Effects of Hypertension and Obesity on the Sympathetic Activation of Heart Failure Patients

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Abstract—Previous studies have shown that congestive heart failure is characterized by sympathetic and reflex dysfunctions. Whether these alterations are potentiated in the presence of obesity and hypertension, two conditions that also display neuroadrenergic abnormalities and markedly increase the risk of heart failure, is unknown. In 14 healthy control subjects (C; age, 55.1±3.0 years; mean±SEM), 13 lean hypertensive subjects (H), 15 obese normotensive subjects (O), 14 lean normotensive subjects with congestive heart failure (CHF, New York Heart Association class II), 14 lean hypertensive subjects with CHF (CHFH), 14 obese normotensive subjects with CHF (CHFO), and 13 obese hypertensive subjects with CHF (CHFOH), all age-matched with C, we measured mean blood pressure (Finapres), heart rate (ECG), and muscle sympathetic nerve traffic (MSNA, microneurography) at rest and during baroreflex testing. Compared with C, body mass index was similarly increased in O, CHFO, and CHFOH, whereas mean blood pressure was similarly increased in HF, CHFH, and CHFOH, and left ventricular ejection fraction (echocardiography) was similarly reduced in CHF, CHFH, CHFO and CHFOH. Compared with C, MSNA was significantly increased in O, H, and CHF (43.0±2.2 versus 54.1±2.8, 53.1±2.5, and 57.4±2.8 bursts/100 heart beats, P<0.01). When O or H was combined with CHF, the MSNA increase was significantly more pronounced and maximal when O and H were concomitantly associated with CHF. Baroreflex sensitivity was reduced in O and H, with a further reduction in CHF and a minimal value in CHFOH. These data show that the sympathetic activation characterizing CHF is markedly potentiated when O and H alone or combined together are associated with a low cardiac output state and that this may depend on an arterial baroreflex impairment. (Hypertension. 2003;42:873-877.)

Key Words: hypertension, essential ■ obesity ■ congestive heart failure ■ sympathetic nervous system ■ autonomic nervous system ■ baroreceptors

Patients with congestive heart failure are characterized by an increase in sympathetic activity whose magnitude is proportional to the heart failure severity, as assessed by clinic or hemodynamic criteria. They are also characterized, however, by large differences in sympathetic activity at each heart failure severity, the reasons for which are poorly understood. This is an important limitation because in heart failure, sympathetic activity is an independent predictor of death second to few or no other factors.

In the present study, we examined whether the increase in sympathetic activity seen in heart failure states of moderate severity depends on the concomitant presence of two conditions known to stimulate sympathetic activity in absence of heart failure, obesity and hypertension. That is, whether in lean and/or normotensive patients with heart failure, sympathetic activity is less than in patients with heart failure displaying an increase in body weight and/or blood pressure (BP). To this aim, sympathetic nerve activity was quantified by microneurography and plasma norepinephrine (NE) in several groups of age-matched patients who had heart failure of similar severity that differed in the presence or absence of obesity, hypertension, or hypertension and obesity combined. The study included an assessment of the baroreceptor ability to restrain sympathetic nerve traffic because the sympathetic activation typical of all 3 conditions has been frequently ascribed to an impairment of the baroreflex.

Methods

Study Population

The study population consisted of 97 male subjects (age ranging from 51 to 61 years) recruited for this investigation between 1998 and 2002. Recruitment criteria consisted of the presence or absence of (1) congestive heart failure as determined by symptoms and alterations in echocardiographic left ventricular structure and function, (2) hypertension as determined by an elevation in BP values (≥140 mm Hg systolic and/or 90 mm Hg diastolic), and (3) normal body weight (body mass index <25 kg/m²) or obesity (body mass index >30 kg/m²). Subjects were excluded from the study if they had (1) secondary hypertension, (2) atrial fibrillation or other major
cardiac arrhythmias, (3) history of myocardial infarction in the 6 months preceding the study or clinical or laboratory evidence of valvular heart disease, (4) history of smoking and/or excessive alcohol consumption, and (5) major concomitant diseases, such as renal insufficiency, diabetes mellitus, or other conditions known to affect autonomic and cardiovascular control. Subjects were classified as (1) healthy lean normotensive subjects or control subjects (n=14), (2) lean hypertensive subjects (n=15), (3) control subjects or obese normotensive subjects (n=25) provided it was regarded as in New York Heart Association (NYHA) class II and had an only modest (2) lean hypertensive subjects (n=15), and (4) patients with congestive heart failure, with or without hypertension and obesity of either ischemic (n=30) or idiopathic (n=25) nature, provided it was regarded as in New York Heart Association (NYHA) class II and had an only modest reduction in left ventricular ejection fraction (35% to 45%). Control, obese normotensive, and lean hypertensive subjects were studied on an outpatient basis; patients with heart failure were hospitalized. In all subjects, cardiovascular drugs were withdrawn for 6 days before the study except for the maintenance of loop diuretics in patients with heart failure. The study protocol was approved by the ethics committee of our institution. All subjects consented to the study after explanation of its nature and purpose.

Measurements

The methodological details of the procedures used to assess sympathetic nerve activity (MSNA, microneurography), plasma NE and PRA (radioimmunoassay), and plasma renin activity (PRA, radioimmunoassay) have been described in previous reports. Mean blood pressure (MBP) was calculated by adding g/kg per minute, each step being maintained for 5 minutes. In all subjects, the drug initially infused was randomly selected, and the end of the first infusion was separated from the beginning of the second one by a recovery time of 45 minutes. SBP, DBP, MBP, MSNA, and HR were averaged for the 5 minutes before infusion and for the 5 minutes of each step infusion. Baroreceptor modulation of MSNA and HR was estimated by calculating (1) the absolute and the percent changes in integrated activity (ie, mean burst amplitude times burst number over time) and (2) the changes in HR in relation to the BP changes induced by each dose of phenylephrine and nitroprusside. The average ratios between MSNA or HR changes and SBP, DBP, or MBP changes were also calculated and summed together separately for MSNA and HR for the 3 infusions of phenylephrine and nitroprusside. These were taken as the measures of MSNA-baroreflex or HR-baroreflex sensitivity during baroreceptor manipulation.

Protocol and Data Analysis

All subjects came to the laboratory in the morning. They were put in the supine position and fitted with intravenous canulas, microelectrodes for MSNA recording, and other measuring devices. Blood samples for NE and PRA assay were then taken, and BP was measured 3 times with a mercury sphygmomanometer. After a 30-minute interval, BP, HR, respiration rate, and MSNA were continuously measured during (1) an initial 10-minute basal state, (2) the intravenous infusion of one vasoactive drug, (3) a 45-minute recovery period followed by a second 10-minute basal state, and (4) the intravenous infusion of the second vasoactive drug.

Data were collected in a quiet room at a constant temperature of 20°C to 21°C. Data were analyzed by a single investigator unaware of the experimental design. Baseline values of each of the above-mentioned parameters from individual subjects were averaged for each group and expressed as mean±SEM. This procedure was also followed for the changes in BP, MSNA, and HR induced by each dose of vasoactive drugs. Comparisons between data obtained in different groups were made by 2-way ANOVA. The 2-tailed t test for unpaired observations was used to locate between-group differences. The Bonferroni correction was used to account for multiple comparisons. A value of P<0.05 was considered statistically significant.

Results

As shown in the Table, the 7 groups of subjects had a similar mean age. Compared with control subjects, body mass index was similarly increased in the 3 groups of subjects with obesity (obese normotensive patients, patients with obesity and heart failure, and patients with obesity, hypertension, and heart failure), whereas BP was similarly increased in the 3 groups of subjects with hypertension (lean hypertensive patients, patients with hypertension and heart failure, and patients with obesity, hypertension, and heart failure). Compared with control subjects, obese normotensive subjects, and with lean hypertensive subjects, LVEF and LVEDD were similarly reduced and increased, respectively, in the 4 groups of patients with heart failure, who also showed a marked increase in PRA (Figure 1). This was not the case for the markers of sympathetic activity,
However, which showed several between-groups differences. (1) Compared with control subjects, MSNA values were greater in obese normotensive subjects, lean hypertensive subjects, and patients with heart failure. (2) In patients with heart failure, the increase was more pronounced with the concomitance of obesity or hypertension and maximal when both conditions were present. NE values showed a similar trend, although the between-group differences were less frequently statistically significant. In the entire study population, there was a significant although modest direct relation between MSNA and PRA values ($r = 0.31$, $P = 0.02$). This was also the case for NE and PRA ($r = 0.25$, $P = 0.05$).

Figure 2 shows that in all groups of patients, MSNA and HR decreased linearly as MBP increased progressively from the lowest value observed with the greatest nitroprusside dose to the highest value observed with the greatest phenylephrine dose, the 3 hypertensive groups (hypertension alone, hypertension and heart failure, and obesity and heart failure) showing a resetting toward higher BP values compared with 4 normotensive groups (lean normotensive, obesity alone, heart failure alone, obesity and heart failure). Figure 3 shows the changes in MBP, HR, and MSNA induced by phenylephrine and nitroprusside in the 7 groups. Compared with control subjects, for similar MBP changes, the HR responses to arterial baroreceptor stimulation and deactivation were reduced in obese normotensive and lean hypertensive subjects, with a further reduction in patients with heart failure and a minimal value in those in whom heart failure was accompanied by obesity and hypertension. This was the case also for the MSNA responses to arterial baroreceptor manipulation with the exception of lean hypertensive subjects, in which they were no less than those of control subjects. Similar data were obtained when calculation of baroreceptor HR and MSNA sensitivity was performed with the use of SBP, DBP, or MBP as indicators of the stimulus to arterial baroreceptors (Figure 4).

Discussion

The present study shows that in congestive heart failure belonging to NYHA class II, sympathetic activity is increased. Data further show, however, that the increase is greater if patients are hypertensive or obese and that the sympathetic activation is even more pronounced if obesity and hypertension are concomitantly present. Thus, the sympathetic activation that occurs in heart failure depends both on heart failure per se and, to a measurable extent, on conditions such as obesity and hypertension that can induce sympathetic activation before heart failure and that do not lose this effect when heart failure occurs. This has clinical relevance because in heart failure, sympathetic activity has an independent negative relation with death.6–9 To know that this activity is likely to be greater when BP is high.
and/or body weight is above normal thus offers a piece of information of prognostic significance that may help proper assessment (and proper management) of overall risk in a substantial fraction of patients.

Our study does not clarify the mechanisms responsible for the greater sympathetic activation observed when heart failure is accompanied by obesity and/or hypertension. The data obtained, however, allow some possibilities to be ruled out and others to be meaningfully discussed. First, we can rule out that the greater sympathetic activities seen when heart failure was associated with hypertension and/or obesity were due to a greater heart failure severity because (1) patients were only selected if the heart failure condition belonged to NYHA class II and (2) the groups that were compared had similar average values of LVEF and LVEDD. Second, we can rule out that differences in drug treatment were responsible because patient hospitalization allowed withdrawal of drugs that are known to affect sympathetic cardiovascular influences (digitalis, β-blockers, ACE inhibitors, and calcium antagonists) and to uniformly maintain patients on diuretics only. Third, we can rule out that a between-group imbalance of patients with ischemic heart failure versus idiopathic cardiomyopathy was involved because when the heart failure severity is matched, these two conditions do not trigger a different degree of sympathetic activation. Fourth, we can on the other hand suggest that because of its clear-cut sympathostimulating effect, angiotensin II is involved because (1) the increase in resting PRA levels and the impairment of baroreflex ability to modulate MSNA were most pronounced in patients with heart failure with than without obesity and hypertension and (2) in all our subjects, PRA showed a significant albeit limited direct relation with MSNA or NE. We can finally suggest, however, that a more important factor involved in the greater sympathoexcitation seen in patients in whom heart failure was accompanied by hypertension and/or obesity is the arterial baroreflex because the impaired ability of baroreceptors to restrain HR and MSNA, known to account for the neurohumoral activation of heart failure, was more pronounced in presence of obesity and hypertension, reaching its maximum when these two conditions occurred together. It should be emphasized that this leaves open the question of the reasons why the baroreflex is progressively impaired from lean to obese and/or hypertensive patients with heart failure, although we can speculate that a progressive increase in arterial stiffness, on which baroreceptor responses to BP stimuli depend, is responsible. We cannot exclude, however, that factors other than baroreflex impairment are also importantly involved because

Figure 3. Changes in heart rate (ΔHR, expressed as b/min) and muscle sympathetic nerve activity (ΔMSNA, expressed as absolute and percent [%] integrated activity [i.a.]) accompanying stepwise increases and reductions in mean blood pressure (ΔMBP) induced by intravenous infusions of phenylephrine and nitroprusside. Data are shown as mean±SEM in the 7 groups of patients of Figure 1. For symbols and explanations see Figure 1.

Figure 4. Sensitivities of baroreceptor–heart rate and baroreceptor–muscle sympathetic nerve activity expressed as average ratios between changes in heart rate (ΔHR) or muscle sympathetic nerve activity (ΔMSNA) and changes in systolic blood pressure (ΔSBP), diastolic blood pressure (ΔDBP), and mean blood pressure (ΔMBP) in the 7 groups of patients of Figure 1. MSNA is expressed as percent (%) and absolute integrated activity (i.a.). Data are shown as mean±SEM. For symbols and explanations see Figure 1.
Despite different degrees of sympathetic activation, patients with heart failure with hypertension or obesity had similar reduction in baroreflex sensitivity. We can speculate, for example, that since sleep apnea is likely to be progressively more common from control to complicated heart failure conditions,23 chemo-
receptor reflexes play a role.24 In addition, other reflexes (cardiopulmonary reflexes), varying degrees of insulin resistance and insulinemia, and greater or smaller participation of central influences are all possible candidates.16,25–26

A final point should be mentioned, namely that in line with observations made in other conditions or diseases,5,11,13,18 the different degrees of sympathetic activation seen in the four heart failure groups were more clear and consistent when quantification of adrenergic activity was based on MSNA than when an indirect marker such as NE was used. This may be due to the fact that differences are more evident at a regional level, that is, on sympathetic modulation of skeletal muscle districts where direct nerve recording is possible. It is more likely to be accounted for, however, by the greater reproducibility of the direct as compared with the indirect humoral measure.18 The latter may be of particular disadvantage in heart failure in which NE levels are determined in similar amounts by secretion from sympathetic nerve terminals and by tissue clearance of this substance.4,27

Perspectives

The results of the present study show that the sympathetic influences of conditions preceding and favoring heart failure do not vanish as heart failure occurs and that clinical data allow some differentiation of the neurohumoral profile of this disease. This, however, concerns patients with heart failure of moderate severity. Whether more severe heart failure is characterized by a greater degree of sympathetic activation might be less in advanced than in moderate heart failure.

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