THE EFFECTS OF PROLONGED STRENUOUS EXERCISE ON BETA-RECEPTOR RESPONSIVENESS IN MALE AND FEMALE TRIATHLETES

by

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ABSTRACT

The purpose of this investigation was to determine whether alterations in β-receptor responsiveness occur as a result of a single bout of prolonged strenuous exercise (PSE), and whether the myocardium of males and females responds differently to PSE. We examined nine male and eight female triathletes during three separate sessions: before, immediately after, and 24h following a half-ironman triathlon. Athletes were assessed during each session using dobutamine stress echocardiography. Steady-state graded infusions of dobutamine were used to assess β-adrenoreceptor responsiveness. Slopes calculated from linear regressions between dobutamine doses and changes in heart rate and contractility for each subject were used as an index of β-adrenoreceptor responsiveness. Fractional shortening decreased from baseline after the race in both males and females, with the decrease greater in males (males: 54.1 ± 2.1 to 50.7 ± 3.4% vs. females: 55.4 ± 2.7 to 53.3 ± 2.5 %). Despite no change in preload, systolic function (stress-shortening relationship) was significantly decreased in males and females following PSE. The amount of dobutamine necessary to increase HR 25 beats·min^{-1} (males: 29.6 ± 6.6 to 42.7 ± 12.9 μg·kg^{-1}·min^{-1} vs. females: 23.5 ± 4.0 to 30.0 ± 7.8 μg·kg^{-1}·min^{-1}) and contractility 10 mmHg·cm^{-2} (males: 20.9 ± 5.1 to 37.0 ± 11.5 μg·kg^{-1}·min^{-1} vs. females: 22.6 ± 6.4 to 30.7 ± 7.2 μg·kg^{-1}·min^{-1}) was significantly greater in both males and females post-race, with the amount of drug necessary to induce this change significantly greater in males. These results provide evidence that an acute bout of PSE results in reduced LV systolic function and dobutamine responsiveness in both males and females and that these alterations occur to a greater extent in males.

Table of Contents

List of Tables

List of Figures

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SCIENTIFIC SUMMARY

The performance of the human body during endurance activities has been a focus of interest for many years. Recent investigations in the area of sport cardiology examining the effects of prolonged exercise on cardiovascular function have reported surprising findings. Two areas of particular interest in sport cardiology include cardiovascular drift and cardiac fatigue. After approximately ten minutes of moderate intensity exercise, cardiovascular drift occurs. This phenomenon is characterized by a progressive decline in stroke volume (SV) and pulmonary and systemic mean arterial pressures. These reductions are accompanied by a parallel increase in heart rate (HR), which enables cardiac output (Q) to be maintained (9). While it has been well documented and generally accepted that cardiovascular drift occurs during prolonged strenuous exercise (PSE), the reasons underlying this occurrence remain highly disputed (22, 23, 37).

Similarly, much debate is centred around the possible mechanisms which are responsible for creating impaired systolic function (cardiac fatigue). Systolic function is both load and contractile dependent, and a change in any one or a combination of factors including preload, afterload or contractility could negatively affect left ventricular (LV) systolic function. While results from several studies suggest that changes in contractility occur during prolonged exercise (14, 15, 17, 29, 34, 39, 40, 52), others have found no such evidence (24, 46, 53, 56). Most investigations conclude that the underlying mechanisms responsible for alterations in LV systolic function need further examination.

Cardiac Fatigue

The occurrence of cardiovascular drift during prolonged exercise may result not only in altered haemodynamic loading of the heart, but also, by decreasing cardiac efficiency, it may contribute to another phenomenon – cardiac fatigue. While it is well known that individuals with underlying cardiac anomalies have an increased risk of sudden death while exercising (59), recent studies have reported

that even healthy individuals with no evidence of underlying cardiovascular pathologies may have impairments in LV performance after prolonged exercise (14, 34, 52, 65).

A reduction in intrinsic pump function with prolonged exercise independent of haemodynamic loading was first suggested by Saltin and Stenberg (50) who observed a decrease in stroke volume (SV) after three hours of exercise, despite a maintenance of blood volume. More recent investigations of prolonged exercise include activities such as running (40, 47, 52), long distance triathlon races (14, 15, 17, 27, 45, 48, 65), and prolonged cycling (19, 24, 30). Cardiac function in these investigations was measured via echocardiography before the exercise period, immediately after the exercise period, and anywhere from 60 minutes to two days post-exercise. Results from each of these studies demonstrated that immediately post-exercise LV contractility was impaired.

While many authors use ejection fraction (EF) and fractional shortening (FS) as indices of contractility, because EF and FS are preload and afterload dependent, interpretation of significantly reduced ejection phase indices does not simply imply that a decrease in contractility occurred. Most investigations rely on the interpretation of end-diastolic volume/diameter (EDV/D) as an indicator of preload, and a decrease in preload has been reported by several authors following PSE (14, 29, 39, 40, 50, 57, 65). While a decrease in preload may negate any changes in contractility, a lack of significant correlation between the change in EDV and the change in FS implies that some factor other than preload may affect contractile performance. Shortening is also afterload dependent, and the majority of the aforementioned studies found either no change (14, 52) or a decrease in wall stress or systolic blood pressure – measures of afterload (30, 65). Several authors have concluded that a decreased or unaltered ventricular shortening in the presence of a decreased systolic blood pressure or wall stress suggest a depressed inotropic state (14, 52, 57, 65).

While many investigations have demonstrated that there is an impairment in contractility following PSE, others involving marathon running (31, 47), and cycling (24, 53) have found no evidence to suggest

that depressed systolic function occurs as a result of PSE. In an attempt to explain the divergent findings between investigations, Perrault et al. (47) suggested that the observed decrease in systolic blood pressure associated with no change in LV EDD may be indicative of impaired LV function. The duration of exercise and/or the extreme environmental conditions associated with these activities, such as Ironman Hawaii, may be factors which compromise LV function more than would normally occur in less severe environments (31). The modality of exercise may also explain these discrepancies (14, 27, 65). For instance, the triathlon may allow athletes to reduce local muscle fatigue by changing muscle groups, while maintaining stress of the myocardium (53). It is plausible that researchers conducting studies involving repetitive motions such as cycling or running may have observed an alteration in contractility, had local muscular fatigue been prevented.

Underlying Mechanisms of Cardiac Fatigue

Several theories attempt to explain the mechanisms causing impaired LV function following PSE. The first mechanism that has been postulated to contribute to cardiac fatigue involves energy metabolism in the heart. Both McKechnie (35) and Seals et al. (52) suggested that LV function impairment could be the result of elevated free fatty acid (FFA) concentrations, leading to depressed myocardial contractility. High levels of FFA are known to suppress glycogen oxidation and may reduce the efficiency of mitochondrial respiration through uncoupling of electron transport (35). Conversely, Goodwin & Taegtmeyer (25) suggested that the glycolytic block imposed by FFA could be bypassed by the substrate lactate, thus improving cardiac energy homeostasis during exercise. This implies that energy metabolism does not contribute to LV dysfunction. Nozawa et al. (41, 42) suggested that a decrease in stroke work (as a result of a decrease in SV and end-systolic pressure) may cause a decrease in myocardial efficiency during prolonged exercise.

An alternative hypothesis put forward by several authors (49, 65) postulates that the increase in catecholamine levels that occurs during exercise may lead to an increased vascular tone and decreased

myocardial blood supply, ultimately resulting in myocardial ischemia. On this note, it is possible that a small compromise in blood flow could induce metabolic acidosis in the myocardium (55). An increase in hydrogen ion concentration has been shown to substantially increase the calcium requirement for myofilament activation and to impair sarcoplasmic reticulum (SR) calcium uptake as well as calcium induced calcium release from the SR (55). O'Brien et al. (43) tested the hypothesis that SR failure is a consistent feature of cardiac and skeletal muscle fatigue, and concluded that failure of calcium sequestration by the SR plays a major role in the pathogenesis of cardiac and muscle fatigue and failure.

Another mechanism proposed to result in a decreased inotropic state is a desensitization of cardiac β-receptors. Investigators have long observed that, in clinical populations (such as those individuals with chronic heart failure) exposure of β-receptors to increased concentrations of catecholamines results in desensitization of these receptors (1, 20, 58). Vanoverschelde et al. (57) proposed that the increased exposure to catecholamines during prolonged exercise may cause a downregulation of β-adrenoreceptor responsiveness, prompting the decline in LV contractility in healthy athletes. Following an endurance run, Maron et al. (32) reported a 5-fold increase in catecholamines from resting levels, an increase which has also been observed following a marathon (12), a 100 km ultra-marathon (44), and a prolonged run to exhaustion (52). Given that prolonged exercise provides a lengthy exposure to these elevated catecholamines, it is possible that there is a down-regulation of β-receptors to below pre-exercising levels (12). This appears to be true in dogs, where prolonged dynamic exercise produced a significant decrease in sensitivity to the effects of β-adrenergic receptor stimulation (21). Recent investigations in humans have also revealed that prolonged exercise alters β-receptor responsiveness (16, 19). Eysmann et al. (19) and Welsh et al. (62) examined β-receptor desensitization following a single bout of PSE, and demonstrated that not only EF was reduced following PSE, but also that this reduction was closely related to a decreased sensitivity to exogenous β-receptor stimulation.

A shift of sarcolemmal β-receptors to an intracellular location following exercise has been demonstrated in rats, suggesting that prolonged exercise may result in β-receptor downregulation, in addition to β-receptor desensitization. Werle et al. (63) investigated the cardiac β-receptor adaptation to physical activity in four groups of rats: 1) control group (remained sedentary), 2) acute endurance exercise group (remained untrained and swam once for two hours), 3) endurance training group (swam continuously for two hours per day for six weeks), and 4) maximal training group (swam three times per day for 2-3 minutes within 3 hours, with 10% of body weight attached to tails for six weeks). They reported a decrease in the number of cardiac β-receptors by 25.5% in the maximal training group, 13.0% in the endurance-training group, and 16.6% in the acute endurance group (63). An early investigation by Butler et al. (5) into β-receptor function in human athletes reported that there were decreases in sympathetic nervous system responsiveness following physical training, and that these results were related to decreases in lymphocyte β-receptor density. They hypothesized that the reductions in receptor density at higher levels of physical fitness were a protective mechanism against the chronic exposure to high concentrations of catecholamines. Human lymphocytes contain β-receptors that are regulated by changes in circulating catecholamines, and many investigations have utilized this non-invasive approach for studying cardiac β-receptor regulation (2, 13, 38). Eysmann et al. (19) also examined lymphocyte β-receptor density following prolonged exercise, but reported no differences between pre- and post-exercising levels. These contradictory results may be due to the accuracy of using lymphocytes β-receptors as a surrogate to cardiac β-receptors, as several investigations have demonstrated that total β-receptor density in the heart is significantly lower than that measured in peripheral lymphocytes (2, 3, 36, 64).

Gender Differences

Several studies have shown that significant sexual dimorphisms exist in neuroendocrine and metabolic responses to physiological stresses (10). In response to exercise, men may have increased catecholamine and norepinephrine responses, as well as enhanced cardiovascular parameters such as systolic and mean arterial pressure (10). Non-invasive measurements of autonomic neural control of heart rate using heart rate variability (HRV) have also indicated that females have greater parasympathetic and less sympathetic control of heart rate than do males at rest and during exercise (18). Several other investigations examining ventricular function have also demonstrated gender differences in cardiovascular regulation, although with conflicting results. Vizgerda et al. (60) established that cardiac myocytes from male rats have an enhanced response to β-adrenergic stimulation. They hypothesized that this could be attributed to augmented β-adrenergic signalling resulting in a greater transsarcolemmal calcium influx (60). This group also reported a twofold greater density of β-receptors in male myocytes compared to female myocytes (60). Similarly, Schaible et al. (51) demonstrated that cardiac function was greater in male rats as opposed to female rats. This finding was not supported by Capasso et al. (6) who reported that isolated papillary muscles from female rats had greater contractile performance than those from male rats. Investigations on humans by Convertino (8) supported the findings of Capasso et al. (6), and suggested that a greater tachycardic response in females during isoproterenol infusion was primarily due to higher β-receptor responsiveness. Ejection fraction (4) and fractional shortening (11) have also been shown to be higher in women compared to men. Interestingly, a recent study examining cardiac performance during PSE in female triathletes did not find a decline in LV systolic function following a 40 km cycle and 10 km run (33). Given that the majority of investigations reporting declines in cardiac performance following PSE include male participants only, as well as the

significant sexual dimorphisms in cardiac function reported in the literature, it is important to examine the gender differences in cardiac performance that may occur following PSE.

STATEMENT OF THE PROBLEM

Although numerous investigations have examined the occurrence of cardiac fatigue during PSE, very few have studied this phenomenon in females. Several studies have shown that significant sexual dimorphisms exist in neuroendocrine and metabolic responses. In response to exercise, men may have increased catecholamine and norepinephrine responses, as well as enhanced cardiovascular parameters such as systolic and mean arterial pressure. Non-invasive measurements of autonomic neural control of heart rate using heart rate variability (HRV) have also indicated that females have greater parasympathetic and less sympathetic control of heart rate than males. Therefore, women may not experience or have as great of a catecholamine-mediated β-receptor desensitization. The purpose of the proposed study was to examine whether alterations in β-adrenergic responsiveness occur in healthy humans in response to a single bout of PSE, and whether the myocardium of males and females responds differently to prolonged physical exertion.

HYPOTHESES

1. As a result of PSE of greater than five hours, both males and females will have decreased myocardial contractility.
2. As a result of PSE, males will have larger alterations in cardiac β-receptor responsiveness relative to females.
3. As a result of greater heart β-receptor alterations, males will exhibit greater evidence of cardiac fatigue relative to females.

RESEARCH METHODS

Participants

Nine male and eight female endurance-trained triathletes were recruited to complete a half-ironman triathlon. All athletes had been exercising regularly 5-7 days per week for a minimum of two years, and all were competing in athletic events on a regular basis. None had any known form of cardiovascular disease. Participant characteristics are shown in Table 1. The study protocol was approved by the Clinical Research Ethics Board of the University of British Columbia and all subjects gave their written consent to participate in this study.

General Protocol

Participants underwent four separate testing days: 1) PRE (familiarization and VO_{2max}), 2) BASE (6 days prior to PSE), 3) POST (immediately following PSE), and 4) REC (24 h following PSE). Participants were instructed to refrain from exercise and abstain from caffeine and other autonomic stimulants such as prescription and non-prescription drugs for at least 48 h before each experimental protocol.

Maximal Exercise

During the PRE session, VO_{2max} and maximum heart rate were determined with a graded maximal cycle ergometer test consisting of 2-minute workload increments. After a standardized 5 minute warm-up period, workload increased by 30 W every minute, during which expired and ventilatory parameters were acquired using a metabolic cart (PhysioDyne, Max-1; USA).

Non- Exercise Conditions

During BASE and REC sessions, two-dimensional and Doppler echocardiography were performed while participants rested supine for 10 min. Continuous incremental infusions of dobutamine were then administered intravenously (see *measurement of β-receptor responsiveness* below).

Prolonged Strenuous Exercise

All athletes completed a half-Ironman triathlon race involving a continuous 1.5 km swim, 90 km cycle, and 21.1 km run. The racing event was conducted during a sunny day (temperature 13°C, precipitation 0

mm and wind speed 12 km·hour^{-1}). Athletes were encouraged to consume fluid *ad libitum* during the race, and data was collected within 15 min of race completion in all participants.

Measurement of β-receptor Responsiveness

During the BASE, POST and REC sessions participants underwent a dobutamine stress test. After acquisition of baseline resting images infusion of the β-receptor agonist dobutamine was commenced where incremental doses of the drug (0, 5, 10, 20, 30, and 40 μg·kg^{-1}·min^{-1}) were administered every three minutes. Continuous HR was measured from an electrocardiogram, and beat-by-beat changes (corrected each minute) in SBP, DBP and MAP were measured non-invasively (Finapres, Ohmeda). Linear regression relationships were constructed relating the increase in HR and contractility to the dose of dobutamine. As previously described (7, 8, 19, 28, 54), the slopes describing the linear stimulus-response relationship between the dose of dobutamine versus HR and contractility provided a measure of the responsiveness of cardiac β-receptors. Differences in slopes, y-intercepts and x-intercepts between BASE, POST and REC conditions were compared by analysing the least squares linear estimates generated by each participant.

Echocardiography

Two-dimensional and Doppler echocardiography were performed during all β-receptor sensitivity assessments. Left ventricular two-dimensional images were obtained in the long axis, short axis (mid-papillary muscles) and apical 2 and 4 chamber views according to the American Society of Echocardiography guidelines. A minimum of three cardiac cycles were averaged for analysis. Left ventricular systolic function was evaluated using ejection fraction, fractional shortening, end-systolic meridional wall stress, and myocardial contractility (SBP/end-systolic cavity area). Pulsed Doppler recordings were employed to assess diastolic filling; in particular, early (E) and atrial (A) peak velocities were measured and the ratio of early to late diastolic filling (E:A) was calculated. Myocardial efficiency was calculated as ((0.38 x stroke work)/pressure volume area) and myocardial oxygen consumption was

calculated as ((1.75x10^{-5} x pressure volume area + .03) x HR) during each dobutamine dose in each condition PRE, POST, and REC).

Statistical Analysis

Differences between echo-Doppler measures of cardiac function, between dobutamine responses at rest and after prolonged exercise were examined using repeated-measures analysis of variance with Tukey post hoc comparisons. The level of significance was set *a priori* at $p < 0.05$. Data are presented as means ± SE at BASE, POST and REC respectively.

RESULTS

Prolonged Strenuous Exercise

All athletes successfully completed the half ironman triathlon with average finishing times of 4h 45min ± 15min for males and 5h 16min ± 21min for females.

Echocardiography at Baseline

At resting baseline (i.e. dobutamine dosage 0 μg·kg^{-1}·min^{-1}) PRE, males and females had normal values for LV cavity dimensions, wall thickness, fractional shortening and wall stress (Table 2). There were no differences between males and females for measures of end-systolic dimension, contractility, fractional shortening, and wall stress at resting baseline ($p<0.05$). However, males had significantly greater end-diastolic dimension (5.4 ± 0.2 vs. 5.0 ± 0.1 cm) and E:A (2.10 ± 0.5 vs. 1.83 ± 0.3) relative to females. At race finish (POST), diastolic dimension (preload) was not changed from baseline measures in either group ($p<0.05$). Systolic dimension and HR were significantly increased in males and females POST, while systolic blood pressure was significantly decreased in both groups. Fractional shortening, myocardial contractility, and wall stress were significantly decreased, while end-systolic dimension was significantly increased POST in males and females (Table 2; dobutamine dosage 0 μg·kg^{-1}·min^{-1}). However, the decrease in fractional shortening and wall stress were significantly greater in males relative to females. The linear, inverse correlation between stress and shortening was displaced downward POST, as measured by a comparison of the y-intercepts, indicating less shortening for a given afterload

in both males and females (Figures 1 and 2). Myocardial VO_2 was significantly higher in males relative to females across all conditions. Myocardial VO_2 was increased POST in both groups. While myocardial efficiency was significantly reduced POST in both males and females, females maintained their efficiency to a greater extent when compared with PRE ($p<.05$; Figure 3). All measures returned to baseline values 24 h following PSE (i.e. during REC).

Cardiovascular Responses to Dobutamine

Contractility increased significantly in response to dobutamine in both groups PRE (Figure 4). However, the increase in contractility was significantly greater in males than in females at the higher doses. Systolic blood pressure increased significantly in response to dobutamine in both groups, but females demonstrated a smaller rise in SBP ($p<0.05$) than did males PRE (Figure 4). Dobutamine induced increases in heart rate in both males and females ($p<0.05$). However, males exhibited a diminished chronotropic response to dobutamine compared with females PRE ($p<0.05$; Figure 4). At race finish (POST), contractility, heart rate, and systolic blood pressure increased in response to dobutamine in males and females (Figure 4). However, the dobutamine induced change in contractility, heart rate and systolic blood pressure (expressed as % change from control to maximum dosage -- i.e. % change from 0 to 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was significantly less POST in males and females when compared to PRE (Figure 5). Additionally, the percent change from PRE to POST was significantly greater in males relative to females (Figure 5). All measures returned to baseline values 24 h following PSE (i.e. during REC). This indicates a gender difference in β-adrenergic mediated cardiovascular changes, both at rest and following PSE, in response to dobutamine.

Chronotropic Responses to β-Adrenergic Stimulation

The chronotropic sensitivity to dobutamine, determined by the slope of the linear portion of the heart rate dobutamine and contractility dobutamine dose-response curve, was significantly greater with a steeper slope in females than in males PRE (Table 3). Dobutamine doses necessary to increase HR were significantly increased following PSE in both males and females; however, the differences were

significantly greater in males (Figure 6). Dobutamine doses necessary to increase contractility were also significantly increased in males and females post race (Figure 7). Males required significantly more dobutamine than females to induce these changes following PSE, as evidenced by increases in slopes and x-intercepts of the dose response relationships between HR, contractility and dobutamine (Table 3).

DISCUSSION

The present study demonstrated that, as has been previously shown LV fractional shortening and contractility are reduced following PSE. This investigation is the first to demonstrate that, although LV systolic function is reduced after PSE in both male and female triathletes, the reduction in cardiac performance occurs to a greater extent in male athletes. Our results also suggest that the decreased inotropic state produced by PSE may, in part, be due to alterations in cardiac β-receptor responsiveness.

Investigators have previously observed that long-term exposure of adrenergic receptors to increased concentrations of catecholamines results in desensitization of these receptors. This phenomenon has clinical relevance for individuals with congestive heart failure, where elevated catecholamines and altered adrenergic responsiveness have been implicated in the pathogenesis of heart failure. Our finding of a decrease in response to dobutamine suggests that a similar mechanism may be functioning in response to physiological stimuli in healthy males and females.

While the detrimental effects of chronically elevated catecholamines on cardiac function have been demonstrated in cardiac patients, few studies have closely examined agonist-induced desensitization with PSE. Friedman et al. (21) demonstrated a decreased cardiac chronotropic responsiveness to isoproterenol after 60 min of exercise in the dog; however, did not assess LV function. In endurance-trained pigs, the diminished chronotropic response was associated with selective downregulation of the β-receptors in the right atrium (26). Recent investigations in humans have also revealed that prolonged exercise may alter β-receptor responsiveness (16, 19). Eysmann et al. (19) examined β-receptor

desensitization using isoproterenol following a single bout of PSE, and demonstrated not only that EF was reduced following prolonged exercise, but also that this reduction was closely related to a decreased sensitivity to exogenous β-receptor stimulation. Welsh et al. (62) recently investigated adrenoreceptor responsiveness following PSE using the β-receptor agonist dobutamine, and reported blunted chronotropic and inotropic responses. Due to its predominantly inotropic stimulation and the ability to be administered as a continuous infusion, the present investigation used dobutamine as a β-agonist. This is the first investigation to assess gender differences in the heart rate, blood pressure and myocardial contractility responses during a continuous inotropic infusion following PSE.

The present investigation also demonstrates a close relationship between the inotropic response to dobutamine and changes in LV EF with prolonged exercise. Several studies have demonstrated that PSE produces transient alterations in LV systolic function and diastolic filling parameters (E:A) that are independent of changing preload and afterload. Our findings are concordant with these reports, and furthermore suggest that reduced systolic function with PSE may, in part, be mediated by impaired adrenergic responsiveness.

While Eysmann et al. (19) and Welsh and coworkers (62) demonstrated that alterations in β-receptor responsiveness occur following PSE, no investigation to our knowledge has examined the potential gender differences in β-receptor responsiveness following a half-ironman triathlon. Several studies have shown that significant sexual dimorphisms exist in neuroendocrine and metabolic responses to physiological stresses (10). In response to exercise, men may have increased catecholamine and norepinephrine responses, as well as enhanced cardiovascular parameters such as systolic and mean arterial pressure (10). These increased sympathetic responses could then result in greater β-receptor desensitization. The present investigation supported these suggestions by demonstrating that men exhibit significantly greater alterations in β-receptor sensitivity relative to females following PSE.

Several limitations need to be considered for this investigation. First, it is possible that baroreflex changes and vagal responses to dobutamine may have affected the observed differences in contractility response. However, Friedman et al. (21) found that the functional desensitization following exercise was evident with and without pretreatment with atropine, suggesting that the phenomenon was unrelated to changes in vagal tone. Furthermore, the functional expression of desensitization to another β-agonist, isoproterenol, during exogenous catecholamine administration has been shown to be independent of baroreceptor reflexes and ganglionic activity (19). This suggests that our findings reflect true impairment of the intrinsic sinus node response to β-adrenergic stimulation.

Second, differences in heart rate between rest and prolonged exercise may have influenced results. Increasing heart rate is known to improve LV performance (52), potentially through a rate-dependent increase in calcium availability. However, because an increase in heart rate is thought to enhance LV performance, our findings of decreased performance may be even more significant.

Finally, the use of human volunteers to assess cardiovascular function is limited, as it is difficult, if not impossible, to assess ventricular inotropic state in humans without removing the heart following intervention. As a result of this limitation, the surrogate measures of ejection fraction, fractional shortening and wall stress were used as indices of contractility.

In conclusion, the present investigation demonstrates that PSE in healthy male and female triathletes is associated with impaired cardiac inotropic responsiveness to dobutamine. This likely represents impairment of the sinus node or right atrial response to β-receptor stimulation, although neither vagal nor baroreceptor influences can be excluded. The inotropic changes are closely related to the decrement in LV EF. These data suggest that the altered cardiac performance which occurs following PSE may be mediated, in part, by impaired cardiac adrenergic responsiveness. Delineation of the mechanisms of such altered responsiveness and its physiological relevance for cardiovascular performance during exercise in healthy adults or in those with diseased hearts requires further investigation.

PRACTICAL IMPLICATIONS

Results from this investigation demonstrate that following prolonged exercise there is a reduction in systolic function, which is mediated by impaired adrenergic responsiveness. Since exercise is so widely prescribed for health promotion, the possibility of transient reductions in heart function occurring as a result of too much exercise has significant implications for both athletic and non-athletic populations. Prolonged exercise may result in myocardial inefficiency and increased myocardial oxygen demands. This may ultimately impact oxygen delivery and endurance performance. In addition to demonstrating a reduction in cardiac function following prolonged exercise, this investigation also established that the myocardium of males responds differently than that of females. This finding may have significant implications not only for individualized training purposes, but also for prescription of exercise for clinical populations. For example, since we have demonstrated that males have greater β-receptor desensitization relative to females following prolonged exercise, it may be beneficial for males to exercise with interval sessions rather than prolonged sessions. Warburton et al. (61) have demonstrated that the same cardiovascular benefit of prolonged sessions can be obtained during a much shorter time period with interval sessions, thus reducing the time the cardiac tissue is exposed to catecholamines, and potentially reducing the occurrence of cardiac fatigue.

Table 1. Selected physiological variables in male and female triathletes

Variable	Males (n= 9)	Females (n= 8)
Age, yr	30 ± 2.6	34 ± 2.6
Height, cm	178 ± 2.6τ	165 ± 2.2
Weight, kg	77.8 ± 3.4τ	63.2 ± 3.3
Body fat, %	13.3 ± 2.3τ	22.4 ±4.1
VO_2max, $mL \cdot kg^{-1} \cdot min^{-1}$	57.5 ± 2.3τ	46.8 ± 2.5

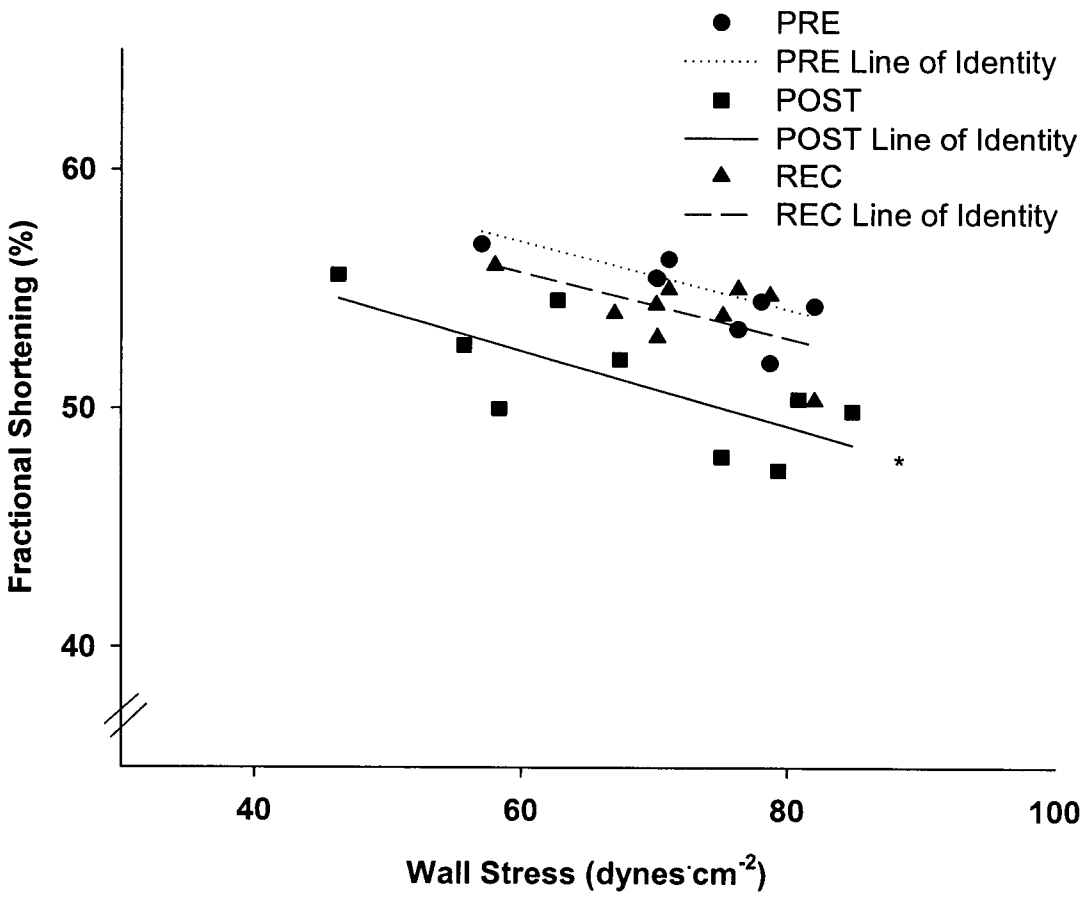
τ $p<0.05$ vs. females. Values are means ± SE.

Table 2. Cardiovascular responses to dobutamine infusion PRE, POST, and REC

	Dobutamine Dosage (μg·kg^{-1}·min^{-1})											
	0		5		10		20		30		40	
Variable	M	F	M	F	M	F	M	F	M	F	M	F
EDD, cm												
PRE	5.4±0.2τ	5.0±0.1	5.4±0.2τ	5.0±0.1	5.4±0.2τ	5.0±0.1	5.4±0.2τ	5.0±0.1	5.4±0.2τ	5.0±0.1	5.4±0.2τ	5.0±0.1
POST	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1
REC	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1	5.4±0.2τ	4.9±0.1
ESD, cm												
PRE	3.0±0.2	3.0±0.2	3.0±0.1	2.9±0.2	2.9±0.1	2.7±0.2	2.5±0.2	2.3±0.2	2.3±0.2	2.1±0.2	2.0±0.1	1.9±0.2
POST	3.7±0.2*τ	3.3±0.1*	3.5±0.2*τ	3.1±0.1*	3.3±0.2*τ	2.8±0.1*	3.1±0.2*τ	2.5±0.1*	2.8±0.2*τ	2.3±0.1*	2.6±0.1*τ	2.1±0.1*
REC	3.1±0.1	2.9±0.2	2.9±0.1	2.8±0.2	2.8±0.1	2.7±0.2	2.5±0.1	2.4±0.2	2.3±0.1	2.2±0.2	2.0±0.2	2.0±0.2
FS, %												
PRE	54.1±0.8	55.4±0.9	59.2±1.5	59.4±1.3	67.8±1.9	64.1±1.4	71.4±2.3	72.1±1.5	75.9±0.9	74.6±1.2	79.6±0.8	76.4±1.2
POST	50.7±1.1*τ	53.3±1.6*	54.0±2.0*τ	57.7±2.0*	59.1±2.0*τ	63.2±1.5	63.6±2.3*τ	68.3±1.7*	71.1±1.2*	72.6±1.2*	73.4±1.3*τ	75.1±0.9*
REC	52.6±1.3	56.7±0.9	59.6±0.7	59.3±1.0	65.7±0.7	63.7±1.3	73.8±1.5	71.8±1.1	77.2±1.5	75.7±1.5	79.2±0.9	77.4±1.3
Cont, mmHg·cm^{-2}												
PRE	11.5±0.6	12.5±0.5	12.7±1.0	13.7±0.5	17.1±0.7	17.2±0.6	21.0±0.7	19.5±0.3	25.9±0.6τ	25.2±0.8	32.6±0.6τ	30.2±0.7
POST	10.3±0.6*	11.8±0.5*	11.7±0.7*	13.9±0.5	12.4±1.1*	15.5±0.7*	15.2±1.7*	18.0±0.9*	19.5±1.8*	23.0±1.6*	22.6±1.8*τ	25.7±1.2*
REC	11.5±0.3	12.3±0.4	12.2±0.3	13.5±0.4	15.0±0.6	18.0±0.7	21.7±1.3	22.7±1.5	26.5±1.3	26.5±2.0	30.1±1.1	30.1±1.8
σ_{ES}, dynes·cm^{-2}												
PRE	74.3±1.6	72.5±3.5	67.4±2.5	68.8±5.1	53.8±3.3	62.7±5.1	52.5±4.1	48.8±5.0	49.8±2.3	45.7±3.8	42.4±1.6	40.4±3.0
POST	67.8±4.4*τ	69.8±5.6*	64.0±4.7*τ	61.7±6.8*	57.3±3.9*τ	53.6±5.2*	56.5±6.9*τ	46.3±4.2*	44.5±3.7*τ	41.0±3.8*	39.6±4.2*	38.6±2.8*
REC	75.9±1.0	72.4±4.5	61.9±2.5	61.6±4.3	53.5±1.9	57.2±3.5	44.0±4.1	49.4±4.0	41.7±4.4	44.0±3.7	39.5±3.5	39.7±2.9

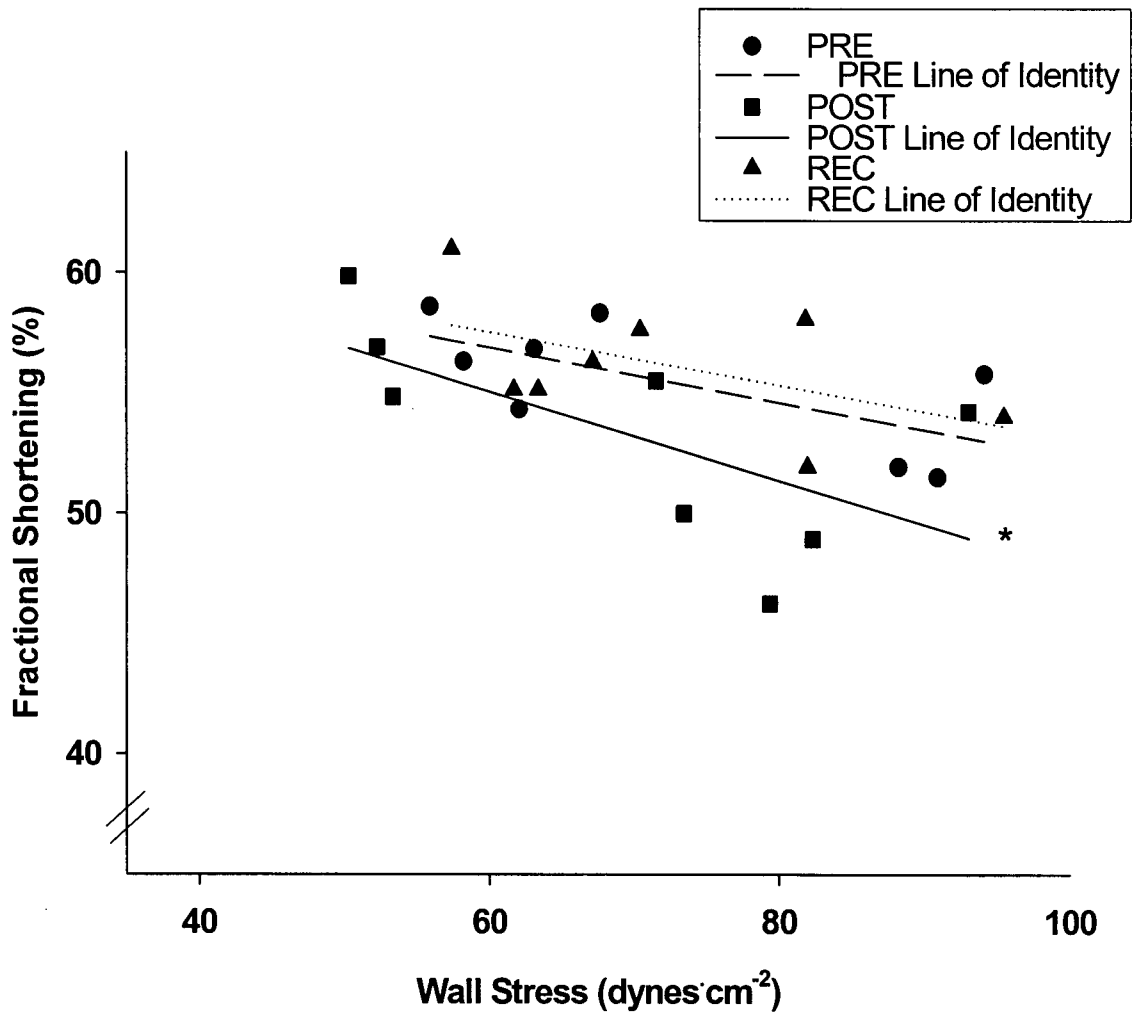
EDD, end-diastolic diameter; ESD, end-systolic diameter; FS, fractional shortening; Cont, contractility; σ_{ES}, end-systolic wall stress. * $p<0.05$ vs. baseline. τ $p<0.05$ vs. females. Values are means ± SE.

Figure 1. Male stress-shortening relationship PRE, POST and REC



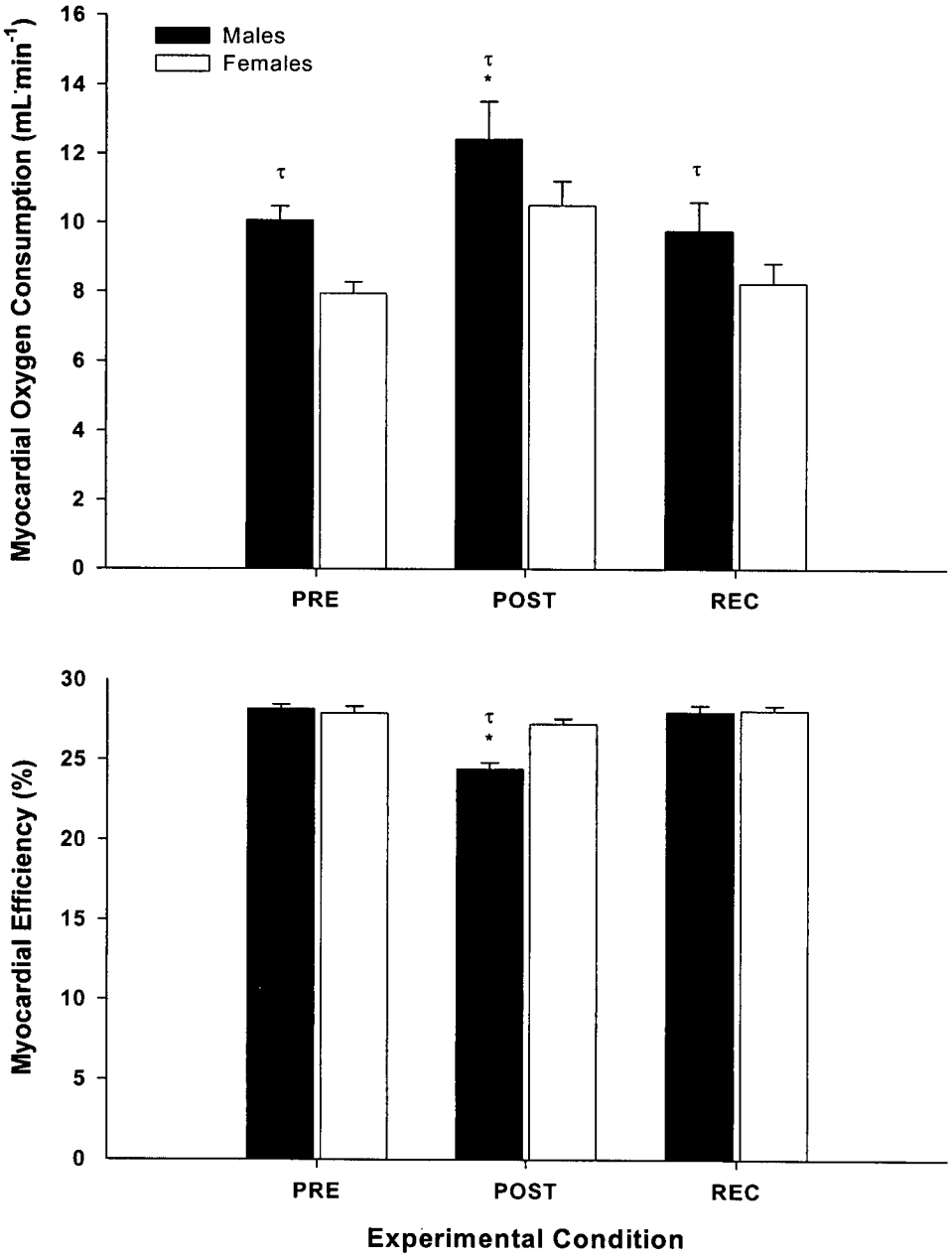
Calculated regression in males for end-systolic wall stress plotted against fractional shortening on pre race, post race and recovery recordings (prior to dobutamine administration). The regression line characterizing the stress-shortening relationship post race is displaced downward (y axis intercepts are lower). * $p<0.05$ vs. baseline.

Figure 2. Female stress-shortening relationship PRE, POST, and REC



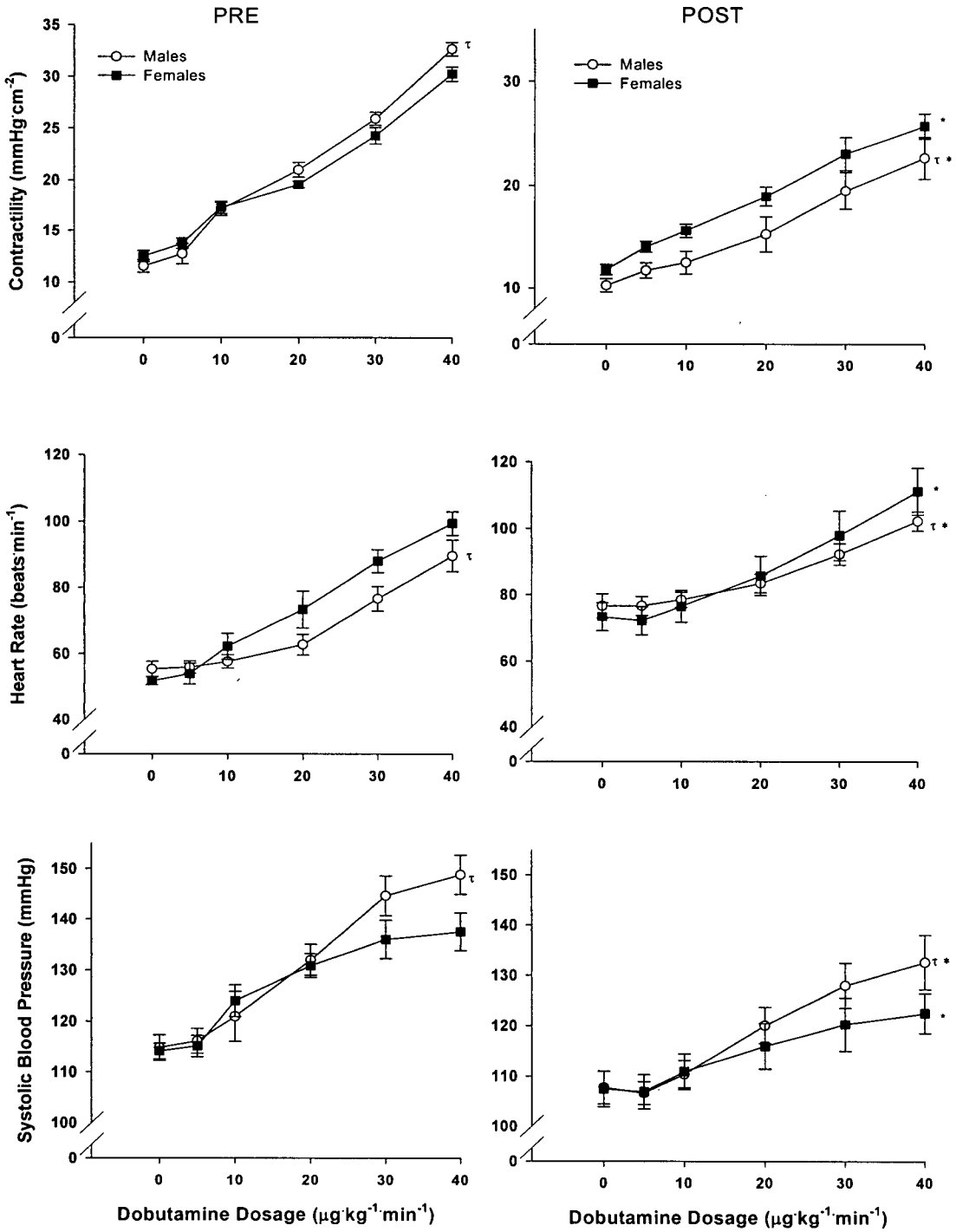
Calculated regression in females for end-systolic wall stress plotted against fractional shortening on pre race, post race and recovery recordings (prior to dobutamine administration). The regression line characterizing the stress shortening relationship post race is displaced downward (y axis intercepts are lower). * $p<0.05$ vs. baseline.

Figure 3. Myocardial mechanoenergetics PRE, POST, and REC



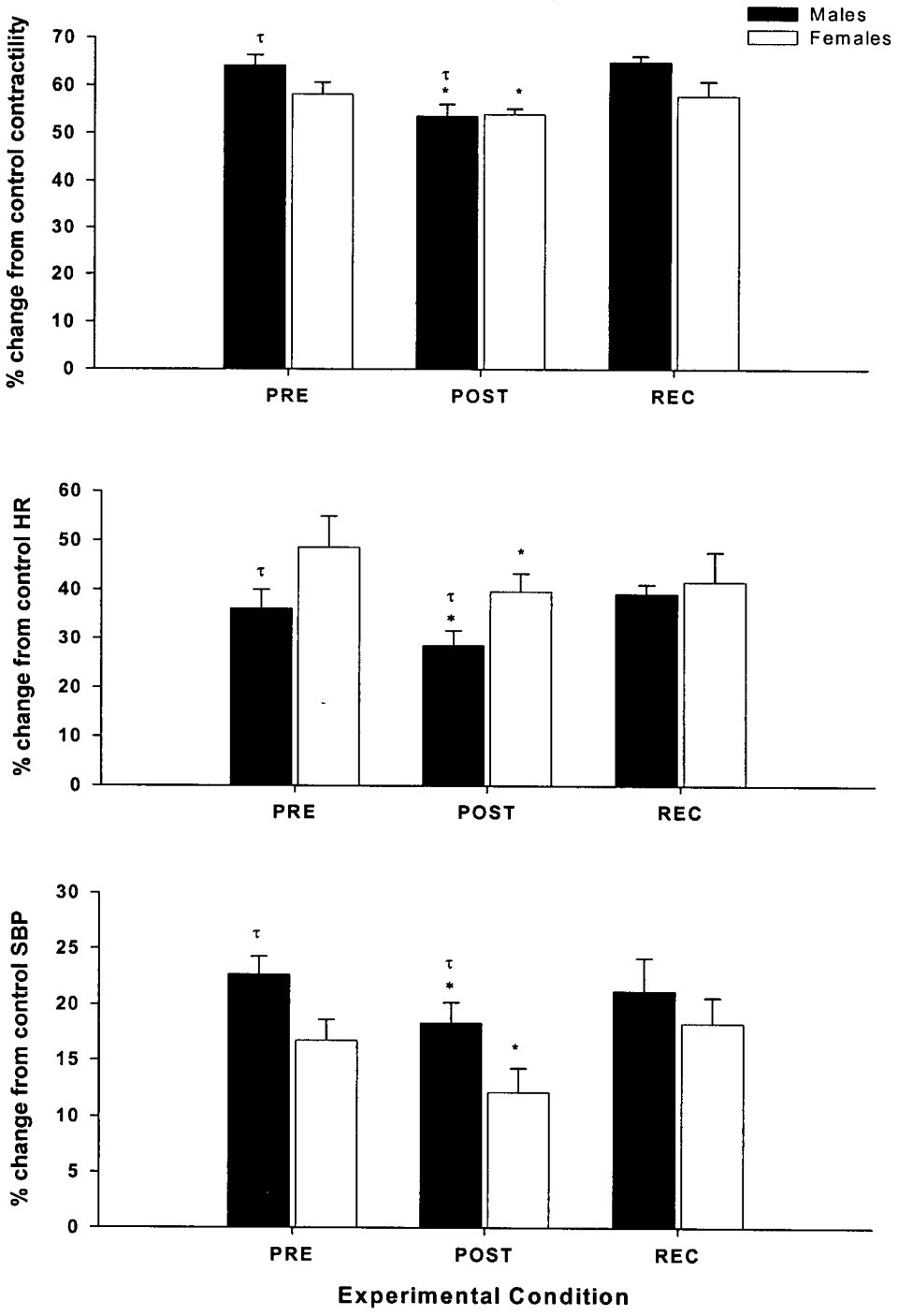
Alterations in myocardial mechanoenergetics characterized by increases in myocardial oxygen consumption in males and females; and decreases in myocardial efficiency in males POST. * $p<0.05$ vs. baseline. τ $p<0.05$ vs. females. Values are means ± SE.

Figure 4. Dobutamine induced cardiovascular changes PRE and POST



Dobutamine increased all variables in both groups however, females showed a greater HR response, while males demonstrated a greater contractility and SBP response PRE and POST. Males also had greater decreases in all variables POST. * $p<0.05$ vs. baseline. τ $p<0.05$ vs. females. Values are means ± SE.

Figure 5. Percent dobutamine induced cardiovascular changes PRE, POST, and REC



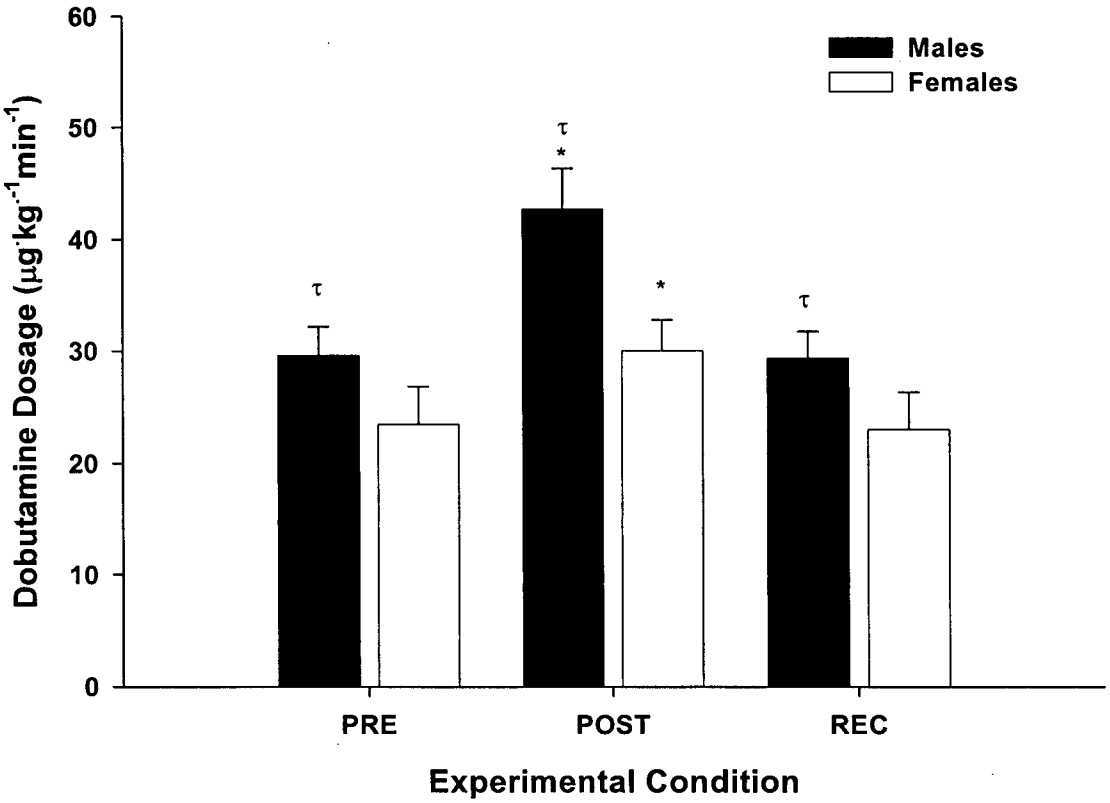
Percent change from 0 to 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in contractility, HR, and SBP was significantly different between males and females PRE and POST. The drop PRE to POST in percent change was significantly greater in males relative to females. * $p<0.05$ vs. baseline. τ $p<0.05$ vs. females. Values are means ± SE.

Table 3. Dose response relationships between HR, contractility and dobutamine

	BASE	POST	REC
X-INTERCEPTS: DOBUTAMINE DOSES ($\mu g \cdot kg^{-1} \cdot min^{-1}$)			
HR, beats/min			
Males	29.6 ± 6.6	42.7 ± 12.9*τ	29.3 ± 5.9
Females	23.5 ± 4	30.0 ± 7.8*	23.4 ± 10.0
Contractility, $mmHg \cdot cm^{-2}$			
Males	20.9 ± 5.1	37.0 ± 11.5*τ	20.4 ± 4.5
Females	22.6 ± 6.4	30.7 ± 7.2*	24.0 ±10.2
SLOPES: β-RECEPTOR RESPONSIVENESS			
HR, beats/min			
Males	0.93 ± 0.33	0.68 ± 0.19*τ	0.96 ± 0.19
Females	1.30 ± 0.48	1.02± 0.31*	1.34 ± 0.46
Contractility, $mmHg \cdot cm^{-2}$			
Males	0.52 ± 0.11	0.31± 0.12*τ	0.52± 0.09
Females	0.46 ± 0.10	0.33 ± 0.09*	0.48 ± 0.14

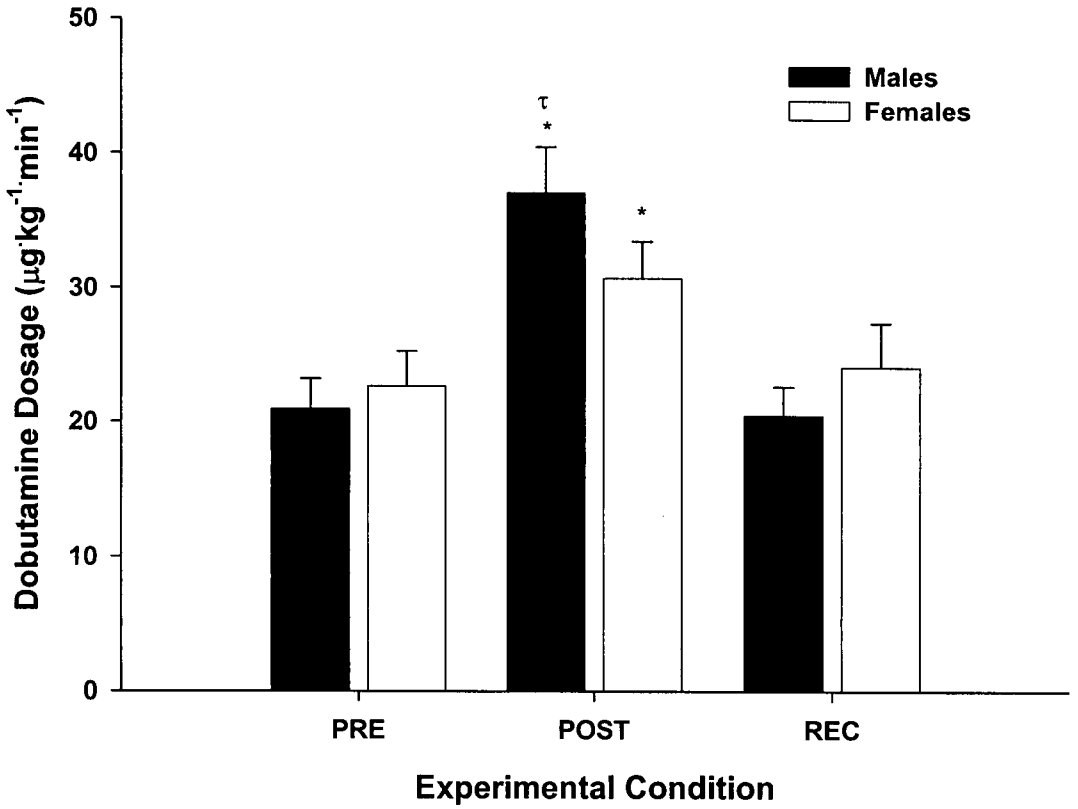
HR, heart rate. * $p<0.05$ vs. baseline. τ $p<0.05$ vs. females. Values are means ± SE.

Figure 6. Dobutamine dose necessary to increase HR 25 beats·min^{-1} PRE, POST, and REC



Differences in chronotropic sensitivity to dobutamine between males and females. * $p<0.05$ vs. baseline. τ $p<0.05$ vs. females. Values are means ± SE.

Figure 7. Dobutamine dose necessary to increase contractility 10 mmHg·cm^{-2} PRE, POST, and REC



Differences in inotropic sensitivity to dobutamine between males and females. * $p<0.05$ vs. baseline. τ $p<0.05$ vs. females. Values are means ± SE.

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