Right Ventricular Dysfunction following Acute Myocardial Infarction in the Absence of Pulmonary Hypertension in the Mouse

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Abstract

**Background:** Cardiac remodelling after AMI is characterized by molecular and cellular mechanisms involving both the ischemic and non-ischemic myocardium. The extent of right ventricular (RV) dilatation and dysfunction and its relation to pulmonary hypertension (PH) following AMI are unknown. The aim of the current study was to evaluate changes in dimensions and function of the RV following acute myocardial infarction (AMI) involving the left ventricle (LV).

**Methods:** We assessed changes in RV dimensions and function 1 week following experimental AMI involving the LV free wall in 10 mice and assessed for LV and RV dimensions and function and for the presence and degree of PH.

**Results:** RV fractional area change and tricuspidal annular plane systolic excursion significantly declined by 33% (P = 0.021) and 28% (P = 0.001) respectively. Right ventricular systolic pressure measured invasively in the mouse was within the normal values and unchanged following AMI.

**Conclusion:** AMI involving the LV and sparing the RV induces a significant acute decline in RV systolic function in the absence of pulmonary hypertension in the mouse indicating that RV dysfunction developed independent of changes in RV afterload.

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**Competing Interests:** The authors have declared that no competing interests exist.

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Introduction

Acute myocardial infarction (AMI) is associated with compensatory mechanisms involving both the left and right ventricles. In experimental models of AMI, right ventricular (RV) hypertrophy occurs even if the RV is initially spared [1]. Hypertrophy and apoptosis of cardiomyocytes both at the site of AMI and at remote unaffected sites of both the LV and the RV are seen in biventricular remodeling following AMI [1–5]. In patients with LV systolic dysfunction and heart failure the presence of signs and/or symptoms of RV failure identify a subgroup of patients with a very poor prognosis [6–10]. The mechanisms leading to RV remodelling and dysfunction following AMI involving the LV are not completely clear, but it is frequently assumed that LV failure causes pulmonary hypertension (PH) and increased RV afterload leading to RV remodelling and dysfunction. In addition, infarction or ischemia of the RV and/or the septum are common in patients with AMI and can also contribute to abnormal RV systolic function. However studies concerning RV remodelling are few and the extent, time and causes for RV dilatation and dysfunction remain unclear [11]. In the current study we evaluated the occurrence and extent of RV dilatation and dysfunction in a mouse model of AMI in which the septum and RV are spared thus eliminating the possibility that RV or septal ischemia/infarction leads to abnormal RV perfusion or mechanics, and in which the RV systolic pressure could be invasively measured. We hypothesized that increased RV afterload due to PH leads to impaired RV function following AMI.

Methods

**Experimental AMI**

Adult male out-bred ICR mice were purchased from Harlan Laboratories (Indianapolis, IN). All animal experiments were conducted under the guidelines on humane use and care of laboratory animals for biomedical research published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1996). The study protocol was approved by the local Institutional Animal Care and Use Committee. Mice underwent experimental myocardial infarction due to permanent coronary artery ligation or sham surgery as previously described [12]. All mice underwent transthoracic echocardiography before surgery and at 2 and 7 days...
and a subgroup of mice also 10 weeks after surgery. Doppler echocardiography was performed with the Vevo770 imaging system (VisualSonics Inc, Toronto, Canada) as previously described and measurements were performed according to the to the American Society of Echocardiography recommendations [13]. The left ventricular (LV) end-diastolic diameter (LVEDD), LV end-systolic diameters (LVESD) were measured at M-mode. LV fractional shortening (LVFS) was calculated. The LV and right ventricle (RV) diastolic and systolic areas were traced in the parasternal short axis mid-ventricular view (Figure 1). The LV and RV fractional area change velocity (LVFAC and RVFAC, respectively), a load- and rate-independent indexes of contractility, were computed dividing the fractional area changes by the rate-corrected ejection time. The tricuspidal annular plane systolic excursion was also measured to quantify right ventricular function. To evaluate for interventricular dysynchrony, we measured the electromechanical delay using (a) Doppler analysis of the pulmonary artery (for the RV) and of the aorta (for the LV) measuring the time between the start of the QRS on the electrocardiogram and the start of the forward flow, and (b) using the M-mode echocardiography of the mitral annulus plane and tricuspid annulus plane systolic excursion and measuring the time between the start of the QRS on the electrocardiogram and the start of the inward motion of the lateral portion of the annulus. The differences between the LV and RV delays were used as measures of dysynchrony. The investigator performing and reading the echocardiogram was blinded to the group allocation.

In an additional group of mice (ligation or sham [N = 5] per group) were deeply sedated and intubated 7 days after surgery, the chest was reopened, the RV or LV apex were punctured and a Millar catheter connected to a pressure transducer to measure RV peak systolic pressure, which is equivalent to pulmonary artery systolic pressure in the absence of pulmonary valve stenosis, or LV end-diastolic pressure. An additional group of mice (ligation or sham [N = 5] per group) underwent measurement of RV peak systolic pressure or LV end-systolic pressure in the absence of pulmonary valve stenosis, or LV end-diastolic pressure. The extent of infarct size was similar using both TTC (29±3% and Masson’s trichrome (28±3%), and in all cases the infarct involved only the anterior and lateral wall while the RV and septum were not involved.

Mice with reperfused AMI showed a significantly smaller infarct size using both TTC (14±2%, P<0.001 vs non-reperfused) and Masson’s trichrome (12±3%, P<0.001 vs non-reperfused) and a smaller decrease in LVFAC (38±4%, P<0.001 vs non-reperfused) yet a similar reduction in RVFAC (30±5%, P = 0.48, Figure 1).

The changes in RVFAC were not statistically correlated with the size of infarct or the changes in LVFAC in the non-reperfused AMI group, in the reperfused AMI group, or in the 2 groups combined (data not shown), whereas LVFAC correlated significantly with infarct size in the 2 groups combined (R = 0.86, P<0.01) but not in the individual groups. RVFAC and LVFAC as absolute values were highly correlated in the 2 groups combined (R = 0.97, P<0.01) but not in the individual groups.

Discussion

Post-infarction cardiac remodelling is characterized by biventricular remodelling. The occurrence of RV dysfunction and failure identifies a subgroup of patients with extremely poor prognosis, however only few clinical studies have systematically addressed RV remodelling following AMI [7–9,15]. Potential mechanisms include ischemia/infarct of the RV, septal dyssynergy, pulmonary hypertension, neurohormonal activation or inflammation [11,16]. Our data shows that a significant degree of RV systolic dysfunction ensues acutely after AMI in the absence of RV dysfunction.
Figure 1. Right ventricular remodeling in AMI. Panel A shows cross-section of the left and right ventricles (apical section) stained with Masson’s trichrome to identify fibrous scar in the infarct. Involvement of a large area of the anterolateral left ventricle free wall (arrows) and sparing of the interventricular septum and right ventricle (N) is evident. Panel B shows an echocardiographic image (short axis view) of the left and right ventricles (mid-ventricular section) in a mouse 7 days after permanent coronary artery ligation. An aneurysm of the anterolateral left ventricular free wall is noted (arrows). The interventricular septum is indicated by (N) and the right ventricular cavity is indicated by (*). Panel C shows a M-mode recording on the tricuspidal annulus plane systolic excursion (TAPSE) obtained from a 4-chamber apical view. Panels D and E show changes in right ventricular fractional area change (RVFAC) and tricuspidal annulus plane systolic excursion (TAPSE) over time in mice with AMI due to permanent coronary ligation and mice with sham operation (N = 10 per group). Panel F shows right ventricular systolic pressure (RVSP) in mice with AMI due to permanent coronary ligation and mice with sham operation 7 days after surgery with no differences noted between the groups (N = 5 per group). Panel G shows the lack of correlation between RVSP and RVFAC in mice with AMI due to permanent coronary ligation and mice with sham operation 7 days after surgery. Panels H and I show data deriving from the model of reperfused AMI as it compares with the non-reperfused AMI: reperfused AMI had a smaller decline in LV systolic function (LVFAC, panel H) yet a similar decline in RV systolic function (RVFAC, panel I).

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ischemia/infarct or septal infarct, and in the absence of pulmonary hypertension. These data are in accordance to data obtained in patients with chronic heart failure in which progressive RV hypertension. These data seem to imply that the LV and RV may be working as a ‘functional syncytium’ and that the two ventricles cannot be dissociated in an independent manner since the architecture of the distinct myocardial bands makes it mandatory for an integrated and unified function of both chambers [18–19].

In conclusion, acute myocardial infarction involving the LV and RV enlarges in the absence of PH [16–17], and call for a refocusing on cellular and molecular events occurring in the RV myocardium rather than in the pulmonary circulation when trying to explain the development of RV failure [11,17]. These data seem also to imply that the LV and RV may be working as a ‘functional

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Footnote for Table 1.

*P<0.05 vs baseline.

Abbreviations: LV- Left ventricular; LVEDD – Left Ventricular End-diastolic Diameter; LVESD – Left Ventricular End-systolic Diameter; LVEF – Left Ventricular Ejection Fraction; LVFAC – Left Ventricular Fractional Area Change; LVFS – Left ventricular systolic pressure; TAPSE – Tricuspid Annulus Plane Systolic Excursion.

References


Author Contributions

Conceived and designed the experiments: SST HJB BWVT EM IS RR FNS AA. Performed the experiments: ST HJB BWVT EM IS RR FNS AA. Analyzed the data: ST HJB BWVT EM IS RR FNS AA. Contributed reagents/materials/analysis tools: SST HJB BWVT EM IS RR FNS AA. Performed the experiments: ST HJB BWVT EM IS RR FNS AA. Contributed reagents/materials/analysis tools: ST HJB BWVT EM IS RR FNS AA.


