Mesenteric lymph duct ligation prevents trauma/hemorrhage shock-induced cardiac contractile dysfunction

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Sambol JT, Lee MA, Caputo FJ, Kawai K, Badami C, Kawai T, Deitch EA, Yatani A. Mesenteric lymph duct ligation prevents trauma/hemorrhage shock-induced cardiac contractile dysfunction. J Appl Physiol 106: 57–65, 2009. First published November 13, 2008; doi:10.1152/japplphysiol.90937.2008.—Clinical and experimental studies have shown that trauma combined with hemorrhage shock (T/HS) is associated with myocardial contractile dysfunction. However, the initial events triggering the cardiac dysfunction are not fully elucidated. Thus we tested the hypothesis that factors carried in intestinal (mesenteric) lymph contribute to negative inotropic effects in rats subjected to a laparotomy (T) plus hemorrhagic shock (HS; mean arterial blood pressure of 30–40 Torr for 90 min) using a Langendorff isolated heart preparation. Left ventricular (LV) function was assessed 24 h after trauma plus sham shock (T/SS) or T/HS by recording the LV developed pressure (LVDP) and the maximal rate of rise in coronary flow rates and Ca^{2+}. Cardiac function was comparable in hearts from naive, T/SS, and T/SS-LDL rats. Both LVDP and +dP/dt_{max} were significantly depressed after T/HS. The T/HS hearts also manifested a blunted responsiveness to increases in coronary flow rates and Ca^{2+}, and this was prevented by LDL preceding T/HS. Although electrocardiograms were normal under physiological conditions, when the T/HS hearts were perfused with low Ca^{2+} levels (~0.5 mM), prolonged P-R intervals and second-degree plus Wenckebach-type atrioventricular blocks were observed. No such changes occurred in the control or T/SS+LDL hearts. The effects of T/HS were similar to those of the Ca^{2+} channel antagonist diltiazem, indicating that an impairment of cellular Ca^{2+} handling contributes to T/HS-induced cardiac dysfunction. In conclusion, gut-derived factors carried in mesenteric lymph are responsible for acute T/HS-induced cardiac dysfunction.

progress has been made in understanding the pathophysiological mechanisms of myocardial contractile dysfunction associated with trauma combined with hemorrhagic shock (T/HS) (26, 34). Experimental hemodynamic studies indicate that the signaling pathways and effector molecules involved in cardiac depression are multifactorial. However, the source(s) of the initial factors involved in the development of altered myocardial function following various forms of shock have not been well established. Yet, identification of the initial (primary) factors that initiate the processes leading to myocardial contractile dysfunction and the development of therapies to block their effects is likely to be more successful than attempts at blocking secondary cardiodepressant factors.

The concept that the gastrointestinal tract (i.e., gut) plays a pivotal pathogenic role in the pathogenesis of the systemic inflammatory response syndrome and multiple organ dysfunction (MODS) following shock is well established (6, 12, 17). Initially, these studies implicated loss of gut barrier function and the subsequent translocation of bacteria and endotoxin as being involved in gut-induced MODS. However, more recently, there is increasing evidence that it is the egress of nonbacterial gut-derived factors carried in the mesenteric lymph that lead to the development of postshock organ failure (25, 42). In fact, Cox et al. (8) recently reported that an isolated episode of intestinal ischemia will lead to myocardial dysfunction in dogs and that this gut-induced effect also appears to be transduced via the intestinal lymphatics. The mechanisms by which these lymphatic borne factors are produced as well as the organs involved in their production seem to involve pancreatic enzymes interacting with the ischemic gut (1, 14, 28). Furthermore, our recent studies measuring cardiac contractility in isolated hearts and myocytes from rats subjected to burn injury (20, 32) have shown that mesenteric lymph generated following burn injury directly causes changes in cardiac contractility, thereby supporting the role of mesenteric lymph as a key factor involved in regulating myocardial contractile dysfunction.

It is conceivable that the same mechanisms of burn injury can be active in T/HS-induced cardiac dysfunction. However, no attempts have been made to date to fully investigate the effects of mesenteric lymph duct ligation (LDL) on T/HS-induced myocardial contractile dysfunction. Thus, to improve our understanding of signaling factors that trigger cardiac dysfunction following T/HS, it becomes important to examine whether mesenteric LDL, which prevents gut-derived intestinal lymph from reaching the systemic circulation, would be pro-

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LYMPH LIGATION IN HEMORRHAGE CARDIAC DYSFUNCTION

tective. Therefore, the primary goal of this study was to test the hypothesis that the gut is the source of these myocardial depressant-inducing factors and that they exit the gut primarily via the intestinal lymphatic system. To accomplish this, we tested the ability of LDL to limit T/HS-induced cardiac contractile dysfunction, since LDL prevents intestinal lymph from reaching the systemic circulation.

Since cellular Ca²⁺ homeostasis is an important regulator of cardiac contractility (4, 18), and altered Ca²⁺ signaling plays an important role in injury conditions such as burns or sepsis (33), the second goal was to determine whether the mechanism of T/HS-induced cardiac dysfunction involves impaired cellular Ca²⁺ handling. In addition, since cardiac stresses such as ischemia and reperfusion are often associated with abnormalities of cardiac rhythm, we also monitored the electrical rhythm (ECG) of the hearts under baseline conditions and in response to changing Ca²⁺. Last, since Ca²⁺ influx through L-type Ca²⁺ channel is a key determinant of cardiac contractility, we examined the effects of the pharmacological L-type Ca²⁺ channel blocker diltiazem on left ventricular developed pressure (LVDP) and ECG simultaneously, to investigate a potential mechanism for T/HS-induced myocardial dysfunction.

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats (250–350g) were used in this study. The animal maintenance protocols and the experiments were approved by the New Jersey Medical School Animal Care and Use Committee. The care and handling of these animals conformed to all guidelines for animal care as outlined by the National Institutes of Health.

Mesenteric lymph ligation and T/HS model. All surgical procedures are performed as previously described (13, 25). The model we utilized was a fixed-pressure hemorrhage shock model combined with tissue trauma in the form of a laparotomy. This model was chosen to better reflect the clinical setting of trauma, where patients experience tissue trauma in the form of a laparotomy. This model was chosen to better mimic the clinical setting of trauma, where patients experience tissue trauma in the form of a laparotomy. This model was chosen to better mimic the clinical setting of trauma, where patients experience tissue trauma in the form of a laparotomy.

Experimental protocols. Five groups of rats were studied: 1) naive noninstrumented controls as well as rats subjected to 2) T/SS, 3) T/SS+LDL, 4) T/HS, and 5) T/HS+LDL. LV systolic pressure and LVEDP were assessed by measuring the intraventricular pressure with a fluid-filled balloon (polyethylene film) that had been inserted into the left ventricle via the mitral valve from the left atrium. This balloon was connected to a pressure transducer (ADInstruments MLT 844). LVDP was calculated as the difference between the peak systolic pressure and LVEDP. The baseline LVEDP was comparable in hearts isolated from all groups.

The maximum rates of LVDP rise (+dP/dt max) and fall (−dP/dt max) were obtained using an electronic differentiator. The ECG was monitored by electrodes attached to the apex and base of the heart (ADInstruments ML 136 Animal Bio Amp). All parameters were stored and analyzed off-line using PowerLab software (ADInstrumets). LV myocardial function was measured at 24 h after T/SS or T/HS. This time point was selected because earlier in vivo heart studies have shown that cardiac output, stroke volume, and ±dP/dt max are significantly depressed in rat hearts 24 h after T/HS (40). Although the Langendorff preparation provides highly reproducible information on the LV systolic and diastolic pressure and their derivatives, one potential limitation is that the assessment of cardiac work parameters that are dependent on intact circulation is not available.

Statistical analysis. Data are means ± SE. Statistical significance was determined using ANOVA to assess differences among the groups for each of the variables. Between-group/condition analyses were conducted using a Student’s t-test. Statistical analysis for ECG parameters reported in Fig. 6B was performed using the Fisher’s exact probability test. P < 0.05 were considered statistically significant.

RESULTS

Because the anesthesia and/or the various procedures performed in the T/SS and T/SS+LDL hearts could have affected cardiac pump function, our initial experiments compared LV contractile function in isolated hearts from naive noninstrumented (control), T/SS, and T/SS+LDL rats. In this experi-

Table 1. Baseline LV function measured in control rats and rats 24 h after T/SS or T/SS+LDL

<table>
<thead>
<tr>
<th>HR, beat/min</th>
<th>LVP, Torr</th>
<th>+dP/dt max, Torr/s</th>
<th>−dP/dt max, Torr/s</th>
<th>n</th>
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<tbody>
<tr>
<td>Control</td>
<td>256.1±8.8</td>
<td>116.3±3.3</td>
<td>3,524±213</td>
<td>2,160±86</td>
</tr>
<tr>
<td>T/SS</td>
<td>273.5±4.6</td>
<td>105.5±6.6</td>
<td>3,320±220</td>
<td>1,841±109</td>
</tr>
<tr>
<td>T/SS+LDL</td>
<td>261.6±12.3</td>
<td>113.6±9.0</td>
<td>3,223±256</td>
<td>2,131±249</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of rats. The baseline left ventricular (LV) heart rate (HR), pressure (LVP), and the maximum rise (+dP/dt max) and fall (−dP/dt max) were measured in naive noninstrumented (control) rats and in rats subjected to trauma and sham shock (T/SS) with or without lymph duct ligation (LDL).
ment, we measured baseline HR, LVDP, and ±dP/dt max, under conditions where the hearts were perfused with KHB (2 mM Ca²⁺) at a constant coronary flow rate of 8 ml/min (36). As summarized in Table 1, we found that none of these LV contractile parameters differed among these groups. Consequently, we pooled the data obtained from naive, T/SS, and T/SS+LDL hearts into one group designated as the control group.

**Effects of T/HS on cardiac contractile function.** Figure 1 shows representative baseline LVDP (A) and ±dP/dt max waveforms (B) recorded from Langendorff-perfused hearts isolated from control (a), T/HS (b), and T/HS+LDL (c) rats. The baseline LVDP of the T/HS hearts were significantly depressed (83 ± 4.2 Torr, n = 9, P < 0.05) compared with those of the control (116 ± 3.3 Torr, n = 15) or T/HS+LDL hearts (117 ± 2.5 Torr, n = 9) as was the rate of contraction and relaxation rates (±dP/dt max) (Fig. 2). These findings in isolated heart preparations were consistent with significant depression of in vivo cardiac function following T/HS (40). In contrast, LDL significantly prevented T/HS-induced changes in LVDP and ±dP/dt max.

We next examined changes in LV contractile parameters in response to changes in coronary flow rates. In this experiment, the hearts were exposed to different coronary flow rates and LV function was analyzed at a steady state (Fig. 2). In all groups, LVDP increased as coronary flow rates increased (Fig. 2A); however, the magnitude of increase was significantly less in the T/HS group than in the control or T/HS+LDL groups. Similarly, in all groups, both the rise (+dP/dt max; Fig. 2B) and fall (−dP/dt max; Fig. 2C) of LVDP were increased with increasing flow rates. However, the hearts from the T/HS group showed significantly lower amplitudes of LVDP, +dP/dt max, and −dP/dt max than the control or T/HS+LDL groups.

Since there are strong links among Ca²⁺ regulation, Ca²⁺ signaling, and heart failure (4, 18), we examined whether T/HS-induced LV dysfunction is associated with altered Ca²⁺ handling. This was accomplished by examining the contractile response to altered perfusate Ca²⁺ (Fig. 3). The control and T/HS+LDL hearts showed a normal physiological response where LVDP, +dP/dt max, and −dP/dt max increased as extracellular Ca²⁺ is acutely elevated. Although the T/HS hearts showed increases in these contractile parameters as the external Ca²⁺ concentration was increased, the magnitudes of the increases were blunted significantly compared with those of the control or T/HS+LDL groups. These results indicate that LV contractile reserve is reduced in T/HS hearts, presumably because responses to Ca²⁺ are impaired, and that lymph duct ligation prevents this response.

**Effects of T/HS on ECG parameters.** To determine whether intrinsic cardiac conduction abnormalities are associated with T/HS induced stress, we continuously recorded ECG signals and studied the effects of changes in perfusate Ca²⁺ concen-
Fig. 3. LV performance to increasing Ca²⁺ concentrations in the perfusate was blunted in the T/HS hearts but not in the T/HS+LDL hearts. Changes in LVDP (A), +dP/dt max (B), and −dP/dt max (C) are shown in response to Ca²⁺ in the perfusate. In control rat hearts, LVDP and ±dP/dt max were increased with an acute increase in Ca²⁺ concentration. The responses to Ca²⁺ were depressed in T/HS but not in the T/HS+LDL hearts. Data are means ± SE (n = 15, 9, and 9 for control, T/HS, and T/HS+LDL groups, respectively).

*P < 0.05 vs. control and T/HS+LDL groups.

Fig. 4. ECG recordings or ECG parameters measured in hearts perfused with 2 mM Ca²⁺ KHB. A typical example of ECG recordings in hearts from control (a), T/HS (b), or T/HS+LDL rats (c) is shown (A). Mean R-R interval (B) and mean PR interval (C) is shown in control, T/HS, and T/HS+LDL hearts. Data are means ± SE (n = 10, 6, and 6 for control, T/HS, and T/HS+LDL groups, respectively).

- R-R interval
- PR interval
- Changed R wave amplitude
- Changes in perfusate Ca²⁺ concentrations (0.5–3 mM) did not cause abnormalities of cardiac rhythm such as premature beats or ventricular tachycardia in either the control or the T/HS hearts. However, a significant prolongation in electrical conduction (prolonged PR interval) occurred in the T/HS group when hearts were perfused with lower Ca²⁺ concentration (Fig. 5C). Therefore, we further analyzed ECG patterns using 0.5 mM Ca²⁺. As shown in Fig. 5A, T/HS hearts demonstrated first-degree AV block (PR interval >60 ms) and Wenckebach-
type AV block as well as episodes of 2:1 AV conduction block. The results are summarized in Fig. 6B. Although the majority of T/HS hearts manifested significant evidence of abnormal ECG with AV conduction block, this did not occur in any of the 10 control or 10 T/HS/LDL heart preparations examined. These ECG results indicate that an impairment of cardiac myocyte Ca\textsuperscript{2+} handling develops following T/HS, and this may contribute to the contractile defect and altered ECG dynamics.

Under physiological conditions, Ca\textsuperscript{2+} influx through voltage-gated L-type Ca\textsuperscript{2+} channels is a key determinant of cardiac contractility and a major factor in AV conduction (4, 29). It is therefore possible that depressed cardiac output and ECG changes observed in T/HS hearts are mediated though TH/S-induced downregulation of L-type Ca\textsuperscript{2+} channel activity. We thus compared the characteristic effects of a Ca\textsuperscript{2+} channel blocker, diltiazem, known to inhibit the voltage-gated L-type subclass of Ca\textsuperscript{2+} channel (37), on LVDP and the ECG of normal hearts with those abnormalities observed in T/HS hearts. A typical tracing of the simultaneous measurement of LVDP and the ECG shows that diltiazem decreased LVDP and induced AV conduction defects in normal hearts (Fig. 7). The magnitude of the decrease in LVDP in normal hearts exposed to a 1 \mu M concentration of diltiazem (40 ± 5%, n = 8) was very similar to that observed in T/HS hearts (Fig. 2). Furthermore, the diltiazem-induced decrease in LVDP was also associated with a prolongation of the PR interval similar to what was observed in the T/HS hearts. In addition, diltiazem induced a Wenckebach-type second-degree AV block in three of the six hearts and 2:1 AV conduction blockade in two of the six hearts tested. These diltiazem effects are in good agreement with the hypothesis that impaired cellular Ca\textsuperscript{2+} handling is associated with downregulation of L-type Ca\textsuperscript{2+} channel and is at least partially responsible for the depressed myocardial contractility and altered ECG dynamics observed in T/HS hearts.

Fig. 5. Effects of changes in perfusate Ca\textsuperscript{2+} concentrations (0.5–3 mM) on ECG parameters showing that PR interval was increased in T/HS hearts at 0.5 mM Ca\textsuperscript{2+} concentrations. A typical example of continuous ECG recordings during the change of perfusate Ca\textsuperscript{2+} from 1 to 3 mM in a control heart is shown (A). The mean voltage of peak R wave (B) and mean PR interval (C) are plotted against perfusate Ca\textsuperscript{2+} concentrations. Data are means ± SE (n = 7, 6, and 5 for control, T/HS, and T/HS+LDL groups, respectively). *P < 0.05 vs. control and T/HS+LDL groups.
LYMPH LIGATION IN HEMORRHAGE CARDIAC DYSFUNCTION

suggest that the cellular mechanisms for altered contractility in T/HS may be different from the common pattern of changes (e.g., loss of SR function) observed in cardiac hypertrophy and heart failure.

DISCUSSION

Myocardial depression following T/HS has been well established in the literature (21, 30, 41). Although the presence of cardiac dysfunction is well described, the mechanism(s) responsible for acute T/HS-induced myocardial contractile dysfunction remain to be fully elucidated. Two major theories have been proposed to explain the pathogenesis of acute myocardial dysfunction in these circumstances. However, because of a lack of supporting experimental evidence, the first theory, which was that burn, trauma, shock, or sepsis-induced myocardial dysfunction was due to decreased myocardial perfusion leading to ischemic injury, has been replaced by a second theory focusing on the inflammatory response (5, 22). The inflammatory theory of myocardial depression postulates that functional rather than structural changes are responsible for depressed contractility and that myocardial depression is mediated by endogenously produced proinflammatory factors (5, 7, 22, 27, 35, 38). This notion of an inflammatory cardiomyopathy is consistent with this fact that these conditions provoke a profound systemic inflammatory response characterized by increased levels of circulating proinflammatory mediators, leukocyte activation, microvascular leakage, and organ failure (12). Based on our experimental studies implicating gut-derived factors carried in the mesenteric lymph as contributing factors to lung and other organ injuries as well as the induction of a systemic inflammatory state after T/HS or burn injury (15), we hypothesized that gut-derived factors might also be involved in acute T/HS-induced cardiac dysfunction.

The current studies documenting that T/HS-induced myocardial contractile dysfunction can be totally abrogated by LDL support the hypothesis that factors contained in T/HS lymph are necessary for the induction of acute myocardial dysfunction after T/HS. This notion that gut-derived factors carried in the mesenteric lymph can cause acute myocardial dysfunction is further supported by our studies in a burn model where LDL prevented ex vivo burn-induced myocardial depression and where burn lymph recreated this myocyte depressant state in vitro (20, 32). On the basis of our previous burn studies showing that the contractile dysfunction of postburn hearts is linked with a decrease in ventricular myocyte Ca\(^{2+}\) transients caused by a decrease in the Ca\(^{2+}\) entry through L-type Ca\(^{2+}\) channels (20), we examined Ca\(^{2+}\) responsiveness of the T/HS hearts. The T/HS hearts had a blunted contractile response to increases in extracellular Ca\(^{2+}\) concentration compared with the control or T/HS+LDL hearts, indicating an impairment of Ca\(^{2+}\) handling. Furthermore, under conditions of low Ca\(^{2+}\), the T/HS hearts, but not the control or T/HS+LDL hearts, displayed ECG evidence of first- and second-degree AV block. The decreased contractile responsiveness to Ca\(^{2+}\) observed in the T/HS hearts is consistent with studies of failing hearts in other conditions, such as chronic heart failure, ventricular hypertrophy, and ischemia-reperfusion injuries, where contractile dysfunction is associated with impaired myocardial Ca\(^{2+}\) homeostasis (18).

Likewise, the ECG findings of a prolonged PR interval and AV conduction abnormalities in the presence of reduced Ca\(^{2+}\) concentration further implicate a role of impaired Ca\(^{2+}\) handling in T/HS-induced myocardial contractile dysfunction. One potential explanation for these Ca\(^{2+}\)-related observations in the T/HS hearts is that L-type Ca\(^{2+}\) channels are altered. This notion is based on the fact that in the mammalian heart, the L-type Ca\(^{2+}\) channel is critically involved in excitation-contraction (EC) coupling and that depolarizations of the sinoatrial and AV nodes are largely dependent on the movement of Ca\(^{2+}\) through the L-type Ca\(^{2+}\) channel (4, 29). Although we are emphasizing the idea that depressed L-type Ca\(^{2+}\) channel function may be present in T/HS hearts, alterations in other components of EC coupling also could lead to electrophysiological and contractile changes. However, consistent with the notion of impaired L-type Ca\(^{2+}\) channel function in the T/HS hearts, we found that normal hearts exposed to the L-type Ca\(^{2+}\) channel blocker diltiazem manifested a decrease in contractility and ECG conduction abnormalities similar to the T/HS hearts. This observation that diltiazem mimicked the effects of T/HS supports the notion that reduced L-type Ca\(^{2+}\) channel

Fig. 6. T/HS hearts exhibit abnormal atrioventricular (AV) conduction at lower external Ca\(^{2+}\) (0.5 mM). A: ECG in control and T/HS hearts: a, normal conduction in control heart; b, first-degree AV block in T/HS heart showing prolonged PR interval; c, second-degree AV block in T/HS heart with a Wenckebach-type AV conduction; and d, 2:1 AV conduction in T/HS heart. B: incidence of first- and second-degree AV block. Numbers (n) correspond to the total number of hearts measured. *P < 0.05 vs. control group. #P < 0.05 vs. T/HS+LDL group.

J Appl Physiol • VOL 106 • JANUARY 2009 • www.jap.org
function may play a role in T/HS-induced myocardial dysfunction.

The mechanism of the functional downregulation of the L-type Ca\textsuperscript{2+} channel is unknown, but it may involve altered L-type Ca\textsuperscript{2+} channel gene transcription, translation, membrane trafficking, or posttranslational modification such as channel phosphorylation or a combination of factors. It is interesting to note that changes in intracellular Ca\textsuperscript{2+} trafficking due to cytokine production have been reported (31), and certain proinflammatory cytokines, such as TNF-\alpha and IL-1, as well as nitric oxide production have been shown to suppress L-type Ca\textsuperscript{2+} currents in rat myocytes and thereby reduce Ca\textsuperscript{2+} transients, resulting in myocyte contractile depression (31). In this study, we are suggesting the idea that changes in cellular Ca\textsuperscript{2+} handling, possibly downregulation of L-type Ca\textsuperscript{2+} channel, may contribute to depressed contractility and abnormal ECG in T/HS hearts. However, there could be alternative explanations for abnormal cardiac function, and further studies that include direct examination of ionic channels involved in the cardiac contraction as well as conduction system are required to prove or refute this point.

The notion that myocardial depression may be caused by circulating factors was proposed as early as 1966 (3), and since then, unidentified myocardial depressant factors have been described in animals subjected to hemorrhagic, cardiogenic, splanchnic, ischemic, and traumatic as well as burn shock, with the gut and/or pancreas being incriminated as their originating source (11, 23). Thus our studies showing that LDL protects against T/HS-induced myocardial dysfunction is consistent with the notion that gut-derived myocardial depressant factors are involved in acute postshock myocardial dysfunction syndromes. These results also support a recent study in dogs showing that ligation of the cisterna chyliae protected against the development of myocardial dysfunction after superior mesenteric artery occlusion (8) as well as studies from the laboratory of Schmid-Schönbein implicating the action of pancreatic enzymes on the ischemic gut as the genesis of factors leading to shock and cardiac dysfunction (1).

Although no attempts have been made to date to isolate the factors in burn or T/HS lymph that are responsible for the acquired contractile dysfunction observed in these conditions, our studies and the work of others indicate that T/HS lymph contains both biologically active, tissue injurious and proinflammatory lipid and protein factors (10, 16, 19). Although we do not know what the biologically active factors are in T/HS lymph, we have excluded a number of putative candidates, including cytokines (9), bacteria, and bacterial products (2). Whatever the factors are in lymph, on the basis of our in vitro burn studies, burn lymph appears to exert a direct depressant effect on normal myocyte contractility and Ca\textsuperscript{2+} transients that are similar to the changes observed in myocytes harvested from burned rats (39). Further studies investigating the effects of T/HS lymph on in vivo cardiac and in vitro myocyte contrac-

**Table 2. LV function measured in isolated rat hearts from control, T/HS, or diltiazem-treated rats**

<table>
<thead>
<tr>
<th></th>
<th>LVP, Torr</th>
<th>+dP/dt\textsubscript{max}, Torr/s</th>
<th>-dP/dt\textsubscript{max}, Torr/s</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>121.0 ± 1.7</td>
<td>3,690 ± 167</td>
<td>2,226 ± 66</td>
<td>15</td>
</tr>
<tr>
<td>T/HS</td>
<td>83.0 ± 4.2*</td>
<td>2,408 ± 273*</td>
<td>1,517 ± 10*</td>
<td>9</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>79.3 ± 4.9*</td>
<td>2,196 ± 108*</td>
<td>1,414 ± 53*</td>
<td>9</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of rats. LV function was measured in control rats, rats subjected to trauma and sham shock (T/SS), and after application of diltiazem (1 \mu M). *P < 0.05 vs. control group.
tily and cellular Ca\textsuperscript{2+} handling as well as on the inflammatory signaling pathways associated with myocardial contractile dysfunction after shock and trauma are required to better elucidate the mechanisms responsible for T/H-induced myocardial dysfunction.

In summary, the results of this study indicate that acute T/H-induced myocardial dysfunction is likely due to gut-derived factors contained in mesenteric lymph and that the impaired contractility of T/H hearts is associated with abnormal myocardial Ca\textsuperscript{2+} handling. As such, these studies support work done in a burn model and support the notion that gut-induced acute myocardial contractile dysfunction may be a reproducible response to conditions leading to splanchnic hypoperfusion such as T/H or major burns. However, future studies to examine the interactions between mesenteric lymph isolated from animals subjected to T/H and cardiac myocyte function are required to further support this notion. In addition, because the present experiments were performed in isolated rat hearts, it will be important to expand and validate these results as well as the potential clinical importance of these observations utilizing large animal models.

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