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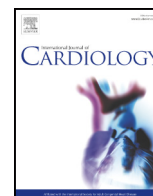
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Role of myocardial collagen degradation and fibrosis in right ventricle dysfunction in transposition of the great arteries after atrial switch

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ABSTRACT

Background: Heart failure is a serious event in patients with transposition of the great arteries (D-TGA) after atrial redirection surgery. We aimed to determine the association between myocardial fibrosis and systolic and diastolic systemic right ventricle (sRV) dysfunction.

Methods: Diastolic and systolic function of sRV was prospectively assessed using echocardiography and cardiac magnetic resonance imaging (CMR) in 48 patients with atrially switched D-TGA and 26 healthy subjects. Diastolic function of the subaortic ventricle was assessed by echocardiography Doppler and DTI. In CMR, ejection fraction of sRV and wall stress defined as the product of the systolic blood pressure and volume/mass ratio were assessed. Fibrosis extent within sRV myocardium was evaluated using gadolinium-enhanced magnetic resonance and serum collagen turnover biomarkers.

Results: Late gadolinium enhancement (LGE) was found in 35% of D-TGA patients, and the collagen degradation biomarker pro-MMP1:TIMP1 ratio was significantly increased in D-TGA patients compared to healthy subjects (1.0×10^{-2} vs. 2.5×10^{-2} , $p = 0.04$). Increase in sRV wall stress was significantly associated with LGE ($p = 0.01$) and pro-MMP1:TIMP1 ratio ($r = 0.77$, $p < 0.01$). After adjustment for age, sex, BMI, blood pressure and cardiac treatment, pro-MMP1:TIMP1 ratio was the strongest determinant of sRVEF ($R^2 = 0.85$, $p < 0.01$). Pro-MMP1:TIMP1 ratio was also significantly correlated with the early diastolic filling parameter E/E' ($r = 0.53$, $p = 0.02$), but this was not anymore the case after adjustment.

Conclusions: Diastolic and systolic sRV dysfunction is related to myocardial collagen degradation and fibrosis. Research in medical therapies that reduce systemic sRV afterload and limit collagen degradation is warranted in this setting.

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1. Introduction

In patients who underwent surgical correction of transposition of the great arteries with a Mustard or Senning procedure (D-TGA), the morphological right ventricle plays the physiological role of a systemic

ventricle (sRV). Heart failure in these patients is a prevalent and life-threatening complication [1]. However, its etiology is not well understood, and treatment options are empirical. As observed in hypertension or aging, myocardial fibrosis may be a major determinant of altered diastolic filling in sRV, and ultimately deteriorate systolic sRV function, which facilitates the development of heart failure (HF) [2–5]. This mechanism was also described in right ventricle failure related to pulmonary arterial hypertension [6]. An improved understanding of the remodelling sRV, and the role of myocardial fibrosis in this condition

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may lead to a novel management strategy more broadly directed to preservation of myocardial health. Our main hypothesis was that chronically elevated systemic wall stress was associated with abnormal myocardial collagen turnover in sRV myocardium, and diastolic and systolic sRV dysfunction, as observed in the LV of hypertensive patients [7].

Cardiac magnetic resonance imaging (CMR) has been validated to measure ventricular wall stress from ventricular volume and systemic pressure [8,9]. Moreover, imaging techniques and serum collagen biomarkers can now be used together as surrogate markers of myocardial fibrosis [3,4,10,11]. In patients with sRV, focal or diffuse areas of dense myocardial fibrosis can be detected by CMR by using late gadolinium enhancement (LGE) sequences, and correlate with poorer ventricular systolic function and worse prognosis [12,13]. Furthermore, a panel of circulating molecules have been proposed as biomarkers of myocardial collagen remodelling [7] (see Supplementary data S1). Accordingly, the goals of this study were to determine the prevalence of myocardial fibrosis by using LGE during CMR and biomarkers of myocardial collagen metabolism in patients with sRV, and to examine the association of myocardial fibrosis markers with sRV wall stress and parameters of sRV systolic and diastolic function.

2. Methods

2.1. Study protocol and population

Study protocol and population have been already reported [14]. Briefly, from February 2011 to March 2012, we conducted a single-centre, cross-sectional, prospective study that included 49 consecutive patients with sRV after atrial switch for D-TGA (Flowchart in Supplemental Methods S2, Fig. 1). These patients were recruited at the cardiology department of our institution. Patients with contraindication for CMR or gadolinium injection ($n = 6$), with residual ventricular septal defect or prosthetic systemic atrioventricular valve, as well as pregnant women were not included in the study ($n = 3$). Twenty-six healthy volunteers, comparable for age and sex with D-TGA patients, were also studied as control. Each volunteer provided his medical history and underwent a complete physical examination, including an electrocardiogram and an echocardiography. The study was performed in accordance with the principles set out in the declaration of Helsinki and was approved by the Ethics Review Board of our institution. Subjects with a stated history of osteoporosis, renal failure or hepatic fibrosis were excluded. All patients and healthy volunteers provided written informed consent to participate in the study (Clinical trial: NCT02066506).

All patients and healthy volunteers underwent CMR, echocardiography and had blood sample within 24 h. B-Type natriuretic peptide (BNP), endothelin-1, fibrinogen, active renin and aldosterone blood concentrations were measured in all subjects. Biomarkers of myocardial collagen metabolism were available in 30 patients and 14 healthy volunteers.

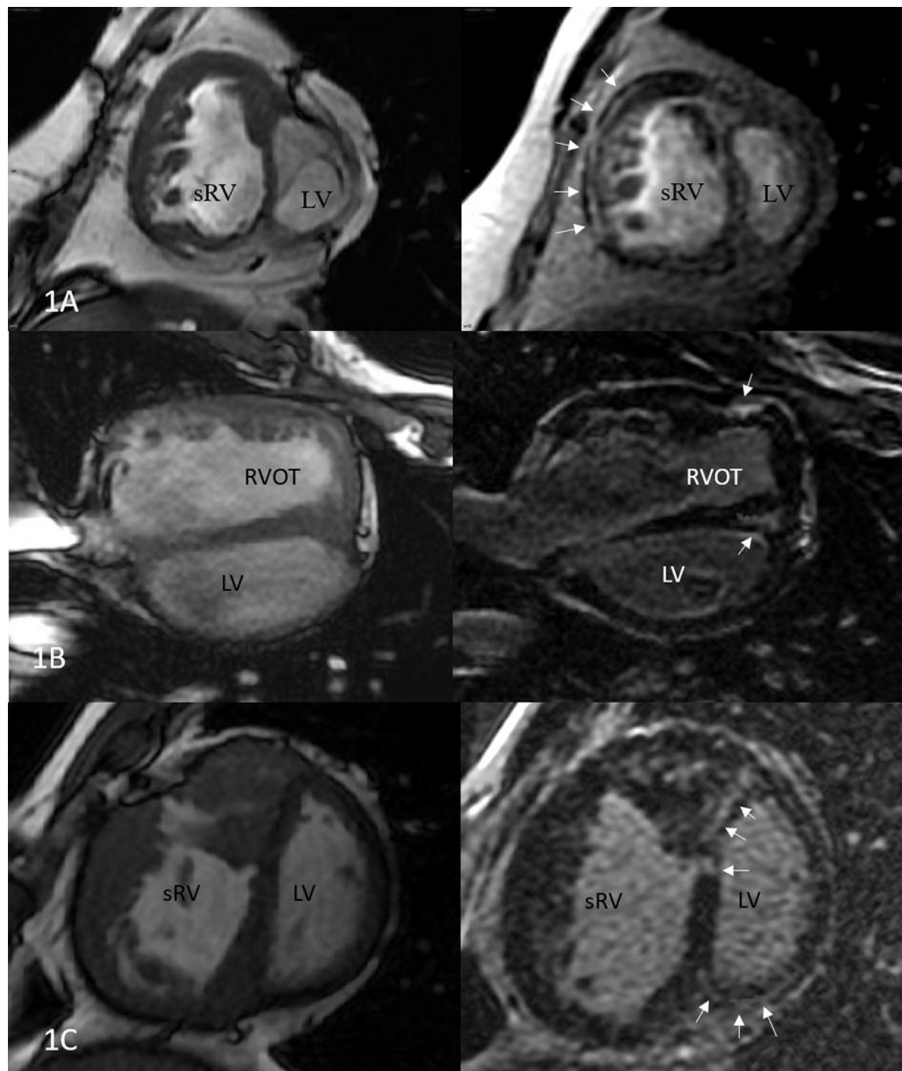


Fig. 1. Late gadolinium lesions in patients with D-TGA. LGE distribution was mainly in the basal segments of the sRV free wall (panel A). Five patients presented LGE at right ventricle outflow tract (panel B) and 2 in the inferior LV wall (panel C). In 10 patients, LGE was observed in the interventricular septum (panel C), although VSD closure was performed in only 2 patients. Panels A, B and C show sRV and sub-pulmonary LV on cine steady-state free-precession sequence on the left, and on 2D segmented inversion-recovery sequences on the right. White arrows show LGE lesions. sRV: systemic right ventricle, LV: sub-pulmonary left ventricle.

2.2. Echocardiography Doppler

Transthoracic echocardiography was performed using a GE-Vingmed Vivid 7 system (Horten, Norway). Echocardiograms were examined by one of the investigator (M.L.), who was blinded to CMR data. Complete two-dimensional, Doppler color-flow, spectral Doppler studies were performed, and tricuspid regurgitation was graded as mild, moderate, or severe, according to the guideline of the American Society of Echocardiography [15–17]. Doppler method was used to measure peak velocity of early (E), late (A) sRV filling flow and deceleration time. Early peak myocardial velocity (E') and isovolumic relaxation time were measured using pulsed Doppler Tissue Imaging, with Doppler sample volume placed in the tricuspid annulus of the RV free wall in D-TGA patients and in lateral LV wall in controls.

2.3. CMR data acquisition

All CMR examinations were performed on a 1.5 T magnet (SignaHDx, GEMS, Waukesha, WI, USA) using a dedicated 8-channel phased array surface cardiac coil. For volumetric and functional imaging, breath hold standard cine steady-state free-precession (SSFP) sequence was applied in axial, short-axis, 2-, 4-, and 3-chamber and RV vertical long-axis views. Short-axis images covering the whole heart without inter-slice gap from apex to base were acquired using the following scan parameters: repetition time = 3.7 ms, echo time = 1.5 ms, flip angle = 50°, pixel size = 0.74 mm × 0.74 mm, slice thickness = 8 mm, views per segment = 12, temporal resolution = 15 ms after applying view sharing. In D-TGA patients, a 3D non-ECG-gated coronal contrast enhanced angiography was further acquired during intravenous injection of 0.2 mmol/kg gadolinium dimeglumine (Dotarem, Villepinte, France) and followed by a second 3D axial angiography in order to evaluate both caval venous baffle and pulmonary veins pathways in two orthogonal views. Late gadolinium enhancement (LGE) images were finally acquired using both 3D and 2D segmented inversion-recovery CMR sequences. For 3D LGE data, 12 to 16 contiguous 6 mm-thick slices were acquired per breath-hold in 3-chamber view and twice in short-axis view, between 8 and 11 min after gadolinium injection. Such acquisitions were followed by 2D acquisition of 8 short-axis slices in 4 to 8 successive breath-holds, between 10 and 16 min, after injection. For each individual patient, the inversion time was optimized to null viable myocardium. LGE 3D and 2D data of each D-TGA patient were visually analysed by an experienced operator (E.M.) blinded to patients' clinical data (collected by M.L.). The presence or absence of LGE was detected by the operator only on the 2D acquisitions but only the presence of myocardial LGE areas previously detected on the 3D acquisitions was taken into account.

2.4. Image analysis

SSFP images analysis was performed, using QMASS software (version 6, Medis, Leiden, the Netherlands), to determine systemic ventricle mass at end-diastole, end-diastolic (ED) and end-systolic (ES) volumes, and ejection fraction. In D-TGA, sRV measurements were performed including the trabeculations as part of the sRV mass. Systemic ventricle remodelling was estimated by the systemic ventricular mass/ED systemic ventricular volume ratio, similarly to LV remodelling evaluation [18]. Wall stress index was estimated according to the following formula: Wall stress = systolic blood pressure × systemic ventricle ES volume / systemic ventricle mass ratio [9], by using simultaneous brachial blood pressure estimate during MR acquisition.

2.5. Measurement of serum biomarkers

Blood samples (serum and plasma) were obtained 12 h after CMR, and processed 60 min after semi-sitting position, spun down and stored at –80 °C before analysis of BNP, active renin, aldosterone, endothelin-1, galectin-3, C-terminal propeptide of type I collagen (PICP), C-terminal telopeptide of type I collagen (ICTP), intact N-terminal propeptide of type 3 collagen (PIIINP), type 1 pro-matrix metalloproteinase (pro-MMP-1), tissue inhibitor of type 1 metalloproteinase (TIMP-1), bone-specific alkaline phosphatase (BAP), fibrinogen and C-reactive protein (CRP). All assays were performed in accordance with manufacturers' instructions (see the Methods section in the Supplementary data S2) by investigators who were unaware of the subjects' clinical status and data.

2.6. Statistical analysis

Patients' characteristics and clinical data were reported as medians and interquartile range for continuous variables, and percent for categorical variables. The Kolmogorov-Smirnov test for normality was performed to determine whether continuous variables were normally distributed, which was the case for each continuous variable. The Mann-Whitney test was used to compare CMR and biological parameters between D-TGA and control subjects, and between D-TGA patients with and without LGE lesions. Spearman coefficient was used to assess univariate association between biological parameters and CMR sRV measurements and echocardiographic diastolic parameters. Potential covariates with clinical relevance, such as age, sex, mean blood pressure, cardiac treatment (beta-blockers, ACE or ARA2), were selected by examining their significance in univariate and multivariate regression models with CMR and echocardiographic parameters of sRV function. All statistical tests were 2-sided, significance was set at $p < 0.05$. All data were analysed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2013).

3. Results

3.1. Subjects

Among the 49 D-TGA subjects reaching the study inclusion criteria, one patient was excluded because of artefacts on velocity-encoded acquisitions and LGE acquisition due to difficulties to hold his breath during the CMR protocol. The demographics history and clinic of the 48 remaining patients are shown in Table 1. Thirteen patients were operated by Mustard operation and 35 by Senning operation. This surgery was combined with ventricular septal defect (VSD) closure in 2 patients, or with aortic coarctation repair in one. Only one patient had undergone additional cardiac surgery after the initial operation to treat a pulmonary veins pathway stenosis. Most patients were NYHA functional class I (85%) and no patient had signs of heart failure. All subjects were in sinus rhythm. Nine patients (19%) received a treatment with beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARB) or diuretics. Moderate to severe tricuspid regurgitation was diagnosed by echocardiography in 2 patients, and no stenosis of the caval baffle and of the pulmonary veins pathway was observed. Biomarkers were measured in 30 D-TGA patients and 14 controls. There was no difference of age, sex ratio, NYHA functional class, systemic ventricle mass, volumes, ejection fraction, LGE lesions, and proportion of patients treated between the groups with and without biomarkers measurements (Supplementary data S3, Table 1).

3.2. Systolic and diastolic function parameters and blood marker levels in D-TGA patients and controls

Parameters of systemic ventricle remodelling, systolic and diastolic function and blood markers levels in D-TGA patients and controls are respectively shown in Supplementary data S3, Table 2. Systemic RV wall stress in D-TGA patients was significantly lower compared to LV wall stress in controls ($p < 0.01$). This result was mainly due to the sRV concentric remodelling with higher mass and lower ES volume of the sRV ventricle compared to LV of controls, associated with a lower systolic blood pressure in D-TGA patients compared to controls. Diastolic sRV function was characterized by an abnormal relaxation with a longer deceleration time (DT) and a longer isovolumic relaxation time (IVRT) compared to healthy subjects, and an impaired sRV filling with a significantly higher E/A and E/E' ratio compared to LV filling of controls.

Bone specific alkaline phosphatases (BAP) as well as the PICP:BAP ratio was similar in D-TGA patients and healthy subjects excluding an influence of bone metabolism in results of myocardial type I collagen

Table 1

Basal characteristics of D-TGA patients. Values are median (IQR), n (%). ACE inhibitors: angiotensin-converting enzyme inhibitors, ARB: angiotensin-II receptor blockers, TGA: transposition of the great arteries, VSD: ventricular septal defect. CMR: Cardiac magnetic resonance imaging.

Patients characteristics ($n = 48$)	
Age at CMR, years	32 (29–35)
Age at repair (months)	8 (2.7–21.7)
Male patients	36 (75%)
Diagnosis	
TGA	43
TGA + VSD	2
TGA + pulmonary stenosis	2
TGA + Aortic coarctation	1
Surgical procedure (Mustard/Senning)	13/35
History of heart failure	3 (6%)
History of atrial arrhythmia	11 (23%)
NYHA functional class I/II/III/IV	41/7/0/0
BMI	23 (21–26)
Treatments	9 (19%)
Beta-blockers	7
ACE inhibitors	2
ARB	2

Table 2

Comparison of patients with and without LGE lesions for hemodynamic biomarkers, biomarkers of collagen, CMR and echocardiographic parameters of sRV systolic and diastolic functions. Values are medians (IQR). BAP: bone-specific alkaline phosphatase BNP: brain natriuretic peptide, DT: deceleration time, ET-1: endothelin-1, ED: end-diastolic, ICTP: C-terminal telopeptide of type I collagen, LGE: late gadolinium enhancement, MMP-1: type 1 pro-matrix metalloproteinase, PICP: C-terminal propeptide of type I collagen, PIIINP: N-terminal propeptide of type 3 collagen, sRV: systemic right ventricle, sRVEF: systemic right ventricle ejection fraction TIMP-1: tissue inhibitor of type 1 metalloproteinase.

	LGE– (n = 31)	LGE+ (n = 17)	p value	
Age at repair (months)	10.0 (2.5–15.0)	46.0 (7.8–26.9)	<0.01	
Age at CMR (years)	31 (27–35)	34 (32–37)	0.02	
Sex ratio M:F	21:10	15:2	0.1	
QRS duration (ms)	90 (80–100)	103 (80–120)	0.06	
Hemodynamic biomarkers, collagen biomarkers				
	Total number of measurements	LGE– (n = 31)	LGE+ (n = 17)	p value
BNP (pg/mL)	48	54 (33–72)	47 (31–55)	0.5
Endothelin-1 (pg/mL)	48	1.7 (1.4–1.9)	1.7 (1.3–2.0)	0.75
Galectin-3 (µg/L)	30	10.6 (10.3–12.5)	15.2 (12.3–15.7)	0.052
Active renin (mUI/L)	48	15.2 (11.1–21.2)	15.3 (11.4–29.5)	0.7
Aldosterone (pg/mL)	48	175 (97–226)	184 (88–304)	0.7
CRP us (mg/L)	48	1.9 (1.0–3.1)	1.6 (2.4–2.9)	0.04
Fibrinogen (g/L)	48	2.8 (2.5–3.1)	2.6 (2.4–2.9)	0.36
Pro-MMP1 (µg/L)	30	3.7 (2.2–7.1)	5.5 (3.9–6.2)	0.32
TIMP1 (µg/L)	30	180 (165–188)	190 (157–206)	0.2
Pro-MMP1/TIMP (ng/µg)	30	0.022 (0.014–0.045)	0.030 (0.024–0.038)	0.3
PICP (µg/L)	30	834 (665–1170)	800 (687–1005)	0.8
ICTP (µg/L)	30	3.6 (3.2–4.2)	4.7 (3.9–5.2)	0.051
PICP/ICTP	30	4.9 (4.1–8.6)	4.7 (3.6–15.8)	0.75
BAP (ng/mL)	30	19.7 (15.4–25.2)	15.6 (12.5–18.1)	0.54
PICP:BAP	30	44.3 (35.4–59.5)	52.6 (10.8–102.0)	0.82
PIIINP (µg/L)	30	4.1 (3.6–5.7)	3.5 (3.2–4.1)	0.2
CMR parameters (total number of measurements = 48)				
		LGE– (n = 31)	LGE+ (n = 17)	p value
ED sRV volume (mL/m ²)	5ML:M ^{2o} (mL) mL/m ²	66 (57–75)	77 (58–88)	0.25
ES sRV volume (mL/m ²)		30 (24–35)	42 (32–51)	0.02
sRV mass (g/m ²)		82 (72–89)	90 (75–105)	0.06
sRVEF (%)		55 (48–60)	44 (38–52)	<0.01
Systemic ventricle wall stress, mm Hg·mL·mg ⁻¹		36.6 (30.6–46.3)	46.9 (40.2–57.0)	0.01
Echocardiographic diastolic parameters (total number of measurements = 48)				
E/A		1.59 (1.96–1.98)	1.57 (1.27–1.96)	0.8
E/E'		11.0 (8.7–19.9)	11.9 (6.4–15.9)	0.5
DT (ms)		198 (168–230)	163 (145–234)	0.2
IVRT (ms)		47 (37–60)	52 (43–78)	0.2

biomarkers. Of note, there was no significant difference in serum levels of fibrosis biomarkers between patients with and without treatment.

3.3. Extent of fibrosis in systemic RV

Areas of LGE were present in 17 patients (35%). Among these, an area of LGE was present in more than one segment in only 5 patients, and LGE distribution was mainly in the basal sRV segments ($n = 9/17$, 54%) and localized along the sRV free wall (7 of the 9 basal localizations). Patients with LGE were significantly older at repair and at CMR exam (Table 2). No significant difference of collagen biomarker levels was observed between patients with and without LGE, except for ICTP and galectin-3 which tended to be higher in the subset of patients with LGE (Table 2). Myocardial collagen turnover biomarkers and LGE were not related to levels of active renin or aldosterone concentrations, even after exclusion of treated patients from analysis, or sRV mass, or sRV mass/volume ratio.

3.4. Association of myocardial fibrosis markers with sRV wall stress and parameters of sRV systolic and diastolic function

A highly significant relation was found between sRV wall stress and pro-MMP1:TIMP1 ratio ($r = 0.77$, $p < 0.01$; Fig. 2A); and sRV wall stress was significantly higher in patients with LGE compared to patients without LGE (Table 2, $p = 0.01$). However, collagen biomarkers, as well as LGE were not significantly associated with either sRV mass (only a trend for LGE, $p = 0.06$) or with sRV mass/volume ratio.

We observed a significant and high correlation of sRVEF with pro-MMP1 concentration ($r = -0.53$, $p < 0.01$) and pro-MMP1:TIMP1 ratio ($r = -0.81$, $p < 0.01$, Fig. 2B). No other association was found between myocardial collagen biomarkers and sRVEF. Moreover, patients with sRV LGE had lower sRVEF (Table 2, $p < 0.001$).

After adjustment for age, sex, blood pressure and cardiac treatment using multiple regression model, pro-MMP1:TIMP1 ratio ($R^2 = 0.85$, $p < 0.01$) and LGE ($R^2 = 0.58$, $p < 0.01$) remained independent associates of sRV EF. When both the pro-MMP1:TIMP1 ratio and LGE were added to the multivariate regression model, pro-MMP1:TIMP1 was the strongest associate of sRVEF.

We found a significant positive correlation of the diastolic parameter E/E' with pro-MMP1:TIMP1 ratio ($r = 0.53$, $p = 0.02$, Fig. 2C), but no significant change of E/E' ratio was found between patients with and without LGE. This correlation was not significant anymore after adjustment for age, sex, blood pressure and treatment. No other relationship between diastolic parameters and fibrosis biomarkers was shown. Diastolic parameters were not significantly associated with sRVEF, mass, remodelling parameters and aldosterone concentration, as well as with active renin concentration, including or not patients with cardiac treatment (beta-blockers, ACE inhibitors, ARB or diuretics).

4. Discussion

We demonstrated here that fibrosis and an excess of myocardial collagen degradation are significantly associated with systolic and

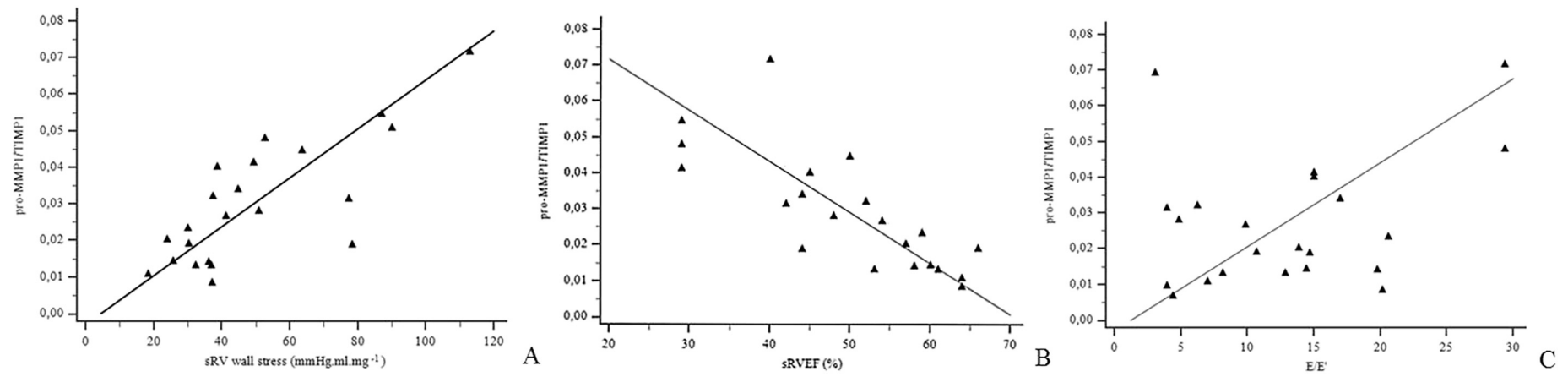


Fig. 2. Scatter diagrams showing significant correlation between A) pro-MMP1:TIMP1 ratio and sRV wall stress ($r = 0.77, p < 0.01$), B) sRV ejection fraction and pro-MMP1:TIMP1 ($r = -0.81, p < 0.01$) and C) pro-MMP1:TIMP1 ratio and the diastolic parameter E/E' ($r = 0.53, p = 0.02$). Pro-MMP1: Type 1 pro-matrix metalloproteinase, sRV: systemic right ventricle, TIMP1: Tissue inhibitor of type 1 metalloproteinase.

diastolic dysfunction of sRV in D-TGA patients after an atrial switch. However, fibrosis was found more strongly associated with systolic dysfunction of sRV than with diastolic dysfunction, even if sRV diastolic echocardiographic parameters (E/E' and IVRT) were significantly different from LV diastolic parameters of healthy subjects.

LGE was relatively frequent in our D-TGA population (35%). The prevalence of sRV LGE in D-TGA after the atrial switch varies greatly, according to studies. However, a majority of the studies report LGE in >40% of D-TGA patients [9,12,13] using late gadolinium imaging and analysis methods similar to ours. There was excellent agreement between the location and extent of RV LGE areas documented *in vivo* by a CMR scan and ventricular focal dense fibrosis in the explanted heart [13,19]. As in other studies [9,12,20], we showed that LGE was significantly associated with decreased sRVEF and increased sRV wall stress [9]. Interestingly, LGE lesions were mainly localized in the basal segments of sRV (for 54%), corresponding to the highest regional sRV wall stress, where sRV diameters are the largest. In parallel, we also found a strong association between the pro-MMP1:TIMP1 ratio and sRV wall stress, as well as sRVEF by multivariate regression analysis. Pro-MMP1:TIMP1 is a biochemical marker of the equilibrium of collagen deposition and degradation within the myocardium [21]. Its augmentation is related to alterations in the perimysial and endomysial collagen network involved in systolic deterioration and geometric dilatation of the left ventricular chamber in hypertensive patients with heart failure [7]. These findings suggest that myocardial collagen network degradation and fibrosis in sRV are related to sRV pressure overload, and they are associated with sRV dysfunction. This association was independent on age, sex, arterial pressure and treatment. As other studies, we found that LGE was more frequent in older patients [9,12]. LGE lesions may progress with time and chronic sRV wall stress. A longitudinal CMR follow-up would be necessary to evaluate progression and impact of fibrosis on sRV function. Additionally, we further found that the presence of LGE was more frequent in late-operated patients. Cyanosis might cause irreversible RV myocardial fibrosis lesions in this condition. We showed that early sRV filling was also significantly related to myocardial collagen degradation by the significant association between the E/E' ratio and the pro-MMP1:TIMP1 ratio. Systemic RV compliance may be impaired when the myocardial collagen network is degraded. Moreover, we found a higher concentration of PIIINP in D-TGA patients compared to control, which can be due to an over-expression of collagen synthesis, which is also observed in these patients. However, this biomarker was not correlated with indices of sRV remodelling (mass or mass/volume ratio) or with diastolic sRV dysfunction.

Abnormal myocardial collagen turnover may be the consequence of longstanding RV pressure overload, as in the LV myocardium of hypertensive patients. LGE lesions may correspond to focal myocardial scarring that is related to regional myocardial ischemia induced by increased regional wall stress (*i.e.* at basal sRV free wall). Moreover, we observed that they are associated with an increase in ICTP, which is another marker of collagen degradation, but not with the pro-MMP1:TIMP1 ratio. It would also be interesting to superpose collagen biomarker results with a diffuse fibrosis index, as proposed by Broberg et al. [22] by using T1 mapping in CMR. Unfortunately, this technique was not available at our site when our study was designed.

Accordingly to our findings, medical therapies reducing systemic afterload and limiting excessive myocardial collagen degradation may be beneficial to sRV failure. Given the growing amount of evidence that myocardial fibrosis has a negative clinical impact on sRV [12,13], investigating medical therapies that reduce fibrosis is warranted. Whereas endocrine secretion of aldosterone was not associated with LGE or collagen turnover dysregulation, drugs that inhibit the transforming growth factor-beta receptor-mediated pathways (*e.g.* angiotensin and aldosterone inhibitors) might be promising for reversing myocardial fibrosis. This is supported by the clinical trial of Dos et al. [23], in which eplerenone trended toward a reduction of PICP, NT-proMMP1 and TIMP1 in an sRV population.

4.1. Limitations

LGE helps diagnose focal myocardial scarring. However, such dense sRV fibrosis is probably associated with homogenous diffuse fibrosis that is not estimated by CMR when using only LGE detection techniques [7,19]. The use of T1 mapping could improve the diagnosis of interstitial fibrosis extends in sRV [22,24]. However, this method needs more validation in RV functional studies. The conventional systemic LV echocardiographic diastolic parameters applied here to the sRV have never been validated by invasive measurements. However, some studies have shown that reduced relaxation reserve of sRV was related to both conventional indices of the diastolic function at echocardiography and speckle tracking [25–27], and we also recently confirmed that impaired sRV filling was related to sRV remodelling using CMR [28]. Because grants and authorisation for collagen biomarker measurements were not obtained at the beginning of the study, which was initially designed to assess sRV remodelling and functioning in TGA patients, these measurements could not be obtained for all subjects. However, they were measured in an acceptable proportion of patients (63%) and healthy subjects (54%) to allow for analysis.

5. Conclusion

Chronic longstanding overload pressure is strongly associated with the degradation of the myocardial collagen network and focal myocardial fibrosis in sRV. These myocardial lesions are associated with systolic and diastolic sRV dysfunction. These findings emphasize the interest in reducing sRV afterload and limiting myocardial collagen degradation, to treat and/or prevent sRV failure. sRV wall stress and myocardial collagen turnover could be new targets of clinical trials in this setting.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.01.100>.

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