PATHOPHYSIOLOGY AND NATURAL HISTORY

CONGESTIVE HEART FAILURE

Reduced aortocoronary sinus extraction of epinephrine in patients with left ventricular failure secondary to long-term pressure or volume overload

COLIN P. ROSE, M.D., PH.D., JOHN H. BURGESS, M.D., AND DANIEL COUSINEAU, M.D., PH.D.

ABSTRACT Heart failure is associated with a reduction in tissue norepinephrine concentration, catecholamine fluorescence, and tyrosine hydroxylase activity. We hypothesized that this attrition of sympathetic nerve function might also be associated with a reduction in the ability of the neuronal membrane to sequester catecholamines. Since the heart does not release epinephrine, the cardiac extraction of epinephrine should be an index of the membrane uptake system. In 12 patients with documented left ventricular failure (pulmonary edema) secondary to mechanical overload and in 10 patients with no history of heart failure, we measured simultaneous plasma catecholamine concentrations in the aorta, coronary sinus, and femoral vein. The aortocoronary sinus extraction of epinephrine was 43 ± 17% in the group with no evidence of heart failure but 0 ± 14% in the group with failure. Net norepinephrine outflow (release minus extraction) was significantly higher in the group with failure, possibly because of reduced extraction. There was neither a reduction in the ability of the lower limb to extract epinephrine nor an increased norepinephrine outflow from the limb. These findings suggest that the sympathetic neuronal membrane uptake system is also depressed in the failing heart and that if the mechanism of catecholamine sequestration in the heart is related to that in the lower limb, the ablation of sympathetic nerve function is specific to the heart and is not a result of a generalized depression of the peripheral sympathetic nervous system.


HEART FAILURE secondary to mechanical overload is associated with a reversible loss of catecholamine fluorescence around the cardiac myocytes. It has been hypothesized that reduction in myocardial catecholamines is the result of a generalized attrition of the sympathetic nervous system secondary to the increased tonic stimulation associated with the peripheral effects of heart failure. However, while tyrosine hydroxylase activity (the rate-limiting step in norepinephrine synthesis) is reduced in the hypertrophied and failing ventricle, it is not reduced in the stellate ganglia.

In addition to releasing norepinephrine, the sympathetic neurons also take up catecholamines via a highly concentrative membrane transport system. If the attrition of myocardial neurons in heart failure affects all neuronal functions and not just norepinephrine synthesis, then the uptake of catecholamines by the neuronal membrane should also be affected. Since norepinephrine is both released and sequestered by the neurons, a reduction in both functions may not be easily detectable by measuring the steady-state arterial and coronary sinus concentrations, but since epinephrine is only extracted and not released by the peripheral sympathetic system, a reduction in neuronal membrane function might be detectable as a reduction in cardiac epinephrine extraction.

Methods

We studied 23 patients referred to the Montreal General Hospital Cardiac Catheterization Laboratory for evaluation of myocardial function or coronary artery disease (table 1). The patients were divided into two groups before cardiac catheterization. One group consisted of 12 patients with clear evidence of left ventricular muscle failure defined as previous radiographically documented pulmonary edema secondary to significant aortic valve or regurgitant mitral valve disease. Patients with significant coronary artery disease or myocardial infarction were excluded so that the cause of the left ventricular
failure could reasonably be assigned to the mechanical lesions. The other group consisted of 10 patients undergoing cardiac catheterization for valve or congenital heart disease with no previously documented pulmonary edema.

All medications were withheld 24 hr before the study. Premedications for catheterization consisted of oral diazepam or intramuscular meperidine. Although some patients in both groups had previously received digoxin, digitalis glycosides only weakly inhibit neuronal membrane uptake of catecholamines at concentrations far exceeding therapeutic levels. To ensure adequate retrograde catheterization, the position of the right heart catheter was confirmed by contrast injection to outline the coronary sinus and by coronary sinus oxygen saturation measurements. The left ventricular end-diastolic pressure was measured in all cases. Ten milliliters of blood was sampled simultaneously from the aorta, coronary sinus, and femoral vein and transferred to ice-cold test tubes that contained glutathione and EGTA. Norepinephrine and epinephrine plasma concentrations were determined in duplicate by the radioenzymatic method of Peuler and Johnson with a few modifications (Cat-a-kit; Upjohn). Statistical significance of the data was determined by Student’s t test.

### Results

Individual and mean values for plasma catecholamines and hemodynamic data in the two groups of patients are given in table 1.

There was a large range of values for plasma catecholamines in both groups, and the only significant difference was in the coronary sinus norepinephrine concentration, which was significantly increased in the group with left ventricular failure. However, when these values are expressed as extraction, (arterial–venous)/arterial, the group with failure showed a highly significant reduction in the myocardial epinephrine extraction and in the norepinephrine overflow, while the extractions across the leg were not significantly different between the two groups (figure 1). The group with failure had a significantly higher left ventricular end-diastolic pressure and there was no signifi-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>NE&lt;sub&gt;A&lt;/sub&gt; (nM)</th>
<th>NE&lt;sub&gt;CS&lt;/sub&gt; (nM)</th>
<th>NE&lt;sub&gt;EV&lt;/sub&gt; (nM)</th>
<th>E&lt;sub&gt;A&lt;/sub&gt; (nM)</th>
<th>E&lt;sub&gt;CS&lt;/sub&gt; (nM)</th>
<th>E&lt;sub&gt;EV&lt;/sub&gt; (nM)</th>
<th>Extraction</th>
<th>LVEDP (mm Hg)</th>
<th>O&lt;sub&gt;2&lt;/sub&gt; sat. (%)</th>
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<td>1.09</td>
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<td>+0.26</td>
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<td>MS</td>
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<td>4.10</td>
<td>0.44</td>
<td>0.28</td>
<td>−0.75</td>
<td>+0.36</td>
<td>13</td>
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<tr>
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<tr>
<td>4</td>
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<td>2.07</td>
<td>1.16 − 0.40 + 0.64</td>
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<tr>
<td>7</td>
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<td>−0.10</td>
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<tr>
<td>8</td>
<td>MR,MS,AR,AS</td>
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<td>0.08</td>
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<td>0.29</td>
<td>−0.21 − 0.03 + 0.56</td>
<td>−0.15</td>
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<tr>
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<td>3.93</td>
<td>1.37</td>
<td>0.74</td>
<td>0.44 − 0.22 + 0.72</td>
<td>+0.08</td>
<td>+0.43</td>
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<td>SD</td>
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<td>± 2.74</td>
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<td>± 2.85</td>
<td>± 1.17</td>
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<td>± 0.37 ± 0.17 ± 5.3 ± 4.4</td>
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</tbody>
</table>

AR = aortic regurgitation; MS = mitral stenosis; AS = aortic stenosis; MR = mitral regurgitation; ASD = atrial septal defect; NE = norepinephrine; E = epinephrine; A = aorta; CS = coronary sinus; FV = femoral vein; LVEDP = left ventricular end-diastolic pressure.
This in vitro observation is in agreement with our in vivo estimate of myocardial catecholamine uptake.

**Mechanism of catecholamine uptake in heart and lower limb.** Transient tracer analysis in the heart had demonstrated that the unidirectional tracer uptake of norepinephrine is identical to the extraction of endogenous epinephrine. We previously found neuronal uptake inhibitors to reduce but not to abolish the tracer extraction of norepinephrine. A similar effect on the extraction of tracer norepinephrine has been observed in the dog hind limb, suggesting that a large fraction of the catecholamine uptake in the heart and the limb can be ascribed to the neuronal membrane uptake system.

Reduced epinephrine extraction could occur in the unsteady state after a transient rise in circulating epinephrine and subsequent release by the terminals. However, if this were the case, then reduced epinephrine extraction should also have been observed across the leg.

**Effect of hypertrophy on coronary blood flow.** We did not measure coronary blood flow, but since the flow per gram of tissue is not increased in cardiac hypertrophy, it is unlikely that increased flow could explain the total inhibition of epinephrine extraction observed in most of the patients with heart failure. In addition, Halter et al. have recently shown that aortic-coronary sinus epinephrine extraction is unaltered in spite of a sevenfold variation in coronary flow.

**Norepinephrine extraction.** The coronary sinus norepinephrine concentration is the arterial norepinephrine concentration plus the net sum of the release (due to cardiac adrenergic stimulation) and uptake of norepinephrine by the sympathetic fibers of the heart. If norepinephrine is being released in the patients with heart failure, there must be some functioning sympathetic fibers and terminals in spite of the absence of uptake of epinephrine. Although we cannot rule out a more pronounced effect of a deficient neuronal uptake on epinephrine extraction compared with norepinephrine, the solution to this apparent paradox possibly lies in the observation that in animals with induced heart failure, the catecholamine fluorescence disappears only around the muscle fibers and is preserved in the connective tissue spaces and around blood vessels. Thus norepinephrine could escape into the blood from these spaces without encountering a large uptake system. On the other hand, epinephrine introduced via the capillaries would encounter virtually no functioning fibers after diffusing into the interstitial space between the muscle fibers. However, it should be noted that in the absence of all apparent membrane uptake, a net overflow of norepinephrine can be obtained with much

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**FIGURE 1.** Comparison of average aortic-coronary sinus percent extractions of epinephrine and norepinephrine for patients with and without clinical left ventricular failure secondary to mechanical overload. A negative extraction indicates net excretion. *p < .01 for the null hypothesis between the two groups. Error bars are SD.

**Discussion**

**Definition of heart failure.** Patients were assigned to groups on the basis of clinical findings. There is no direct relationship between left ventricular contractility and clinical findings, but there is no other test or measurement that is generally accepted as an unequivocal index of contractility. We have therefore assumed that those patients with pulmonary edema in the absence of any other cause had reduced left ventricular contractility secondary to long-term pressure or volume overload. Even with this imprecise definition, every one of these patients had a myocardial epinephrine extraction below normal average by at least 1 SD. The groups can be separated by the left ventricular end-diastolic pressure but there is a large range in both groups.

Using a clinical definition of heart failure, Petch and Nayler found reduced labeled norepinephrine and epinephrine uptake in left ventricular papillary muscle removed at operation for mitral valve replacement.
less total release than in the normal situation, in which there is both a large release and large uptake of norepinephrine.

Conclusion

Although extraneuronal uptake of catecholamines could be partially involved, the data suggest that in addition to a reduction in cardiac sympathetic neuronal enzyme activity in heart failure secondary to mechanical overload, there is also a reduction in the capacity of the neuronal membrane to sequester catecholamines. This attrition of neuronal membrane function appears to be specific to the heart and is not a result of a generalized depression of the peripheral sympathetic system.

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References

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