Cardiac Norepinephrine Kinetics in Hypertrophic Cardiomyopathy

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We examined the uptake and release of norepinephrine in the cardiac circulation and other regional vascular beds in 11 patients with hypertrophic cardiomyopathy (HCM) and in 10 control subjects during simultaneous infusion of tracer-labeled norepinephrine and isoproterenol. Cardiac neuronal uptake of norepinephrine was assessed by comparing regional removal of tracer-labeled norepinephrine with that of tracer-labeled isoproterenol (which is not a substrate for neuronal uptake) and by the relation between production of dihydroxyphenylglycol (DHPG), an exclusively intraneuronal metabolite of norepinephrine, and regional spillover of norepinephrine. Cardiac extraction of norepinephrine averaged 59±17% in the patients with HCM, significantly less than in the control subjects (79±13%, p<0.05), whereas cardiac extraction of isoproterenol was similar in the two groups (13±23% versus 13±14%), indicating that neuronal uptake of norepinephrine was decreased in the patients with HCM. The cardiac arteriovenous difference in norepinephrine was significantly larger in the patients with HCM than in the control subjects (73±77 versus 13±50 pg/ml, p<0.05), as was the product of the arteriovenous difference in norepinephrine and coronary blood flow (7.3±7.3 versus 0.8±3.0 ng/min, p<0.05). The slope of the line relating cardiac DHPG production to cardiac norepinephrine spillover was less in the patients with HCM (p<0.005), indicating that the increased arteriovenous difference in norepinephrine in HCM was not due to increased norepinephrine release (which would have been accompanied by increased DHPG production) but rather due to decreased neuronal uptake and metabolism of norepinephrine. The impairment in cardiac neuronal norepinephrine uptake can explain several morphologic and pathophysiologic features of this disease. (Circulation 1989;79:836–844)

Hypertrophic cardiomyopathy (HCM) is characterized by an increase in myocardial mass in the absence of cardiac or systemic abnormalities that could result in secondary myocardial hypertrophy.1 Several clinical features of this disease, including a hyperdynamic left ventricular contraction pattern, reduced coronary flow reserve, a propensity for ventricular and atrial arrhythmias, and amelioration of symptoms by β-adrenoceptor blocking agents2–6 suggest the possibility of underlying hyperactivity of the sympathetic nervous system. It has been hypothesized that such an abnormality may contribute to the development of ventricular hypertrophy in HCM7,8 as well as in other diseases, such as systemic hypertension.9,10 Treatment of hypertensive patients or experimental animals with antihypertensive agents that act at the sympathetic neuroeffector junction can produce regression of cardiac hypertrophy.11,12 Moreover, administration of the sympathetic neurotransmitter, norepinephrine, can cause hypertrophy of cultured rat myocytes13 and biventricular hypertrophy in experimental animals, even at doses that do not cause systemic hypertension.12,14

Despite the theoretic appeal, a definite link between altered sympathetic nervous function and cardiac hypertrophy in general and HCM in particular has not been proved. Specifically, tissue norepinephrine concentration in biopsy samples15,16 and coronary arteriovenous differences in plasma norepinephrine have not been reported to be elevated in patients with HCM.17

In a given regional vascular bed, however, norepinephrine is both released and removed from the circulation (Figure 1). Abnormalities in release or
uptake of norepinephrine in the coronary circulation of patients with HCM, therefore, may not be detected by measuring arteriovenous differences in plasma norepinephrine. In the present study, we applied recently developed methods using simultaneous intravenous infusions of tracer-labeled norepinephrine and tracer-labeled isoproterenol to evaluate norepinephrine release and neuronal uptake in the cardiac and other regional vascular beds. Because isoproterenol is not a substrate for neuronal uptake, the difference in extraction of norepinephrine and isoproterenol was used to quantify neuronal uptake activity. In addition, we analyzed regional production of dihydroxyphenylglycol (DHPG), the main intraneuronal metabolite of norepinephrine, to provide another index of regional neuronal uptake of norepinephrine.

Methods

Study Subjects

Patients were referred to the Cardiology Branch of the National Heart, Lung, and Blood Institute for evaluation. Eleven patients had HCM as defined previously. Patients with HCM were compared with 10 control subjects without cardiac hypertrophy who underwent diagnostic cardiac catheterization for evaluation of chest pain. Patients with coronary artery disease (defined as angiographic narrowing of more than 50% of the lumen of any major epicardial vessel), valvular heart disease, infiltrative cardiomyopathy, or dilated cardiomyopathy were excluded from both groups. Patients had M-mode and two-dimensional echocardiographic studies by an Advanced Technology Laboratory Mark 500 (Bellevue, Washington) or Diasonics CV-400 mechanical sector scanner (South San Francisco, California). Measurements were performed according to previously described methods.

Among the patients with HCM, there were eight men and three women (mean age, 42±16 years). The patients with HCM had symptoms of angina or dyspnea for an average of 4.6±2.5 years. Before hospitalization at the National Institutes of Health, eight patients were receiving calcium channel antagonists and six were receiving β-blocking agents. These medications were discontinued at the time of admission. Echocardiographic data and baseline hemodynamic data are listed in the Table.

Among the control subjects, there were six women and four men (mean age, 49±7 years). All control subjects had chest pain for an average of 3.8±3.6 years. Before hospitalization at the National Institutes of Health, nine control subjects were receiving calcium channel antagonists, one was receiving a β-blocking agent, and two were receiving nitrates. These medications were discontinued at the time of admission. Six control subjects had evidence of microvascular angina, and four had no definite abnormality of coronary flow reserve. At rest, control subjects with microvascular angina were similar to those without microvascular angina with respect to coronary blood flow and hemodynamics and so these subjects were grouped for comparison with the patients with HCM.

The protocol was reviewed and approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute and by the Radiation Safety and the Radiopharmacy Committees of the National Institutes of Health. All patients gave informed consent before cardiac catheterization.

Cardiac Catheterization Procedure

Cardioactive medications were discontinued at least 48 hours before cardiac catheterization. Patients were studied in the morning after an overnight fast. Caffeine-containing beverages and tobacco prod-
TABLE. Echocardiographic and Hemodynamic Data in Patients With Hypertrophic Cardiomyopathy and Control Subjects

<table>
<thead>
<tr>
<th>Echocardiography</th>
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<td>Septum (mm)</td>
<td>LV FW (mm)</td>
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<td>Patients with hypertrophic cardiomyopathy</td>
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<td>Mean</td>
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<td>SD</td>
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Control subjects

| | | | | | | | | |
|1 | 13 | 13 | 77 | 118 | 150/10 | 0 | 10 | 80 | 1.1 |
|2 | 11 | 11 | 48 | 90 | 120/12 | 0 | 6 | 84 | — |
|3 | 9 | 9 | 82 | 87 | 108/12 | 0 | 10 | 89 | 2.3 |
|4 | 10 | 10 | 70 | 104 | 110/16 | 0 | 14 | 96 | 1.6 |
|5 | 10 | 10 | 75 | 95 | 122/18 | 0 | 14 | 95 | 1.1 |
|6 | 9 | 9 | 82 | 112 | 150/12 | 0 | 4 | 44 | 1.8 |
|7 | 10 | 10 | 85 | 118 | 140/7 | 0 | 9 | 62 | — |
|8 | 12 | 11 | 62 | 95 | 125/15 | 0 | 12 | 69 | 1.3 |
|9 | 11 | 10 | 94 | 106 | 140/16 | 0 | 8 | 58 | 2.6 |
|10 | 10 | 10 | 85 | 90 | 130/14 | 0 | 8 | 66 | 2.5 |
|Mean | 11 | 11 | 73 | 99 | 130/13 | 0 | 10 | 69 | 1.8 |
|SD | 1 | 1 | 14 | 14 | 15/3 | 0 | 3 | 17 | 0.6 |

LV, left ventricular; FW, free wall; HR, heart rate; MAP, mean arterial pressure; gradient, left ventricular outflow gradient; PCWP, pulmonary capillary wedge pressure; CBF, coronary blood flow; FBF, forearm blood flow.

Products were probed for 8 hours before the study. Each patient was premedicated with oral diazepam (10 mg) 1 hour before study.

Coronary arteriography was performed to confirm the absence of epicardial coronary artery disease, and left ventriculography was performed. At least 15 minutes were allowed between contrast injection and hemodynamic or metabolic studies.23

Systemic pressure was measured with an indwelling 20-g brachial artery catheter. Pulmonary arterial and pulmonary capillary wedge pressures were measured with a balloon-tipped thermodilution catheter. Left ventricular pressure was measured in the patients with HCM using a pigtail catheter with a single end-hole and in the control patients using an angiographic pigtail catheter.

A thermolюdation coronary sinus catheter (Elecath Corp, Rahway, New Jersey) was positioned via the right internal jugular vein with the tip of the catheter at the junction of the great cardiac vein (GCV) and the anterior interventricular vein. Manual injection of contrast dye was used to confirm proper positioning of the catheter, and constant position was confirmed by repeatedly checking the relation of the catheter to bone landmarks.24 Coronary blood flow from the anterior circulation was measured by thermodilution as previously described.25,26 This method allowed measurement of absolute coronary blood flow in the anterior circulation of the heart, which is the anatomic location of hypertrophy in most patients with HCM. In addition, the thermodilution catheter system allowed GCV blood sampling required for assessment of regional norepinephrine kinetics.

An indwelling catheter in the antecubital vein and catheter-introducing sheaths in the femoral vein and the internal jugular vein were used for blood sampling from other specific vascular regions. Forearm blood flow was measured using forearm plethysmography as previously described.27

**Tracer Infusion**

To quantify neuronal and extraneuronal uptake of catecholamines, patients received tracer doses of $^{3}$H-l-norepinephrine and $^{3}$H-d,l-isoproterenol. The radionuclides were prepared for human use by the
National Institutes of Health radiopharmacy in 50 
µCi (about 5 ml) aliquots and stored at −70 °C until 
used. For each study, 50 µCi tritiated ring-labeled 
l-norepinephrine (New England Nuclear, Boston, 
Massachusetts) and 50 µCi tritiated d,l-isoproterenol 
(New England Nuclear or Amersham, Arlington 
Heights, Illinois) were combined to achieve a final 
radioactivity concentration of 100 µCi in about 60 
ml 5% dextrose in water. The infusion was admini-
stered at a rate of 90 ml/min for 20 minutes to 
ensure steady-state blood levels of labeled cate-
cholamines.18 The total norepinephrine dose was 
about 0.19 µg and the total isoproterenol dose was 
about 1.1 µg. The infusion did not result in any 
hemodynamic changes.18,19

Sample Collection and Analysis

Blood samples (7 ml) were obtained from the 
 femoral artery, GCV, brachial vein, femoral vein, 
and internal jugular vein at 20 minutes during the 
infusion of the labeled catecholamines. Samples 
were transferred to chilled, evacuated, heparinized 
glass tubes and placed on ice. The plasma was 
separated by refrigerated centrifugation and stored 
at −70 °C until assayed.

Concentrations of norepinephrine, isoproterenol, 
and dihydroxyphenylglycol (DHPG) were mea-
sured using batch alumina extraction followed by 
high-performance liquid chromatography with elec-
trochemical detection. Concentrations of tritiated 
norepinephrine and isoproterenol were measured by 
collecting fractions of the column eluate at times 
corresponding to the elution of the standards fol-
lowed by quantification of the tritium in the frac-
tions using liquid scintillation spectroscopy.19,20,28

Norepinephrine Kinetics Calculations

Regional arteriovenous differences in norepineph-
rine (pg/ml) were calculated as venous norepineph-
rine minus arterial norepinephrine. The regional 
arteriovenous (AV) difference multiplied by blood 
flow (termed the “regional AV production rate,” 
ng/min) was calculated as follows:

Regional AV production rate = 
\[ \frac{[N_{E_a} - N_{E_v}]}{X} \times \text{blood flow} \] (1)

where NEa is venous norepinephrine concentra-
tion (pg/ml), NEv is arterial norepinephrine concen-
tration (pg/ml), and blood flow is GCV blood flow (ml/ 
in min) or forearm blood flow (ml/min/100 ml).

Arterial and venous concentrations of tracer-
labeled norepinephrine were used to calculate the 
regional percent extraction of norepinephrine. 
Because isoproterenol is not a substrate for neu-
ronal uptake, the arterial and venous concentra-
tions of tracer-labeled isoproterenol were used to 
calculate extraction due to nonneuronal uptake of 
norepinephrine. The difference between the regional 
extractions of labeled norepinephrine and that of 
labeled isoproterenol has been previously shown to 
reflect neuronal uptake of norepinephrine.18,19 The 
regional percent extractions of labeled norepine-
phrine and labeled isoproterenol were calculated as 
follows:

\[
\text{Percent extraction (NE)} = \left[ \frac{[3HNE_{a} - 3HNE_{v}]}{3HNE_{a}} \right] \times 100 \quad (2)
\]

\[
\text{Percent extraction (ISO)} = \left[ \frac{[3HISO_{a} - 3HISO_{v}]}{3HISO_{a}} \right] \times 100 \quad (3)
\]

where \( 3HNE_{a} \) and \( 3HNE_{v} \) are arterial and venous 
concentration of tritiated norepinephrine, respec-
tively (dpm/ml), and \( 3HISO_{a} \) and \( 3HISO_{v} \) are arterial 
and venous concentrations of tritiated isoproter-
enol, respectively (dpm/ml).

The total regional removal rate of norepinephrine 
(pg/min) was calculated as follows:

\[
\text{Regional removal rate} = \text{NE} \times \text{percent extraction (NE)} \times \text{blood flow} \quad (4)
\]

The regional spillover rate of norepinephrine (pg/ 
min), reflecting the entry of norepinephrine into the 
regional circulation, was calculated from the regional 
AV production rate and the regional removal rate as 
follows:

\[
\text{Regional spillover rate = regional AV production} \quad (5)
\]

\[
\text{rate + regional removal rate}
\]

Total body clearance (l/min/m²) and spillover of 
norepinephrine (ng/min/m²) were calculated as 
follows:

\[
\text{Total body clearance (NE)} = \frac{3HNE \text{ infusion rate}}{3HNE_{a}/m² \text{ BSA}} \quad (6)
\]

\[
\text{Total body spillover (NE)} = \frac{\text{total body clearance (NE)} \times \text{NE}_{a}/m² \text{ BSA}}{7}
\]

where 3HNE is tritiated norepinephrine and BSA is 
body surface area.

DHPG Kinetics Calculations

The regional arteriovenous difference in DHPG 
concentration (pg/ml) was calculated as venous 
DHPG minus arterial DHPG. The regional AV 
difference in DHPG, multiplied by blood flow 
(termed the regional DHPG production rate, pg/ 
min), was calculated as follows:

\[
\text{Regional DHPG production rate} = \frac{[\text{DHPG}_{a} - \text{DHPG}_{v}]}{X} \times \text{blood flow} \quad (8)
\]

where DHPGa is venous DHPG concentration (pg/ml) 
and DHPGv is arterial DHPG concentration (pg/ml).

Statistical Analysis

Results were expressed as mean±SD in the text 
and table and as mean±SEM in the figures. Patient 
groups were compared with two-tailed, unpaired 
t tests. Relations between variables were tested 
with simple linear regression and multiple linear 
regression analysis. A p value of 0.05 defined 
statistical significance.
Results

Cardiac Norepinephrine Kinetics

The cardiac arteriovenous difference in norepinephrine averaged 73 ± 77 pg/ml in the patients with HCM, significantly more than in the control subjects (13 ± 50 pg/ml). Coronary blood flow averaged 94 ± 31 ml/min in the patients with HCM, significantly higher than in the control subjects (69 ± 17 ml/min). The cardiac AV production rate of norepinephrine averaged 7.3 ± 7.3 ng/min in the patients with HCM, significantly more than in the control subjects (0.8 ± 3.0 ng/min).

The percent extraction of labeled norepinephrine in the heart averaged 59 ± 17% in the patients with HCM, significantly less than in the control subjects (79 ± 13%). The percent extraction of labeled isoproterenol in the patients with HCM did not differ from the control subjects (13 ± 23% versus 13 ± 14%). The percent extraction of norepinephrine reflecting neuronal uptake (percent extraction of norepinephrine minus percent extraction of isoproterenol) averaged 46 ± 19% in the patients with HCM, significantly less than in the control subjects (65 ± 18%, Figure 2A).

Arterial norepinephrine in the patients with HCM did not differ significantly from that in the control subjects (249 ± 107 versus 199 ± 61 pg/ml). Despite the lower percent extraction, the cardiac removal rate of norepinephrine in the patients with HCM did not differ from that of the control subjects (12.6 ± 6.3 versus 10.5 ± 3.6 ng/min) because of the higher coronary blood flow in the patients with HCM. The cardiac spillover rate of norepinephrine in the patients with HCM was 19.9 ± 12.4 ng/min, more than in the control subjects (11.3 ± 5.3 ng/min, p = 0.06); the difference, however, did not reach statistical significance.

Ten of the 11 patients with HCM had left ventricular outflow obstruction, with a mean pressure gradient of 67 ± 38 mm Hg (Table 1). The percent extraction of norepinephrine in the patients with HCM was unrelated to the severity of obstruction or peak left ventricular pressure (Figure 3A), pulmonary capillary wedge pressure, mean arterial pressure, or coronary blood flow (Figure 4A). In contrast, the cardiac AV difference in norepinephrine (R = 0.71, p < 0.05), cardiac AV production rate (R = 0.68, p < 0.05), and cardiac spillover rate of norepinephrine (R = 0.63, p < 0.05) were all significantly correlated with the peak left ventricular pressure in the patients with HCM. The relation of cardiac spillover rate and peak left ventricular pressure in the patients with HCM is shown in Figure 3B.

Cardiac DHPG Kinetics

The arterial DHPG level averaged 1,063 ± 299 pg/ml in the patients with HCM, significantly more than in the control subjects (694 ± 202 pg/ml, p < 0.005). In contrast, the cardiac AV difference in DHPG averaged 394 ± 181 pg/ml in the patients with HCM, significantly less than in the control subjects (732 ± 378 pg/ml, p < 0.05). Because of the higher coronary blood flow in the patients with HCM, however, the cardiac DHPG production rate in the patients with HCM did not differ significantly from that of the control subjects (36.7 ± 18.2 versus 49.5 ± 23.1 ng/min). As indicated in Figure 5, cardiac DHPG production correlated with norepinephrine spillover in both study groups. The slope of the relation of DHPG production and norepinephrine spillover was significantly less in the patients with HCM (p < 0.005, Figure 5). Thus, for any given norepinephrine spillover rate, DHPG production rate was less in the patients with HCM.

Forearm Norepinephrine Kinetics

The forearm AV difference in norepinephrine in the patients with HCM was significantly less than in
the control patients (41 ± 69 versus 138 ± 111 pg/ml). Forearm blood flow in the patients with HCM averaged 3.0 ± 0.7 ml/min/100 ml, significantly higher than in the control subjects (1.8 ± 0.6 ml/min/100 ml). The forearm AV production rate of norepinephrine did not differ significantly in the patients with HCM compared with the control subjects (88 ± 151 versus 156 ± 188 pg/min/100 ml).

In the forearm, the percent extraction of tritiated norepinephrine averaged 55 ± 11% in the patients with HCM and 68 ± 12% in the control subjects, and the percent extraction of tritiated isoproterenol averaged 44 ± 13% in the patients with HCM and 55 ± 14% in the control subjects. Thus, the proportion of arterial norepinephrine that was removed by neuronal uptake in the forearm did not differ significantly in the patients with HCM compared with the control subjects (9 ± 8% versus 14 ± 6%, Figure 2B). In both groups, the percent extraction of norepinephrine in the forearm (by both neuronal and extraneuronal uptake) correlated negatively with forearm blood flow (Figure 4B).

**Forearm DHPG Kinetics**

The AV difference in DHPG in the forearm averaged 57 ± 69 pg/ml in the patients with HCM, significantly less than in the control subjects (264 ± 184 pg/ml, *p* < 0.01). The forearm DHPG production rate in the patients with HCM did not differ significantly from that of the control subjects (117 ± 174 versus 374 ± 280 pg/min/100 ml). In the forearm, the DHPG production rate was not related to norepinephrine spillover in either study group.

**AV Differences in Catechols in Other Circulatory Beds**

The AV difference in norepinephrine in the patients with HCM did not differ significantly from the control subjects in the femoral circulation (−7.6 ± 33.3 versus 2.3 ± 48.6 pg/ml) or the cranial circulation (14.6 ± 33.4 versus 37.1 ± 35.5 pg/ml). The percent extraction of norepinephrine in the two groups also did not differ significantly in the femoral
circulation (57 ± 15% versus 62 ± 8%) or the cranial circulation (40 ± 14% versus 38 ± 10%). Similarly, the AV difference in DHPG in the patients with HCM did not differ significantly from the control subjects in the femoral circulation (14.8 ± 143.2 versus 93.3 ± 186.4 pg/ml) or the cranial circulation (196.1 ± 123.3 versus 183.3 ± 159.8 pg/ml).

**Total Body Clearance and Spillover of Norepinephrine**

Total body clearance of norepinephrine did not differ in the patients with HCM compared with control subjects (1.3 ± 0.3 versus 1.2 ± 0.4 l/min/m²). Total body spillover of norepinephrine was 329 ± 162 ng/min/m³ in the patients with HCM, significantly higher than in the control subjects (242 ± 134 ng/min/m³).

**Discussion**

The findings of this investigation indicate that neuronal uptake of norepinephrine is impaired in the hearts of patients with HCM. As a result of this impairment in norepinephrine uptake, patients with HCM exhibited a significantly larger cardiac AV difference in norepinephrine and a larger cardiac AV production rate of norepinephrine (the product of the AV difference and blood flow).

Impaired neuronal uptake of norepinephrine in patients with HCM was suggested by the pattern of regional extraction of labeled norepinephrine and isoproterenol. Because norepinephrine is removed from the bloodstream by both neuronal and nonneuronal tissues and the synthetic catecholamine, isoproterenol, is not a substrate for neuronal uptake, the difference between the percent extraction of circulating norepinephrine and that of isoproterenol was used to quantify neuronal uptake. This approach has been validated in the human arm and heart by the observation that regional extraction of norepinephrine after treatment with desipramine (which blocks neuronal uptake) is similar to that of isoproterenol without desipramine treatment. We recently reported that the human heart is exceptionally dependent on neuronal uptake for in vivo removal of circulating norepinephrine. Whereas the percent extraction of circulating norepinephrine by neuronal uptake averaged 14% in the arm and 7% in the leg, it averaged approximately 70% in the heart. Based on the differences in percent extraction of norepinephrine and isoproterenol between the patients with HCM and the control subjects, we estimated that neuronal uptake of norepinephrine was reduced by about one third in the hearts of patients with HCM.

The AV difference in norepinephrine was significantly larger in the patients with HCM; the AV production rate of norepinephrine was approximately 15 times greater in the patients with HCM; and spillover of released norepinephrine tended to be higher in the patients with HCM. The larger AV increment and production rate of norepinephrine in the patients with HCM appeared to be primarily due to defective neuronal uptake.

Impaired neuronal uptake of norepinephrine in patients with HCM was also suggested by the relation between the cardiac production rate of DHPG and the rate of norepinephrine spillover. DHPG is formed from the deamination of axoplasmonic norepinephrine, which derives from neuronal uptake and leakage from neuronal vesicles. The slope of the relation between DHPG production and norepinephrine spillover probably reflects neuronal norepinephrine uptake activity, and the y intercept probably reflects vesicular leakage. This relation assumes that the two study groups were similar with respect to extraction of circulating plasma DHPG. As shown in Figure 5, for any given amount of cardiac norepinephrine spillover, cardiac DHPG production was less in the patients with HCM, suggesting reduced neuronal uptake of norepinephrine.

Because of this defect, any stimulus that would increase cardiac sympathetic tone would be expected to exaggerate increments in norepinephrine at cardiac adrenoceptors. Levy and Blattberg and Masuda and Levy found that inhibition of neuronal uptake with cocaine or desipramine augmented cardiac responses to infused norepinephrine and prolonged responses to cardiac sympathetic nerve stimulation. The possibility that a similar exaggerated response to sympathetic stimulation occurs in patients with HCM is an area of current investigation.

Reduced cardiac neuronal uptake of norepinephrine was noted despite the markedly higher myocardial mass in the patients with HCM. Correcting norepinephrine uptake for the greater myocardial mass exhibited by the patients with HCM would have resulted in an even larger difference from the control subjects in terms of calculated neuronal uptake per unit mass of myocardium. We chose to not perform this calculation because of the inability...
to measure muscle mass in the specific region of myocardium drained by the GCV.

As in the heart, the percent extraction of norepinephrine was less in the forearm circulation in the patients with HCM than in the control subjects. This did not necessarily mean, however, that patients with HCM had a diffuse abnormality of neuronal uptake. The patients with HCM had higher rates of forearm blood flow than the control subjects. Previous studies in this laboratory have shown that percent extraction of norepinephrine in the forearm circulation is inversely related to forearm blood flow.

This inverse relation was confirmed in the present study (Figure 4). The significantly higher forearm blood flow in the patients with HCM could explain the lower percent extraction of norepinephrine in the forearm circulation of the patients with HCM. In contrast with the arm, the percent extraction of norepinephrine in the heart was unrelated to regional blood flow. The higher forearm blood flow in the patients with HCM is unexplained and, to our knowledge, has not been reported previously.

In both study groups, forearm extraction of isoproterenol was only slightly less than that of norepinephrine, consistent with the previous findings that neuronal uptake accounts for only a small proportion of norepinephrine removal in the forearm. Only a small amount of DHPG was produced in the forearm, and the DHPG production rate and norepinephrine spillover rate were unrelated in the forearm. The forearm, therefore, may not be a suitable region to detect small abnormalities in neuronal uptake and the present data do not allow conclusions about whether neuronal norepinephrine uptake is impaired in the forearms of the patients with HCM. Nevertheless, the finding that total body spillover of norepinephrine and arterial DHPG were similarly increased in the patients with HCM argues against a diffuse abnormality of neuronal norepinephrine uptake.

Left ventricular systolic and diastolic pressures and pulmonary artery pressure were higher and mean arterial pressure was lower in the patients with HCM compared with the control subjects. These hemodynamic abnormalities were unrelated to the reduction in neuronal norepinephrine uptake in the patients with HCM. In contrast, the cardiac spillover rate of norepinephrine, the cardiac AV difference in norepinephrine, and the cardiac production rate of norepinephrine all correlated positively with peak left ventricular pressure. It is not possible to discern whether the increases in left ventricular pressure in the patients with HCM were the cause or the result of the alterations in norepinephrine kinetics.

Abnormalities in norepinephrine kinetics have been noted in patients with dilated cardiomyopathy. However, systemic levels of norepinephrine were often markedly elevated in these patients, indicating generalized sympathetic activation to compensate for severe congestive heart failure. Results about whether cardiac norepinephrine uptake is impaired in dilated cardiomyopathy have been inconsistent. No previous study has analyzed regional norepinephrine kinetics in patients with HCM. A study of the cardiac AV difference in plasma norepinephrine indicated no significant increase in patients with HCM, and studies of myocardial norepinephrine and adrenoceptor density in HCM were inconclusive.

Norepinephrine induces myocardial hypertrophy and may differentially affect the ventricular septum compared with the right and left ventricular free walls. Norepinephrine also induces vascular smooth muscle hypertrophy and hyperplasia and diffuse myocardial scarring, common morphologic features of HCM. Catecholamine stimulation also increases myocardial contractility and decreases the threshold for atrial and ventricular arrhythmias, common clinical features of HCM. The present findings therefore suggest that abnormalities in norepinephrine kinetics may play a role in the morphogenesis and pathophysiology of this disease.

References


KEY WORDS: myocardial hypertrophy • norepinephrine • hypertrophic cardiomyopathy
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