Norepinephrine Turnover Is Increased in Suprabulbar Subcortical Brain Regions and Is Related to Whole-Body Sympathetic Activity in Human Heart Failure

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Background—Although it is established that heightened sympathetic drive exists in congestive heart failure (CHF), the reflex processes by which this may occur and the sites in the central nervous system that may be responsible for mediating this process are not yet fully elucidated.

Methods and Results—Eight patients with moderate to severe CHF and 8 healthy control subjects underwent simultaneous arterial and bilateral internal jugular venous blood sampling and cerebral venous blood pool scanning for anatomical determination of the origin of internal jugular venous blood flow. We estimated sympathetic nervous activity by measuring total body norepinephrine (NE) spillover using radiotracer methodology and determined brain NE turnover by measuring the internal jugular overflow of NE and its lipophilic metabolites, 3-methoxy-4-hydroxyphenylglycol and 3,4-dihydroxyphenylglycol. Suprabulbar subcortical turnover of NE was significantly greater in CHF patients than in the healthy group (2.77 ± 0.75 versus 0.66 ± 0.40 nmol/min, P < 0.05). There was a significant positive correlation between suprabulbar subcortical turnover of NE and total body NE spillover (r = 0.62, P = 0.01).

Conclusions—This study, for the first time, demonstrates elevated suprabulbar subcortical noradrenergic activity in human CHF and identifies a positive correlation between this and the level of whole-body NE spillover. The findings suggest that the activation of noradrenergic neurons projecting rostrally from the brain stem mediates sympathetic nervous stimulation in CHF. (Circulation. 2002;105:1031-1033.)

Key Words: heart failure • brain • nervous system, sympathetic • norepinephrine

High sympathetic tone has been correlated with poor outcome in heart failure.1–3 Although the role of the sympathetic nervous system in the pathophysiology of congestive heart failure (CHF) has been established, the nature of the afferent signals and the sites of origin of the efferent signals from the central nervous system that are responsible for the heightened sympathetic tone have not been fully elucidated.

Our group previously demonstrated a positive correlation between pulmonary artery pressures and cardiac norepinephrine (NE) spillover rate in CHF patients. Further, we have shown that a positive correlation exists between brain NE turnover, a measure of central noradrenergic neuronal activity, and cardiac NE spillover rate. These 2 findings combined suggest the existence of a reflex link, consisting of afferent neural traffic from the cardiopulmonary receptors and sympathetic efferent outflow from the brain driven by sympathoexcitatory noradrenergic neurons.

In the present study, our aim was to investigate this reflex further by first attempting to locate better the sites in the central nervous system that are responsible for the efferent signals; in addition, we wished to investigate the relationship between central NE turnover and global sympathetic activity.

Methods

Subject Characteristics

Results from studies performed on 8 CHF patients (aged 51.9 ± 5.6 years) and 8 healthy volunteers (aged 55.3 ± 9.5 years) form the basis for this report. The CHF group had markedly impaired left ventricular function (ejection fraction of 24.5 ± 7.2%). The mean pulmonary capillary wedge pressure in this group was 22.7 ± 1.8 mm Hg. All patients were on standard anti-failure therapy, which consisted of digoxin (n = 8), diuretics (n = 8), and an angiotensin-converting enzyme inhibitor (n = 8). Five CHF patients were also on carvedilol. The healthy control subjects were recruited by advertisement in the general community. The study was performed with the approval of the Alfred Hospital Ethics Review Committee, and all the subjects gave written informed consent.

Catheterization Protocol

All studies were performed in the morning after a light breakfast. After a priming bolus of 12 μCi of 1-[ring-2,5,6-3H] NE (New England Nuclear; specific activity, 40 to 50 μCi/mmol) via a peripheral vein, an infusion was commenced at 0.7 Ci/m²·min to maintain plateau plasma concentrations during the study. To ensure steady-state levels of the isotope, we waited at least 45 minutes after commencing the infusion before performing baseline blood sampling. Under local anesthesia, the radial artery was cannulated (3F, 5cm, Cook) for arterial pressure monitoring and blood sampling. Venous introducer sheaths were placed in the antecubital fossae bilaterally. In the patients with CHF, a pulmonary artery thermodilution...
catheter (7F, Arrow, Arrow International) was advanced under fluoroscopic control to the pulmonary circulation to measure right-sided heart pressures, pulmonary capillary wedge pressure, and cardiac output. Subsequently in these patients and the healthy control subjects, coronary sinus thermodilution catheters (Webster CCS 7/8U 90A, Webster Laboratories) were introduced bilaterally via the antecubital venous sheaths. These were manipulated into both the right and left internal jugular veins (IJV) above the confluence of the facial veins for jugular venous blood sampling and for the determination of jugular blood flow by thermodilution.4-6 The tip of the catheter was placed beyond the mandibular angle, upstream to the point of entry of any venous tributaries from the tissues of the face to minimize contamination of the cerebral venous effluent.

Cerebral Venous Blood Flow Lateralization
Using a technetium-99 cerebral venous sinus scan to delineate the pattern of venous drainage in individual subjects, subcortical and cortical neurotransmitter turnover can be distinguished.6 The usual pattern is for the right IJV to have the superior sagittal sinus as its major tributary and the cerebral cortex as its predominant field of drainage. This we designate the “dominant” or “cortical” IJV. In this situation, the suprabulbar subcortical venous drainage from regions such as the hypothalamus and amygdala is into the left IJV, and we designate this the “nondominant” or “subcortical” IJV (Figure 1). Venous drainage from the medulla oblongata is primarily into the veins of the spinal cord and dural venous sinuses, not the IJVs.6 Sometimes the venous sinus drainage pattern is reversed, with cortical venous drainage into the left IJV. Another normal variant is that the drainage is nonlateralizing, with ready admixture of blood occurring at the confluence of the sagittal and straight sinuses. In this report, only data from subjects with cerebral venous lateralization is presented.

Neurochemical Measures of Sympathetic Activity
Whole-body sympathetic nervous activity was determined by the principle of isotope dilution, as previously described.6 Venous arterial plasma concentration differences combined with IJV flow were used, in accordance with the Fick principle, to determine metabolite spillover from the brain. The central nervous system noradrenergic turnover was estimated by summing the IJV spillover of NE, 3-methoxy-4-hydroxyphenylglycol (MHPG), and 3,4-dihydroxyphenylglycol.4-6

Biochemical Assays
NE, dihydroxyphenylglycol, and MHPG concentrations were measured with high-performance liquid chromatography, according to previous methods.9 Fractions from the effluent containing tritium-labeled NE were assayed by liquid scintillation spectroscopy.

Statistical Analysis
Data are presented as mean±SEM, unless otherwise stated. Data were normally distributed, and statistical analysis was performed using Student’s t test (SigmaStat version 2.03). Relations between continuous variables were examined using the least-squares method of linear regression. P<0.05 was considered statistically significant.

Results
IJV Blood Flow and Its Origin
In the control and CHF groups, 6 of 8 patients had right and 2 of 8 subjects had left cortical drainage, respectively. Internal jugular blood flows were not significantly different between the 2 groups (CHF: cortical, 405±80 mL/min; subcortical, 318±115 mL/min; controls: cortical, 436±60 mL/min; subcortical 284±40 mL/min).

Central Noradrenergic Activity
As presented in Figure 1, suprabulbar subcortical NE turnover was greater in CHF patients than in the control group (2.77±0.75 versus 0.66±0.40 nmol/min; P<0.05). When examining the relationship between cortical and subcortical noradrenergic activity, there was evidence of a significant increase in suprabulbar subcortical noradrenergic activity in CHF (0.64±0.59 versus 2.77±0.75 nmol/min for cortical versus subcortical flow; P<0.05). This relationship did not exist in the control group (1.37±0.54 versus 0.66±0.40 nmol/min for cortical versus subcortical flow; P=NS).

Relationship Between Brain NE Turnover and Peripheral Sympathetic Activity
As presented in Figure 2, when data from the subcortical vein in all 16 subjects was analyzed, a significant positive correlation was
observed between total body NE spillover and suprabulbar subcortical NE turnover ($y=2.12+0.47x; r=0.62, P=0.01$).

**Hemodynamic Correlates of Sympathetic Activity**

Data are available from 8 patients to study the relationship between cardiac filling pressures and central noradrenergic activity. No significant correlation was observed between pulmonary capillary wedge pressure and brain NE turnover in either the cortical or suprabulbar subcortical areas.

**Discussion**

Although the pathophysiological role of the sympathetic nervous system in CHF is widely accepted,1-3 an understanding of the mechanisms responsible for the heightened sympathetic drive remains elusive. Identifying these mechanisms may allow for early therapeutic intervention and ensuing clinical benefit.

Using methodologies such as the retrograde transsynaptic transport of live pseudorabies virus,10 a substantial body of evidence now exists from animal studies showing that groups of NE-releasing neurons in the brain stem and forebrain, assorted into nuclei designated A1 to A7, innervate all levels of sympathetic nervous outflow.11 In humans, techniques to examine central sympathetic function are limited to measuring the overflow of NE and its metabolites from the brain.12 After the demonstration by Maas et al12 that central nervous system neuronal activity of stumptailed monkeys could be studied by direct IJV blood sampling for MHPG, the major central nervous system metabolite of NE, this technique has been applied to humans.4-6 At present, it is the “gold standard” for measuring central noradrenergic activity.

In the present study, NE turnover was increased in the suprabulbar subcortical areas in CHF patients when compared with a healthy, age-matched control group. Furthermore, subcortical NE turnover was significantly greater than in the cortex in CHF, but this differentiation did not exist in the control subjects. In addition, there was a strong positive correlation between suprabulbar subcortical NE turnover and global sympathetic activity.

In the present study, we were unable to demonstrate a correlation between cardiac filling pressures and suprabulbar subcortical brain NE turnover. This was somewhat surprising given the earlier observation in the rat that cardiopulmonary volume afferents project to the noradrenergic nuclei of the locus ceruleus (A6) and the firing rate of locus ceruleus neurons is changed by alterations in cardiopulmonary pressures.13 There are two possible explanations for this observed lack of correlation. First, CHF therapy may distort any relationship that may exist between filling pressures and central monoamine turnover. Second, the sympathetic nervous stimulation in CHF may result from a state of desensitization of low-pressure baroreflexes, thereby forming a basis for withdrawal of tonic inhibition of peripheral sympathetic activity.14

**Conclusions**

This study examines the central origins and regulatory mechanisms underlying the heightened sympathetic drive in human heart failure. We have shown that neuronal NE turnover in suprabulbar subcortical regions of the brain is increased and positively correlated with the level of whole-body NE spillover in human CHF. The findings support the hypothesis that the activation of noradrenergic neurons projecting rostrally from the brain stem mediates the sympathetic nervous stimulation present in CHF.

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