Endurance training reduces renal vasoconstriction to orthostatic stress

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Conboy EE, Fogelman AE, Sauder CL, Ray CA. Endurance training reduces renal vasoconstriction to orthostatic stress. Am J Physiol Renal Physiol 298: F279–F284, 2010. First published November 18, 2009; doi:10.1152/ajprenal.00447.2009.—Endurance training has been associated with increased orthostatic intolerance. The purpose of the present study was to test the hypothesis that endurance training reduces renal vasoconstriction to orthostatic stress. Blood pressure, heart rate, and renal blood flow velocity were measured during a 25-min 60° head-up tilt (HUT) test before and after 8 wk of endurance training in eight healthy sedentary subjects (26 ± 1 yr). Training elicited a 21 ± 3% increase in peak oxygen uptake (VO2peak) and a reduction in heart rate at rest of 8 ± 2 beats/min. During HUT, heart rate progressively increased (~20 beats/min) over the 25-min HUT trial both before and after training. Systolic arterial blood pressure during HUT was unchanged with training, whereas diastolic arterial blood pressure was lower at the end of HUT after training. Before training renal blood flow velocity (Δ14 ± 5 cm/s) and renal vascular conductance (Δ22 ± 7%) decreased during HUT, whereas after training renal blood flow velocity (Δ2 ± 5 cm/s) and renal vascular conductance (Δ1 ± 12%) did not change significantly during HUT. Renal blood flow velocity and vascular conductance responses to HUT did not change in control subjects during the 8-wk period. These results demonstrate that endurance training reduces renal vasoconstriction during an orthostatic challenge and may contribute to training-induced orthostatic intolerance.

renal vascular conductance; head-up tilt

CARDIAC OUTPUT declines ~20% when humans assume an upright posture. Therefore, increases in peripheral resistance must occur to maintain blood pressure during standing. The renal vasculature is one of the most important vascular beds for increasing total peripheral resistance upon standing (17). Renal vascular resistance has been shown to increase ~30% during head-up tilt (HUT) (8, 15). Another important role of the renal vasculature is observed during exercise, when renal and splanchnic vasoconstriction counteracts the vasodilation of the skeletal muscle to minimize a decrease in blood pressure (16).

Some previous cross-sectional studies suggest that highly trained endurance athletes appear to be more susceptible to orthostatic intolerance than healthy sedentary individuals. It has been hypothesized that this increased susceptibility to orthostatic intolerance could be caused by either increased aerobic capacity or a hereditary predisposition for both increased aerobic capacity and orthostatic intolerance. Although there is evidence to support the hypothesis that increased aerobic capacity is associated with orthostatic intolerance, a mechanism for this association is equivocal (4).

It has been established that trained humans and animals exhibit less vasoconstriction in both splanchnic and renal vasculature in response to the same acute dynamic exercise modality with which they were trained (5–7, 12, 17, 21). However, the response of human renal vasculature to HUT before and after training has not been examined. The aim of this study was to determine the effect of endurance training on renal vascular responses to orthostatic stress. It was hypothesized that renal vasoconstrictor responses to HUT would be attenuated after endurance training. This reduced renal vasoconstriction may contribute to orthostatic hypotension in endurance-trained athletes.

METHODS

Subjects. Sixteen healthy, sedentary young volunteers (6 men and 10 women) participated in the study. Participants had a mean ± SE age of 26 ± 1 yr, height of 169 ± 3 cm, and weight of 68 ± 5 kg. All subjects were nonsmokers, nonobese, normotensive, not participating in any regular physical activity program, and not taking any medications that would influence the results of the study. Women taking oral contraceptives participated in the study, and all women were tested on or close to the same day during their menstrual cycle throughout the study; however, phase of menstrual cycle was not controlled for between subjects. Additionally, all subjects were fasted for at least 8 h before the experimental protocol. All subjects received a physical examination before participation. Written informed consent was obtained from all subjects after verbal explanation of the experimental protocol. The Institutional Review Board of the Pennsylvania State University College of Medicine approved this study.

Experimental protocol. Training subjects (7 women and 1 man) were randomly assigned to 8 wk of either running or stationary cycling training. Endurance training consisted of running or biking 4 times/wk for 8 wk. Training sessions were 1 h. Subjects wore a Polar heart rate monitor (Polar S610; Polar Electro; New York, NY) during all exercising sessions to ensure that target heart rates were maintained. VO2peak was determined by maximal graded exercise test on a cycle ergometer (Lode; workload increased 30 W every minute to fatigue). VO2 was measured continuously during the graded exercise test (True One 2400, Parvo Medics). VO2peak was accepted as the highest value obtained during the last 30 s of the graded exercise test. All experimental procedures were replicated for each subject at the end of 8 wk.

Head-up tilt test. Before and after 8 wk of endurance training, subjects performed a 25-min 60° HUT test on a separate day from

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Table 1. Exercise training programs for running and stationary cycling during supine rest (baseline) and throughout the HUT test.

<table>
<thead>
<tr>
<th>Week</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20-min Run</td>
<td>20-min Run</td>
<td>20-min Run</td>
<td>20-min Run</td>
</tr>
<tr>
<td>2</td>
<td>25-min Run</td>
<td>25-min Run</td>
<td>25-min Run</td>
<td>Hill intervals (3×)</td>
</tr>
<tr>
<td>3</td>
<td>35-min Run</td>
<td>Hill intervals (4×)</td>
<td>35-min Run</td>
<td>Sprint intervals (4×)</td>
</tr>
<tr>
<td>4</td>
<td>45-min Run</td>
<td>Hill intervals (5×)</td>
<td>45-min Run</td>
<td>Sprint intervals (5×)</td>
</tr>
<tr>
<td>5</td>
<td>55-min Run</td>
<td>Hill intervals (5×)</td>
<td>55-min Run</td>
<td>Sprint intervals (6×)</td>
</tr>
<tr>
<td>6</td>
<td>60-min Run</td>
<td>Hill intervals (6×)</td>
<td>60-min Run</td>
<td>Sprint intervals (6×)</td>
</tr>
<tr>
<td>7</td>
<td>60-min Run</td>
<td>Hill intervals (6×)</td>
<td>60-min Run</td>
<td>Sprint intervals (6×)</td>
</tr>
<tr>
<td>8</td>
<td>60-min Run</td>
<td>Hill intervals (7×)</td>
<td>60-min Run</td>
<td>Sprint intervals (6×)</td>
</tr>
</tbody>
</table>

Session 1: 25-min Run 25-min Run 25-min Run
Sprint intervals (4×)
Hill intervals (3×)

Session 2: 45-min Run Hill intervals (5×)
Sprint intervals (5×)

Session 3: 55-min Run Hill intervals (6×)
Sprint intervals (6×)

Session 4: 60-min Run Hill intervals (7×)
Sprint intervals (6×)

Stationary cycling

Sprint interval = 30-s sprint, 1-min recovery, 1-min sprint, 2-min recovery performed on flat course; hill interval = uphill sprint and downhill recovery on a 0.1-mi course at 6% grade (weeks 2–5) or 10% grade (weeks 6–8); bike interval = increased power output for 30 s, 1-min recovery, 1-min increased power output, 2-min recovery.

\( \dot{V}O_{2\text{peak}} \) testing. Renal blood flow velocity (RBFV) was determined during supine rest (baseline) and throughout the HUT test.

Subjects lay supine on a tilt table and were instrumented for the study. Subjects then rested in a dimly lit, quiet laboratory maintained at 21–23°C for 20 min. Baseline measurements (heart rate, arterial blood pressure, and RBFV) were made for 5 min, followed by a 25-min passive HUT and a 5-min recovery period in the supine position. The tilt test was terminated if the subject completed 25 min of HUT; if the subject began to feel presyncopal symptoms including lightheadedness, nausea, vomiting, excessive heat, sweating; if the subject’s systolic blood pressure decreased >25 mmHg; or if the subject’s diastolic blood pressure decreased <70 mmHg; or if the subject’s systolic blood pressure decreased >25 mmHg. Subjects who did not complete 25 min of HUT before training were excluded from this study.

Renal vascular responsiveness. Renal vascular responsiveness to α-adrenergic stimulation was determined in five trained and four control subjects. RBFV was measured in the supine position by Doppler ultrasound before and after steady-state intravenous infusions of phenylephrine. Baseline measurements were taken for 5 min. Phenylephrine infusion commenced at a rate of 0.5 μg·kg\(^{-1} \cdot \text{min}^{-1}\) for 5 min and was increased by 0.5 μg·kg\(^{-1} \cdot \text{min}^{-1}\) every 5 min. Phenylephrine infusions were stopped if blood pressure increased >30 mmHg from baseline or if heart rate was <40 beats/min.

Measurements. Resting heart rate and brachial arterial blood pressure were collected after 20 min of rest in the supine position in a dimly lit room (Dinamap, General Electric, Waukesha, WI).

Doppler ultrasound (HDI 5000, ATL Ultrasound, Bothell, WA) was used to measure RBFV. All arteries were scanned by the anterior abdominal approach with a curved-array transducer (2–5 MHz) with a 2.5-MHz pulsed Doppler frequency. The probe isonation angle to the artery was ≤60°. The focal zone was set at the depth of the artery. The transducer was held in the same place to record velocity tracings during each trial, and the data were obtained in the same phase of the respiratory cycle. Continuous measurements of RBFV were taken during baseline and during HUT at minutes 1–5, 9–10, 14–15, 19–20, and 24–25.

Continuous measurements of blood pressure and heart rate were made by finger plethysmography with a Finometer blood pressure monitor (Finapres Medical Systems).

Data analysis. Blood pressure and heart rate were analyzed off-line with Chart software (ADInstruments, Newcastle, Australia). Doppler ultrasound tracings were analyzed with the software of the ATL to obtain mean blood velocity for each cardiac cycle. Because of technological limitations it is not possible to accurately measure the diameter of the arteries in the present study with the ATL Doppler ultrasound machine; therefore an index of renal vascular conductance (RVC) was calculated by dividing the respective artery blood velocity by mean arterial blood pressure of the given trial. A paired t-test was used to compare baseline and HUT values.

RESULTS

\( \dot{V}O_{2\text{peak}} \) (ml·kg\(^{-1} \cdot \text{min}^{-1}\)) was increased by 21 ± 3% after 8 wk of endurance training, with no significant change in body weight (Table 2). \( \dot{V}O_{2\text{peak}} \) did not change in the control subjects (Table 2). Resting heart rates were significantly decreased in trained subjects compared with control subjects after 8 wk (Δ8 ± 2 and Δ3 ± 2 beats/min, respectively; Table 2). Resting brachial blood pressure did not significantly change in either the trained or the control subjects (Table 2).

Heart rate significantly increased with HUT before and after training (Fig. 1), and heart rate responses to HUT were not altered with training. However, heart rate was significantly higher at baseline and during HUT before training compared with after training. Heart rate significantly increased during HUT in control subjects before and after 8 wk, but heart rate responses were not different between the two visits. Systolic arterial blood pressure was not significantly affected by training (train × tilt; P = 0.87; Fig. 1). However, diastolic arterial blood pressure was significantly lower during the end of HUT after training (77 ± 8 and 69 ± 3 mmHg for before and after training, respectively, for minutes 24 and 25, P < 0.001; Fig.
Arterial blood pressure was not changed in the control group during the 8-wk period (Fig. 1). RBFV and RVC decreased during HUT before training (22% and 5 cm/s, respectively) but did not change in response to HUT after training (2% and 12%, respectively; Fig. 2). The decrease in RBFV and RVC in control subjects during HUT was not different before and after 8 wk (Fig. 2).

Only data from phenylephrine infusions at 0.5 and 1.0 g·kg\(^{-1}\)·min\(^{-1}\) are reported because most subjects did not tolerate higher infusion rates. Mean arterial pressure at rest in the trained (75 and 74 mmHg) and control (86 and 82 mmHg) groups were not significantly different before and after training, respectively. During phenylephrine infusion blood pressure increased as a function of dose for both control and training groups, but there were no differences in blood pressure response to phenylephrine before and after training (P = 0.36 and P = 0.44, respectively). RVC decreased as a function of dose during phenylephrine infusions in all subjects, but the response was not different before and after training for both the trained and control subjects (Fig. 3).

**DISCUSSION**

The major finding of this study is that endurance training elicits a blunted vasoconstriction of the renal artery during HUT. This is the first study to report a significant attenuation in renal vasoconstriction to HUT in humans in response to endurance training. This insight into the effects of exercise training on the renal vasculature expands our understanding of the effects of exercise training on humans. Moreover, it provides a possible explanation why some endurance athletes have been reported to be more orthostatically intolerant than sedentary subjects (4).

These findings are consistent with both animal and human studies that have demonstrated decreased vasoconstriction of the renal vasculature during exercise in trained compared with sedentary subjects. However, the response to phenylephrine did not differ before and after training for both the trained and control subjects (Fig. 3).

### Table 2. Baseline measurements in trained and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trained (n = 8)</th>
<th>Control (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>VO(_2)peak, mL·kg(^{-1})·min(^{-1})</td>
<td>32 ± 1</td>
<td>39 ± 1*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63 ± 5</td>
<td>62 ± 5</td>
</tr>
<tr>
<td>Systolic pressure, mmHg</td>
<td>109 ± 3</td>
<td>104 ± 2</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>78 ± 2</td>
<td>75 ± 2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60 ± 3</td>
<td>52 ± 2*</td>
</tr>
<tr>
<td>RVC, cm·s(^{-1})·mmHg(^{-1})</td>
<td>0.81 ± 0.09</td>
<td>0.68 ± 0.05*</td>
</tr>
</tbody>
</table>

Values are means ± SE. VO\(_2\)peak, peak oxygen uptake; MAP, mean arterial blood pressure; RVC, renal vascular conductance. *Significantly different from before training, †significantly different from trained (P < 0.05).
untrained individuals (5–7, 12, 17, 21). Because both exercise
and HUT activate the sympathetic nervous system, it is there-
fore likely that the same or a similar mechanism is responsible
for the observed attenuation of vasoconstriction in both con-
ditions. There are two plausible mechanisms for the effects of
exercise training on renal blood flow during HUT. Less renal
vasoconstriction in the trained state could be a result of
decreased sympathetic outflow to the renal vasculature, or a
decreased vascular response to the plasma norepinephrine (NE)
concentration. Evidence that supports the former mechanism
demonstrates lower plasma NE levels at the same exercise
intensity after training (23). Meredith et al. (13) demonstrated
that endurance training selectively lowered resting renal NE
spillover, suggesting that the renal sympathetic nerves had
reduced firing rates. This reduction in nerve activation supports
our finding of decreased vasoconstriction in trained subjects. If
the decrease in renal vasoconstriction is due to decreased
vascular responsiveness to NE, it may be a result of training-
induced decreases in α-adrenergic receptors or decreased in-
tracellular signaling (5–7, 12, 17, 21). However, there was a
comparable decrease in RVC to phenylephrine infusions before
and after training, suggesting that renal vascular responsiveness to
α-adrenergic receptor stimulation is not altered with training. It is
possible that vascular responses to other substances may be
altered with training (e.g., angiotensin II). Additionally, the in-
crease in arterial blood pressure elicited by phenylephrine infusion
could mediate a myogenic vascular response. The myogenic
response to pressure changes could confound our interpretation.
However, because blood pressure responses were comparable to
phenylephrine infusion before and after training in both the
control and training groups this would suggest that this mecha-
nism is not likely to have influenced our results and interpretation
with respect to exercise training.

Wallin et al. (22) demonstrated that there was a significant
positive correlation between muscle sympathetic nerve activity
(MSNA) and renal NE spillover in humans. This finding

Fig. 2. Renal blood flow velocity (RBFV; top) and renal vascular conductance (RVC; bot-
tom) differences before and after 8 wk in both trained and control groups during head-up tilt.
Values are means ± SE.

Fig. 3. RVC to infusions of phenylephrine at 0.5 and 1.0 μg·kg⁻¹·min⁻¹. RVC was de-
creased as a function of drug dose. More importantly, RVC responses were not differ-
ent before and after 8 wk in both trained (n = 5) and control (n = 4) groups. Values are
means ± SE. *Significantly different from baseline (P < 0.05). †There was a linear dose
response to phenylephrine (P = 0.0007 for trained and P = 0.009 for control groups).
indicates that in healthy humans the resting renal sympathetic nerve activity (RSNA) is similar or proportional to MSNA. With this association between MSNA and RSNA established, the training-induced MSNA reduction during leg exercise training suggests that there is a concurrent reduction in RSNA during training (14). Additionally, other studies have found that training is associated with an attenuation of exercise-induced increases of MSNA (14, 19, 20). Therefore, the lack of renal vasoconstriction that we observed in the present study is likely a result of training-induced RSNA reductions.

DiCarlo and Bishop (1) demonstrated that 8 wk of endurance training in rabbits significantly attenuates arterial baroreflex control of RSNA. In a follow-up study they concluded that training enhances the inhibitory influence of cardiac afferents on the arterial baroreflex regulation of RSNA (2). Although their results were observed in resting animals, our present study in humans demonstrates a similar effect during HUT. Therefore, an attenuation of renal vasoconstriction during HUT may be related to changes in the sensitivity of cardiac afferents following training.

Another possible mechanism for the decrease in vasoconstriction is activation of the vestibulosympathetic reflex (VSR) with training. We have demonstrated (18) that engagement of the VSR can elicit renal vasoconstriction. If the VSR is attenuated after endurance training, this would cause less renal vasoconstriction.

Training reduced both heart rate and diastolic arterial pressure during HUT. One potential explanation for this lower blood pressure is that the decrease in renal vasoconstriction results in a decrease in total peripheral resistance at a time when cardiac output is lower, resulting in a lower blood pressure.

Our results are clinically relevant because the association we demonstrated between RVC during HUT and exercise training may help to further our understanding of orthostatic intolerance. Levine et al. (9) have provided evidence that endurance athletes may have a diminished tolerance to orthostatic stress compared with moderately fit or sedentary subjects. They suggest that maximal aerobic capacity is a poor predictor for orthostatic intolerance because the association does not seem to fit a simple, linear pattern. There are potentially multiple factors that contribute to cardiovascular regulation during orthostasis. Fu et al. (3) have expanded on this concept by suggesting that humans have an individual, intrinsic, and limited sympathetically mediated vasoconstrictor reserve that could affect the maintenance of orthostatic tolerance. Furthermore, they suggest that physical fitness may be one important factor underlying individual differences in vasoconstrictor reserve. Our study demonstrates that endurance training causes attenuated renal vasoconstriction; this is one factor that may contribute to endurance training-associated orthostatic intolerance.

In the present study Doppler ultrasound could not measure renal artery diameter. Thus we are unable to be certain that HUT did not elicit changes in renal diameter. There is some evidence to suggest that pharmacologically mediated renal vasoconstriction (11) and vasodilation (10) do not alter diameter of the renal artery. Furthermore, the vessel we examined was a conduit and not a resistance vessel. Therefore, it is unlikely that changes in renal artery diameter during HUT influenced the results of the study. However, if differences in renal diameters occur as the result of exercise training this could affect our results and subsequent interpretation.

In summary, the renal vasoconstrictor response to HUT was attenuated after 8 wk of endurance training in humans. This attenuation of renal vasoconstriction may be one contributing factor for endurance training-induced orthostatic intolerance when it occurs in susceptible subjects.

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DISCLOSURES

No conflicts of interest are declared by the authors.

REFERENCES


