_4$ = sRV-HF vs sLV-HF.

Table 2
Echocardiographic measurements.

	All sRV patients n = 87	sRV no HF n = 58	sRV-HF n = 29	sLV-HF n = 30	P-value$_1$	P-value$_2$	P-value$_3$	P-value$_4$
Systemic ventricle *complete, n (%)*								
Systemic AV-regurgitation > 2, *sRV 85 (98), sLV 29 (97)*	15 (17)	9 (16)	6 (22)	1 (3)	**<0.001**	**0.034**	**0.010**	**<0.001**
sysAPSE (cm) *sRV 83 (95), sLV 25 (83)*	1.3 (1.0–1.5)	1.3 (1.0–1.5)	1.1 (0.9–1.5)	1.2 ± 0.3	0.247	0.140	0.245	0.650
sysFAC (%) *sRV 72 (83), sLV 25 (83)*	26 (21–36)	26 (22–37)	22 (20–32)	28 ± 8	0.132	0.056	0.690	0.115
sysS' (cm/s) *sRV 59 (68), sLV 24 (80)*	4.2 (3.5–4.9)	4.2 (3.5–5.5)	4.2 (3.4–4.8)	5.6 ± 1.5	**0.001**	0.740	**0.001**	**0.001**
sysGLS > -12 (%) sRV 58 (67), sLV 24 (80)	27 (47)	14 (24)	13 (72)	4 (17)	**0.001**	**0.009**	0.136	**<0.001**
sysSept strain (%) sRV 66 (76), sLV 24 (80)	−11.8 ± 2.8	−12.4 ± 2.8	−10.6 ± 2.7	−11.3 ± 4.2	0.100	**0.026**	0.432	0.311
sysLat strain (%) sRV 66 (76), sLV 23 (77)	−12.7 ± 2.8	−13.2 ± 4.0	−11.5 ± 4.1	−10.1 ± 5.0	**0.008**	**0.046**	**0.005**	0.370
sysGLS (%) sRV 58 (67), sLV 24 (80)	−12.2 ± 2.8	−12.6 ± 2.8	−11.2 ± 2.6	−9.7 ± 4.1	**0.005**	**0.047**	**0.003**	0.296
sysSept strain rate (/s) sRV 65 (75), sLV 24 (80)	−0.68 ± 0.17	−0.70 ± 18	−0.64 ± 0.18	−0.67 ± 0.15	0.576	0.359	0.449	0.768
sysLat strain rate (/s) sRV 59 (68), sLV 23 (77)	−0.74 ± 0.21	−0.76 ± 0.22	−0.69 ± 0.18	−0.62 ± 0.24	0.056	0.266	**0.019**	0.303
sysPeak systolic strain rate (/s) sRV 58 (67), sLV, 23 (77)	−0.69 ± 0.15	−0.71 ± 0.16	−0.65 ± 0.14	−0.53 ± 0.16	**<0.001**	0.203	**<0.001**	**0.043**
Subpulmonary ventricle *complete, n (%)*								
IVSd (cm) *sRV 60 (69), sLV 25 (83)*	0.90 (0.60–0.80)	0.87 (0.74–1.04)	0.93 (0.76–1.08)	1.10 (1.0–1.20)	**<0.001**	0.306	**<0.001**	**0.030**
spID (cm) *sRV 68 (78)*	3.5 (2.9–3.9)	3.4 (2.9–3.9)	3.9 (3.3–5.7)	/	/	**0.030**	/	/
spPWd (cm) *sRV 62 (71)*	0.78 (0.60–1.00)	0.71 (0.59–0.91)	0.93 (0.76–1.20)	/	/	**0.006**	/	/
spAPSE (cm) *sRV 74 (85), sLV 25 (83)*	2.0 ± 0.4	2.1 ± 0.4	1.7 ± 0.5	1.7 (1.6–2.1)	**<0.001**	**0.003**	**0.001**	0.884
spFAC (%) *sRV 64 (74)*	57 (46–64)	59 (51–70)	47 (38–58)	49 (44–56)	**<0.001**	**0.002**	**0.003**	0.673
spEF (%) *sRV 61 (70)*	66 ± 13	70 ± 10	59 ± 14	/	/	**0.011**	/	/
spS' (cm/s) *sRV (52 (60)*	7.7 ± 2.2	7.9 ± 2.2	7.2 ± 2.3	/	/	0.461	/	/
spLat strain (%) *sRV 45 (52), 23 (77)*	−19.6 ± 5.7	−20.2 ± 5.2	−18.3 ± 6.7	−21.0 ± 8.1	0.444	0.342	0.578	0.248
spLat strain rate (/s) *sRV 46 (53), sLV 23 (77)*	−1.42 ± 0.44	−1.5 ± 0.39	−1.2 ± 0.46	−1.3 ± 0.40	0.053	**0.016**	0.170	0.359

AV = atrioventricular; APSE = annular plane systolic excursion; FAC = fractional area change, S' = peak lateral annular systolic velocity; GLS = global longitudinal strain; IVSd = interventricular septum in diastole; IDd = internal diameter in diastole; PWd = posterior wall in diastole; EF = ejection fraction; sys = systemic; sp = subpulmonary; P-value$_1$ = sRV no HF vs sRV-HF vs sLV-HF, P-value$_2$ = sRV no HF vs sRV-HF, P-value$_3$ = sRV no HF vs sLV-HF, P-value$_4$ = sRV-HF vs sLV-HF.

and lateral strain rate (−1.2/s ± 0.46 vs −1.5/s ± 0.39, P = 0.016). The subpulmonary (left) ventricle of sRV-HF patients had a significantly lower APSE (spAPSE, 1.7 cm ± 0.5 vs 2.1 cm ± 0.4, P = 0.003), FAC (spFAC 47 % (IQR 38–58) vs 59 % (IQR 51–70), P = 0.002) and EF (spEF, 59 % ± 14 vs 70 % ± 10, P = 0.011). Additionally, the posterior wall (spPWd) and the diastolic diameter (spIDd) of the subpulmonary ventricle were enlarged in sRV-HF patients (0.93 cm (0.76–1.20) vs 0.71 (0.59–0.91), P = 0.006 and 3.9 cm (3.3–5.7) vs 3.4 cm (2.9–3.9), P = 0.030, respectively).

Another possible explanation for the remodeling of the subpulmonary LV are associated defects such as baffle leak or stenosis, residual shunts or pulmonary stenosis or insufficiency. We did not detect any significant baffle leakage, baffle obstruction or residual shunt on echocardiography. While we observed pulmonary valve insufficiency, these cases were deemed not hemodynamically significant as all were graded 2/4 or lower and were similar between sRV patients with and without HF. In addition, we measured increased gradients over the pulmonary valve in some patients, but all were mild gradients and therefore not hemodynamically significant. Furthermore, the gradients were comparable between sRV patients with and without HF. Therefore, the remodeling of the subpulmonary LV secondary to other defects is less likely in our patient cohort.

3.2. Comparisons between sRV-HF and sLV-HF patients

Overall, the sLV-HF cohort was older (68 vs 44 years, P < 0.001) and despite a comparable number of symptomatic patients in both groups, sRV-HF patients were less likely to receive HF therapy (Table S1). Surprisingly, inflammatory markers were higher in the sRV-HF group: NLR (3.7 (2.2–4.9) vs 2.5 (1.7–3.3), P = 0.044) and CRP (2.5 mg/dL (1.0–4.3) vs 0.85 mg/dL (0.6–2.0), P = 0.006) (Table 1). There was no significant difference in levels of NT-proBNP (921 (365–1452) vs 675 (369 = 1404) ng/L, P = 0.505) between both groups.

Comparing both systemic ventricles, the sRV-HF patients had more regurgitation of the systemic AV valve (22 % vs 3 %, P < 0.001), a lower S' (4.2 (3.4–4.8) vs 5.6 ± 1.5, P = 0.001) and more patients had a strain lower than −12 % (14 sRV-HF patients vs 4 sLV-HF patients, P < 0.001). In contrast, the peak systolic strain rate was lower in sLV-HF patients (−0.65/s ± 0.14 vs. −0.53/s ± 0.16, P = 0.043) and sLV-HF patients had a more hypertrophied interventricular septum (0.93 cm (0.76–1.08) vs. 1.10 cm (1.00–1.20), P = 0.030) (Table 2).

3.3. Correlations between echocardiographic measurements and biomarkers

Heatmaps for the three different groups between inflammatory markers and echocardiographic measurements are represented in Fig. 1. For sRV patients without HF, there was no significant correlation between laboratory parameters and systolic function of the systemic (right) ventricle and only weak to moderate correlations between NT-proBNP and LV posterior wall thickness (r = 0.339, P = 0.023) and NLR and S' (r = 0.471, P = 0.004) of the subpulmonary (left) ventricle. For these analyses NT-proBNP was log-transformed.

For sRV-HF patients, there was a moderate correlation between NT-proBNP and the septal strain of the systemic (right) ventricle (r = 0.597, P = 0.005). In contrast, stronger correlations were found between NT-proBNP and systolic function of the subpulmonary (left) ventricle: with spAPSE (r = −0.467, P = 0.025), spFAC (r = −0.567, P = 0.011), spEF (r = −0.509, P = 0.022) and lateral strain rate (r = 0.618, P = 0.016). Higher NT-proBNP levels also correlated moderately with dilatation of the subpulmonary LV (spIDd, r = 0.538, P = 0.018). Of interest, there were moderate to strong correlations between inflammation markers and subpulmonary systolic function: NLR with spFAC (r = −0.581, P = 0.012), RDW with spFAC (r = −0.711, P = 0.001), spEF (r = −0.620, P = 0.004), and lateral strain rate (r = 0.547, P = 0.037).

For sLV-HF patients, there were significant correlations between NT-proBNP and systolic function of the systemic (left) ventricle: with sysEF (r = −0.620, P = 0.001), sysFAC (r = −0.692, P < 0.001), sysS' (r = −0.411, P = 0.046), sysLat strain (r = 0.444, P = 0.030) and peak systolic strain rate (r = 0.582, P = 0.004). Regarding inflammatory markers, only CRP correlated moderately with the lateral strain of the subpulmonary (right) ventricle (r = 0.461, P = 0.027).

3.4. Univariate linear regression analysis

In the sRV-HF group, there was a positive association between NT-proBNP and sysSept strain ($\beta 1$ = 0.0014 CI (0.0001–0.0027), P = 0.025) and spFAC ($\beta 1$ = −0.1 CI (−0.0136 – 0.0058), P < 0.001) (Fig. 2). One association was found between NT-proBNP and sysFAC in the sLV patients ($\beta 1$ = −9.0038 CI (−0069 to −0.0006), P = 0.021), but no associations were found between NT-proBNP and systolic function in sRV patients without HF (Fig. 2).

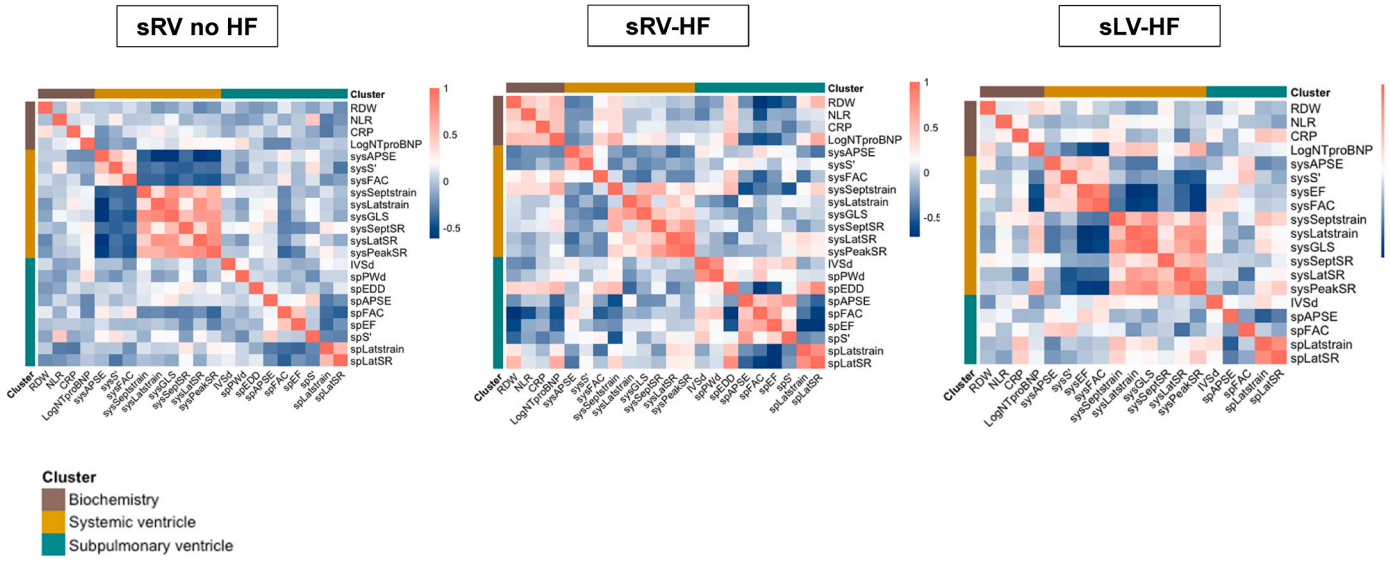

Fig. 1. Heatmap showing Spearman correlation analysis between echocardiographic measurements and biomarkers for each group separately.

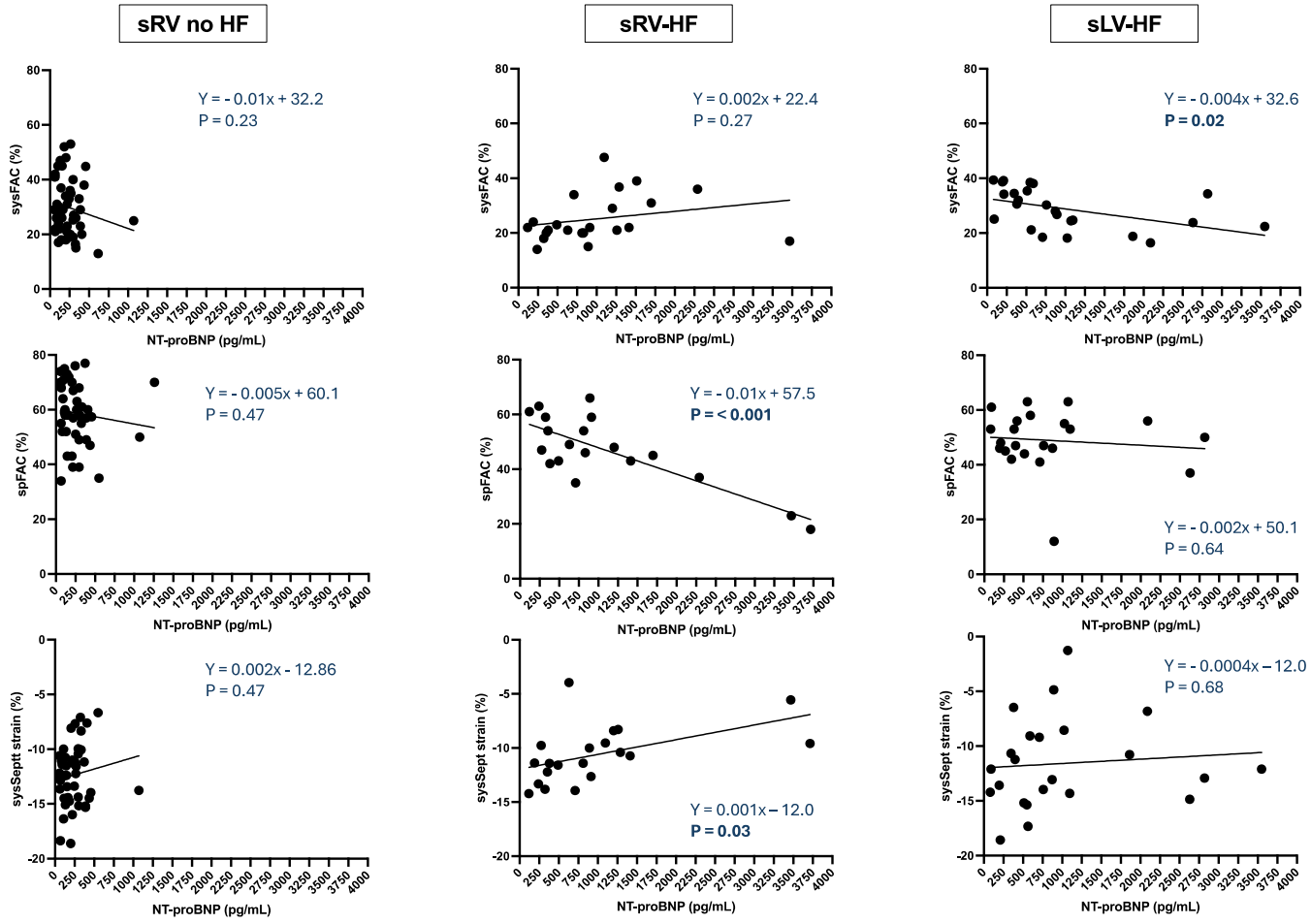

Fig. 2. Univariate linear regression between NT-proBNP and systolic function of the subpulmonary and systemic ventricle in the 3 groups.

4. Discussion

The data in this study indicates that sRV patients with a diagnosis of HF have worse subpulmonary LV function when compared to sRV patients without HF. This association is stronger than that observed for systolic sRV function between these two groups. Moreover, sRV-HF patients had higher inflammatory biomarkers when compared to sRV-no HF patients and sLV-HF patients.

4.1. Subpulmonary LV function is related to clinical HF in sRV patients

Given the rapid clinical decline once sRV patients progress to HF and the limited evidence-based treatment options' [9], early detection of HF is important. Although systemic RV systolic function has been related to exercise capacity, other studies [10] failed to show an association between sRV systolic function at rest and exercise capacity. Only recently the importance of the subpulmonary LV is being recognized: worse systolic function of the subpulmonary LV and a larger volume were related to impaired clinical outcome [11] and lower exercise capacity [12] respectively. Additionally, size and function of the subpulmonary ventricle were stronger predictors of clinical outcome than the standard performance parameters of the sRV [13]. The observation that there is more extensive fibrosis in the subpulmonary LV compared to the systemic RV further underlines the importance of the LV in sRV patients [14,15]. Our study confirms that sRV-HF patients have more remodeling and a lower systolic function of the subpulmonary LV. Additionally, dilatation and systolic function of the subpulmonary LV correlated more strongly with HF severity (NT-proBNP levels) compared to the systemic RV suggesting that the failing subpulmonary LV contributes more to clinical HF than the systemic RV.

Although we also noted differences in systemic RV systolic function these differences were less pronounced than those for the subpulmonary LV. Indeed, sRV-HF patients had a lower strain of the systemic RV compared to sRV patients without HF. Still, the lower deformation values of sRV patients without HF underscore the difficulty of using these values to make a HF diagnosis in patients with a systemic RV and reflects the lack of association between these measures and outcome noted in other studies [3,16].

We can only speculate on the cause of subpulmonary LV dysfunction in sRV-HF patients which is probably multifactorial. Firstly, comparable to the mechanism of subpulmonary RV dysfunction in acquired LV failure [17], postcapillary pulmonary hypertension secondary to elevated systemic RV end-diastolic pressures could lead to increased pressure load to the subpulmonary LV and subsequent dysfunction. While we did not measure pulmonary pressures in our study, it is likely that our sRV-HF patients have either post-capillary or combined pre- and postcapillary pulmonary hypertension [18,19] especially when natriuretic peptides are elevated [18]. Secondly, adverse mechanical ventriculo-ventricular interaction (VV interaction), can cause a septal shift (due to increased afterload for the systemic RV), and disturbance of shared myocardial fibers which may cause subpulmonary LV dysfunction through unfavorable ventricular interdependence [20–22]. Indeed, there is evidence that subpulmonary LV outflow tract obstruction protects against the development of HF, possibly by deviating the septum towards the sRV, preventing the development of systemic AV valve regurgitation [23]. Besides septal displacement, a reduced septal

function and reduced septal myocardial work has also been reported and may lead to impaired sRV function (and through VV interaction consequentially to subpulmonary LV function) [24]. Cardiac dyssynchrony in the systemic RV (when present), is another mechanism that could potentially lead to subpulmonary LV dysfunction through electrical VV interaction [21]. In our study, correlations between systemic RV and subpulmonary LV function were limited, suggesting that elevated pulmonary pressures rather than VV interaction contributed to subpulmonary LV dysfunction.

4.2. sRV-HF patients have elevated inflammation

In contrast to abundant evidence for the presence of inflammation in acquired HF [25], a role for inflammation in HF in ACHD patients is less clear. Chronic inflammation markers, RDW and hs-CRP, have a prognostic role in the ACHD population in general [26–30] and in the sRV population specifically [16] suggesting a potential involvement of inflammation in adverse outcome in ACHD patients. Our study is the first to indicate that NLR, a surrogate marker of systemic inflammation and known predictor of mortality and cardiac events in many cardiovascular diseases including HF, has importance in ACHD. Our study suggests a possible role for inflammation in HF as we show that sRV-HF patients have higher levels of inflammatory markers than sRV patients without HF and sLV-HF patients. Whether the reason for increased inflammation in sRV-HF patients compared to sLV-HF patients is due to undertreatment of HF (more sLV-HF patients received HF medication) or indicating that a different treatment approach is warranted (ex. anti-inflammatory therapies) requires further study.

It remains unclear if inflammation plays a causal role in the development of HF or if it is an epiphenomenon reflecting ongoing cardiovascular disease. In line with previous data [16]., we failed to show any correlation between inflammatory markers and systolic function of the systemic RV. However, we did find stronger correlations between RDW and systolic function of the subpulmonary ventricle, again suggesting an important role for the subpulmonary LV in HF in sRV patients.

The paucity of correlations between inflammatory markers and echocardiographic measurements of systolic function could have multiple reasons. It is possible that inflammation in HF is a more chronic and low-grade process where its consequences on cardiac function are only seen after the transition from inflamed tissue to the development of fibrosis. Correlations between markers of fibrosis and ventricular function of the systemic RV shown earlier in TGA patients [31] could support this theory. Alternatively, comparable to acquired HF, the pathophysiology of inflammation in HF in sRV patients is probably complex. More HF-specific cytokines (rather than general markers of inflammation) may correlate better with ventricular function. Lastly, conventional echocardiography may not be sensitive enough to detect changes in ventricular function secondary to inflammation. Nonetheless, sRV-HF patients do have more inflammation. Regardless of inflammation being a mediator or bystander in the underlying HF process, determining the inflammatory status in sRV patients could be helpful in assessing HF in these patients.

5. Limitations

The study was performed at a single tertiary center and hence is subjective to selection bias possibly favoring a sicker sRV and sLV-HF patient population. Given the lack of a universal definition for HF in the ACHD population, our definition could differ from the ones used in other studies. However, by combining clinical characteristics of HF with at least one more objective marker (biochemistry or echocardiography) we aimed to define HF as accurately as possible. The majority of our cohort (70 %) was male, reflecting the higher prevalence of TGA in males. We could only perform all strain measurements in approximately 70 % patients due to insufficient image quality. The sLV-HF patients differ from the sRV patients not only in age but also in the presence of cardiovascular risk factors. However, cardiovascular risk factors are inherently linked to most of the etiologies leading to HF in normal heart anatomy. Lastly, we did not correct for multiple testing or for a potential influence of pharmacological therapy on biomarkers. Therefore, we cannot exclude a potential effect of treatment on the correlations found between biomarkers and echocardiographic function, especially in those patients with sLV-HF.

6. Conclusion

sRV-HF patients have more remodeling and a lower systolic function of the subpulmonary LV compared to sRV patients without HF. Status of the subpulmonary LV correlated more strongly with severity of HF than the systemic RV. Additionally, sRV-HF patients have more inflammation compared to sRV patients without HF and sLV-HF patients. We therefore suggest a systematic evaluation of the subpulmonary LV together with assessment of the inflammatory status in sRV patients to detect HF at an earlier timepoint.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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CRediT authorship contribution statement

Valérie Spalart: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Aleksandra Cieplucha:** Writing – review & editing, Formal analysis. **Werner Budts:** Writing – review & editing, Data curation. **Pieter De Meester:** Writing – review & editing. **Els Troost:** Writing – review & editing. **Thilo Witsch:** Writing – review & editing. **Walter Droogne:** Writing – review & editing. **Lucas NL Van Aelst:** Writing – review & editing. **Magalie Ladouceur:** Writing – review & editing. **Kimberly Martinod:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Alexander Van De Bruaene:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper; two of the authors (WB, ML) serve as EB Members of the IJCCHD, but have not been involved with the handling of this paper.

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Appendix A. Supplementary data

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