Cardiorenal epinephrine kinetics: evidence for neuronal release in the human heart

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Johansson, Mats, Bengt Rundqvist, Graeme Eisenhofer, and Peter Friberg. Cardiorenal epinephrine kinetics: evidence for neuronal release in the human heart. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2178–H2185, 1997.—There are experimental data suggesting that epinephrine (Epi) may act as a cotransmitter in sympathetic nerves, stimulating presynaptic β2-receptors and enhancing norepinephrine (NE) release. To examine neuronal Epi release, patients with congestive heart failure and hypertension and healthy subjects were examined with the isotope-dilution method. At baseline, small cardiac and renal Epi spillovers were found in patients. During intense supine exercise, cardiac NE and Epi spillovers increased concomitantly with similar magnitude, whereas no renal Epi spillover could be detected. Blockade of neuronal uptake caused a consistent decrease in both cardiac and renal fractional extractions of NE and Epi. The present study demonstrates baseline cardiorenal Epi release in patients with congestive heart failure and renal Epi release in hypertensive patients. Furthermore, Epi is removed by neuronal uptake in both the heart and kidney, and cardiac Epi spillover increases during exercise. This study, in contrast to other results, provides evidence for cardiac neuronal Epi release.

EPINEPHRINE (Epi) is secreted by the adrenal medulla in response to different physiological stimuli such as exercise, mental stress, and hypoglycemia (16). More than 90% of circulating Epi is derived from the adrenal medulla (2). Although Epi has been demonstrated to act as a neurotransmitter in the central nervous system (24), there is uncertainty about its physiological role in peripheral sympathetic neurons. Experiments have indicated that Epi may act as a cotransmitter, being incorporated into postganglionic sympathetic nerves and released with norepinephrine (NE) up to 24 h after its uptake (22, 23). Furthermore, infusion of pharmacological doses of Epi has been shown to promote noradrenergic transmission (21), probably by stimulating prejunctional β2-receptors. Hence Epi released from sympathetic nerves in the periphery may be of clinical importance in congestive heart failure (CHF) and hypertension, contributing to increased sympathetic nerve activity. Therefore, the main purpose of the present study was to investigate cardiac and renal handling of catecholamines in humans, with an emphasis on neuronal Epi release.

In addition to baseline studies, cycling exercise was performed to stimulate sympathetic nerves (11, 25), possibly revealing neuronal cardiorenal Epi release. To examine whether Epi is recaptured neuronally, an intravenous infusion of desipramine (DMI) was used to block neuronal uptake (uptake 1). Simultaneous infusions of [3H]NE and [3H]Epi in conjunction with simultaneous sampling of arterial, coronary, and renal venous blood allowed direct comparison between both NE and Epi handling in the heart and kidney.

MATERIALS AND METHODS

Subjects

Data on the study population are given in Tables 1 and 2. Hypertensive patients. These patients (n = 17) were undergoing a clinical investigation for renovascular hypertension involving renal vein blood sampling for the assessment of plasma renin activity. Unilateral renal artery stenosis (RAS) and renin-dependent hypertension were diagnosed in six patients according to criteria previously described in detail (17). CHF patients. These patients (n = 28) were investigated hemodynamically with right heart catheterization to determine the severity of heart failure. The clinical characteristics of these patients are shown in Table 1. Most patients had moderate to severe heart failure (New York Heart Association III-IV).

Healthy subjects. These subjects (n = 12) were younger than the patients in the other study groups (35 ± 2 vs. 56 ± 1 (SE) yr). None had a history of neurological or cardiovascular disease. A comprehensive clinical evaluation in conjunction with hematology and routine serum biochemistry testing indicated that all parameters were within the normal range. All studies were approved by the local ethical and isotope committees at Sahlgrenska University Hospital (Sweden), and all subjects gave their consent to participate in the study.

Catheterization

The subjects were studied in the morning in a catheterization laboratory. Generally, drugs with cardiorenal effects were withheld for 12 h before the investigations. In some patients, diuretics and/or nitrates were given on clinical indication. The subjects refrained from smoking and coffee drinking for 12 h preceding the study. The patients undergoing investigation for RAS were hospitalized 4 days before catheterization and maintained on a low-salt diet. A cannula was introduced percutaneously into the left radial artery for blood pressure monitoring and blood sampling. The right renal vein was catheterized via either a femoral vein or the right internal jugular vein with the Seldinger technique. In patients undergoing investigation for RAS, both renal veins were catheterized. The renal vein catheters were positioned under fluoroscopic control, with the positions confirmed by means of oxygen saturation. In CHF patients and healthy subjects, the right kidney was examined.

In CHF patients and healthy subjects, a coronary sinus catheter was inserted via the right internal jugular vein into the coronary sinus. Coronary sinus blood flow was determined by the retrograde thermodilution technique (15).
Table 1. Data on study population

<table>
<thead>
<tr>
<th>Renin-dependent hypertension</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>Non-renin-dependent hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>28</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>19</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>9</td>
</tr>
<tr>
<td>NYHA I–II</td>
<td>11</td>
</tr>
<tr>
<td>NYHA III–IV</td>
<td>17</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>28 (12–47)*</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>12</td>
</tr>
</tbody>
</table>

Values are no. of subjects except * denotes mean value (range). †Classification of congestive heart failure (CHF) according to New York Heart Association (NYHA).

Infusions

p-Aminohippuric acid (Merck Sharp & Dohme, Philadelphia, PA) and tracer doses of [3H]NE (L-2,5,6-[3H]NE; 40–60 Ci/mmol) and Epi (L-N-methyl-[3H]Epi; 65–70 Ci/mmol; New England Nuclear, Boston, MA) were infused into a peripheral vein. An infusion rate of 1.0–1.5 µCi/min was used for the radiolabeled catecholamines.

Experimental Protocol

Baseline blood samples were taken simultaneously from a radial artery, the coronary sinus, and one or both renal vein(s) at steady state 30 min after the infusions were started. Samples were collected into ice-chilled tubes containing heparin or EDTA and glutathione. The plasma was separated by centrifugation and stored at −80°C until assayed for catecholamines. Renal plasma flow (RPF) was derived from the total infusion clearance of p-aminohippuric acid corrected for renal fractional extraction. In hypertensive patients, separate renal function and RPF were assessed by gamma camera renography, and in the other study groups, RPF in the right kidney was assumed to be 50% of total RPF.

Neuronal Ruptake Blockade

DMI hydrochloride (Ciba-Geigy, Göteborg, Sweden) was administered intravenously to inhibit neuronal uptake of NE and Epi in patients with CHF (n = 9), the heart transplant recipient, and the healthy subjects (n = 10). Infusions of DMI lasted 15–30 min, yielding a cumulative dose of 0.25–0.5 mg/kg, which was achieved at the time of arterial and renal vein blood sampling.

Dynamic Exercise

Supine cycling was carried out in a subgroup of CHF patients (n = 14) and in healthy subjects (n = 11). Workload was set at 50% of the maximum working capacity as assessed from a previous exercise test (cycling sitting on ergometer bicycle with load increments of 10 W/min and a test duration of 10 min). Arterial, coronary sinus, and renal venous blood samples were drawn during the last minute of the 10-min exercise.

Catecholamine Assays

Cardiac and renal catecholamine extractions were calculated as ([3H]CA − [3H]CV)/[3H]CA, where [3H]CA and [3H]CV are the plasma concentrations of [3H]-labeled catecholamine in the arterial and coronary or renal venous plasma, respectively.

The specific activity of the catecholamines was estimated from [3H]C/C, where [3H]C is the plasma concentration of [3H]-labeled catecholamine in disintegrations per minute (dpm) per milliliter and C is the plasma concentration of endogenous catecholamine in picomoles per milliliter. The decreasing specific activity from artery to vein is due to organ release of endogenous catecholamine according to the isotope-dilution concept (7). Thus the decrease in specific activity across the heart or kidney reflects regional catecholamine release.

The regional catecholamine spillover was estimated with Fick’s principle corrected for the fractional extraction across the organ examined (10) according to the formula IR/SAA, where IR is the infusion rate of [3H]-labeled catecholamine in dpm/min and SAA is the specific activity of the catecholamine in arterial plasma (in dpm/pmol).

Statistical Methods

Results are expressed as means ± SE. Student’s t-tests for paired and unpaired observations were used. Parameters not normally distributed were logarithmically transformed before the parametric test. If a nonnormal distribution was retained, the Wilcoxon signed-rank test for paired comparisons or the Mann-Whitney U-test for unpaired comparisons was used. For comparisons between groups, analysis of variance (ANOVA) was used, with post hoc testing according to Scheffé. The relationship between two variables was assessed by calculating the rank correlation coefficient according to Spearman. Statistical significance was defined as P < 0.05.

RESULTS

Baseline Measurements

Heart rate was higher in the patient groups compared with control subjects (P < 0.05; Table 2). Coro-
Cardiovascular sinus plasma flow was similar in CHF patients and healthy subjects. RPF was reduced by ~50% in hypertensive and CHF patients relative to healthy subjects \((P < 0.01; \text{Table 2})\). The plasma concentration of NE was elevated in CHF and hypertensive patients compared with healthy subjects \((P < 0.05)\), whereas arterial Epi concentration showed no significant difference among the groups \((P > 0.05)\). Total body NE spillover was higher in hypertensive patients compared with healthy subjects \((P < 0.01)\) and CHF patients \((P < 0.05)\), whereas total body Epi spillover was similar in the study groups \((P > 0.05)\).

Specific activity for both NE and Epi fell substantially across the heart and kidney \((P < 0.01)\). The cardiorenal decrease in specific activity for Epi was confined to the patients, whereas the healthy subjects did not show a significant decrease.

Cardiac NE spillover was markedly increased in the CHF patients compared with the healthy control subjects \((P < 0.01)\), and renal NE spillover was slightly higher in the patient groups compared with the healthy subjects, but the difference did not reach statistical significance \((P > 0.05)\). Cardiac and renal Epi spillovers

### Table 3. Arterial plasma [NE] and [Epi] and cardiac, renal, and total body catecholamine spillover in CHF and hypertensive patients and healthy subjects at baseline conditions

<table>
<thead>
<tr>
<th></th>
<th>CHF Patients ((n = 28))</th>
<th>Hypertensive Patients ((n = 15))</th>
<th>Healthy Subjects ((n = 12))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial [NE], pmol/ml</td>
<td>2.42 ± 0.25*</td>
<td>3.24 ± 0.45†</td>
<td>1.06 ± 0.07</td>
</tr>
<tr>
<td>NE spillover, pmol/min</td>
<td>286 ± 40†</td>
<td>84 ± 15</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>1,016 ± 99</td>
<td>1,209 ± 215</td>
<td>697 ± 48</td>
</tr>
<tr>
<td>Renal</td>
<td>1,489 ± 391</td>
<td>6,502 ± 920†</td>
<td>2,972 ± 222</td>
</tr>
<tr>
<td>Total body</td>
<td>4,489 ± 391</td>
<td>6,502 ± 920†</td>
<td>2,972 ± 222</td>
</tr>
<tr>
<td>Arterial [Epi], pmol/l</td>
<td>0.50 ± 0.05</td>
<td>0.39 ± 0.09</td>
<td>0.33 ± 0.12</td>
</tr>
<tr>
<td>Epi spillover, pmol/min</td>
<td>8 ± 1*</td>
<td>0 ± 1</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>54 ± 13*</td>
<td>24 ± 10</td>
<td>4 ± 17</td>
</tr>
<tr>
<td>Renal</td>
<td>1,001 ± 118</td>
<td>737 ± 120</td>
<td>918 ± 339</td>
</tr>
</tbody>
</table>

Values are means ± SE; \(n\), no. of subjects. [NE], norepinephrine concentration; [Epi], epinephrine concentration; renal, both kidneys together. Significant difference from healthy subjects: *\(P < 0.05\); †\(P < 0.01\). ‡Significant difference from CHF patients, \(P < 0.05\).

Fig. 1. Individual values of decrement in specific activity (SA) across coronary circulation (top) and renal circulation (bottom) for norepinephrine (NE; left) and epinephrine (Epi; right). Horizontal bars, group mean value. Decreasing SA from arteries to veins indicates dilution of \(^{3}H\)NE or \(^{3}H\)Epi by endogenously released catecholamines from heart or kidney. All subjects are shown together. For Epi, decreases in cardiorenal SA were confined to patient group. **Significant decrease from artery, \(P < 0.01\).
Neuronal Reuptake Blockade

For all subjects taken together, mean arterial blood pressure, heart rate, and RPF increased after DMI administration (P < 0.05). Coronary venous plasma flow remained unchanged in response to neuronal uptake 1 blockade. Data for the different study groups are presented in Table 4.

Total body NE spillover decreased slightly after DMI administration (P < 0.05), whereas total body Epi spillover did not change. Cardiac NE spillover was unchanged, whereas Epi spillover fell (P < 0.01) and could not be detected in the heart after DMI. The renal spillovers of both NE and Epi decreased after DMI administration (P < 0.05). Values for the different study groups are presented in Table 5.

The fractional cardiac and renal extractions of [3H]NE and [3H]Epi decreased after inhibition of neuronal uptake (P < 0.01; Fig. 3). Cardiac and renal NE extractions fell by 54 and 24%, respectively (absolute values), whereas Epi extractions fell by 50 and 15%, respectively. Thus the decrease was more pronounced in the heart (P < 0.01), indicating a stronger dependence of neuronal uptake for both NE and Epi in the heart compared with the kidney. Renal NE extraction fell more than Epi extraction after DMI administration, whereas the reduction was similar for the cardiac extractions of NE and Epi.

The reduction in cardiac extractions of NE and Epi was more pronounced in the healthy subjects compared with the CHF patients (62 ± 1 vs. 45 ± 3% for NE and 60 ± 2 vs. 29 ± 10% for Epi; P < 0.01 for both). Fractional renal Epi extraction decreased more in the group of healthy subjects (18 ± 2 vs. 9 ± 2%; P < 0.05), whereas the reduction in NE extraction did not differ among the groups.

Dynamic Exercise

For all subjects taken together, mean arterial pressure, heart rate, and coronary plasma flow increased during supine cycling (P < 0.05), whereas RPF tended to decrease (P < 0.05; Table 4).

Table 4. Change in MAP, HR, CSPF, and RPF after blockade of neuronal uptake and after supine cycling in CHF patients and healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>∆MAP, mmHg</th>
<th>∆HR, beats/min</th>
<th>∆CSPF, ml/min</th>
<th>∆RPF, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Desipramine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF patients</td>
<td>4 ± 2</td>
<td>7 ± 4</td>
<td>7 ± 6</td>
<td>-2 ± 7‡</td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>12 ± 5*</td>
<td>9 ± 2†</td>
<td>12 ± 11</td>
<td>37 ± 7†</td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF patients</td>
<td>11 ± 2†‡</td>
<td>44 ± 6†‡</td>
<td>82 ± 15†</td>
<td>-12 ± 12</td>
</tr>
<tr>
<td>(n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>2 ± 2</td>
<td>68 ± 4‡</td>
<td>142 ± 39†</td>
<td>-38 ± 13*‡</td>
</tr>
<tr>
<td>(n = 11)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects who participated in intervention. ∆, Change. Desipramine used for blockade of neuronal uptake. Significant difference from baseline: *P < 0.05; †P < 0.01. ‡Significant difference from healthy subjects, P < 0.05.
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to decrease slightly during exercise. Values for the different study groups are presented in Table 5. Values for the different study groups are presented in Table 5. The increment in total body NE and Epi spillovers during exercise were more pronounced in the healthy subjects compared with the CHF patients (P < 0.05). The arterial Epi concentration during exercise did not differ between the CHF patients and healthy subjects.

Cardiac spillover of both NE and Epi increased during exercise, and there was a strong correlation between the change in cardiac NE and Epi spillovers

Table 5. Change in total body, cardiac, and renal NE and Epi spillover after blockade of neuronal uptake and during supine cycling in CHF patients and healthy subjects

<table>
<thead>
<tr>
<th>Desipramine</th>
<th>Total Body</th>
<th>Cardiac</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF patients (n = 9)</td>
<td>ΔNE spillover</td>
<td>ΔEpi spillover</td>
<td>ΔNE spillover</td>
</tr>
<tr>
<td>Healthy subjects (n = 9)</td>
<td>-90 ± 393</td>
<td>20 ± 140</td>
<td>-26 ± 43</td>
</tr>
<tr>
<td>CHF patients (n = 14)</td>
<td>7,266 ± 1,258‡</td>
<td>439 ± 112§</td>
<td>946 ± 177†</td>
</tr>
<tr>
<td>Healthy subjects (n = 11)</td>
<td>10,506 ± 1,372†</td>
<td>4,331 ± 1,219†</td>
<td>1,213 ± 152†</td>
</tr>
</tbody>
</table>

Values are means ± SE in pmol/min; n, no. of subjects who participated in intervention. Four desipramine-treated CHF patients received [3H]Epi infusion. Renal Epi spillover was measured during exercise in 4 CHF patients. Significant difference from baseline: *P < 0.05; †P < 0.01. Significant difference from healthy subjects: ‡P < 0.05; §P < 0.01.
during exercise (Figs. 4 and 5). This relationship was similar for the patients and healthy subjects. A strong correlation was also found between total body NE and Epi spillovers ($r = 0.65; P < 0.01$).

**DISCUSSION**

In the present study, dilution of $[^3H]$Epi across the heart provides evidence for cardiac Epi release in CHF patients under baseline conditions. Moreover, increased cardiac Epi spillover during marked activation of the sympathetic nervous system is consistent with the notion that Epi is being released from cardiac sympathetic neurons in humans. Furthermore, the present data suggest that Epi is handled neuronally in both the heart and kidney because neuronal uptake blockade clearly reduced the cardiac and renal extraction fractions of $[^3H]$Epi.

These results are at variance with the findings of Kaye et al. (18). They found a net overflow of Epi across the heart in patients with CHF but no increase during supine cycling. Furthermore, no relationship between cardiac NE and Epi spillovers was found, and the authors therefore concluded that cardiac Epi release is of nonneuronal origin. Explanations for these differences are not obvious. The level of sympathetic nerve activation during cycling exercise appeared similar in the two studies, as indicated by similar increments in total body NE spillover. The larger number of subjects performing cycling exercise in the present study ($n = 24$ vs. 15 in the study by Kaye et al.) in conjunction with a solid and consistent increase in cardiac Epi spillover (22 of 24 subjects) during exercise supports the concept of neuronal cardiac Epi release. Moreover, we found a close correlation between the increase in cardiac NE and Epi spillovers during exercise, similar to the relationship observed between the change in overall NE and Epi spillovers during exercise. The vast majority of the latter is released from the adrenal medulla as a consequence to stimulation by regional sympathetic nerves.

In another study, increased cardiac Epi spillover was seen during exercise in younger healthy subjects, whereas no increase could be detected in older subjects (8). This is in agreement with the present findings where cardiac Epi spillover increased only in the younger group of healthy subjects. It is possible that Epi is only released during states of markedly increased sympathetic drive. Hence, in CHF patients with increased sympathetic nerve activity at baseline, cardiac Epi spillover was detected, whereas no Epi spillover could be detected in healthy subjects. In contrast, when sympathetic outflow increased during dynamic exercise, an increase in cardiac Epi spillover was observed in the healthy subjects but not in CHF patients. An attenuated increase in cardiac NE spillover during exercise has been shown in CHF patients (25), and our data further support such a reduced adrenergic responsiveness in these patients. One may speculate that depleted intraneuronal catecholamine stores due to increased catecholamine turnover may play a role.
Cardiac NE and Epi extractions fell similarly after DMI administration. This contrasts to previous studies (1, 3) in which a stronger dependence on neuronal uptake for NE compared with Epi in the heart was found. Interestingly, cardiac Epi spillover decreased after DMI administration, supporting the concept of a neuronal origin for Epi spilling over from the heart. This decrease could be due to either reduced central sympathetic outflow after DMI administration (12) or inhibition of neuronal uptake of Epi. Both explanations do support a neuronal origin of cardiac Epi release, with the latter suggesting that circulating Epi is extracted and released by cardiac sympathetic nerves.

Consistently decreasing specific activity of Epi across the kidney in conjunction with a significant renal Epi spillover in CHF and hypertensive patients at baseline supports the concept of renal Epi release. Contamination of adrenal medullary blood has been proposed as an explanation for renal Epi spillover in two previous studies (4, 18) where the number of kidneys studied was smaller compared with the present study. However, this explanation here seems unlikely because the detected renal Epi release in most patients was measured in the right renal vein, and drainage of the right adrenal gland blood does not converge into the renal vein in the normal case. Contamination of adrenal blood was clearly identified by a highly elevated Epi concentration in renal venous blood in some patients (mostly left renal venous blood samples). None of these patients was included in this study. Moreover, individuals with detectable renal Epi spillovers did not, on average, have a higher renal NE spillover than other subjects. Hence an adrenal source to the renal Epi release observed in the present study seems unlikely.

Although total body NE and Epi spillovers and renal NE spillover increased at least twofold during cycling (evidence for overall and regional increases in the sympathoadrenal activity), there was no detectable renal Epi release. In addition, there was no correlation between renal NE and Epi spillovers at baseline or during exercise. Taken together, these data suggest other, nonneuronal sources constituting the low renal Epi spillover at baseline.

Both renal [3H]NE and [3H]Epi extractions fell significantly after DMI administration. The more pronounced decrease in NE extraction indicates that NE is removed more efficiently compared with Epi by neuronal uptake in the kidney. Renal Epi spillover decreased after blockade of neuronal uptake, suggesting a dependence of neuronal uptake in the inactivation of released Epi. This observation supports the concept of neuronal release of extracted circulating Epi by the kidney. However, the absence of renal Epi release during exercise is difficult to explain in the context of neuronal Epi release. Theoretically, it could be due to depleted neuronal Epi deposits during exercise. Although extraneuronal release of Epi in the kidney is plausible, it is hard to explain the fall in renal Epi spillover after DMI administration without having some Epi release from sympathetic nerves.

It is unclear whether some of the Epi released by the heart and kidney may have been synthesized within the organs. However, phenylethanolamine-N-methyltransferase (PNMT; an enzyme necessary for Epi synthesis) has been found in the glomeruli and tubules in the rat kidney, suggesting local Epi synthesis (27). Epi may be synthesized by neuroendocrine cells in the kidney, but immunohistochemistry results suggest that these cells only contain a minor part of the renal PNMT (20). Thus regional Epi synthesis is probably of minor importance compared with extraction of circulating Epi. The latter mechanism is also supported by an increased plasma concentration of Epi in the patient group compared with healthy subjects and positive correlations between circulating plasma Epi concentration and cardiorenal Epi spillover at baseline.

Study Limitation

Age affects catecholamine kinetics, and differences between healthy subjects and patients have to be interpreted with caution because the groups were not age matched. Hence it is possible that the cardiorenal Epi release found only in patients at baseline could be due to older age compared with healthy subjects rather than the consequence of hypertension or CHF. Although age perhaps will affect baseline Epi spillover, a concomitant increase in cardiac NE and Epi spillovers during exercise was seen among both younger and older subjects. Thus the main finding of neuronal Epi release in the human heart remains unaffected by age.

Perspectives

Epi may participate in the development of increased sympathetic nerve activity associated with high mortality in CHF (19, 26). Moreover, it may, by presynaptic facilitation of NE release, contribute to an activated sympathetic nervous system often observed in the early stages of primary hypertension and may play a role in the pathogenesis of the process (9, 13, 14). Although this study demonstrates Epi release in the human heart and kidney, it cannot establish the pathophysiological role of Epi, but the results may be the impetus for further studies.

In summary, the present study demonstrates cardiorenal neuronal uptake of Epi and provides evidence for neuronal Epi release in the human heart.

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