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Gender differences in autonomic cardiovascular regulation: spectral, hormonal, and hemodynamic indexes

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Evans, Joyce M., Michael G. Ziegler, Abhijit R. Patwardhan, J. Blaine Ott, Charles S. Kim, Fabio M. Leonelli, and Charles F. Knapp. Gender differences in autonomic cardiovascular regulation: spectral, hormonal, and hemodynamic indexes. *J Appl Physiol* 91: 2611–2618, 2001.—The autonomic nervous system drives variability in heart rate, vascular tone, cardiac ejection, and arterial pressure, but gender differences in autonomic regulation of the latter three parameters are not well documented. In addition to mean values, we used spectral analysis to calculate variability in arterial pressure, heart rate (R-R interval, RRI), stroke volume, and total peripheral resistance (TPR) and measured circulating levels of catecholamines and pancreatic polypeptide in two groups of 25 ± 1.2-yr-old, healthy men and healthy follicular-phase women (40 total subjects, 10 men and 10 women per group). *Group 1* subjects were studied supine, before and after β- and muscarinic autonomic blockades, administered singly and together on separate days of study. *Group 2* subjects were studied supine and drug free with the additional measurement of skin perfusion. In the unblocked state, we found that circulating levels of epinephrine and total spectral power of stroke volume, TPR, and skin perfusion ranged from two to six times greater in men than in women. The difference (men > women) in spectral power of TPR was maintained after β- and muscarinic blockades, suggesting that the greater oscillations of vascular resistance in men may be α-adrenergically mediated. Men exhibited muscarinic buffering of mean TPR whereas women exhibited β-adrenergic buffering of mean TPR as well as TPR and heart rate oscillations. Women had a greater distribution of RRI power in the breathing frequency range and a less negative slope of ln RRI power vs. ln frequency, both indicators that parasympathetic stimuli were the dominant influence on women's heart rate variability. The results of our study suggest a predominance of sympathetic vascular regulation in men compared with a dominant parasympathetic influence on heart rate regulation in women.

catecholamines; spectral power; stroke volume; peripheral resistance; atropine; propranolol; autonomic balance; skin perfusion; arterial pressure; heart rate

BALANCE BETWEEN SYMPATHETIC and parasympathetic tone is a significant component of cardiovascular regulation. Changes in autonomic balance may accompany natural development processes as well as the onset of some diseases. Therefore knowledge concerning such changes may provide important information about health. Spectral power associated with heart rate oscillations, expressed as R-R interval (RRI) variability, is the tool most frequently used to demonstrate differences in autonomic balance in human regulation of heart rate as a function of age (17, 20, 23), smoking history (20), exercise history (4, 10, 25), and presence of chronic cardiovascular disease (14, 27). Measures of autonomic regulation include high- (breathing) frequency (HF; parasympathetic index) and low-frequency (LF; sympathetic index) spectral powers of RRI as well as ratios between LF and HF powers (indexes of autonomic balance). From these studies, a consensus has emerged implicating diminished parasympathetic control of heart rate as a contributor to increased risk of cardiovascular incidents: aging, smoking, lack of routine exercise, and a diagnosis of coronary artery disease are characterized by either lower values of HF (0.15–0.45 Hz) spectral power of RRI, higher values of LF (0.04–0.15 Hz) spectral power of RRI, or increased ratio of low to high power compared with values from their respective control groups (4, 10, 14, 17, 20, 23, 25, 27).

Studies of gender differences in autonomic regulation indicate that women demonstrate significantly greater HF RRI spectral power than do age-control men (10, 18, 23, 25). Indications of enhanced parasympathetic input to cardiac regulation appear to be not only greater in women but also protective during periods of cardiac stress; i.e., in response to brief coronary occlusions, indexes of vagal activation were greater and incidences of ventricular ectopy were less in women compared with men (1).

In addition to parasympathetic dominance in control of heart rate, women demonstrated lower, low-frequency spectral power of muscle sympathetic nerve activity and arterial blood pressure (AP) than men of the same age (2, 19). These results, together with epidemiologic studies, led us to hypothesize that a

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significant component of women's cardiovascular advantage over men may result not only from greater relative parasympathetic input to the heart but also from lesser sympathetic input to vascular regulation (2, 17, 19, 23).

Because the autonomic balance of vascular regulation in men and women is basically undetermined, we monitored hormonal indexes of autonomic activity simultaneous with mean values and spectral power indexes of arterial pressure (AP), heart rate, stroke volume (SV), total peripheral resistance (TPR), and skin perfusion in normal young men and women. Subjects were studied supine, before and after β- and muscarinic autonomic blockades administered singly and together on separate days of study.

METHODS

Subjects

We studied two groups of subjects, each group consisted of 10 young women in the follicular phase of the menstrual cycle and 10 young men. Each subject in *group 1* was studied twice, 1 mo apart, to allow time for drug effects to dissipate. Data were taken once from an additional 10 men and 10 women (*group 2*) while supine and drug free for gender comparisons of skin perfusion and absolute values of catecholamine levels (absolute values of catecholamines in *group 1* men were questionable because of thawing of stored samples). All subjects were healthy, nonobese volunteers whose blood pressures at screening were in the second and third quartiles of blood pressure distribution for their age. Table 1 lists gender, anthropometric, racial, and exercise characteristics for each group. All subjects gave written consent to this protocol approved both by the local Institutional Review Board and by the Advisory Committee of the General Clinical Research Center (GCRC).

Experimental Protocol

Subjects were admitted to the GCRC at the University of Kentucky on the evening before each study. At 7:00 AM, a venous catheter (Jelco, 20 gauge) was placed in an antecubital vein. Subjects were then given a no-fat, low-protein breakfast and walked for the next 20 min. When the subjects returned to the GCRC, electrical impedance leads were attached to monitor electrocardiogram (ECG), SV, cardiac output (CO) and end-diastolic volume (BoMed, Cardiodynamic Monitor). Beat-to-beat AP was measured by finger cuff (Finapres, Ohmeda) and skin perfusion of the palm of the hand by laser Doppler (Perimed). Beat-by-beat calculations of TPR were made from the ratio AP/CO.

Table 1. *Anthropometric, ethnic and exercise characteristics of study volunteers*

	Group 1		Group 2	
	10 Men	10 Women	10 Men	10 Women
Age, yr	24.9 ± 0.8	25.2 ± 0.7	25.2 ± 1.0	26.5 ± 1.3
Weight, kg	73.5 ± 1.8	66.2 ± 2.5*	77.6 ± 3.4	70.9 ± 2.9*
Height, m	175 ± 1.4	162 ± 2.1*	178.8 ± 1.8	166.8 ± 2.7*
Body surface area, m^2	1.89 ± 0.02	1.69 ± 0.03*	1.88 ± 0.02	1.71 ± 0.02*
Ethnicity	8 White 2 Asian	9 White 1 Asian	7 White 3 Asian	7 White 3 Black
Exercise, h/wk	4.5 ± 0.7	3.5 ± 0.7	4.2 ± 0.5	3.2 ± 0.6

Values are means ± SE. *Men's values significantly greater than women's, $P < 0.05$.

Autonomic Blockades (Group 1)

Before β-blockade, a bolus injection of isoproterenol (1, 2 or 5 μg) sufficient to evoke a >15 beat/min increase in heart rate was given. Propranolol was then infused in 0.025 mg/kg increments up to 0.2 mg/kg or until the same dosage of isoproterenol given above failed to increase heart rate. β-Blockade was tested periodically, and subsequent dosages of propranolol were administered as needed throughout the experiment. Subjects had muscarinic blockade with atropine sulfate infused in 0.005 mg/kg increments up to 0.04 mg/kg or until the subsequent dose failed to produce a change in heart rate. After the atropine, a 20-min period to allow for recovery from excess vagal tachycardia was observed before data collection (9, 23). Subsequent recovery of respiratory sinus arrhythmia or a decrease in heart rate was used to indicate the need for additional dosages of atropine. This usually resulted in an additional dosage of ~0.02 mg/kg atropine given ~1 h after the original dosage. The order of administration of propranolol and atropine was alternated in each subject. Whichever drug was given first on the first day of study was given last on the second day of study. Because women were studied in the follicular phase of their menstrual cycle, the two study days were separated by a month.

Hormonal Assays

Ten milliliters of blood were drawn during the last 2 min of each 20-min period of supine rest and were immediately spun in a refrigerated centrifuge. Plasma was extracted and frozen until subsequent delivery to the laboratories that performed the assays. Plasma norepinephrine and epinephrine (to assess sympathetic activity) were determined by Dr. Michael Ziegler, Department of Medicine, University of California, San Diego, CA by using radioenzymatic assay with a sensitivity of 6 pg/ml and an intra-assay coefficient of variation of 13% (15). Pancreatic polypeptide (PPP; to assess parasympathetic activity) was determined by Dr. George Greeley, Department of Surgery, University of Texas, Galveston, TX (28).

Data Analysis

The analysis of hemodynamic data included mean levels of each variable averaged over each 20-min supine rest period. After verification of finger cuff pressure measurement with arm cuff measurement, servo adjustments of the finger cuff were stopped for the 20 min of data recording. The spectral contents of each variable were computed by use of two nonparametric techniques: spectral power is reported as total power and power in specific frequency ranges, Welch technique (21). Fractal and harmonic powers in the same specific frequency ranges were computed by using the coarse graining spectral analysis technique reported by Yamamoto and Hughson (31).

Spectral estimation. All signals were digitized on-line at the rate of 200 samples/s. A computer program was used to detect peaks of the R-wave in the ECG, from which RRIs were computed (22). All other variables were processed synchronous with the cardiac rhythm; the AP signal was integrated with each cardiac cycle to obtain beat-to-beat mean blood pressure. Artifacts were filtered from the original time series as necessary. Because information regarding auto-

Table 2. *Unblocked catecholamine and pancreatic polypeptide levels of study subjects*

	Group 1		Group 2	
	10 Men	10 Women	10 Men	10 Women
Epinephrine, pg/ml		7.7 ± 1	22.7 ± 4.2†	9.9 ± 1.4
Norepinephrine, pg/ml		153 ± 11	171 ± 14	162 ± 14
Pancreatic polypeptide, pg/ml	57 ± 3*	43 ± 4		

Values are means ± SE. Men's values significantly greater than women's: *$P < 0.05$, †$P < 0.01$.

nomic regulation is contained in frequencies below 0.5 Hz, we low-pass filtered and resampled the resulting piecewise constant time series at the rate of 5 samples/s. New time series of the remaining variables, either measured or calculated, were constructed from the beat-to-beat values, similar to RRI and blood pressure time series. Artifacts and premature ventricular contractions in the beat-to-beat series were removed by use of linear interpolation between the data preceding and succeeding these periods. Spectral information from the 20-min data record was computed from 200-s segment (50% overlap) averages.

Recent evidence suggests that the self-similar or fractal component of the variability in heart rate may be a more sensitive indicator of changes in underlying physiological function (5). We assessed the fractal component of the total variability in heart rate and other variables using the coarse graining spectral analysis algorithm of Yamamoto and Hughson (31). Fractal variability was computed from the cross-spectrum estimated between the time series and its rescaled sample. Contributions from harmonically related components were reduced by orthogonalizing the phases of individual segments. The fractal component was subtracted from total spectral variability to yield a better estimate of the harmonic content for comparison with spectral estimates.

Spectra from heart rate displayed distribution of power in three frequency regions, centered about 0.03 Hz (very low frequency; VLF), 0.1 Hz (LF), and 0.25 Hz (HF). Hence, spectral powers of all variables were binned into three regions encompassing these spectral peaks. The VLF, LF, and HF bandwidths were selected as 0.006–0.07 Hz (VLF), 0.07–0.15 Hz (LF), and 0.15–0.45 Hz (HF). Spectral powers were computed by integrating the spectrum within the VLF, LF, and HF bandwidths.

Statistical analysis. A two-factor, repeated-measures ANOVA was used on each cardiovascular variable to assess effects of level of blockade (unblocked, β-, muscarinic, and combined), gender differences, and blockade-gender interactions. Catecholamine and PPP levels, anthropometric data, and spectral power of skin perfusion were compared by *t*-test.

RESULTS

Subjects

Anthropometric, ethnic, and exercise characteristics of the study volunteers are given in Table 1. In both groups, men's height, weight, and body surface area were significantly greater than women's. Age, exercise history, and blood pressures at screening were not different between men and women.

Hormonal Assays

Epinephrine. In the unblocked state, men had higher ($P < 0.01$) levels of epinephrine at rest than did women (Table 2). Propranolol increased ($P < 0.002$) epinephrine levels in all women and in all but one man; the average increase in epinephrine was 16.7 ± 4.1 pg/ml.

Norepinephrine. There was no gender difference in norepinephrine levels, nor was there a significant norepinephrine response to β- or muscarinic blockade in either men or women (not shown).

PPP. Men had greater unblocked resting values of PPP than did women ($P < 0.05$; Table 2). Muscarinic blockade lowered men's resting PPP to the same level (41 ± 8 pg/ml) as women's (40 ± 4 pg/ml). β-Blockade had no significant effect on PPP.

Mean Values

Hemodynamic means ± SE for *group 1* men and women at each level of autonomic blockade are given in Table 3: *day A* consisted of 20-min segments of data taken before muscarinic blockade, after muscarinic blockade, and after the addition of β-blockade to muscarinic blockade, and *day B* consisted of 20-min segments of data taken before β-blockade, after β-blockade, and after the addition of muscarinic to β-blockade. There were no significant gender differences for resting mean values of any variable in the unblocked state. In

Table 3. *Hemodynamic variables for the 10 men and 10 women of group 1*

Day and Blockade State	Arterial Pressure, mmHg		Heart Rate, beats/min		Peripheral Resistance, mmHg·l^{-1}·min		Stroke Volume, ml	
	Men	Women	Men	Women	Men	Women	Men	Women
A								
Premuscarinic	82.6 ± 3.9	78.2 ± 2.0	59.6 ± 2.5	63.9 ± 3.1	13.1 ± 0.2	12.1 ± 1.1	116.5 ± 11.2	106.8 ± 7.3
Muscarinic	100.6 ± 7.1*	88.1 ± 3.0*†	87.9 ± 3.9*	92.6 ± 2.6*	16.2 ± 1.5*	12.9 ± 0.9	76.5 ± 7.7*	77.9 ± 6.0*
Musc + beta	89.1 ± 4.3*	84.4 ± 2.4	71.4 ± 2.2*	77.1 ± 1.9	15.5 ± 1.7	12.8 ± 1.2	89.2 ± 9.6	91.9 ± 6.7
B								
Prebeta	86.8 ± 2.9	80.5 ± 1.4	60.0 ± 2.1	65.3 ± 2.3	14.5 ± 1.7	11.2 ± 1.1	110.6 ± 10.7	118 ± 8.5
Beta	84.3 ± 4.7	83.6 ± 1.7	55.1 ± 2.3*	56.7 ± 2.7*	14.8 ± 1.4	14.2 ± 1.7*	110.1 ± 7.0	112.1 ± 7.6
Beta + musc	86 ± 3.8	80.3 ± 1.4	83.7 ± 2.8*	83.7 ± 2.2*	14.8 ± 1.6	11.4 ± 1.0*	75.7 ± 6.2*	89.8 ± 7.0

Values are means ± SE. Each subject was studied on 2 days (~1 month apart): on *day A,* muscarinic blockade (musc) preceded β (beta) blockade; on *day B,* β-blockade preceded muscarinic blockade. *Day A* and *day B* were alternated for subjects. †Significant gender difference in the same blockade state ($P < 0.05$). *Significant change from the preceding blockade state ($P < 0.05$).

addition, HR responses to combined muscarinic and β-blockades indicated that intrinsic heart rates were not different between men and women. There were, however, several significant ($P < 0.05$) gender-by-blockade interactions: muscarinic blockade increased AP and TPR more in men than in women, whereas β-blockade increased TPR in women with no effect in men. In addition to data contained in Table 3, β-blockade decreased CO by 12 ± 2% in women ($P < 0.05$) without a significant effect in men.

Spectral Power (Welch Spectra)

Variability in heart rate. Resting, averaged, unblocked spectral power of RRI was not different between men and women in any frequency region (Fig. 1*A*). β-Blockade increased spectral power in LF (0.07–0.15 Hz, $P < 0.05$) and HF (0.15–0.5 Hz, $P < 0.001$) ranges in women but not in men. The VLF peak was significantly increased by β-blockade in women but, when averaged over the frequency range, was not significantly different from that of β-blocked men. In all cases, muscarinic blockade reduced RRI power to nearly zero ($P < 0.005$). Data for muscarinic blockade alone and combined muscarinic plus β-blockade states were similar to the combined β-plus muscarinic blockade results shown here. In the unblocked state, (VLF+LF)/HF was significantly greater in men than in women ($P < 0.02$, Table 4).

Variability in TPR. Resting, averaged spectral power of TPR for the same subjects in the same three stages of autonomic blockade is shown in Fig. 1*B*. Women had significantly less spectral power of TPR than men ($P < 0.003$ in all frequency ranges). Similar to HR, β-blockade increased LF and HF power in women ($P < 0.05$) but not in men. The addition of muscarinic blockade to β-blockade resulted in decreased LF ($P < 0.04$) and HF ($P < 0.008$) spectral powers of TPR in women.

Variability in AP. Women exhibited a greater percentage of spectral power in the higher frequency range (HF/Total, $P < 0.02$) because of less spectral power in the lower frequency ranges. Neither blockade had significant effects (data not shown).

Variability in SV. Resting, averaged spectral power of SV for the same subjects in the same three stages of blockade is shown in Fig. 1*C*. As with TPR and AP, women had less spectral power than men; these levels were significantly lower in the LF ($P < 0.01$) and VLF ($P < 0.003$) ranges. The addition of muscarinic blockade decreased spectral power ~60% in LF ($P < 0.01$) and VLF ($P < 0.002$) ranges in men. β-Blockade had no significant effect on SV power for either men or women.

Variability in skin perfusion. Unblocked resting spectral power of perfusion of the skin is shown for *group 2* subjects in Fig. 2. The peak value of unblocked skin perfusion spectral power was sixfold greater in men than in women ($P < 0.01$). This spectral peak occurred between 0.01 and 0.03 Hz in all subjects. Relative contributions/modulations from β- and muscarinic activity were not assessed in this group of subjects.

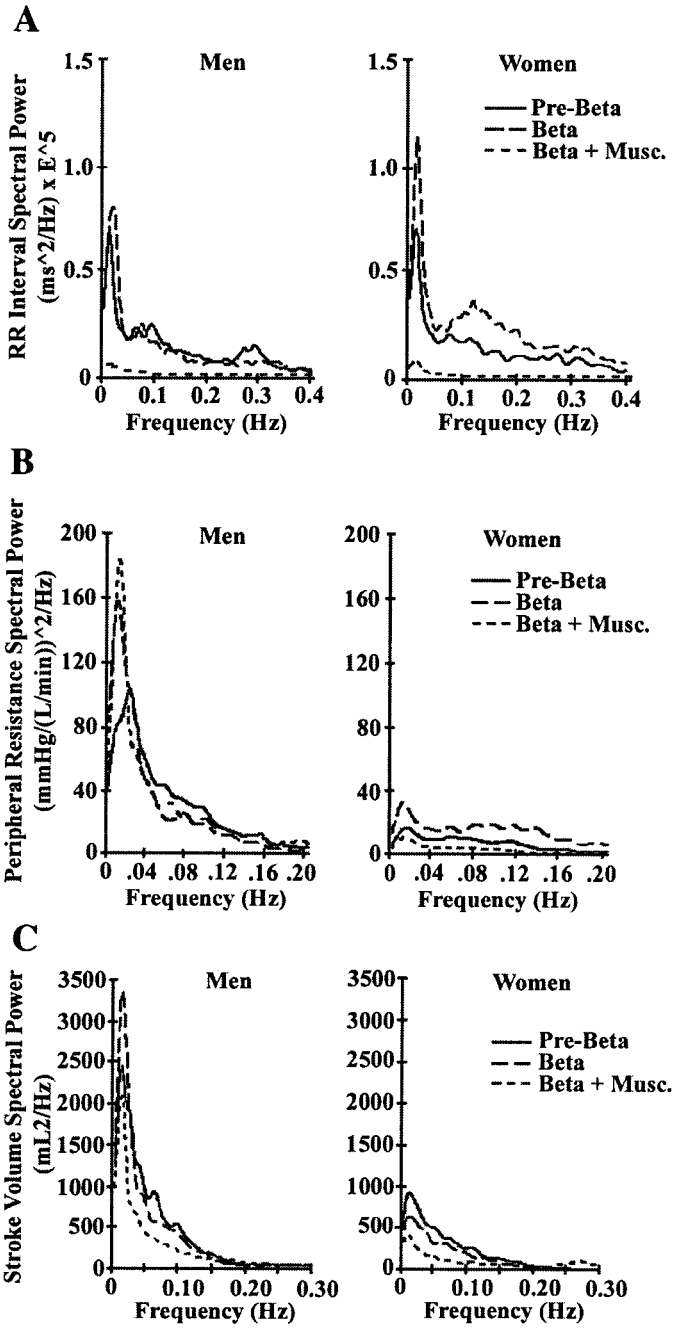

Fig. 1. *A*: resting R-R interval spectral power (Welch technique) averaged for 10 men and women of *group 1*. Data presented are for pre-β, β, and β plus muscarinic (Musc.) blockade states. See text and Table 4 for statistical results. *B*: averaged resting peripheral resistance spectral power (Welch technique) for the 10 men and women of *group 1*. Data presented are for pre-β, β, and β plus muscarinic states. See text for statistical results. *C*: resting stroke volume spectral power (Welch technique) for the 10 men and women of *group 1*. Data presented are for pre-β, β, and β plus muscarinic states. See text for statistical results.

Spectral Power (Coarse Graining Analysis)

The only variable for which Welch techniques did not indicate a robust gender difference was RRI. We therefore attempted to increase the sensitivity of our assay by applying coarse graining techniques to separate

Table 4. *Resting heart rate and heart rate spectral power in 10 men and 10 women*

	Unblocked		Blocked	
	Men	Women	Men	Women
Mean heart rate, beats/min	60.6 ± 2.1	65.6 ± 2.8	77.8 ± 2.5*	80.7 ± 2.0*
	Welch spectral results			
Total	23.7 ± 6.76	19.4 ± 5.54	1.95 ± 0.51*	1.55 ± 0.40*
VLF (<0.07 Hz)	8.08 ± 1.73	5.03 ± 1.20	1.17 ± 0.30*	0.96 ± 0.21*
LF (0.07–0.15 Hz)	8.33 ± 2.05	6.45 ± 1.87	0.63 ± 0.20*	0.47 ± 0.17*
HF (0.15–0.5 Hz)	7.28 ± 3.55	7.86 ± 2.64	0.15 ± 0.04*	0.15 ± 0.04*
HF/Total	0.25 ± 0.04	0.33 ± 0.04	0.10 ± 0.01*	0.19 ± 0.08*
(VLF + LF)/HF	4.30 ± 1.07	2.92 ± 1.03†	12.2 ± 1.90*	9.20 ± 1.20*
	Coarse graining results			
Fractal power				
Total	1,258 ± 228	925 ± 184	123 ± 38*	125 ± 41*
%	72 ± 2	69.0 ± 1	68 ± 3	65 ± 5
Slope (ln power vs. ln frequency)	−1.04 ± 0.08	−0.77 ± 0.06†	−1.56 ± 0.06*	−1.47 ± 0.04*
Harmonic power				
VLF (<0.07 Hz)	160 ± 23	154 ± 56	46 ± 13*	39 ± 12*
LF (0.07–0.15 Hz)	124 ± 28	95 ± 23	18 ± 6*	10 ± 4*
HF (0.05–0.5 Hz)	176 ± 65	174 ± 36	4 ± 1*	4 ± 1*
HF/Total	0.07 ± 0.01	0.13 ± 0.01†	0.024 ± 0.004*	0.035 ± 0.006*†
(VLF + LF)/HF	5.5 ± 1.4	1.85 ± 0.3†	19.2 ± 4.2*	15.8 ± 4.0*

Values are means ± SE. VLF, LF, and HF, very low, low, and high frequency, respectively. Values for Welch spectral and coarse graining results are in arbitrary units. Unblocked data are preblockade values averaged over both days of study. Blocked data are averages of combined muscarinic and β-blockades for both days of study. *Significant effect of blockade; †significant difference between men and women, $P < 0.02$.

fractal from harmonic components of HR spectra. Mean values of heart rate, Welch spectral results, and fractal and harmonic components of RRI for unblocked and blocked subjects from *group 1* are given in Table 4. From the fractal analysis, we determined that women had a less steep slope of fractal power vs. frequency than did men. Harmonic analysis indicated higher values of the parasympathetic index (HF/total) and lower values of the sympathetic index (VLF+LF)/HF in women compared with men. Combined blockade changed each spectral power index, but the gender difference in the proportion of power in the HF range was maintained after combined blockade.

DISCUSSION

Men and women demonstrated statistically significant differences in indexes of sympathetic and parasympathetic autonomic activity. Men had higher resting levels of epinephrine and greater spectral power associated with cardiac ejection, TPR, heart rate, and skin perfusion, indicating greater sympathetic activity in regulation of blood flow as well as heart rate. Women had markers of parasympathetic dominance in the regulation of heart rate (spectral indexes). Women's β-adrenergic activity buffered peripheral vascular variability, and muscarinic activity was the major source of women's heart rate variability. In men, muscarinic activity contributed more than half of SV variability, but served to buffer mean AP and TPR as well as HF TPR variability.

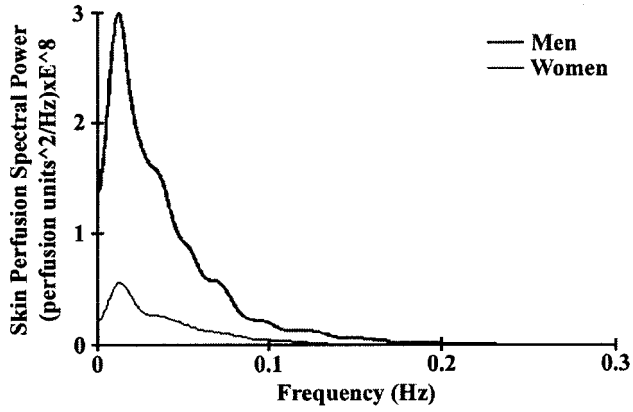

Fig. 2. Averages of unblocked, resting skin perfusion spectral power for the 10 men and women of *group 2*. See text for statistical results.

Sympathetic Indexes

Kennedy and Ziegler (15) found a highly significant, within-subject correlation of TPR with plasma norepinephrine in supine resting men and women of the same age group as those of the present study. Our study finds significantly higher levels of epinephrine and slightly higher levels of norepinephrine, mean blood pressure, and mean TPR in men than in women. The overall low levels of catecholamines in both genders, however, indicated that the blood samples were acquired from subjects in a nonstressed state and are therefore representative of resting values.

Spectral power was a sensitive indicator of gender differences in variables other than heart rate. Total power and/or lower (0–0.15 Hz) frequency power of TPR, SV, heart rate, and skin perfusion were significantly elevated in men compared with women. Spectral power of TPR in men was more than double that of women, and neither β- nor muscarinic blockades diminished TPR power. This gender effect was clear in

both modes of measurement: laser Doppler (skin perfusion) and thoracic impedance (SV, TPR, and CO). α-Adrenergic-mediated vasoconstriction seems the most likely source of this difference, although neuropeptide Y, endothelin, intrinsic vascular tone, and low-frequency modulation of respiratory activity are other possibilities.

β-Blockade increased mean values and LF and HF spectral power of TPR in women but not in men. This increase in TPR variability suggests that tonic β-adrenergic buffering of α-adrenergic vasomotion and/or vasoconstriction may be a significant component of blood pressure regulation in women but not in men (8, 16). Similar to the women's response to β-blockade, muscarinic blockade increased HF power of TPR, mean TPR, and mean AP in men, indicating that tonic muscarinic activity buffered men's peripheral vasoconstriction. In addition, a significant portion of SV variability in men was due to muscarinic activity. Interactions between autonomic branches in the regulation of TPR and SV was not totally unexpected because we previously demonstrated that β-adrenergic and muscarinic vasodilation buffered α-adrenergic-induced increases in mean blood pressure in dogs (6, 7).

Our unblocked men had significantly greater RRI values of (VLF+LF)/HF than did women (both Welch and coarse graining techniques), thereby supporting results from other studies that showed that the balance of autonomic input regulating heart rate was shifted toward sympathetic dominance in men compared with women (17, 18). It has been suggested that this sympathetic dominance of male cardiovascular control could contribute to earlier cardiovascular disease in men (12).

Parasympathetic Indexes

Women had *1*) significantly greater distribution of RRI power in the HF region as well as *2*) a less negative slope of ln RRI power vs. ln frequency. These indexes, derived after separation of fractal from harmonic components of spectral power, have previously been interpreted as markers of parasympathetic influence (32). Other analysis techniques determined a greater ratio of HF to LF power (17, 26, 27) and an increased complexity of RRI dynamics in women compared with men (26). Results from these studies were also interpreted as indications of parasympathetic dominance in the regulation of HR in women compared with men.

The hormonal index of parasympathetic influence, PPP, was higher in our men, and mean heart rate was slightly lower in our women, both previously reported (3). What at first appears to be a dichotomy between the hormonal and mean value indexes compared with the spectral indexes disappears, however, if men's higher sympathetic activity was balanced by increased parasympathetic activity to prevent increased heart rate. It also supports the concept that total power is probably an index for overall neural control of heart rate whereas ratios of power are most useful as measures of autonomic balance.

Harmonic And Fractal Indexes

Other laboratories have determined that decomposing RRI spectral power into its harmonic and fractal components increases the ability to interpret autonomic input to heart rate regulation (5, 30, 32). In studies from these laboratories, atropine increased mean HR, decreased HF harmonic power, and increased the slope of ln RRI power vs. ln frequency (32), whereas β-blockade had no effect on fractal power indexes and increased the ratio of LF to HF harmonic power (31). Our results are similar; we found that both fractal and harmonic components of RRI power were predominately a function of autonomic muscarinic activity. After muscarinic blockade, fractal power decreased by an order of magnitude, and harmonic power in each frequency range was decreased, ranging from a factor of 6 for VLF power to 40 for HF power with no difference between men and women.

Coarse graining the data to separate harmonic from fractal components enhanced detection of gender-related differences in autonomic regulation of heart rate. Neither raw power nor ratios of raw spectral power (Welch) were specific enough to establish gender differences in parasympathetic regulation in this small group of subjects even though this technique has been reported to be sufficient for larger groups (2, 17, 23).

Limitations

This study involved only young, healthy subjects. Autonomic influences change with age, so further studies, particularly in older age groups, should be carried out. In addition, our data were taken from supine subjects and cannot be used to predict gender differences in response to stress; autonomic tone during stress or exercise might be quite different. The baseline conditions of subjects before starting a study is always a concern. For that reason, our subjects spent the night before each study in the GCRC. Before the study, however, we needed to counteract the effects of overnight bed rest and fasting; therefore, subjects in this study simulated ordinary activity by eating a small meal and walking for 20 min. The low levels of catecholamines and PPP indicated that neither the food nor the exercise activated autonomic activity above that normally found in a resting, fasted state. Body size could also be a factor in results, particularly spectral power results. Normalization of spectral power measures by body surface area did not, however, change the significance of gender differences in cardiovascular variables.

Noninvasive measurements, such as impedance cardiography, can be a concern with respect to accuracy of absolute values. We used impedance cardiography to assess changes in SV, CO, and peripheral resistance. Previous studies in our laboratory (11) indicated that

end-diastolic volume determinations from ECG-gated, magnetic resonance images acquired at rest and in response to lower body negative pressure correlated significantly with both impedance ($P < 0.004$) and echocardiographic ($P < 0.03$) determinations. In addition, mean values of SV were not different between men and women, but LF variability about the mean was much greater for men than for women, suggesting that gender differences are not an artifact of impedance measurement. Spontaneous breathing could influence spectral power of SV in the HF range. However, gender differences in SV were most pronounced in the lower frequency ranges, suggesting source(s) other than respiration for this difference. Finally, gender differences in spectral power derived from impedance measurements of flow were supported by spectral power results from independent modalities of flow: laser Doppler (skin perfusion) and ultrasonic Doppler (radial artery flow, not presented).

In summary, hormonal, hemodynamic, and spectral power values of peripheral vascular variables indicated that men exhibited greater autonomic sympathetic activity than did women. Increased male sympathetic activity was pronounced in TPR, SV, and skin perfusion; its effect on heart rate was balanced by increased parasympathetic activity. The balance of autonomic activity in the regulation of heart rate in women was tilted toward parasympathetic dominance. Finally, peripheral vascular autonomic activity had a β-adrenergic component in women and a muscarinic component in men, both of which appeared to be important components in buffering tonic vasoconstriction.

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