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Effects of environmental stress following myocardial infarction on behavioral measures and heart failure progression: The influence of isolated and group housing conditions

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HIGHLIGHTS

- We tested whether social isolation or crowding increases the risk of heart failure.
- Responses to housing manipulation were examined in a post-myocardial infarction model.
- Open field testing was valid to determine stress-responses following myocardial infarction.
- Myocardial infarction did not increase behavioral stress-responses compared to sham.
- The post-infarction heart failure risk was not influenced by isolation or crowding.

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ABSTRACT

Background: Heart failure (HF) prognosis is negatively influenced by adverse environmental conditions associated with psychological distress and depression. The underlying mechanisms are not well understood because of insufficient experimental control in prior clinical and epidemiological studies. Using a validated animal model we examined whether distress-producing environmental manipulations (social isolation and crowding) increase HF progression following myocardial infarction (MI).
Methods: MI was induced using coronary artery ligation in 8-week old male Wistar rats (N = 52) and results were compared to sham surgery (N = 24). Housing conditions were randomly assigned at 5 days post MI or sham surgery (1/cage = isolation, 2/cage = standard reference condition, or 4/cage = crowding) and continued for 17 weeks until the end of observation. The open field test was used to test behavioral responses. Echocardiograms were obtained at weeks 8 and 16, and left ventricular (LV) weight at week 17.
Results: Housing conditions increased behavioral markers of distress ($p = 0.046$) with the strongest effects for the isolated (1/cage) ($p = 0.022$). MI did not increase distress-related behaviors compared to sham. MI-surgery resulted in characteristic HF indices (left ventricular ejection fraction (LVEF) at week 16 = 46 ± 12% vs. 80 ± 7% in sham, $p < 0.001$). Housing condition was not related to LVEF or LV weight ($p > 0.10$).
Conclusions: Adverse environmental conditions, particularly isolated housing, produce increases in some of the behavioral indicators of distress. No effects of housing were found on post-MI progression of HF. The distress–HF associations observed in humans may therefore reflect common underlying factors rather than an independent causal pathway. Stronger environmental challenges may be needed in future animal research examining distress as related HF progression.

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1. Introduction

Clinical and population-based studies have demonstrated an increase in heart failure (HF) over the past decades [1,2]. This increase is attributable to the improved post-myocardial infarction (MI) survival as a consequence of early detection, thrombolysis and early revascularization as well as the aging of the population [1,3,4]. HF is a common consequence of MI and related to loss of contractile muscle and scar formation, subsequently resulting in poor left ventricular (LV) function and HF. Determinants of HF can be systematically investigated using experimental post-MI models [5–7]. These post-MI HF models are well validated in rats and other rodents [8,9] and provide effective procedures to systematically investigate the interaction between biological and behavioral factors as predictors of HF progression.

Accumulating evidence suggests that psychosocial factors, particularly psychological distress [9–11], are associated with increased risk of HF [12,13]. Adverse effects of distress are also observed for other adverse cardiovascular health outcomes such as incident MI and post-MI mortality [14–17]. These elevated cardiovascular risks are observed following prolonged psychological distress such as distress experienced during exhaustion [18,19] and depression [13,20,21] as well as milder forms of chronic distress [22,23]. However, the direction of causal pathways is complicated to discern when assessing human clinical or epidemiological studies, because it cannot be ruled out that underlying disease accounts for the association between psychosocial factors and disease progression. Psychological distress and its biobehavioral correlates can be systematically studied using animal models that change social and/or environmental factors (e.g., [24,25] for studies in rats). Manipulation of the housing condition is a well-established paradigm to induce distress in rodent models [26–28] and can be used to differentiate the effects of social isolation and crowding on biobehavioral and HF-related functional measures compared to the standard condition in which animals are housed in pairs.

This investigation used a combination of a post-MI model that is known to result in progressive HF with alterations in housing to examine the effects of sustained distress on HF progression. We examined whether MI results in increased vulnerability to develop distress-related behaviors following adverse housing conditions: individually housed/social isolation or housed in groups of 4/crowding versus the usual housing condition in pairs. We then tested the hypothesis that animals in the two adverse housing conditions are more likely to develop HF as evidenced by echocardiographically determined left ventricular function and structural changes on histopathology, compared to animals housed in the usual housing condition.

2. Methods

Studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (NIH 85-23) and the Institutional Animal Care and Use Committee regulations of the University of Maryland. The post-MI HF model quantifies the magnitude to which surviving myocardium remote from the scar becomes dysfunctional, subsequently resulting in expansion of the left ventricle, deteriorated contractile function and HF. Heart failure typically develops within 8 to 16 weeks following surgery-induced MI [5–7].

2.1. Procedure

Animals (male Wistar rats) had continuous access to food, were weighed every week, and were maintained on a reverse 12 h:12 h light:dark cycle (lights off at 7 AM). MI was produced by coronary ligation surgery (N = 52) and sham surgery (N = 24) was used for control purposes as detailed below. Five days after surgery, animals were assigned to one (single: social isolation condition), two (paired: reference condition), or four (group: crowding condition) rats per cage until completion of the study at 17 weeks. To determine the change in cardiac structure and function over time, repeated echocardiographic assessments were obtained at 8 and 16 weeks post-surgery. Prior studies have shown that reduced cardiac function can already be observed at 8 weeks but is consistently present at 16 weeks using a coronary ligation-induced MI model in rats [5–7]. Tissue and blood samples were obtained following terminal surgery at 17 weeks.

2.2. Surgical procedure

Heart failure was induced by a validated MI model as previously described [5–7]. Briefly, eight week old male Wistar rats weighing ~250 g were anesthetized with 1.5–2.0% isoflurane, intubated and ventilated. An infarct was induced by ligation of two adjacent sections of the left coronary artery. To ensure that MI was induced, the electrocardiogram had to show development of Q waves in response to coronary ligation. Animals receiving sham surgery were subjected to the same surgical procedure without coronary artery ligation. The success rate for this surgery was 80% in ligated rats and 95% in sham rats. After surgery, the animals were housed separately for 5 days until fully recovered and then randomized to the housing condition.

A total of 52 animals underwent MI surgery and 24 animals sham surgery. During the 17 week post-surgery follow-up 8 animals died (3 in the sham group and 5 in the infarcted group): 2 animals were euthanized because of severe infection or substantial loss of weight, 1 animal died before the 8-week echocardiogram, 3 animals died between weeks 8 and 16 before the second echocardiogram, and 2 animals just prior to terminal surgery. Animals stayed in the same pairs or group in the 2/cage and 4/cage conditions and replaced only if the death occurred within 6 weeks of surgery (N = 2 in the 2/cage and N = 1 in the 4/cage condition). Later replacements were not done because the advantages of consistent group size are outweighed by the disadvantages of bias resulting from changing the animal group composition.

2.3. Housing condition manipulation

The housing condition manipulation was selected to best serve the aims of the present project because (1) of its known effects on behavioral indices of distress; (2) the established effect on the hypothalamic–pituitary–adrenal axis, catecholamines, and neuroendocrine and immune system responses; and (3) to minimize confounding by pain, injury and exertion, which all may influence HF biology independent of psychological distress.

Animals were housed in one of three conditions: individually, in pairs (usual care) or in groups of four. For the 2/cage and 4/cage conditions, animals were kept in the same group throughout the experiment. If an animal in these conditions died then a replacement was made to maintain the group size if the death occurred within 6 weeks (see above). The cage size was consistent for all three groups (15 by 25 cm). Randomization to the housing condition occurred at five days post-surgery, to allow for wound healing prior to exposure to other animals. Because of the long-term housing conditions in the 4/cage group, Veterinarian Services required frequent change of cages because of soiling and ammonia accumulation (three times per week). This frequency of cage changes was also used for the other experimental groups.

2.4. Echocardiography

Left ventricular (LV) function was evaluated by echocardiography at eight and sixteen weeks following surgery using a Vevo 770 High-Resolution Imaging System (Toronto, Ontario, Canada) as previously described [6,7,29–32]. The RMV™ 716 Scanhead transducer was used with a 40-MHz linear array. The rats were anesthetized with 1.5–2.0% isoflurane by mask, the chest shaved, the animal situated in the supine position on a warming pad.