Mast cell stabilization improves cardiac contractile function following hemorrhagic shock and resuscitation

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Cardiac contractile dysfunction following HS/R is well established (31, 32), and previous work of our laboratory has demonstrated a significant depression in cardiac contractile function with concomitant HS-induced increases in cardiac TNF-α. Although the mechanism of cardiac dysfunction following HS/R is incompletely understood, various cardiodepressant cytokines have been implicated as possible mediators of the dysfunction, including TNF-α, IL-1β, and IL-6 (17, 31). Although the local production of cardiac stress-activated cytokines has been demonstrated, the exact cell source has not been fully elucidated. There is emerging evidence to suggest that resident cardiac mast cells have the ability to store, produce, and release these cytokines via degranulation in response to stress (7, 9).

The exact role of mast cells in HS is not completely understood. Recent research in HS has focused on mast cell granule contents as potential mediators of disease following HS, with compelling evidence to suggest that HS is a sufficient stimulus for the activation of mast cells in the rat lung (14), stomach wall (5), and hypothalamus (34). In addition, mast cells have been implicated in various cardiac pathologies, including atherosclerosis (16), myocardial ischemia (33), myocardial infarction (12), and chronic volume overload (3). The wide range of mast cell granule contents and their perivascular nature suggest that these cells may be able to respond rapidly to local and/or systemic stressful events or stimuli and release their contents directly into the blood to then act either locally or remotely.

Two distinct subpopulations of mast cells exist: the mucosal mast cell and the connective tissue mast cell (CTMC) (10). The rat heart contains a resident mast cell population derived from CD34+ pluripotent stem cells (23) and classified as CTMCs (18). This type of mast cell can be identified immunohistochemically or immunofluorescently through staining using a CTMC granule-specific enzyme, rat mast cell protease-1 (RMCP-1) (4). These mast cells have the ability to produce and release cytokines including TNF-α, IL-1, and IL-6, in addition to other biological mediators such as histamine, chymase, carboxypeptidase, and hexosaminidase (9, 23).

Recent research has implicated mast cells in various cardiac pathologies, including atherosclerosis (16), myocardial ischemia (33), myocardial infarction (12), and systolic pressure overload (11). No previous work has been published on the role of mast cells in cardiac dysfunction following HS.

The goal of this study was to determine whether HS is a sufficient stimulus to activate cardiac mast cells and whether...
mast cell degranulation plays a role in the cardiac contractile dysfunction noted following HS. Specific CTMC stabilizers were administered to animals 15 min before the onset of HS. Verification of mast cell degranulation and stabilization was done by quantifying serum levels of β-hexosaminidase. In addition, mast cell immunofluorescence using RMCP-1 was used to assess the degranulation and stabilization of these potentially cardiodepressant cells.

METHODS

Animal care. The animal studies were approved by the Animal Care Committee, and all animals were maintained in an accredited facility and cared for in accordance with the recommendations of the Canadian Council on Animal Care, the requirement of the Animals for Research Act of the Province of Ontario, and the regulations of the Animal Care Committee, University Health Network, and the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, Revised 1996). All animal protocols conformed to the Canadian Council on Animal Care, the requirement of the Animals for Care and Use of Laboratory Animals (NIH Publication No. 85-23, Revised 1996).

Surgical procedure. Adult male Sprague-Dawley rats weighing 350 to 400 g (Charles River, Wilmington, MA) were pretreated intramuscularly with atropine sulfate (25 μg/kg) and anesthetized intraperitoneally with pentobarbital sodium (50 mg/kg). Catheters (22 gauge) were placed in the tail vein and carotid artery, and a tracheostomy (14-gauge catheter) was performed. Venous access was used for the administration of supplemental anesthetic, return of withdrawn blood, and the administration of fluid during resuscitation (Ringer lactate solution). The carotid artery was utilized for the measurement of mean arterial blood pressure (MAP; Hewlett-Packard model 78304A; Palo Alto, CA) and the removal of blood for the induction and maintenance of HS. The animals were allowed to stabilize for 30 min until hemorrhage was induced. The animals were maintained on room air and spontaneous ventilation throughout the experimental period.

HS model. Hemorrhage was induced by the removal of blood through the carotid artery over a 5-min period to reduce the MAP to 40 mmHg. MAP was maintained at 40 mmHg for predetermined time intervals by the continuous removal of blood from the carotid artery. Following the HS period, the animals were resuscitated with their shed blood and additional Ringer lactate solution (10 ml/kg) over a 5-min period to return the MAP to preshock (PS) levels. The animals were then monitored up to 2 h, during which supplemental Ringer lactate solution was given as required to maintain the MAP at PS levels. After the 2-h resuscitation period, hearts were excised for either biochemical analysis or the assessment of cardiac contractile function.

Information design and groups. To determine a role for cardiac mast cells in the contractile dysfunction following HS/R, selective CTMC stabilizers were administered to rats 15 min before HS. Rats were randomly assigned to one of four groups (n = 7/group): 1) sham-operated control rats, 2) HS + saline (1 mg/kg iv), 3) HS + ketotifen (1 mg/kg iv), and 4) HS + cromolyn (5 mg/kg iv, repeated hourly).

In a second series of animals, the biochemical verification of mast cell degranulation was assessed by quantifying serum β-hexosaminidase throughout the experimental protocol. The rats were divided into the same four groups (n = 10/group). Blood was withdrawn from the carotid artery at the following predetermined time points: 25 min of PS, 30 min of shock (HS30), 60 min of shock (HS60), 60 min of shock + 10 min of resuscitation, 60 min of shock + 60 min of resuscitation, and 60 min of shock + 120 min of resuscitation.

Assessment of left ventricular function. Following 60 min of hemorrhage and 2 h of resuscitation, heparin (200 IU iv) was given to prevent coagulation and the hearts were rapidly excised and placed in 4°C Krebs-Henseleit bicarbonate (KHB) buffer. The KHB buffer used in this study is similar to that previously reported with isolated heart muscle preparations (22). The solution contained (in mM) 118 NaCl, 4.7 KCl, 21 NaHCO3, 1.25 CaCl2, 1.2 MgSO4, 1.2 KH2PO4, and 11 glucose. All solutions were prepared daily with deionized water and bubbled with 95% O2-5% CO2. The pH of the solution was 7.4, and the temperature was maintained at 37°C. The ascending aorta was cannulated with an 18-gauge cannula that was subsequently connected through glass tubing to a KHB buffer reservoir for the perfusion of the coronary circulation at a constant pressure of 120 cmH2O. Intraventricular pressure was measured with a saline-filled latex balloon attached to a polyethylene tube and threaded into the left ventricular chamber through the left auricle. Left ventricular pressure was measured with a mini pressure transducer (Gould Electronics, Valley View, OH) attached to the balloon cannula. The values of left ventricular maximal pressure increase and decrease over time (+dP/dtmax and −dP/dtmax, respectively) were obtained using an electronic differentiator (model 13-4615-17; Gould Electronics) and recorded using a Windo-Graph chart recording system (Gould Electronics).

A Starling relationship for the different groups was determined by plotting left ventricular peak systolic pressure (PSP), +dP/dtmax (a measure of contractility), and −dP/dtmax (a measure of relaxation) against the physical parameter of increasing left ventricular volume.

The relationship between left ventricular capacity and balloon volume was determined by plotting the pressure-volume relationship of the isolated balloon. All experiments were performed on the linear portion of the balloon pressure-volume curve.

Quantification of total serum β-hexosaminidase. β-Hexosaminidase is one of the many acid hydrolases histochemically identified in mast cell granules (27). It has been shown to be released in parallel with histamine following immunologic mast cell activation with anti-rat F(ab)2 and has subsequently been accepted as a marker of mast cell activation and degranulation (30). In our model, serum β-hexosaminidase levels were measured at predetermined time points. At the time points discussed in Experimental design and groups, 0.2 ml of blood was withdrawn from the carotid arterial line. Total β-hexosaminidase was measured by the fluorometric analysis of the degradation product of the synthetic substrate 4-methylumbelliferonyl-N-acetyl-α-d-glucosaminide (MUG). Briefly, 25 μl of serum were incubated with 25 μl of 3.2 mM MUG dissolved in 1× citrate buffer (pH 4.1) for 20 min. The reaction was stopped by the addition of 200 μl of 10 mM 2-amino-ethylcarbazole dissolved in 1× citrate buffer (pH 4.1), and the fluorescence of 4-methylumbelliferone, the degradation product, was determined by fluorimetry with an excitation wavelength of 365 nm and an emission wavelength of 450 nm.

Mast cell histology. To verify mast cell degranulation histologically, hearts from animals at 60 min into sham operation (Sham60) or HS60 with or without a mast cell stabilizer were used. The hearts were rapidly excised and flushed free of residual blood by the administration of ice-cold Ringer lactate solution. A portion of the base and the apex of the heart, along with the atria, were removed. The hearts were placed in Carnoy’s fixative (60% ethanol, 30% chloroform, and 10% acetic acid) for 24 h, followed by a transfer to absolute ethanol for long-term storage. Routine paraffin embedding was performed, and 4-μm sections were made using a Microm HM 325 microtome. Ten levels in each heart were cut 100 μm apart to allow a global representation of mast cell density. The levels were cut beginning at the apex and progressing to the base of the heart. At each level, one section was made. The sections were stained with 0.1% toluidine blue for mast cell identification. Briefly, paraffin sections were deparaffinized, hydrated, and rinsed in deionized water. Sections were placed in 1% acetic alcohol and rinsed in 1× citrate buffer (pH 4.1), and the fluorescence of 4-methylumbelliferone, the degradation product, was determined by fluorimetry with an excitation wavelength of 365 nm and an emission wavelength of 450 nm.

Mast cell staining. Immunofluorescence was performed on rat heart tissue, and images were obtained using confocal microscopy. The hearts were excised and flushed as described in Mast cell immunofluorescence.
Statistical comparisons were performed using SPSS 10 Statistical Software for Windows (SPSS, Chicago, IL). Analyses included an ordinary t-test and one-way ANOVA followed by a Student-Newman-Keuls post hoc test for multiple pairwise comparisons, as well as repeated-measures ANOVA followed by a Bonferroni post hoc test. A probability of <0.05 was considered significant.

RESULTS

In vivo response to HS/R. The in vivo MAP response to HS/R is demonstrated in Fig. 1, whereas Table 1 indicates the blood volumes removed and fluid volumes replaced. The animals in the HS groups underwent a similar injury as evidenced by the reductions in MAP. However, during resuscitation, the MAP is significantly improved at several time points in the cromolyn- and ketotifen-treated compared with saline-treated animals (P < 0.05). The mean volume of blood withdrawn to induce HS is the same in each group; however, the volume of resuscitation fluid required in the HS + cromolyn and HS + ketotifen groups is approximately half of that required for the HS groups (Table 1). This trend was significant in the cromolyn-treated animals (P < 0.05 vs. saline).

Table 1. Shed blood volumes and resuscitation fluid requirements

<table>
<thead>
<tr>
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<th>HS + Saline</th>
<th>HS + Ketotifen</th>
<th>HS + Cromolyn</th>
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<tbody>
<tr>
<td>Blood withdrawn</td>
<td></td>
<td></td>
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<tr>
<td>during HS, ml</td>
<td>15.14±0.61</td>
<td>15.11±0.65</td>
<td>15.21±0.56</td>
</tr>
<tr>
<td>Resuscitation volume, ml/kg body wt</td>
<td>49.91±9.24</td>
<td>29.94±2.53</td>
<td>22.42±2.87*</td>
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</table>

Values are means ± SE. Shed blood volumes demonstrate no statistical difference, yet the resuscitation volumes required in the ketotifen- and cromolyn-treated groups are roughly half of those required in the saline-treated group. This trend is statistically significant with cromolyn treatment. *P < 0.05 vs. hemorrhagic shock (HS) + saline.

Mast cell stabilization and cardiac function following HS/R. The myocardial functional data following 60 min of HS and 2 h of resuscitation depict a significant depression in contractile function in the HS + saline-treated compared with the sham-treated animals in all measured variables (PSP, +dP/dt\text{max}, and −dP/dt\text{max}, Fig. 2). Ketotifen or cromolyn treatment significantly reduced the contractile dysfunction, as evidenced by the improvements in PSP and +dP/dt. Mast cell stabilization also produced an initial significant improvement in relaxation, as measured by −dP/dt, which gradually lost significance. Overall, cromolyn treatment displayed a more potent effect by returning function closer to sham-operated values than the treatment with ketotifen.

Changes in diastolic function were not statistically significant between any of the experimental groups; however, a trend toward diastolic dysfunction in the HS + saline and the drug-treated animals was evident (Fig. 3). Ketotifen administration showed a slight initial improvement in diastolic function, which gradually progressed to dysfunction.

Serum β-hexosaminidase throughout HS/R. Serum levels of β-hexosaminidase were not altered from baseline to HS30 between the four groups (Fig. 4). Following 60 min of HS, a significant increase in serum β-hexosaminidase was observed, which remained significantly elevated throughout resuscitation. Both ketotifen and cromolyn treatment significantly inhibited the rise of serum β-hexosaminidase. Cromolyn treatment displayed a more potent ability to prevent mast cell degranulation during HS, although the difference in the inhibition between the two drugs was not statistically different.

Mast cell histology. The mast cell density in the HS hearts was significantly elevated compared with that of the control hearts (1.92 ± 0.03 vs. 1.84 ± 0.05 cells/mm²), and the administration of ketotifen or cromolyn did not significantly reduce the mast cell numbers (1.71 ± 0.08 and 1.69 ± 0.08 cells/mm², respectively; Fig. 5).

Basic histology demonstrated differences in cardiac mast cell morphology between the sham-, HS + saline-, and drug-treated animals. Figure 6, D–F, depicts cardiac mast cells from HS + saline-treated animals. There is evidence of granule extrusion from the cells, indicating degranulation. In comparison, Fig. 6, G–I, depicts cardiac mast cells from HS + ketotifen-treated animals, whereas Fig. 6, J–L, displays cardiac mast cells from HS + cromolyn-treated animals and demonstrates little evidence of degranulation. Treated cardiac mast...
cells resemble more closely the sham-treated mast cells based on the staining intensity of their cytoplasm and the absence of granule extrusion from the cells.

Mast cell immunofluorescence allowed for the visualization of mast cell degranulation (Figs. 7 and 8). In Fig. 7, FITC-avidin-stained mast cells are clearly evident in Sham0 (A–C), Sham60 (D–F), and HS60 (G–I) animals. RMCP-1-positive cardiac mast cells are evident in Fig. 8 from Sham0 (A–C), Sham60 (D–F), and HS60 (G–I) animals. Evidence of mast cell degranulation occurring at HS60 is displayed in both the FITC- and RMCP-1-stained mast cells. No evidence of mast cell degranulation was seen in the sham-operated animals using either the FITC or RMCP-1 stain at PS or at Sham60.

**DISCUSSION**

This study defines a role for mast cells and mast cell degranulation mediators in the development of cardiac contractile dysfunction following HS/R. Each investigational method indicated a role for mast cells in HS-induced cardiac contractile dysfunction.

Animals pretreated with mast cell stabilizing agents showed improvements in cardiac function following HS/R, as demonstrated by improvements in PSP, $\frac{dP}{dt}$, and $\frac{dP}{dt}$ max. The

![Fig. 2](image1.png)

**Fig. 2.** Myocardial contractile function assessment at increasing left ventricular volume. A: peak systolic pressure. B: maximal pressure increase over time ($\frac{dP}{dt}$ max). C: maximal pressure decrease over time ($\frac{dP}{dt}$ min). Sham-operated controls; ■, HS + saline; ∆, HS + ketotifen; ▲, HS + cromolyn. Values expressed as means ± SE (n = 7 hearts/group). *P < 0.05, sham vs. HS + saline; +P < 0.05, HS + cromolyn vs. HS + saline; #P < 0.05, HS + ketotifen vs. HS + saline.

![Fig. 3](image2.png)

**Fig. 3.** Myocardial diastolic function following mast cell stabilization. Sham-operated controls; ■, HS + saline; ∆, HS + ketotifen; ▲, HS + cromolyn. All values are expressed as means ± SE (n = 7 hearts/group).

![Fig. 4](image3.png)

**Fig. 4.** Serum levels of β-hexosaminidase throughout hemorrhagic shock and resuscitation. White bar, sham-operated controls; black bar, HS + saline; light gray bar, HS + ketotifen; dark gray bar, HS + cromolyn. *P < 0.05 vs. HS + saline at 25 min of PS; #P < 0.05 vs. all other groups at the same time point. PS5, 5 min of PS.
quantification of serum β-hexosaminidase confirmed the in vivo inhibition of mast cell granule release coincident with improved cardiac function. Histological evidence demonstrated that rats have a resident cardiac mast cell population that degranulated and were inhibited from degranulation by the stabilizing agents (cromolyn and ketotifen) employed in this study. Immunohistochemistry using mast cell antibodies provided the direct visualization of cardiac mast cell degranulation after HS60. These results indicate that HS is a sufficient stimulus to activate cardiac mast cell degranulation and raise the serum hexosaminidase level. The inhibition of connective tissue-type mast cell degranulation significantly improves cardiac contractile function coincident with normal serum hexosaminidase levels. Mast cell stabilization affects the entire mast cell population, and it is likely that improvements in cardiac function may be due to the reduced secretion of mast cell granule contents in both the heart as well as the systemic mast cell population.

Using our model of HS/R, we successfully identified a resident cardiac mast cell population using toluidine blue, FITC-avidin, and RMCP-1 antibodies. All staining methods provided evidence of cardiac mast cell degranulation during HS. In the past, immunohistochemical staining for RMCP-1 has identified rat cardiac mast cells and classified them as CTMCs (30). Our present data using immunofluorescent staining for RMCP-1 displayed analogous results confirming the presence of this mast cell subtype in the rat heart. Degranulated cardiac mast cells were observed at 60 min of HS (Fig. 8, G–I), whereas mast cells from control hearts (Sham0 and Sham60) lacked evidence of degranulation. These findings were noted in both the FITC- and RMCP-1-stained hearts. There was a distinct difference in immunofluorescent cardiac mast cell morphology between mast cells from sham-operated (Sham0 and Sham60; Fig. 8) versus the HS60 groups. The cells visualized at HS60 displayed a nonconventional mast cell shape with evidence of granule extrusion. Furthermore, counting cardiac mast cells stained with toluidine blue indicated that the cardiac mast cell density in the HS + saline-treated animals was significantly elevated compared with that of the sham-operated animals. When mast cell stabilizers were administered, the rise in mast cell numbers at 60 min of HS was not reduced. The mechanism(s) underlying the increased density of mast cells in heart failure or cardiac dysfunction, in our model or other models, remains unknown. These results suggest that HS is a sufficient stimulus to activate cardiac mast cells and support recent research, which has demonstrated mast cell activation and hyperplasia in various organs following HS (5, 14, 27).

A role for cardiac mast cells in the failing myocardium has recently garnered much attention. Although the exact roles of...
mast cell granule mediators in heart failure or dysfunction are not completely understood, a role for mast cells has been demonstrated by the findings of increased numbers of cardiac mast cells in various cardiac pathologies including chronic volume overload (2). The subsequent inhibition of mast cells resulted in reduced mast cell numbers and improved ventricular diastolic function (2). Mast cell granular content involvement in cardiac disease pathogenesis has also been described in myocardial ischemia. Lodoxamide administration, before and during ligation of the left circumflex coronary artery, significantly reduced myocardial infarct size compared with that of saline-treated hearts (13). The authors attributed this improvement in infarct size to the inhibition of the release of mediators from mast cells. Other authors have also described the role of mast cell mediators in ischemia-reperfusion-induced cardiac injury (7, 25).

Hemorrhage-induced cardiac dysfunction has been well documented in our laboratory. Investigations into the mechanisms of the dysfunction have indicated that both TNF-α and adrenergic signaling pathways may be involved. Cardiac contractile dysfunction was improved by 90%, and the translocation of NF-κB to the nucleus after HS was prevented following α1-adrenergic blockade with prazosin hydrochloride (21, 31). Coupled with the knowledge that α1-adrenergic receptors have been localized to cardiac mast cells (29), future studies are needed to investigate the link between α-adrenergic stimulation and mast cell activation to provide insight into the HS-specific agents responsible for mast cell activation and the development of cardiac contractile dysfunction following HS/R.

Evidence linking mast cell granular content release to depressed cardiac function following HS was noted by the administration of mast cell stabilizing agents to rats 15 min

Fig. 7. FITC-avidin immunofluorescent staining of cardiac mast cells. Immunofluorescent determination of cardiac mast cell degranulation is shown. Mast cells stained with FITC-avidin were identified in sham operation before shock (Sham0; A–C), Sham60 (D–F), and HS60 (G–I) hearts. HS60 cardiac mast cells stained with FITC-avidin indicate degranulation. Images were taken at ×400 (n = 3 hearts/group).
before the onset of HS, as well as the quantification of serum β-hexosaminidase. The gradually rising levels of serum β-hexosaminidase during HS provided a quantitative measure of degranulation, whereas the abolishment of this rise with the administration of mast cell stabilizers signified the inhibition of degranulation. Following 60 min of HS and 120 min of resuscitation, hearts were harvested and cardiac function was assessed. Cardiac functional assessment performed at the end of the resuscitation period indicated a significant prevention of cardiac dysfunction in both mast cell stabilizer groups, indicated by the shift in the function curves upward and to the left compared with that of the HS saline function curves.

Although both ketotifen and cromolyn administration improved systolic function, it was noted that cromolyn was more effective in protecting against the HS-induced systolic dysfunction. We speculate that the mechanism of action of these two drugs may explain this phenomenon. Ketotifen is a second generation histamine H1 receptor antagonist, and the exact mechanism of action of ketotifen has been linked to the ability of the drug to block the calcium influx into the mast cell, which is essential for granule exocytosis (8, 35). Unlike ketotifen, the mechanism of action of cromolyn does not include the blockade of calcium influx. Its exact mechanism remains undefined; however, research has shown that mast cell membranes contain a cromolyn-binding protein (20). The activity of cromolyn seems to be involved in degranulation events occurring before calcium entry into the cell (19). Based on this information, it seems likely that any mast cell-stabilizing drug that alters calcium channel flux may prevent the myocardium from achieving optimal contractile function. Although there was no significant depression in diastolic function, there was a trend toward a decreased diastolic function in the HS + saline-treated animals, indicated by a shift in the diastolic function curves upward and to the left compared with the sham-operated

Fig. 8. Rat mast cell protease-1 (RMCP-1) immunofluorescent staining of cardiac mast cell. Immunofluorescent determination of cardiac mast cell degranulation is shown. RMCP-1-positive mast cells were identified in Sham0 (A–C), Sham60 (D–F), and HS60 (G–I) hearts. HS60 cardiac mast cells stained with anti-RMCP-1 antibodies indicate degranulation. Images were taken at ×400 (n = 3 hearts/group).
diastolic function. Treatment with the mast cell stabilizing agents did not significantly improve diastolic function, although initially cromolyn treatment indicated a return of diastolic function toward sham-operated levels. Although this study has indicated a reduced left ventricle compliance during HS, which is consistent with previous published work from our laboratory (31), and no improvement in left ventricle compliance following mast cell inhibition, other studies have described an improved left ventricle compliance following mast cell inhibition (2, 3). It is possible that the signaling pathways that activate mast cells in an acute low-flow state such as HS differ significantly from those activated during states of chronic volume overload, which may explain the differences in mast cell mediators in these two models. Future studies are needed to investigate whether acute alterations in the myocardial levels of matrix metalloproteinase activity and fibrillar collagen concentration develop in this model of HS/R. Differences in these two models with respect to diastolic function may also be related to the acute versus chronic nature of the types of dysfunction being investigated. The ability of mast cell stabilizing agents to improve cardiac function likely results from the inhibition of the release of negative inotropic agents from mast cell granules. In fact, a cardioprotective effect of ketotifen in an animal model of doxorubicin-induced myocardial damage has been described. The exact mechanism of cardioprotection from ketotifen is unknown; however, its ability to block the release of cardiotoxic compounds from mast cells has been suggested as a potential mechanism (36).

Overall, this study has demonstrated a clear role for cardiac mast cells in the contractile dysfunction resulting from HS/R. We have demonstrated 1) the presence of connective tissue-type mast cells in the rat heart, 2) histologically and enzymatically that 60 min of HS is sufficient for the activation of cardiac mast cells, and 3) that the stabilization of mast cells inhibited granule content release while protecting against the HS-induced contractile dysfunction. These results imply that the stabilization of mast cells during HS may become a future therapeutic intervention for maintaining optimal cardiac function during HS, with the potential to reduce the morbidity and mortality associated with HS/R.

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GRANTS

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