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Effect of temperature on isoproterenol-induced increases in left ventricular developed pressure

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ABSTRACT

The goal of this project was to determine the effects of elevated cardiac temperature on preload-dependent and preload-independent regulation of left ventricular developed pressure (LVDP) in Langendorff-perfused, electrically paced (420 bpm), Sprague-Dawley rat hearts. LVDP responses to steady-state isoproterenol infusions (10^{-8} M) were determined at 37, 38, 39, and 40 °C. Preload-dependent LVDP was determined at 37 and 40 °C. Isoproterenol-induced LVDP and preload-dependent LVDP time controls were conducted in a separate group maintained at 37 °C. The percent increase in LVDP during isoproterenol infusion significantly decreased at 40 °C to 42 ± 6 (SE), compared to 55 ± 9, 55 ± 6, and 53 ± 7% at 37, 38, and 39 °C, respectively. No significant differences were observed in the percent increase in LVDP to isoproterenol among the corresponding time controls (50 ± 6, 47 ± 3, 56 ± 4, and 56 ± 5%). Preload-dependent LVDP decreased across the experimental protocol, but there were no cardiac temperature effects. These data indicate that β-adrenergic mediated contractility is not altered by moderate heating from normothermia but is compromised at very high temperatures (40 °C). Cardiac temperatures from 37 to 40 °C do not alter the inherent preload-dependent LVDP, indicating that the Frank–Starling relation is not directly affected within this temperature range.

1. Introduction

Passive heat stress increases cardiac output primarily via increases in heart rate (Crandall and Gonzalez-Alonso, 2010; Johnson and Proppe, 1996; Rowell, 1983). The chronotropic effect of temperature has been widely documented in both hypothermic and hyperthermic conditions (Badeer, 1951; Clark, 1920; Garrey and Townsend, 1948; Knowlton and Starling, 1912). Using combinations of passive heat stress, anticholinergics, and β-adrenergic antagonism, Gorman and Proppe (1984) identified an 8.4 ± 0.8 bpm increase per 1.0 °C increase in internal temperature in primates. Heart rate increases are due, in part, to increases in cardiac temperature, and the remainder of the response (~60% of response) is due to stress-induced increases in sympathetic nervous system outflow to the heart (Gorman and Proppe, 1984).

Unlike heart rate, the direct effect of cardiac temperature experienced during passive heat stress on stroke volume is unclear. Stroke volume does not appreciably change during passive heat stress, despite evidence of increased systolic function (Wilson and Crandall, 2011). It is unknown if there is simply an increase in sympathetic mediated contractility or if there is an interaction between heating and the adrenergic responses in the heart that mediated this increased systolic function. During passive heat stress, plasma catecholamine to cardiac index correlations are decreased compared to heart rate, suggesting that stroke volume is not as tightly correlated to sympathetic responses (Kim et al., 1979). Temperature (cooling and re-warming) can induce functional changes in cardiac β-adrenergic receptor responses (Broadley and Williams, 1983; Han et al., 2008), and thus it is possible that heating could cause similar interactive effects on inotropy, thereby altering stroke volume. Passive heat stress decreases left-ventricular filling time and preload as well as afterload (Wilson and Crandall, 2011), which decreases and increases stroke volume, respectively (Klabunde, 2011). Increases in heart rate can contribute to increases in the strength of contractions via the Bowditch effect (Janssen and Periasamy, 2007). Therefore, to determine the mechanism by which cardiac temperature alters stroke volume, multiple stroke volume regulatory factors (e.g. inotropy, chronotropy, preload, and afterload) need to be controlled or standardized, which is not possible in humans.

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The purpose of this study was to determine how increases in cardiac temperature within the range observed during human passive heat stress alter ventricular pressure development in isolated rat hearts. The use of a Langendorff preparation permitted heart rate and preload to hold constant while changing ventricular inotropy with a β-adrenergic receptor agonist. This model also permitted study of preload dependent changes in ventricular developed pressure, which is the basis for the Frank–Starling relation. Two hypotheses were addressed by this study: (1) isoproterenol-induced left ventricular developed pressure (LVDP) will be attenuated during severe heating; and (2) heating will not alter preload-dependent LVDP compared to time/temperature controls. The rationale for these hypotheses is based, in part, on: (a) previous observations that 20, 37, and >41.5 °C did not change inherent force-length relations in heart strip preparation and that the highest temperature caused decreased force of epinephrine-induced contraction (Moore et al., 1966), and (b) the need to define the cardiac responses to temperature changes that occur during passive heat stresses (Wilson and Crandall, 2011).

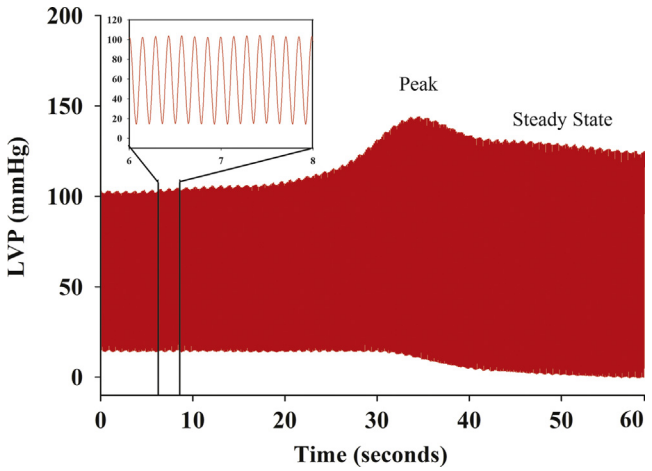

Fig. 1. Representative tracing of isoproterenol-induced change in left-ventricular developed pressure during Phase I (37 °C). Insert is 2 s of baseline data enlarged to show systolic and diastolic pressures.

2. Methods

2.1. Animals and isolated heart preparation

The use of animals was approved by the Institutional Animal Care and Use Committee of Ohio University. Forty male Sprague-Dawley rats (275–325 g) were heparinized (1000 IU, i.p.) and anesthetized with pentobarbital sodium (65 mg/kg, i.p.) for extensive preliminary studies and experimental protocols. Hearts were rapidly excised, immediately placed in an ice-cold bath of buffer solution, and the aortas cannulated. The hearts were hung on a custom Langendorff perfusion apparatus (glassware: Radnoti, Monrovia, CA; peristaltic pump and pump head: Masterflex L/S, Cole-Parmer Instruments, Vernon Hills, IL; thermal circulator water baths: Isotemp 8005, Fisher Scientific, Pittsburg, PA), and the coronary arteries were perfused with 37 °C Krebs–Henseleit buffer at a coronary flow rate that produced a coronary perfusion pressure of 70–80 mmHg. This flow rate was then maintained throughout the experiment, and therefore, changes in coronary perfusion pressure were directly proportional to changes in coronary vascular resistance. The left atrium was then removed and a balloon-tipped catheter was inserted into the left ventricle through the mitral valve opening. Hearts were paced (SD9, Grass Technologies, Warwick, RI) at 420 bpm to ensure that infusion of isoproterenol did not increase the heart rate above the paced level and to prevent the positive chronotropic effect of sinoatrial node temperature (Johnson and Proppe, 1996). The balloon (Radnoti, Monrovia, CA) within the left ventricle was initially inflated with water to a volume of 100 μl, and LVDP was measured. The balloon was then deflated in 20 μl decrements to determine the relationship between LVDP and balloon volume (ventricular preload). A balloon volume that corresponded to the beginning of the LVDP plateau was selected as the preload condition to be maintained throughout both protocols until the effects of preload on LVDP were determined again at the end of the protocols.

2.2. Protocols

Following equilibration for ~20 min, one of 2 protocols was initiated. Protocol 1 (Heated Group): To mimic stress conditions, a steady-state infusion of the β-adrenergic agonist isoproterenol (10^{-8} M) was given for 90 s while the perfusate and bath temperatures were set at 37 °C (Phase I). Immediately following this, the temperature setting of the bath was increased and held at 38 °C for 10.5 min at which point isoproterenol was again administered (Phase II). The isoproterenol response was quantified at both the peak response and during the steady-state response near the end of the infusion period (Fig. 1). This process was repeated at 39 and 40 °C (Phases III and IV). Ten hearts successfully completed this protocol. All temperatures were verified via external 400 series YSI thermistors connected to a meter (Tele-thermometer, YSI, Yellow Springs, OH). Following the last isoproterenol infusion at the end of Phase IV, and while the heart temperature was being maintained at 40 °C, the ventricular balloon volume was inflated to 100 μl then decreased by 20 μl decrements in order to quantify the effects of changing ventricular preload volume on LVDP. The effects of preload changes on LVDP were compared to values collected at the various balloon volumes prior to Phase I, while temperature was maintained at 37 °C.

Protocol #2 (Control Group): The control group of hearts was subjected to the same procedures as the heated group (Protocol #1) for evaluating preload effects on LVDP (before and after Phases I through IV) and isoproterenol infusions (Phases I through IV) except that the temperature was held at a constant 37 °C for all 4 Phases. Eight hearts successfully completed this protocol.

2.3. Drugs and chemicals

All chemicals and drugs were purchased from Sigma (St. Louis, MO). The basic Krebs–Henseleit buffer solution consisting of (mM): NaCl 100, KCl 4.74, KH_2PO_4 1.19, $MgSO_4$ 1.18, $CaCl_2$ 2.54, $NaHCO_3$ 19.3 and glucose 11.1. The buffer was equilibrated with 95% O_2 and 5% CO_2, and the pH was adjusted to 7.4 at 37 °C. Isoproterenol was dissolved in distilled water at concentrations 20 times the final desired concentration and infused into the coronary perfusion line at 5% of coronary flow, which produced both a peak and steady-state response. Preliminary experiments indicated that a final isoproterenol concentration of 10^{-8} M produced about a half-maximal increase in LVDP; therefore, this concentration was infused in all experiments.

2.4. Statistics

Heart rate, coronary perfusion pressure, and LVDP data were continuously collected at 100 Hz (PowerLab 8/30, ADInstruments Inc., Colorado Springs, CO) and stored in a computer workstation. The baseline data for the 2 groups were compared using a two-tailed Student's *t*-test (Excel, Microsoft, Redmond, WA). All functional data were analyzed by a one-way (temperature by time) repeated measures ANOVA for each protocol. Frank–Starling data

Table 1
Baseline comparisons between the heated and time control groups. No significant differences between groups were noted. Where CPP, coronary perfusion pressure; LV, left ventricular, value in parenthesis is the number of rats per group. Values are means ± SE.

Group	Rat weight (grams)	CPP (mmHg)	Coronary Flow (mL/min)	LV Volume (μL)
Control	294 ± 4 (8)	82.3 ± 4.0 (8)	15.9 ± 0.9 (8)	65.0 ± 6.5 (8)
Heated	284 ± 7 (10)	81.1 ± 4.6 (10)	17.1 ± 1.2 (9)	71.3 ± 6.9 (9)

were analyzed by a two-way (pre-post by inflated volume) repeated measures ANOVA (SigmaStat, Systat Software, San Jose, CA). A p-value of less than 0.05 was considered significant.

3. Results

After preliminary studies, data from 18 isolated hearts were obtained for all time points across all conditions—eight hearts in the control group (37 °C throughout phases I–IV) and 10 hearts in the experimental group (Phase I=37, Phase II=38, Phase III=39, and Phase IV=40 °C). Rat weights and baseline values measured prior to Phase I were not statistically different between the 2 groups (Table 1). The different sample sizes ($n=9$ vs. 10) for control coronary flow and balloon volume in the heated hearts resulted from a short glitch in the electronic recording and annotation for one of the 10 hearts. Because preload and coronary flow were still optimized, data obtained during the rest of the protocol in this one heart were still valid.

Baseline LVDP decreased across time in both the control and experimental groups ($p<0.001$; Fig. 2A); however, the magnitude of decline in LVDP was not significantly different between the control and heated groups. Steady-state LVDP responses to isoproterenol infusion decreased with each increase in temperature ($p<0.001$ across time and $p<0.05$ between each progressive phase; Fig. 2A). Although the control group also changed ($p=0.017$), the only significant decrease in LVDP responses to isoproterenol was observed between Phases I and IV ($p<0.05$). Given that both the baseline and drug responses were changing during treatment, we also calculated the percent increase in LVDP during each isoproterenol infusion. Incremental heating did not change the percent increase in LVDP to isoproterenol until Phase IV, where 40 °C was significantly lower than the 3 previous temperatures ($p<0.05$; Fig. 2B). No significant changes were observed in percent change in the control group ($p=0.106$; Fig. 2B). Peak LVDP responses were similar to steady-state LVDP responses, decreasing as temperature increased ($p<0.001$), incremental decreases were observed after Phase II ($p<0.05$), and no differences were observed in the control group ($p=0.141$; Fig. 3A). The percent increase in peak LVDP trended lower ($p=0.098$) and was not different in the control group ($p=0.369$; Fig. 3B).

Prior to initiating Phase I of the protocols, both groups showed similar increases in LVDP with increasing left ventricular volume. The relationships between left ventricular volume and LVDP were depressed in both groups after completing Phase IV of the protocols. The depression was similar in magnitude in both the control and heated groups (Fig. 4).

4. Discussion

The primary findings of the study were that percent increase in LVDP during isoproterenol infusion significantly decreased at 40 °C, compared to 37–39 °C with no significant differences observed in corresponding time controls. These data indicate that

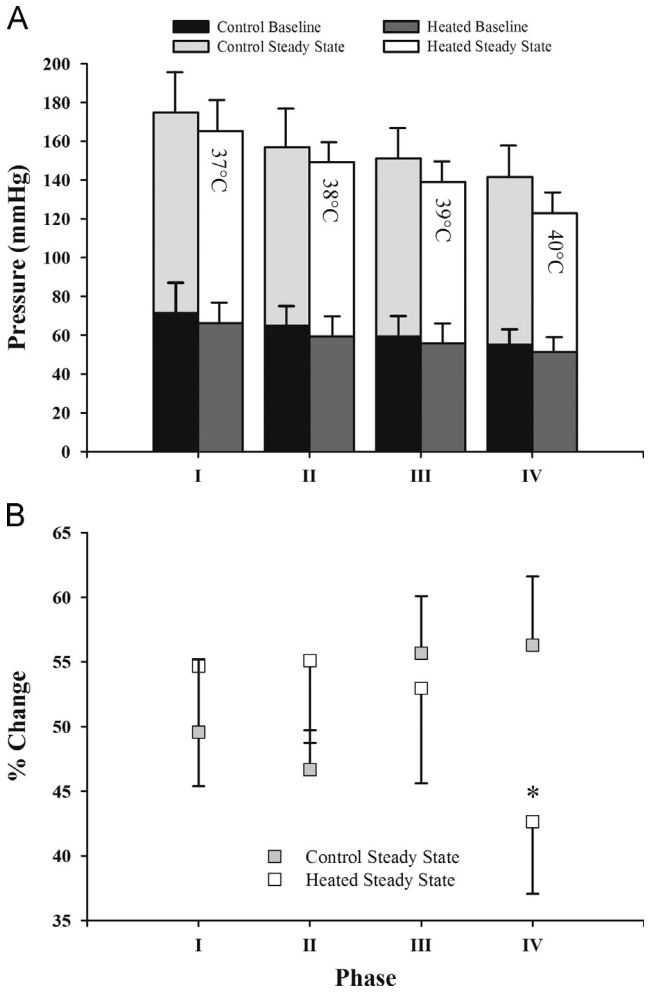

Fig. 2. Left ventricular developed pressure during the steady-state infusion portion of isoproterenol with Panel A providing the absolute numbers and Panel B the percent change. The control group was maintained at 37 °C throughout Phases I–IV; heated refers to the group where temperature was increased 1 °C per phase. * indicates $p<0.05$ compared to Phases I–III in the heated group.

β-adrenergic mediated contractility is not altered by moderate heating but becomes compromised during severe heating. Cardiac temperatures equivalent to those used in human passive heat stress do not alter the inherent preload-dependent LVDP, indicating a preservation of the Frank–Starling relation. Combining these isolated heart data with previous passive heat stress data in humans (Wilson and Crandall, 2011) suggests the working hypothesis that the increase in systolic function observed during passive heat stress is not mediated by heat-induced augmentation of β-agonist-induced positive inotropy or via the Frank–Starling mechanism, but instead appears to be directly related to heat-induced increases in the sympathetic nervous system.

Our study indicates that there is no direct cardiac temperature effect on preload-independent regulation of LVDP at temperatures between 37 and 39 °C. However, when cardiac temperature was increased from 39 to 40 °C, there was ~20% reduction in LVDP. At 40 °C, hearts were unable to generate the same force compared to cooler temperatures or to time controls. These data indicate that during a severe heat stress, the inability to maintain or increase stroke volume may be related, in part, to decreased force development. This is especially important given that heat stress, especially when combined with orthostatic stress, causes decreases in central blood volume, pulmonary capillary wedge

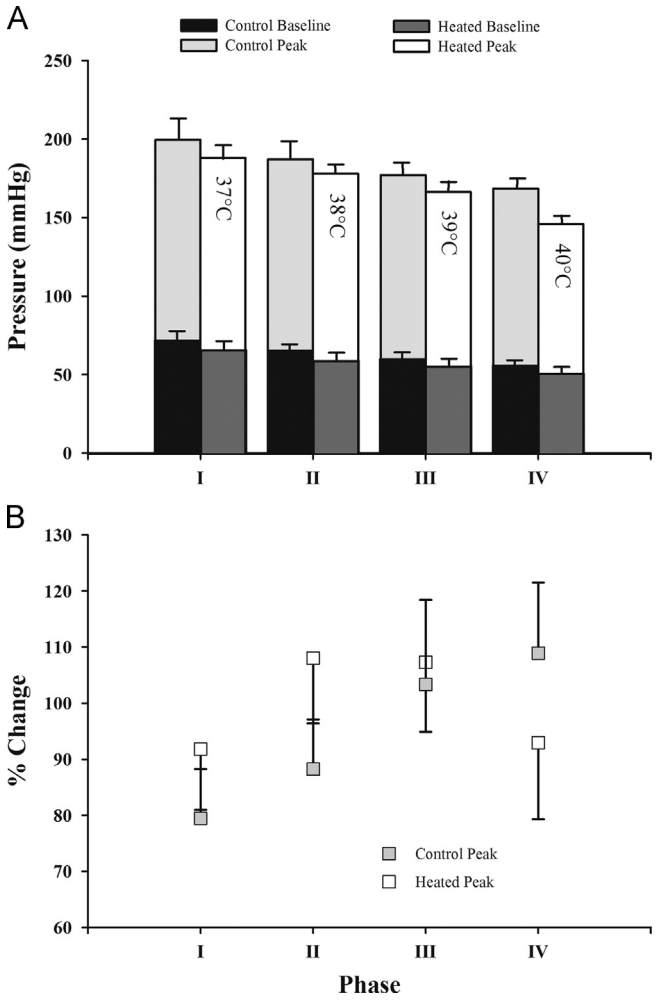

Fig. 3. Left-ventricular developed pressure during the peak response of isoproterenol with Panel A providing the absolute numbers and Panel B the percent change. The control group was maintained at 37 °C throughout Phases I–IV; heated refers to the group where temperature was increased 1 °C per phase.

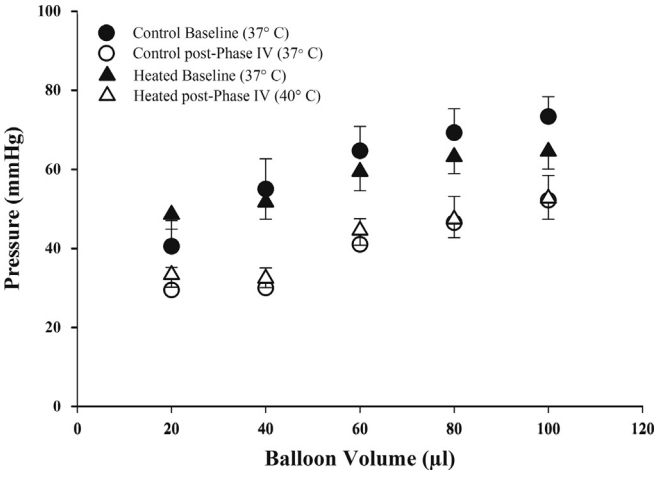

Fig. 4. Left-ventricular developed pressure responses to changes in balloon volume (preload) prior to Phase I (Baseline) and at the end of Phase IV (post-Phase IV) of the protocols. Data are shown for both the heated (Protocol 1) and control (Protocol 2) hearts. To generate these data, balloon volumes were first set to 100 µl and then decreased by 20 µl decrements.

pressure, and left-ventricular end-diastolic volume (Bundgaard-Nielsen et al., 2010; Crandall et al., 2008, 2012; Nelson et al., 2010, 2011; Wilson et al., 2009).

Directly increasing cardiac temperature results in a decrease (Hiranandani et al., 2006; Janssen et al., 2002; Saeki et al., 2000; Templeton et al., 1974) or no change (Cohen et al., 2007) in force production, developed tension, maximal rate of rise of left ventricular pressure, or LVDP. The present study utilized a very narrow range of temperatures (37–40 °C) that are experienced during human passive whole-body heat stress; in contrast other groups used more extreme temperatures to maximize effects and to demonstrate changes during hyperthermia and pyrexia. We also utilized greater precision in temperature increases (1 °C), while other groups either did not use a gradient approach or used larger increases in temperature. This is important as mild passive heat stress (0.6–1.0 °C) shows much different physiological effects than severe passive heat stress (1.5–2.0 °C) in humans (Lucas et al., 2010). Our study also used non-heat acclimated rats; Cohen et al. (2007) observed that heat-acclimated rat hearts show augmentations in force compared to heat stress naive rats. Heat acclimation causes a number of physiological and phenotypical changes that preserve and augment the cardiovascular system response to heat stress (Horowitz, 2003). Thus, it is possible that the hearts from acclimated animals may have a different preload-independent regulation of LVDP.

The temperature independent decline in LVDP over time (Fig. 2) is commonly found in Langendorff-perfused hearts and is associated with a rise in coronary perfusion pressure (from baseline value of 82 to 120 mmHg in control and from 81 to 114 mmHg in heated rat hearts, respectively). Increasing coronary perfusion pressure reflects an increase in coronary vascular resistance because the hearts were perfused under constant flow conditions; therefore, changes in coronary flow cannot account for the gradual decline in LVDP over time. Because baseline LVDP declined during the protocol, it is not surprising that the absolute change in LVDP during isoproterenol infusion also declined. When the LVDP responses to isoproterenol were expressed as a percent increase above baseline, the responses to isoproterenol did not decline over time in either group except for when the temperature was raised from 39 to 40 °C in the experimental group. To account for this potential bias, this study employed time control hearts.

Data from the present study indicate a lack of an effect of cardiac temperature on preload-dependent regulation of LVDP between 37 and 40 °C. This indicates that temperature did not alter Frank–Starling relations compared to time matched controls. This result is in contrast to Saeki, et al. (2000) who observed decreases in left-ventricular end-systolic pressure-volume relations during increased cardiac temperature from 36 to 41 °C. It is possible at these very high temperatures (1 °C higher than what we used) may depress the Frank–Starling relation, but temperatures of 41 °C are rare and close to the temperature (41.5 °C) at which cardiovascular collapse begins in rodents (Gordon, 1993). Data also indicate that experimental time in itself caused a downward shift in these relations. This may have been due to small amounts of edema which can result with increasing coronary perfusion pressure observed in both temperature and control groups. Decreased ventricular wall compliance caused by edema may have contributed to the decline in preload-dependent increases in LVDP during the course of the experiment. Thus, if there were small temperature effects, they were not robust enough to manifest themselves in our experimental paradigm.

There are a few inherent limitations in Langendorff-perfused hearts in addition to the increase in coronary perfusion pressure stated above. There may have been an order effect in the heated group as the temperature was increased in a linear fashion for experimental reasons, thus all of the 40 °C testing occurred during the last phase of the experiment. In preliminary studies it was difficult to cool a heated heart between phases without introducing other errors and a variable time course. To help control for phase in this study, we used time control animals.

In response to the question posed in the classic review of Johnson and Proppe (1996) as to whether direct heating of the myocardium contributes to any change in the cardiac contractility during heating, the answer appears to be "no" unless temperature nears 40 °C. This question was developed because, as stated above, stroke volume does not appreciably change during passive heat stress despite decreases in preload. This suggests an increase in systolic function during passive heat stress. A number of studies using different measures and methods confirm this assertion: (1) increases in ejection fraction via radionucleotide angiography (Crandall et al., 2008); (2) increases in peak systolic velocities, isovolumic acceleration, and peak left ventricular twisting rates via tissue Doppler and cardiac magnetic resonance imaging (Brothers et al., 2009; Nelson et al., 2010, 2011); (3) decreases in left ventricular ejection time (Frey and Kenney, 1979); (4) increase in the maximal rate of rise of left ventricular pressure (Goodyer, 1965); and (5) inotropic shifts in the Frank–Starling relation via pulmonary artery catheterization (Bundgaard-Nielsen et al., 2010; Wilson et al., 2009). These observations, combined with data from this experiment, form a working hypothesis: passive heat stress-induced increases in systolic function are not mediated by either preload-independent interactions or preload-dependent regulation but rather are directly related to increases in cardiac sympathetic outflow and/or catecholamine release from adrenal medulla. This sympathetic nervous system activation maintains stroke volume even during conditions of reduced preload and left-ventricular filling time.

In conclusion, this study was designed to determine the direct effects of elevated temperature on left ventricular contractile function under conditions of constant heart rate, ventricular preload, and coronary flow. The primary observations were that preload-independent LVDP was preserved until 39 °C with no significant differences observed in corresponding time controls and that cardiac temperatures did not alter the inherent preload-dependent LVDP. These data indicate that β-adrenergic mediated contractility is compromised only during severe heating; however, even severe heating does not affect the inherent Frank–Starling relation.

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