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**Systolic dysfunction in infarcted mice does not necessarily lead to heart failure:
need to refine preclinical models**

Villalba-Orero, infarcted mice do not over signs of heart failure.

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ABSTRACT

Heart failure (HF) is a major cause of death and hospitalization worldwide. Despite advances in reducing mortality, prognosis remains poor and prevalence has reached epidemic proportions. The limitations of available preclinical models represent a major hurdle in the development of new therapies. Myocardial infarction (MI) is a main cause of HF in humans and mouse models of MI are often used to study HF mechanisms and experimental treatments. We investigated whether MI in mice constitutes an appropriate model of HF. Permanent ligation of the left coronary artery induced severe and persistent systolic dysfunction and ventricular dilatation. Mouse follow up for 10 months showed no significant evidence of lung congestion or other pulmonary defects associated with HF. No difference was observed in the capacity of infarcted mice to exercise compared to control animals. These results indicate that severe cardiac dysfunction in mice is not sufficient to demonstrate the presence of HF.

Heart failure (HF) is a major cause of death and disability. Despite advances, prognosis remains poor, and the underlying mechanisms are not completely understood. Recent reports highlight methodological shortcomings in HF evaluation in preclinical studies, which preclude the development of new treatments[1, 2]. HF is a complex syndrome, characterized by fluid retention, breathlessness and tiredness[2]. In mice, symptoms are difficult to evaluate and the presence of HF is often assumed based on cardiac dysfunction. Myocardial infarction (MI) is a major cause of HF in humans and around 25% of patients develop HF within the first 4 years after a first MI[3]. Therefore, MI is often used as a model of HF in mice [1]. Systolic dysfunction in mice after infarction is well proven, however, HF is seldom assessed. Here we investigated whether MI in mice actually results in the development of HF.

Seventeen 20-week-old male C57BL/6 mice underwent permanent occlusion of the left descending anterior coronary artery (MI group) and eight unoperated mice were used as controls (Ctl group). Cardiac function was analyzed by echocardiography. Only mice with left ventricular ejection fraction (LVEF) <45% and at least two akinetic cardiac segments at day 5 post-infarction were retained (n=13). Animals were analyzed every month for 10 months. Mouse lung ultrasound (MoLUS) score was used to evaluate pulmonary changes associated to HF[4]. Since fatigue is one of the symptoms used to diagnose HF in humans, we used metabolic cages and a treadmill to determine exercise tolerance post-infarction.

Myocardial infarction caused a sustained decrease in LVEF (Fig 1a). Similarly, infarct size, and the wall motion score index did not change significantly over time in the MI group (Fig. 1b, 1c). Infarcted mice showed progressive left ventricular dilatation, as observed by the increase in left ventricle end-diastolic volume (Fig. 1d). Despite evident cardiac dysfunction and remodeling, MoLUS analysis revealed only minor changes

associated with pulmonary congestion, edema or effusion, and none of the infarcted mice reached a MoLUS score >10.5, which is indicative of HF (Fig. 1e) [4]. Accordingly, the lung water content was not significantly increased in MI mice 10 months post-infarction (Fig. 1f).

Infarcted and control mice showed similar food and water consumption (Ctl: 11.27 ± 1.84 g, MI: 13.88 ± 9.98 g; Ctl: 9.19 ± 1.47 ml, MI: 8.23 ± 1.80 ml; respectively) and similar O₂ and CO₂ exchange (Ctl: 19.57 ± 2.67 ml/min/kg, MI: 19.58 ± 2.11 ml/min/kg; Ctl: 18.13 ± 2.60 ml/min/kg, MI: 17.84 ± 2.04 ml/min/kg; respectively). Voluntary activity and rearing showed no differences between groups. Compared to young uninjured mice, distance run on the treadmill was lower in both, control and infarcted mice, likely due to age. Infarcted mice showed no decrease in exercise capacity (Fig. 1g-i).

In summary, our results indicate that although MI causes systolic dysfunction in mice, it does not actually lead to HF, at least within the first ten months post-infarction. While the mouse MI is a valuable tool to study heart repair, remodeling and dysfunction[2], it does not replicate human HF syndrome. Our results reinforce the need to demonstrate the actual development of HF in basic and translational animal models.

Compliance and Ethical Standards

Funding

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

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Figure legend

Long-term physiological parameters of mice following myocardial infarction. (a-d) : Control (Ctl) and infarcted (MI) mice were investigated by echocardiography at 1, 6 and 10 months in order to determine (a) LVEF, (b) infarct size, represented as the number of segments affected, (c) wall motion score index, using a 12-segment model scored as 1:normal; 2: hypokinetic, 3:akinetic, 4:dyskinetic and 5:aneurysmal (WMSI, dashed line indicates basal score) and (d) left ventricular end-diastolic volume (LVEDV). (e) Mouse lung ultrasound (MoLUS) was used to assess lung congestion. The dashed line indicates a MoLUS score threshold of 10.5, above which HF is considered to be reliable. (f) Lung water content in Ctl and MI mice at 10 months post-infarction. (g-i) Spontaneous activity and exercise tolerance in Ctl and MI mice 10 months post-infarction as determined by (g) locomotor activity, (h) total rearing count and (i) total running capacity (dashed line indicates distance run by 4-month old mice, as a reference). *** $P < 0.001$ compared to the Ctl group and [#] $P < 0.05$ compared to previous time points using one-way (b, c) or two-way (a, d, e) ANOVA followed by Tukey correction, or unpaired t-test (f-i).

