Right Ventricular Involvement and Recovery after Acute Stress-Induced (Tako-tsubo) Cardiomyopathy

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Abstract:

Acute stress-induced (Tako-tsubo) Cardiomyopathy is an increasingly recognised but insufficiently characterised syndrome. Here we investigate the pathophysiology of right ventricular (RV) involvement in Tako-tsubo and its recovery time-course. We prospectively recruited 31 Tako-tsubo patients with predominantly ST-elevation ECG and 18 controls of similar gender, age and comorbidity distribution. Patients underwent echocardiography and cardiac magnetic resonance (CMR) imaging on a 3T Philips scanner in the acute phase (day 0-3 post presentation) and at 4 months follow-up. Visually, Echocardiography was able to identify only 52% of patients who showed RV wall motion abnormalities on CMR. Only CMR-derived RV EF (p=0.01) and Echocardiography-estimated Pulmonary artery Pressure (p=0.01) identify RV functional involvement in the acute phase. Although RV ejection fraction normalises in the majority of patients by 4 months, acutely there is RV myocardial edema in both functioning and malfunctioning segments, as measured by prolonged native T1 mapping (p=0.02 for both vs controls) and this persists at 4 months in the acutely malfunctioning segments (p=0.002 vs controls). The extra-cellular volume fraction was significantly increased acutely in all RV segments and remained increased at follow up compared to controls (p=0.004 for all). In conclusion, in a Tako-tsubo population presenting predominantly with ST-elevation ECG, we demonstrate that although RV functional involvement is seen in only half of patients, RV myocardial edema is present acutely throughout the RV myocardium in all patients and results in microscopic fibrosis at 4 months follow-up.

Keyword list: acute stress induced cardiomyopathy, Tako-tsubo, right ventricle

Acute stress induced (Tako-tsubo) cardiomyopathy is an increasingly recognized clinical syndrome. Whilst classically viewed as an acute disorder of the left ventricular (LV) systolic function (often triggered by intense emotional of physical trauma), right ventricular (RV) involvement has been increasingly described [1,2,3,4,5]. Although it is not uniformly clear if RV involvement portends a worse outcome, involvement of the RV has been associated with greater LV dysfunction, more frequent complications[1,2,6] or prolonged hospital stay[1,5,6,7]. We have previously demonstrated that the initial LV dysfunction in Tako-tsubo is accompanied by a significant degree of LV myocardial oedema[8,9] and profound LV energetic impairment[8] with incomplete resolution of both after 4 months. Although RV dysfunction appears to characterise those with a worse spectrum of LV dysfunction, the nature of the pathophysiology underlying the RV involvement is unknown and the recovery time-course of the RV has not been described. In the current study we investigated in a prospectively recruited, predominantly ST-elevation Tako-tsubo population: 1) the prevalence and extent of RV functional involvement, 2) the RV myocardial tissue characteristics and 3) the recovery time-course of the RV at 4 months follow-up.

Methods:

Thirty-one consecutive consenting patients (28 women, median age 64 years, (range 41-84 years) who met the Mayo Clinic criteria[10] for Tako-tsubo were recruited from Aberdeen Royal Infirmary between 2013-2015. All patients were initially suspected of myocardial infarction and most were brought in by Scottish Ambulance Service via the primary percutaneous coronary intervention service. Patients were studied in the acute phase (day 0-3 after presentation) and re-studied

after 4 months. Eighteen controls of similar age (mean 63 years, range 47-80 years), gender (16 women) and comorbidity distribution were also recruited. The study was approved by the North of Scotland Research Ethics Committee and all subjects provided informed consent.

Echocardiography was performed using a Vingmed E9 system (GE Healthcare, Norway) with a 2.5 MHz probe. Standard images were acquired from parasternal, apical and subcostal views. Tissue Doppler images of the RV (at lateral tricuspid annular level) were used to derive E', A' and S' indices.

A 3T Philips Achieva (Best, The Netherlands) was used for cardiac magnetic resonance (CMR) imaging. After localisers, 2,3 and 4-chamber views and a full short axis cine stack were acquired, as well as a full short axis stack of native and post-contrast 3-3-5 Modified Look-Locker Imaging T1 mapping[11].

Both Echo and CMR images were each analysed by a pair of two independent expert observers (CS, AR, CN and JS) blinded to each other, to the other imaging modality and for T1 mapping to the order of the scan. Qualitative interpretation (wall motion score) was resolved by adjudication/agreement with a third expert. All quantitative analyses were subjected to inter-observer variability. Echo images were analyzed offline using Echopac (GE Healthcare, Norway). Pulmonary artery pressure (PaP) was derived from the maximum tricuspid regurgitation velocity as measured by the formula $4v^2$+estimated right atrial pressure depending on the inferior vena cava collapse during inspiration. A simple index of RV longitudinal function was also measured as Tricuspid annular pan-systolic excursion

(TAPSE) as previously described[12]. The CMR images were analysed in CMR Tools (Cardiovascular Imaging Solutions, London, UK) for computation of LV volumes and mass, RV volumes and to derive volumetric Ejection Fractions for the two ventricles. RV Wall motion score index was obtained using a 6 segment model where the basal, mid-cavity and apical slices were each divided into anterior and posterior segments (**Figure 1A**). Each segment was scored for functional status (1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic). T1 maps were generated using Philips' RelaxMap, quality controlled with chi-square maps and imported into Image J (NIH, USA) where pre and post contrast T1 values for the RV myocardium were generated for each of the 6 segments[13]. To avoid the difficulties posed by the thin RV wall and possible partial volume effect, all T1 map images were co-registered with the exact spatially corresponding cine sequences in the following manner: the RV boundaries were carefully delineated manually on magnified cine images, then inwardly eroded by at least 2 pixels in order to avoid blood on the endocardial side or fat on the epicardial side and finally the ROI's thus obtained were imported into the corresponding T1 map images for deriving pre and post-contrast T1 values. Extracellular volume fraction (ECV) was calculated according to the formula:

$$ECV = (1 - hematocrit)\frac{\left(\frac{1}{T1_{myo\ post}} - \frac{1}{T1_{myo\ pre}}\right)}{\left(\frac{1}{T1_{blood\ post}} - \frac{1}{T1_{blood\ pre}}\right)}$$

A repeat Echocardiogram and CMR were scheduled at 4 months and achieved in 28 patients due to death (2) and device implant (1).

Data are presented as mean±SD or median (range) if not normally distributed. Comparisons between controls and patients or between patients at baseline and follow-up were performed using independent/paired Students' *t* test or Mann Whitney

rank-sum/Wilcoxon signed-rank tests depending on the data distribution. In order to account for multiple comparisons the *p* value chosen for statistical significance was Bonferroni-adjusted depending on the number of variables compared between groups. Inter-observer variabilities were calculated as mean±SD of the percentage ratios between differences and means of the 2 independently measured variables.

Results

General characteristics are shown in **Table 1.** In this study cohort most patients were middle-age and elderly women, with a preceding emotional trigger, presenting with ST-elevation ECG's, modest Troponin rise and apical-type ballooning. The controls were chosen to be similar in age and gender distribution to the Tako-tsubo patients, and to have a comparable cardiac past medical history/therapy. Typically, Tako-tsubo patients were given the emergency therapy required for a presumed myocardial infarction until the diagnosis of Tako-tsubo was established at cardiac catheterisation; after this, medication was re-established as before presentation in each case.

RV systolic wall motion was assessed on a segmental basis as presented in **Figure 1A**. Tako-tsubo patients were grouped according to the wall motion score index (WMSI) on CMR images as those with RV involvement (RV+, mean WMSI 1.5±0.3, n=16) and without RV involvement (RV-, WMSI=1, n=15). There was no difference between the RV+ and RV- groups with regard to age, past medical history, heart rate or systolic/diastolic blood pressure at presentation (p=ns for all). **Figure 1B** shows a typical example of RV dyskinesia. In all cases, only the apical and mid-cavity RV segments were seen to be involved. Of note, Echocardiography was able

to identify a wall motion abnormality in only 9 patients in the RV+ group (52%). **Table 2** shows that in both groups there was a significant improvement in LV EF at 4 months compared to baseline ($p<0.01$ in both). The RV+ group had decreased RV EF ($p=0.01$), decreased TAPSE ($p=0.002$) and increased PaP ($p=0.01$) acutely compared to follow-up and also compared to controls (all $p<0.01$). The RV- group also showed a decreased TAPSE acutely compared to controls ($p=0.002$), which improved at follow up ($p=0.001$ vs acute).

On T1 mapping assessment, individual RV segments from Tako-tsubo patients were grouped according to their WMS during acute presentation and compared to those of the control group. **Table 3** shows that native T1 was significantly prolonged during acute presentation in segments with abnormal wall motion and also in segments with normal wall motion ($p=0.02$ for both), suggesting that acutely there is a degree of myocardial edema present throughout the RV. The segments showing wall motion abnormalities during the acute phase continued to have a significantly prolonged precontrast T1 even at 4 months follow-up ($p=0.002$ compared to controls). Similarly, the post-contrast T1 values were significantly shorter at acute presentation study compared to controls, irrespective of their wall motion ($p=0.004$ for both). The ECV was significantly increased acutely in all RV segments and remained increased at follow up compared to controls ($p=0.002$ for all). An example is shown in **Figure 2**.

The average inter-observer variabilities for Echo, CMR and T1 mapping measurements were: 4±2%, 3±1% and 5±3% respectively.

Discussion: Firstly, we demonstrate that CMR is superior to standard Echocardiography in detecting RV functional involvement in acute Tako-tsubo. This is not surprising since CMR is the accepted gold standard for RV assessment and

thus it is possible that previous studies may have underestimated the extent of RV involvement in this condition. A reduced RV EF and increased PaP characterise the RV+ group, in keeping with previous observations[3,4,5]. Interestingly, in our study, the group designated RV- by visual assessment of wall motion also showed a modest but significantly reduced TAPSE acutely, which improved at follow-up, suggesting discrete abnormalities in the long axis function of the RV even in this group. A previous report showed that RV global longitudinal strain was able to distinguishing RV involvement on Echocardiography, whereas TAPSE was not[4]. It is possible that our patient cohort who presented predominantly as ST-elevation ECG's were diagnosed and scanned at an earlier stage. Additionally, while our findings may characterize a most severe spectrum of Tako-tsubo disease, they cannot be extrapolated to the less severe clinical presentations.

Secondly, a significant finding of this study is that of myocardial edema, involving the RV and present beyond the boundaries of the dysfunctional myocardium during the acute phase, similar to the LV pattern of involvement that we recently described[14]. Taken together, these findings are the first evidence to suggest that Tako-tsubo is a condition that affects the whole ventricular myocardium. This supports the concept that Tako-tsubo is a more systemic condition than previously thought, with a provoking stimulus that is capable to affect the entire left and right ventricular myocardium. Despite these striking findings of pan-myocardial edema, Tako-tsubo shows specific localization of functional involvement in both the RV and LV myocardium, since often the apex and part of the mid-cavity myocardium is dyskinetic whereas the base of the heart is hyperkinetic. Previous authors have already suggested that an explanation for the differential functional responses of myocardial territories may lie in the distribution and relative proportions of the beta-

adrenergic receptors within the LV myocardium[15], although this has never been investigated in the human RV. We further demonstrate that RV myocardial edema also shows incomplete resolution at 4 months follow-up, persisting in the segments which showed impaired contractility during the acute phase.

Another important observation is that RV involvement does not appear to have any systemic haemodynamic consequences in those with clear RV wall motion abnormalities in the acute phase, as there were no differences in systemic blood pressure or heart rate between groups. This observation suggests that factors other than hemodynamic status may dictate a worse clinical course for those who manifest functional RV involvement. Taken together, our data show that not only the pathophysiology of Tako-tsubo is distinctively different form that of acute coronary syndromes, but also that the clinical markers for identifying patients at high risk may also be different. These findings also support a primary myocardial inflammatory hypothesis as a response to stress. Further research is needed to define the type of inflammation associated with Tako-tsubo and this may pave the way to suitable therapies.

Thirdly, we show that the RV myocardium continues to have an increased ECV at 4 months in all segments, irrespective of their functional involvement during the acute phase. This suggests that a degree of microscopic myocardial fibrosis develops in the RV of these patients, as previously shown in myocardial biopsies from the LV by other authors[16]. This is also in keeping with clinical reports of Tako-tsubo patients remaining symptomatic in longer term and builds further to the growing body of evidence that an episode of acute Tako-tsubo leaves a signature in the myocardium.

In keeping with observations already made at 1.5T magnetic field[17], the T1 values we measured in the RV in our study at 3T are indeed different from those measured in the LV[8], due to the different proportions of myocytes and collagen found even in the normal RV. Even though we report RV T1 mapping values at 3T for the first time, it is unlikely that the higher pre-contrast and lower post-contrast T1 values in the RV are a reflection of the patients' comorbidities (in general Tako-tsubo patients are "healthier" compared to coronary artery disease patients) – and our control population was well matched to avoid this confounder. Finally, the current study is proof of concept work and thus it enrolled a small number of patients, therefore these findings will need confirmation in future larger studies.

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FIGURE LEGENDS:

Figure 1: A - Schematic representation of the RV segmentation for wall motion score interpretation; the segmental WMS were: 1.7, 1.4, 1.4, 1.3, 1, 1 for segments 1,2,3,4,5 and 6 respectively.

Figure 1: B – Typical End-diastolic (ED) and End-systolic (ES) frames demonstrating LV and RV (arrows) apical ballooning, large pleural effusions are also seen.

Figure 2: Pre and post contrast T1 maps in a control (a,b) and an ASC patient with functional RV involvement (c,d) demonstrating normal RV versus RV wall edema during the acute scan (hues of orange vs hues of yellow-green) and normal RV versus microscopic fibrosis at follow-up scan (hues of blue vs hues of yellow-green). The respective numeric mapping scales are shown on the right.

Table 1. Clinical characteristics of the Tako-tsubo patients and controls

Clinical Characteristics	Tako-tsubo (n=31)	Controls (n=18)
Past medical history		
Hypertension	7 (22%)	4 (22%)
Prior coronary artery disease	1 (3%)	-
Diabetes mellitus	2 (6%)	-
Thyroid disease	8 (26%)	5 (27%)
Mental health disorder	9 (29%)	-
Previous Tako-tsubo	6 (19%)	-
Smoker	11 (35%)	6 (33%)
Alcohol abuser	3 (9%)	-
Body mass index>25 kg/m^2	16 (51%)	9 (50%)
Clinical presentation		
Chest pain	25 (81%)	
Syncope/pre-syncope	4 (13%)	
Ventricular tachycardia	2 (6%)	
Precipitating emotional stressor	27 (87%)	
No stressor	4(13%)	
Heart rate at presentation [bpm, mean±SD]	80±14	
Systolic blood pressure at presentation [mm Hg, mean±SD]	125±23	
Diastolic blood pressure at presentation [mm Hg, mean±SD]	79±17	
ECG changes at presentation		
ST-elevation	25 (81%)	
T wave inversion	4 (12%)	
LBBB	2 (7%)	
Troponin I (ng/ml)		
At presentation [median, (range)]	1.28 (<0.04, 10.93)	
12 hour [median, (range)]	3.45 (0.22, 11.97)	

C-reactive protein [median, (range)]	21.5 (<4, 75)	
Coronary disease at angiography		
Left anterior descending <50%	6 (19%)	
Left circumflex <50%	1 (3%)	
Right coronary artery <50%	6 (19%)	
Left ventricular angiogram		
Apical ballooning	26 (84%)	
Mid-cavity ballooning	5 (16%)	
Drug history		
Aspirin	3 (9%)	-
Beta-blocker	1 (3%)	-
ACE inhibitor	6 (19%)	2 (11%)
Calcium channel blocker	3 (9%)	-
Statin	4 (12%)	-
Diuretic	5 (16%)	3 (16%)

Data are shown as n (%) unless otherwise stated.

Table 2

Table 2. Imaging Characteristics of Tako-tsubo patients with and without Right ventricular involvement (RV+/-) and healthy controls

	Controls	Acute study (day 0-3)		Follow up (4 months)	
		RV+	RV-	RV+	RV-
	n=18	n=16	n=15	n=14	n=14
Cardiac Magnetic Resonance					
Left ventricular end-diastolic volume (ml)	133±14	126±35	131±22	122±21	127±16
Left ventricular end-diastolic volume index (ml/m^2)	73±6	80±20	74±13	78±12	71±10
Left ventricular end-systolic volume (ml)	45±8	67±30†	57±20†	45±15*	45±11*
Left ventricular end-systolic volume index (ml/m^2)	24±4	42±18†	32±12†	28±9*	25±7*
Left ventricular mass (g)	121±13	137±16†	134±18†	125±17*	118±18*
Left ventricular mass index (g/m^2)	66±10	84±10†	77±17†	75±11*	70±14*
Left ventricular ejection fraction (%)	67±4	48±10†	60±8†	63±6*	64±6*
Right ventricular end-diastolic volume (ml)	100±20	121±23	107±22	111±20	107±26
Right ventricular end-diastolic volume index (ml/m^2)	58±9	66±12	58±10	60±10	58±13
Right ventricular end-systolic volume (ml)	44±7	43±15	38±7	38±15	34±9

Right ventricular end-systolic volume index (ml/m^2)	25±4	25±10	20±4	22±10	18±4
Right ventricular ejection fraction (%)	63±5	57±11†	63±9	66±11*	67±8
Echocardiography					
Right ventricular E' (cm/s)	0.14±0.01	0.09±0.04	0.10±0.04	0.12±0.02	0.11±0.03
Right ventricular A' (cm/s)	0.16±0.01	0.17±0.05	0.14±0.05	0.13±0.05	0.15±0.04
Right ventricular S' (cm/s)	0.13±0.01	0.09±0.02	0.12±0.03	0.12±0.03*	0.12±0.03
Tricuspid annular pan-systolic excursion (cm)	2.6±0.1	1.7±0.4†	2.0±0.3†	2.4±0.5*	2.6±0.4*
Pulmonary artery Pressure - estimated (mm Hg)	24±7	43±15†	31±6	33±8*	29±6

All data shown as mean±SD.

$*$ $p \leq 0.01$ acute study vs follow-up (paired *t*-test)

† $p \leq 0.01$ acute study vs controls

Table 3: Native and post-contrast Right Ventricular T1 mapping values and extracellular volume fraction from segments with normal or abnormal wall motion from Tako-tsubo patients compared to all segments form controls. Native T1 mapping is indicative of edema whereas extracellular volume fraction is indicative of microscopic myocardial fibrosis.

	Controls	Acute study (day 0-3)	Follow up (4 months)
Native Right Ventricular T1 mapping - normal wall motion (ms)	1310±92	1399±88*	1356±58
Native Right Ventricular T1 mapping - abnormal wall motion (ms)	-	1459±128*	1478±88*
Post-contrast Right Ventricular T1 mapping - normal wall motion (ms)	523±42	484±40*	501±42
Post-contrast Right Ventricular T1 mapping abnormal wall motion (ms)	-	456±17*	478±47
Right ventricular Extracellular volume fraction normal wall motion (%)	0.33±0.03	0.40±0.04*	0.41±0.05*
Right ventricular Extracellular volume fraction abnormal wall motion (%)	-	0.42±0.04*	0.42±0.05*

∗ $p<0.03$ acute or follow-up study vs healthy control myocardium

Figure

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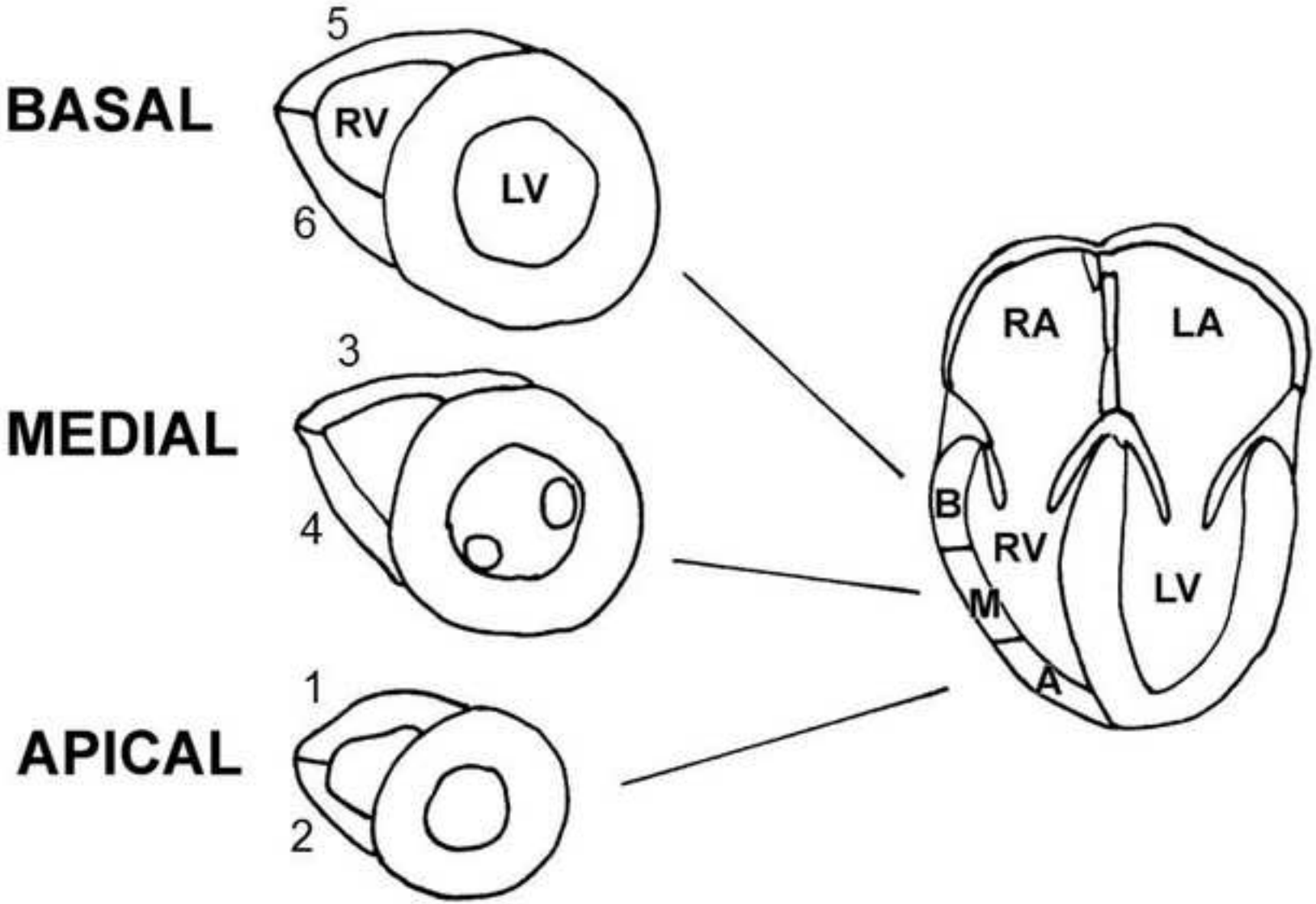

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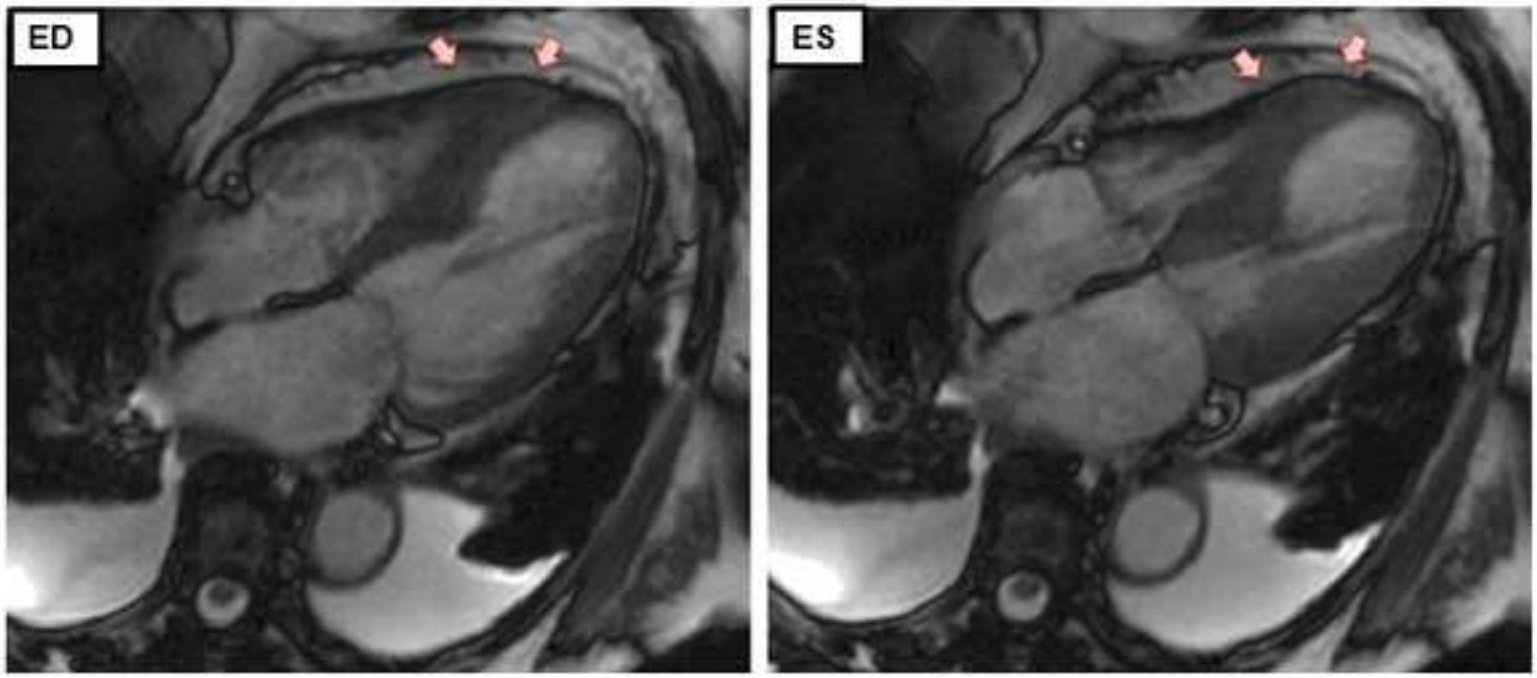

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