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Sex Differences in Orthostatic Tolerance Are Mainly Explained by Blood Volume and Oxygen Carrying Capacity

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OBJECTIVES: The reduced orthostatic tolerance (OT) that is characteristic of the female sex may be explained by multiple phenotypic differences between sexes. This study aimed to elucidate the mechanistic role of blood volume (BV) and oxygen carrying capacity on sex differences in OT.

DESIGN: Experimental intervention.

SETTING: University of Calgary, Main Campus, Calgary, AB, Canada.

SUBJECTS: Healthy women and men ($n = 90$) throughout the adult lifespan (20–89 yr) matched by age and physical activity.

INTERVENTIONS: Incremental lower body negative pressure (LBNP) in all individuals. Blood withdrawal and oxygen carrying capacity reduction in men to match with women's levels.

MEASUREMENTS AND MAIN RESULTS: Transthoracic echocardiography and central blood pressures were assessed throughout incremental LBNP for 1 hour or until presyncope. Blood uniformization resulted in a precise sex match of BV and oxygen carrying capacity ($p \geq 0.598$). A third of women (14/45) and two thirds of men (31/45) prior to blood uniformization completed the orthostatic test without presyncopal symptoms (p-for-sex < 0.001). After blood uniformization, seven out of 45 men completed the test (p-for-sex $= 0.081$). Left ventricular end-diastolic volume (LVEDV) and stroke volume (SV) were progressively reduced with LBNP in both sexes, with women showing markedly lower volumes than men ($p < 0.001$). Blood uniformization did not eliminate sex differences in LVEDV and SV.

CONCLUSIONS: Sex differences in OT are not present when BV and oxygen carrying capacity are experimentally matched between sexes throughout the adult lifespan.

KEY WORDS: blood volume; female sex; older age; orthostatic tolerance; oxygen carrying capacity

The capacity to withstand the upright posture is remarkably diverse among healthy individuals (1, 2). Increasing gravitational stress on the cardiovascular system inexorably leads to syncope in humans, yet some individuals reach their limit of orthostatic tolerance (OT) well in advance than others (3). A consistent gap between sexes is long known to exist, with women commonly presenting lower OT compared with men (4). Far from irrelevant, impaired OT may contribute to the increased risk of falls (up to 50% increment) in women relative to men throughout the adult lifespan (5–8). Outstanding research efforts have identified a plethora of anthropometrical, autonomic, cardiovascular and hematological factors potentially underpinning sex differences in OT (9, 10). A number of potentially contributing factors cannot be safely manipulated in humans, yet certain phenotypic variables may be experimentally modified in order to assess their influence in OT (11). Notably, fluid-related

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factors such as blood volume (BV), which is generally lower in women versus men even when adjusted by anthropometrical differences (12, 13), can be carefully manipulated (14). BV is a fundamental circulatory variable that primarily determines venous return, cardiac filling, and output (15), thus possibly holding a major contributing role in OT (11). Likewise, another key hematological variable determining oxygen delivery, that is, blood oxygen carrying capacity, can be experimentally modulated and matched between sexes (16). The extent to which major sex-specific blood variables, that is, BV and oxygen carrying capacity, explain sex differences in OT can thus be addressed.

Accordingly, the aim of the present study was to experimentally determine the role of sex differences in BV and oxygen carrying capacity in OT, cardiac volumetric and functional responses in healthy women and men throughout the adult lifespan.

METHODS

Detailed experimental methods are included in the **Supplemental Material File** (http://links.lww.com/CCX/A883).

Participants

Ninety healthy women and men throughout the adult lifespan (20–89 yr) were recruited via electronic/printed advertisements on community notice boards in the city of Calgary. Moderate-to-vigorous physical activity levels were determined from established questionnaires as previously described (17). Inclusion criteria comprised healthy status, absence of current medical symptoms, and no history of cardiac, pulmonary, or neuromuscular diseases. Individuals fulfilling the above criteria but having donated blood within 3 months prior to the study were excluded. The study was approved by the Conjoint Health Research Ethics Board (REB18-1654) of the University of Calgary and conducted in accordance with the declaration of Helsinki. Prior to the start of the experiments, informed oral and written consents were obtained from all participants.

Experimental Design

Participants were required to report to our laboratory at least once, depending on sex and a voluntary familiarization visit. Each man was assessed twice, prior to and after blood uniformization relative to a previously assessed woman with similar age and physical activity level (one-to-one matching). Time of day of testing sessions was kept consistent for each men and women-men matched pair with a minimum of 48 hours and a maximum of 7 days between the first (baseline) and second (blood uniformization) sessions. All individuals were instructed to avoid strenuous exercise, alcohol and caffeine from 24 hr prior to testing, as well as to maintain their usual baseline activity and daily dietary habits throughout the study. All measurements were performed in fasting conditions (≥ 4 hr) in a quiet room with controlled temperature between 22°C and 23°C. Prior to testing, the participants completed demographic and clinical questionnaires and rested in supine position for 20 minutes in order to stabilize cardiovascular, hemodynamic, and hematological variables.

Measurements

Hemoglobin mass and BV were determined via the carbon monoxide (CO) rebreathing technique. Transthoracic echocardiography and central hemodynamics were noninvasively assessed using high-resolution ultrasound (Mindray Medical M9, Mahwah, NJ) and the volume-clamped method (Finapres Medical Systems, Enschede, The Netherlands). The OT test was performed in a lower body negative pressure (LBNP) chamber designed to facilitate echocardiography via left lateral tilting. The negative pressure inside the chamber was increased every 10 minutes by –10 mm Hg, from 0 to –50 mm Hg. The test was terminated immediately after completion of the last 10 minutes LBNP (–50 mm Hg) level or in the presence of presyncope.

RESULTS

Baseline Characteristics

Main general characteristics of the study participants are presented in **Table 1**. All individuals were nonsmokers and nonobese (body mass index < 30 kg/m^2). Age and physical activity levels were matched between women and men. As expected, women presented smaller anthropometric indices (height, weight, body surface area [BSA]) compared with men ($p < 0.001$). Likewise, hematological variables fell within normal age- and sex-related levels, with women presenting lower hemoglobin concentration, hematocrit, and BV

TABLE 1.
Baseline Characteristics of Study Subjects

Variable	Women	Men
n	45	45
Age (yr)	54.4 ± 16.0	53.5 ± 18.9
Height (cm)	164.8 ± 7.2	178.3 ± 7.6[a]
Weight (kg)	62.5 ± 9.1	79.5 ± 10.8[a]
Body surface area (m^2)	1.68 ± 0.14	1.97 ± 0.15[a]
Mean arterial pressure (mm Hg)	96.9 ± 16.6	97.4 ± 15.4
Moderate-to-vigorous physical activity (hr/wk)	5.8 ± 2.9	6.8 ± 4.0
Smoking (%)	0	0
Blood		
Hemoglobin concentration (g/dL)	13.3 ± 0.7	15.0 ± 1.0[a]
Carboxyhemoglobin (%)	0.8 ± 0.3	0.9 ± 0.2
Effective hemoglobin concentration (g/dL)	12.0 ± 0.6	13.5 ± 0.9[a]
Hematocrit (%)	41 ± 2	46 ± 3[a]
Plasma volume (mL/kg)	49 ± 6	48 ± 6
RBC volume (mL/kg)	34 ± 5	41 ± 5[a]
Blood volume (mL/kg)	83 ± 10	88 ± 10[a]
Resting echocardiography		
Heart rate (beats/min)	58.7 ± 8.1	57.3 ± 7.2
Right atrial (mL/m^2)	18.4 ± 7.1	20.4 ± 6.2
Right ventricle end-diastolic area (cm^2/m^2)	10.8 ± 2.3	11.2 ± 2.1
Right ventricle end-systolic area (cm^2/m^2)	5.0 ± 1.6	5.0 ± 1.8
Left atrial (mL/m^2)	22.5 ± 9.7	22.4 ± 8.6
Left ventricular end-diastolic volume (mL/m^2)	46.4 ± 9.3	54.9 ± 13.8[a]
Left ventricular end-systolic volume (mL/m^2)	13.5 ± 4.7	16.9 ± 6.6[a]
Left ventricular ejection fraction (%)	71.1 ± 7.9	69.6 ± 6.7
Stroke volume (mL/m^2)	32.9 ± 7.3	38.0 ± 9.3[a]
Cardiac output ($L/min/m^2$)	2.0 ± 0.6	2.2 ± 0.6[a]

[a]$p < 0.05$, men vs women.
Data are presented as mean ± SD.

than men ($p < 0.001$). BV per unit body weight was positively associated with body mass index in women ($r = 0.63$; $p < 0.001$) and men ($r = 0.58$; $p < 0.001$). Age was not significantly associated with OT time or BV per unit of body weight in women and men ($p \geq 0.115$). With respect to resting cardiac variables, smaller left ventricular (LV) volumes, stroke volume (SV), and cardiac output adjusted by BSA were noted in women compared with men ($p \leq 0.022$). Resting central blood pressures did not differ between sexes, whereas systemic vascular resistance (SVR) was elevated in women compared with men ($p = 0.001$).

Blood Uniformization

The manipulation of blood oxygen carrying capacity in men resulted in a precise match of effective hemoglobin between sexes (12.0 ± 0.6 vs 12.0 ± 0.8 g/dL; $p = 0.598$). Likewise, no differences in BV per kg of body weight were present between women and men after blood withdrawal (83 ± 10 vs 83 ± 9 mL/kg; $p = 0.743$). It should be noted that BV per kg of body weight measured via CO-rebreathing yields higher values compared with dye dilution methods (e.g., indocyanine green) (18). The average absolute BV removed

from men was 510.6 ± 191.1 mL, approximately equivalent to a standard blood donation (19). Blood withdrawal in men did not alter hemoglobin concentration (15.0 ± 1.0 vs 15.0 ± 0.9 g/dL; p = 0.598) nor hematocrit (46.0 ± 2.9 vs 45.8 ± 2.5 g/dL; p = 0.598), which remained elevated relative to women ($p < 0.001$).

Orthostatic Tolerance

Figure 1 illustrates the frequency distribution of women and men (prior to and after blood uniformization) throughout the orthostatic test as well as the OT time. Before blood uniformization, all women and men reached moderate LBNP levels (–20 mm Hg). From –30 to –50 mm Hg, a decreasing number of women and men completed each LBNP stage, with women being outnumbered by men at all levels ($p \leq 0.043$) (Fig. 1*A*). Approximately a third of women (14/45) and two thirds of men (31/45) (p-for-sex < 0.001) completed the entire orthostatic test without signs and symptoms of presyncope. After blood uniformization, men did not outnumber women at any LBNP level. Indeed, only seven out of 45 men completed the test after blood uniformization (p-for-sex = 0.081). The average OT time was shorter in women compared with men before blood uniformization (51.3 ± 8.9 vs

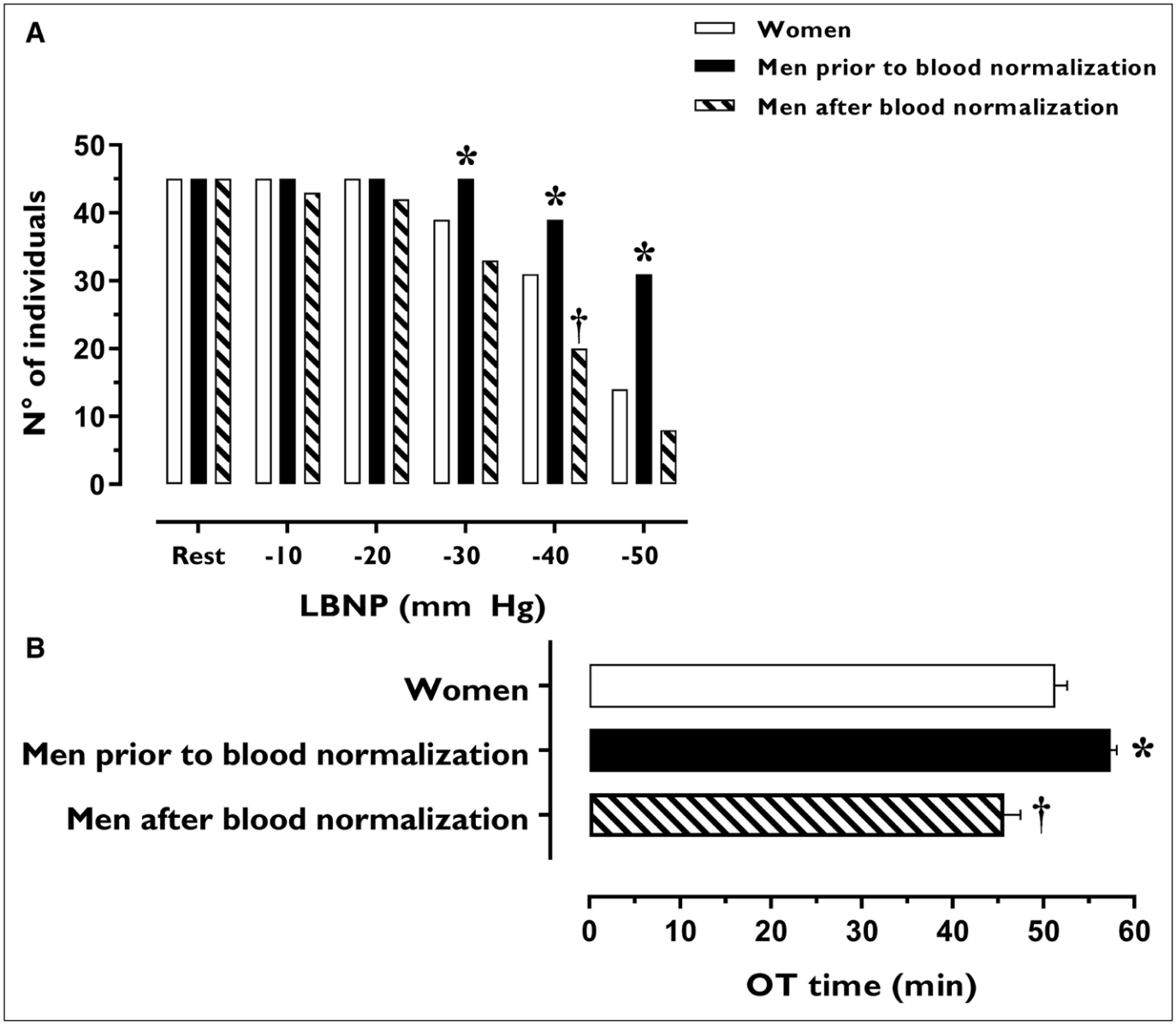

Figure 1. Frequency distribution of women and men prior to and after blood uniformization at each completed lower body negative pressure (LBNP) level (**A**) and orthostatic tolerance (OT) time (**B**). *$p < 0.05$ between women and men prior to blood uniformization. †$p < 0.05$ between women and men after blood uniformization. Data are expressed as n or mean ± SEM.

57.4 ± 4.7 min; $p < 0.001$), whereas women's time was longer relative to men after blood uniformization (51.3 ± 8.9 vs 45.7 ± 11.9 min; $p = 0.014$) (Fig. 1*B*).

Cardiac Structure, Function, and Hemodynamics During Orthostatic Stress

Right and left cardiac volumes and output at each completed LBNP level are presented in **Figure 2**. Right and left cardiac volumes were substantially decreased along with increasing LBNP levels in both women and men before blood uniformization ($p < 0.001$). Furthermore, right atrial and LV volumes (left ventricular end-diastolic volume [LVEDV], left ventricular end-systolic volume [LVESV]) were lower in women compared with men during the orthostatic test ($p \leq 0.003$). Similarly, SV and cardiac output were markedly lower in women compared with men prior to blood uniformization ($p < 0.001$). After blood uniformization, main LV volumes and output (LVEDV, SV, and cardiac output) remained elevated in men compared with women ($p \leq 0.047$). Likewise, SVR was augmented in women relative to men prior to and after blood uniformization ($p \leq 0.002$) (**Fig. 3**). Between-sex comparisons in individuals reaching presyncope revealed that sex differences in right atrial volume, LVESV and SVR are abolished after blood uniformization in men at the individual-specific LBNP level closer to presyncope ($p \geq 0.199$) (**Fig. 4**).

DISCUSSION

This main purpose of the present study was to experimentally assess the role of BV and oxygen carrying capacity on sex differences in OT. The main findings are: 1) the match of BV and oxygen carrying capacity between women and men abolishes sex differences in OT; 2) sex differences in LV filling and output remain after blood uniformization; 3) prior to presyncope, SVR is augmented in women compared with men prior to, but not after blood uniformization.

The growing emphasis on understanding biomedical sciences in a sex-specific manner is warranted by the recognition of quantitative as well as qualitative sex divergences in clinically relevant phenotypic variables (20–23). In this respect, the strong relationship between low OT in women and increasing risk of falls, plausibly entailing adverse consequences for hard clinical outcomes, merits further research (8, 24). Consistent with prevalent findings in the literature (9, 10),

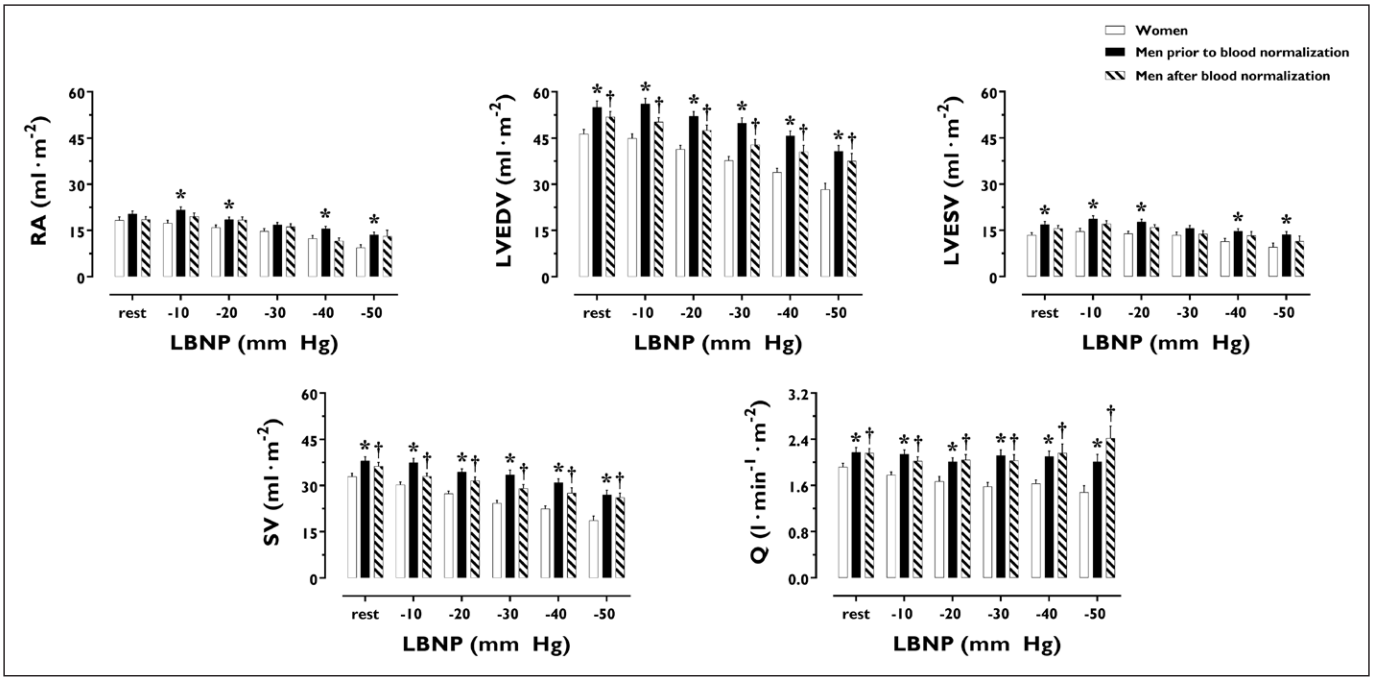

Figure 2. Cardiac volumes and function during progressive lower body negative pressure (LBNP) in women and men prior to and after blood uniformization. *$p < 0.05$ between women and men prior to blood uniformization. †$p < 0.05$ between women and men after blood uniformization. Data are expressed as mean ± SEM. LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, Q = cardiac output, RA = right atrial, SV = stroke volume.

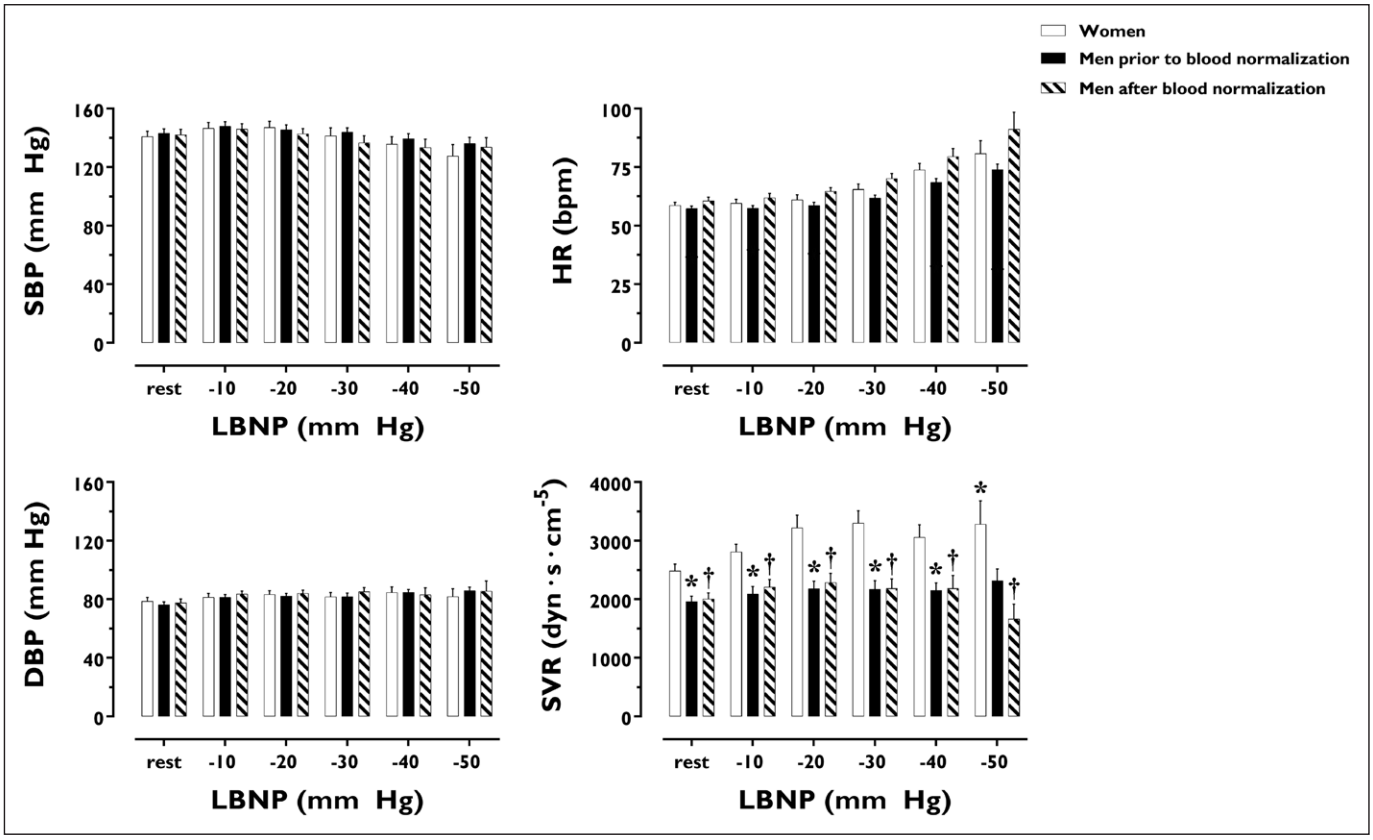

Figure 3. Central blood pressures and peripheral resistance during progressive lower body negative pressure (LBNP) in women and men prior to and after blood uniformization. *$p < 0.05$ between women and men prior to blood uniformization. †$p < 0.05$ between women and men after blood uniformization. Data are expressed as mean ± SEM. DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure, SVR = systemic vascular resistance.

we found markedly lower OT in women compared with men matched by age and physical activity levels. Specifically, ~50% less women reach the highest level of LBNP relative to men. Such a pronounced gap in OT may be explained by differences in fundamental phenotypic variables. Herein, a precise match of key blood variables, BV and oxygen carrying capacity, between women and men eliminated sex differences in OT. Indeed, after blood uniformization, a substantially reduced number of men (n = 7) were able to finish the orthostatic test, while their OT time was shorter compared with women. Of note, differences OT time between sexes prior to and after blood uniformization (± 6 min) approximately correspond with the effects of interventions involving the ingestion of a volume of fluid (500 mL) similar to the BV removed in the present study (11). BV seems to play a prominent, albeit not exclusive, role in determining increases and decreases in OT. The positive prospect is that BV is amenable to modification, for example, via exercise training or specific physical maneuvers such as head-up sleep, and thus plausibly translated into effective targets to improve or preserve hemodynamic stability in the general population (25–29).

The potential mechanisms underlying the effects of blood uniformization on OT require examination. Conforming to well established physiologic principles, blood plays a primary role as a hemodynamic "driver" of the circulatory system. The more blood fills the system, particularly the heart, the greater the myocardial capacity to increase SV until a plateau is reached, conforming to the Frank-Starling mechanism (30, 31). A sex-specific ventricular filling and SV has been suggested as a key mechanical divergence underlying sex differences in OT (32). Namely, similar sex differences in LVEDV and SV at presyncope to those identified in the present study (20–30% decrements in women vs men) have been previously associated with corresponding differences in OT time (–5 min in women vs men) (32). Unexpectedly, LV volumes (LVEDV, SV, cardiac output) remained elevated prior to presyncope in

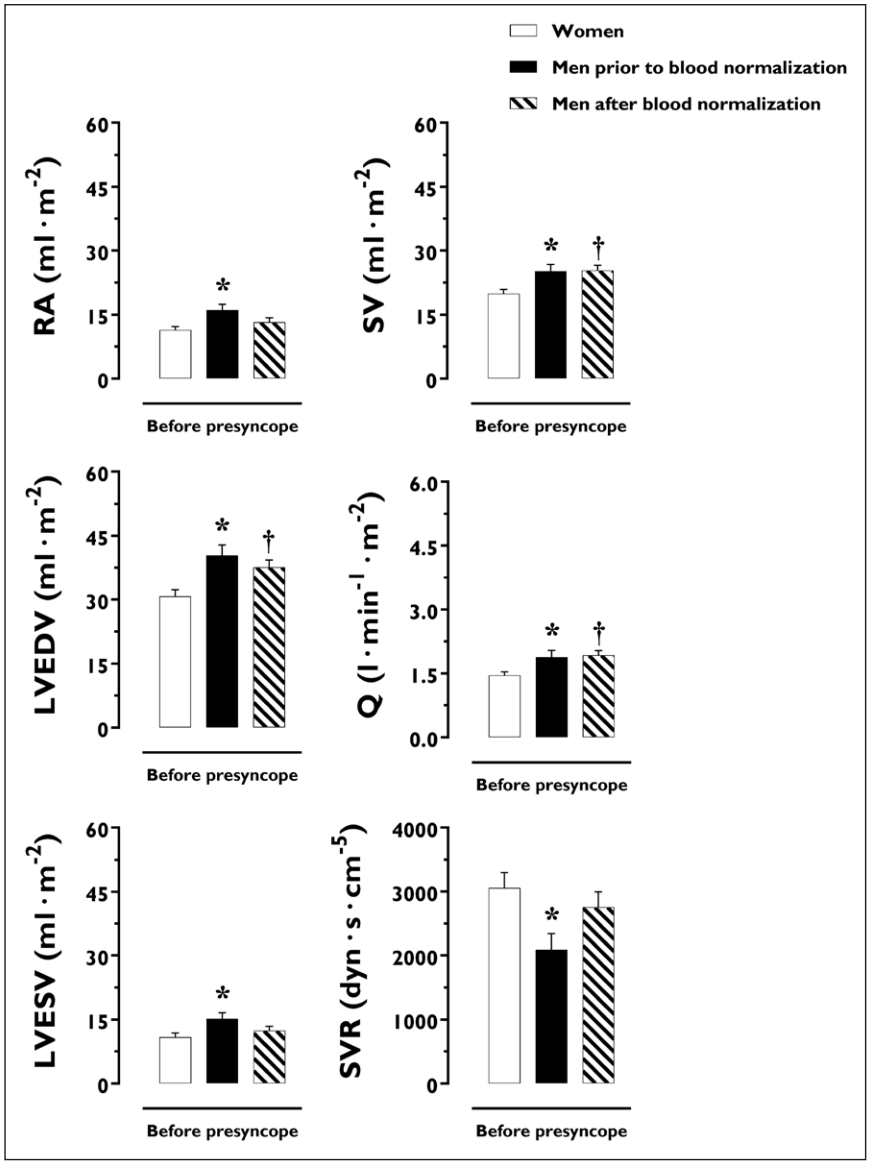

Figure 4. Main cardiac and hemodynamic variables prior to presyncope in women and men prior to and after blood uniformization. *$p < 0.05$ between women and men prior to blood uniformization. †$p < 0.05$ between women and men after blood uniformization. Data are expressed as mean ± SEM. LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, Q = cardiac output, RA = right atrial, SV = stroke volume, SVR = systemic vascular resistance.

men after blood uniformization (Fig. 2). In this respect, the matching of blood oxygen carrying capacity between women and men generally involves a ~10% reduction of effective hemoglobin concentration in the latter (33, 34), which entails a relative state of hypoxia and compensatory vasodilation (16, 35). Accordingly, reduced oxygen carrying capacity may have facilitated peripheral blood flow in men after blood uniformization, concurring with previous studies combining hypoxia and orthostatic stimuli (36). Yet, in those men that could not complete the orthostatic test due to presyncope, blood uniformization induced an increase in SVR reaching the values observed in women (Fig. 4). This was accompanied by a decrease in LVESV also matching women's level, plausibly reflecting augmented ventricular contractibility (37). Hence, certain peripheral and central responses under autonomic control were comparable between sexes after blood uniformization in individuals experiencing presyncope. These findings suggest that hematological determinants of OT interact with central and peripheral sympathetic activation, both being generally lower in women compared with men presenting with intact hematological variables (38, 39). In addition, sex differences in intrinsic peripheral vascular functions (e.g., vascular capacitance, compliance) to a given LBNP stimuli have been previously identified and could contribute to central hemodynamic responses (40–42). Further experimental research is needed to elucidate the independent role of sex differences in the sympathetic reserve and vascular function during orthostatic challenges.

Consideration shall be given to the administration of CO in the present study. The use of CO to experimentally manipulate blood oxygen carrying capacity has deep roots in human physiology (16, 43–45). CO rebreathing resulting in up to 18% decrements in oxygen carrying capacity does not alter hematological (blood pH, bicarbonate, electrolytes, hemoglobin concentration) and biophysical (temperature) characteristics of blood (16). As predicted, proportional reductions in oxygen carrying capacity and aerobic capacity are found after CO rebreathing in healthy individuals (45, 46). The CO administered essentially remains in the circulation and even in the presence of large hemodynamic alterations, there is no diffusion into the tissue (16). In this line, the hemodynamic (vasodilatory- and perfusion-related)

effects of reduced blood oxygen content induced by low oxygen breathing (hypoxic hypoxia) are similar to those elicited by CO-mediated hypoxia (16). In fact, hypoxia, per se, do not substantially alter blood pressure responses to high LBNP (–30 to –50 mm Hg) or head-up tilt in normobaric conditions in healthy women and men (47, 48). Collectively considered, the reduction of oxygen carrying capacity via CO is not deemed to compound the intrinsic consequences of hypoxia in men (49). Molecular investigations will be needed to unravel sex-specific signaling pathways linking oxygen carrying capacity with hemodynamic regulation and OT (23).

Healthy individuals were included in order to limit the influence of disease-related confounding factors. Whether the present findings can be extrapolated to particular pathologic conditions will need to be determined by further experimental and clinical investigations. Second, the investigators that performed the analyses, but not the study participants, were blinded to the experimental condition. Provided that a blinded intervention for phlebotomy and CO rebreathing could be successfully implemented, the main outcomes of the study are not thought to be altered by an hypothetical nocebo effect when standard signs and symptoms of presyncope are strictly observed (50). Finally, the potential effects of blood withdrawal on neurohormonal compensating mechanisms were not assessed in the present study.

CONCLUSIONS

The present study indicates that blood uniformization between men and women largely eliminate differences in OT. The match of BV and oxygen carrying capacity between sexes was not paralleled by that of main cardiac outcomes. In contrast, prior to presyncope, a similar SVR level was detected in both sexes after blood uniformization, suggesting the interplay of blood with autonomic responses determining OT. Further studies are needed to unravel the blood-dependent signaling pathways determining sex differences in OT throughout the lifespan.

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Dr. Montero involved in conception and design of experiments. All authors involved in collection, analysis, and interpretation. All authors involved in drafting the article or revising it critically for important intellectual content.

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All data relevant to this study are presented in the article.

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