Myocardial Presynaptic and Postsynaptic Autonomic Dysfunction in Hypertrophic Cardiomyopathy

Michael Schäfers, David Dutka, Christopher G. Rhodes, Adriaan A. Lammertsma, Flemming Hermansen, Otmar Schober, Paolo G. Camici

Abstract—Although hypertrophic cardiomyopathy (HCM) is genetically determined, several other factors, including autonomic dysfunction, may play a role in the phenotypic expression. A recent study using positron emission tomography with $[^{11}C]CGP$ 12177 ($[^{11}C]CGP$) demonstrated that β-adrenoceptor (BAR) density is reduced in HCM and is correlated with disease progression. This present study tested the hypothesis that this downregulation is associated with reduced catecholamine reuptake (uptake 1) by myocardial sympathetic nerve terminals leading to increased local norepinephrine concentration. Myocardial presynaptic catecholamine reuptake was assessed by measuring the volume of distribution ($V_d$) of the catecholamine analogue $[^{11}C]$hydroxyephedrine ($[^{11}C]$HED) in 9 unrelated HCM patients aged 45±15 years. The maximum number of binding sites ($B_{max}$) for myocardial βAR, density was measured in 13 unrelated HCM patients aged 40±12 years using the nonselective β blocker $[^{11}C]CGP$. Six patients were studied with both $[^{11}C]$HED and $[^{11}C]CGP$. Comparison was made with two groups of healthy control subjects for each ligand ($[^{11}C]$HED, n=10, aged 35±8 years; $[^{11}C]CGP$, n=19, aged 44±16 years). Myocardial $V_d$ of $[^{11}C]$HED (33.4±4.3 mL/g tissue) and βAR density (7.3±2.6 pmol/g tissue) were significantly reduced in HCM patients compared with control subjects (71.0±18.8 mL/g tissue, $P<.001$, and 10.2±2.9 pmol/g tissue, $P=.008$, respectively). These results are consistent with our hypothesis that myocardial βAR downregulation in HCM is associated with an impaired uptake-1 mechanism and hence increased local catecholamine levels. (Circ Res. 1998;82:57-62.)

Key Words: cardiomyopathy, hypertrophic ▪ autonomic dysfunction ▪ catecholamines ▪ beta adrenoceptors ▪ positron emission tomography

Most cases of HCM are familial with an autosomal dominant pattern and mutation of genes that encode myocardial contractile proteins.1–4 Although this is the case in the majority of HCM patients, there is considerable variation in the clinical manifestations of the disease that may not be always evident in obligate carriers.5,6 It has been hypothesized that other factors could play a role in the phenotypic expression of this condition. Some clinical features of HCM, such as left ventricular hypercontractility, the propensity to tachyarrhythmias,7 and the positive therapeutic effect of β blockers,8 suggest an involvement of the autonomic nervous system with increased sympathetic activity.

Accordingly, using the nonselective β blocker $[^{11}C]CGP$ with PET, we have previously demonstrated9 that myocardial βAR density is reduced in patients with HCM compared with normal control subjects. In addition, using the same technique, we have recently demonstrated that a negative correlation exists between the density of myocardial βARs and left ventricular function in patients with HCM.10 Receptor down-regulation is normally a reaction to increased agonist concentration in the target tissue. In principle, an increased tissue norepinephrine concentration could result from increased neurotransmitter release from the nerve terminals and/or from an impaired neurotransmitter reuptake into the nerve terminal (uptake 1). The latter process can be assessed noninvasively with PET using the catecholamine analogue $[^{11}C]$HED.

We therefore tested the hypothesis that the downregulation of myocardial βAR in HCM is associated with reduced catecholamine reuptake by the myocardial sympathetic nerve terminals using PET studies with $[^{11}C]$HED and $[^{11}C]CGP$ in patients with HCM and in healthy control subjects.

Materials and Methods

Study Population

Patients

Sixteen unrelated HCM patients, aged 43±14 years, of a total of 120 attending the Hammersmith Hospital were identified as suitable for study (Table 1). All underwent preliminary screening, which included full history and clinical examination, ECG, and echocardiogram. Since treatment with β blockers is known to affect myocardial βAR density, the main exclusion criterion of the present study was a current or past history of treatment with β blockers. In addition, patients who had taken amiodarone during the last year were excluded because of questions about its sympatholytic activity. In all 16 patients, left
ventricular hypertrophy was asymmetrical and most marked in the septum in all cases. All patients were clinically stable, and none had current or past evidence of left ventricular failure. Patients receiving current or past evidence of left ventricular failure. Patients receiving

Selected Abbreviations and Acronyms

- $bAR$ = $\beta$-adrenoceptor
- BGO = bismuth germanate
- CGP = CGP 12177
- COV = coefficient of variation
- FWHM = full width at half maximum
- HCM = hypertrophic cardiomyopathy
- HED = hydroxyephedrine
- PET = positron emission tomography
- ROI = region of interest
- $V_d$ = volume of distribution

Control Subjects

Two groups of age- and sex-matched healthy control subjects were studied to limit radiation exposure. Ten subjects (aged 35–6 years) served as controls for $[^{11}C]CGP$, and a second group of 19 subjects (aged 45±16 years) served as controls for $[^11C]CGP$. All control subjects had no history of cardiac disease, a low risk profile, and normal physical examination. All had normal resting ECGs and negative exercise tests in response to a high workload.

All subjects gave written informed consent to the protocol, which was approved by the Hammersmith Hospital Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee (ARASC).

Study Protocol

Myocardial $bAR$ density was derived from the maximum number of binding sites ($B_{max}$) obtained from the $[^{11}C]CGP$ scan in 13 patients (aged 40±12 years), and transporter-mediated neuronal catecholamine uptake was determined by measuring the $V_d$ of $[^{11}C]HED$ in 9 patients (aged 45±15 years). In 6 patients, both scans were performed. Plasma catecholamines were measured at three points during each study, and venous blood samples were taken with the subject in the supine position at baseline ($\pm$ 30 minutes after the insertion of the venous cannula) and at 30 and 60 minutes thereafter.

PET

The $[^{11}C]CGP$ and $[^{11}C]HED$ PET scans were performed with the subjects positioned on the bed of an ECAT 931–08/12 positron emission tomograph (Siemens/CTI Inc) with simultaneous acquisition of 15 planes. First, a rectilinear scan was performed using an external ring source filled with $^{68}$Ge. This scan was used to position the left ventricle as close as possible to the center of the axial and transaxial fields of view of the scanner. After final positioning, a 20-minute transmission scan was performed, and the attenuation correction coefficients for each line of response in the emission sinograms were calculated from this scan. The transmission scan was followed by the measurement of myocardial blood volume using inhaled oxygen-15–labeled carbon monoxide ($C^{15}O$) and 10 minutes later (to allow for decay of radioactivity) by the measurement of myocardial blood flow by means of oxygen-15–labeled water ($H_2^{15}O$) as described previously. The $H_2^{15}O$ scan was also used to calculate tissue fraction, defined as the proportion of tissue within a given ROI that is capable of rapidly exchanging water. After another 10 minutes, either the $[^{11}C]CGP$ or $[^{11}C]HED$ scan was carried out as described below. Six HCM patients had both $[^{11}C]CGP$ and $[^{11}C]HED$ scans performed on different days.

$[^{11}C]HED$ Scan

$[^{11}C]HED$ was prepared by direct $N$-methylolation of metaraminol with $[^{11}C]$methyl iodide in sulfoxide as previously reported. An intravenous infusion of $[^{11}C]HED$ (350±24 MBq) was given over a 2-minute period. A 38-frame dynamic emission scan of 65-minute duration was used to define the temporal distribution of the tracer in the myocardium. This scan consisted of a 30-s background frame before the infusion of $[^{11}C]HED$, followed by six 5-s frames, six 10-s frames, three 20-s frames, four 30-s frames, five 60-s frames, four 150-s frames.

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<th>TABLE 1. Clinical and Echocardiographic Results in HCM Patients</th>
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IVS indicates interventricular septum; PW, posterior wall; LVEDD/LVESD, left ventricular end-diastolic/end-systolic diameter; FS, fractional shortening; LVOT, left ventricular outflow tract velocity; and E:A, early-to-late transmitral flow velocity ratio.
and nine 300-s frames. Arterialized venous blood was sampled continuously from the antecubital vein of a heated hand using a peristaltic withdrawal pump, and the whole-blood radioactivity concentration was monitored using a BGO detection system. In addition, typically, 10 blood samples were taken manually during the scan for the measurement of plasma metabolite concentrations and whole-blood–to–plasma [\(^{11}\)C]HED concentration ratios and to calibrate the on-line detection system.\(^a\)

\[^{11}\text{C}]\text{CGP Scan}\n
\[^{11}\text{C}]\text{CGP} was prepared as reported previously.\(^b\) The measurement of myocardial \(\beta\)-AR density was performed according to a double-injection protocol described by Delforge et al\(^b\) and modified by us.\(^a\) Briefly, the first dose of high specific activity \[^{11}\text{C}]\text{CGP} (159±29 MBq, 5.7±2.3 \mu\text{g}) was infused intravenously over 2 minutes, followed by 30 minutes later by a second low specific activity injection (300±67 MBq, 28.6±5.8 \mu\text{g}) infused over 2 minutes. A 55-frame dynamic emission scan was used to measure the temporal and spatial distribution of the tracer in vivo. During the 30-minute period after the start of the first injection, 24 time frames (eight 15-s, four 30-s, two 60-s, two 120-s, and eight 150-s frames) were acquired. The second injection was then given, and the scan was completed with another group of 30 frames, analogous to the sequence after the first injection, but extended by six 150-s frames. Venous blood was continuously withdrawn and passed through a BGO counting system to assess changes in \[^{11}\text{C}]\text{CGP} blood concentration with time.\(^b\) This information was used to correct the \[^{11}\text{C}]\text{CGP} scan for vascular activity. Five calibration blood samples were taken manually during this period and assayed for \(^{11}\text{C}\text{ activity in a well counter, which was cross-calibrated with the scanner.\(^a\)\n
PET Data Analysis

All sinograms were normalized, corrected for attenuation, and then reconstructed to provide transaxial images with a spatial resolution of 8.4-mm FWHM and a slice thickness of 6.6-mm FWHM. Data acquisition and initial processing were performed using dedicated array processors on a MicroVax II computer (Digital Equipment Corp). Images were then transferred to a SUN workstation (SUN Microsystems Inc) and further analyzed by dedicated software developed under the Matlab mathematical software package (The MathWorks Inc). Images were resliced by defining the heart axis in the vertical and horizontal long-axis views. Thin short-axis slices perpendicular to the heart axis were then constructed and displayed. To define the length of the heart, the first (apical) and last (basal) slices containing left ventricular myocardium were identified from this series of short-axis slices. In order to have a fixed number of 12 slices for each study, a new slice thickness was determined by dividing the heart length by twelve. The final set of short-axis slices was then obtained by taking into account the new calculated slice thickness in the reslicing process. In each of the resliced short-axis slices, inner and outer myocardial borders were defined by manual tracing, and additional lines through the anterior and inferior septum were drawn on each slice. For the regional analysis, ROIs were defined by dividing the left ventricular myocardium into a 14-segment bull’s-eye scheme as follows. First, the myocardial area between the anterior and inferior septal lines of the apical slice was defined as a septal quadrant, and the remaining myocardium was divided into anterior, lateral, and posterior quadrants. The midventricular and basal slices were divided into five ROIs each (ROIs 5 to 14) by further dividing the septal quadrant into equal anterior and inferior ROIs. The ROIs from the 12 resliced short-axis slices were then reduced in number by averaging the corresponding regions in the apical (1–4), midventricular (5–8), and basal (9–12) slices. In a further step, a whole-heart ROI was created by taking into account the new calculated slice thickness in the reslicing process. In each of the resliced short-axis slices, inner and outer myocardial borders were defined by manual tracing, and additional lines through the anterior and inferior septum were drawn on each slice. For the regional analysis, ROIs were defined by dividing the left ventricular myocardium into a 14-segment bull’s-eye scheme as follows. First, the myocardial area between the anterior and inferior septal lines of the apical slice was defined as a septal quadrant, and the remaining myocardium was divided into anterior, lateral, and posterior quadrants. The midventricular and basal slices were divided into five ROIs each (ROIs 5 to 14) by further dividing the septal quadrant into equal anterior and inferior ROIs. The ROIs from the 12 resliced short-axis slices were then reduced in number by averaging the corresponding regions in the apical (1–4), midventricular (5–8), and basal (9–12) slices. In a further step, a whole-heart ROI was created by averaging all pixels within the area between the outer and inner traces for all 12 slices. These ROIs were then applied to all emission images of the different scans.\(^a\)

Volume of Distribution of [\(^{11}\text{C}]\text{HED}\n
The analysis of the myocardial time–activity curves was based on the assessment of \(V_d\) using a single tissue compartment model and least-squares nonlinear regression analysis to provide influx and efflux rate constants (\(K_i\) and \(K_e\), respectively), where \(V_d = K_i / K_e\). A correction was included to account for spillover of radioactivity from arterial blood into the myocardium. The input function was obtained jointly from the data obtained from the BGO counting system (for times >15 minutes) and from an ROI situated over the left atrium for time points between 0 and 15 minutes. This combination was necessary because of a significant apparent loss of \[^{11}\text{C}]\text{HED} from arterialized blood early in the studies and the progressive increase in spillover from the myocardial tissue into the left atrial ROI during the later phases of the study. The part of the BGO curve representing the late phase was used to correct for the spillover of radioactivity into the left atrium. Plasma metabolite concentrations, determined using HPLC, were used to provide the corrected plasma \[^{11}\text{C}]\text{HED} input functions. The resulting values of \(V_d\) were then corrected for partial volume and wall motion effects using the measured values of tissue fraction (milliliters of exchangeable tissue per milliliter of ROI, obtained from the H\(^2\)O scan).\(^c\) The values of \(V_d\) were then converted from mL/mL tissue to mL/g tissue by dividing by 1.04 (myocardial tissue density).\(^d\)

Measurement of Myocardial \(\beta\)-AR Density

Myocardial time–activity curves were corrected for radioactive decay and for vascular activity using the regional values of blood volume and the radioactive concentration of blood samples taken throughout the dynamic scan. The sections of the curve corresponding to the two slow clearance phases, which represent the dissociation of \[^{11}\text{C}]\text{CGP} bound to \(\beta\)-AR, were exponentially extrapolated back to the start of the infusions. \(\beta\)-AR density was then determined as the maximum number of available specific \[^{11}\text{C}]\text{CGP} binding sites per gram of tissue (\(B_{\text{max}}\)) in the ROIs as reported previously.\(^e\) The resulting values of myocardial \(\beta\)-AR density were then divided by 1.04 (myocardial tissue density) to convert from pmol/mL tissue to pmol/g tissue.

Statistics

All measured values are expressed as mean±SD. Differences in variances between data in the two studied groups were tested by Levene’s test for equality of variances. For statistical analysis of differences in age, plasma catecholamine levels, ROI size, global \(\beta\)-AR density, global \(V_d\) of \[^{11}\text{C}]\text{HED}, and myocardial blood flow between HCM patients and control subjects, two-tailed unpaired \(t\) tests for equal/unequal variances were performed. Correlation between the global \(\beta\)-AR density and \(V_d\) of \[^{11}\text{C}]\text{HED} and between the PET studies and the echocardiographic findings were tested using linear regression analysis. The regional distribution of global \(\beta\)-AR density and the \(V_d\) of \[^{11}\text{C}]\text{HED} was calculated using COV over all 14 bull’s-eye segments for each study. Differences in COV between HCM patients and control subjects were then tested by two-tailed \(t\) tests for equal/unequal variances. A value of \(P<.05\) was considered to be statistically significant.

Results

Heart rate and blood pressure at baseline were not significantly different between HCM patients and control subjects, and there was no significant change in these parameters during both the \[^{11}\text{C}]\text{HED} and \[^{11}\text{C}]\text{CGP} scans, confirming no pharmacological effect of the tracers (Table 2). Baseline plasma catecholamines were similar in patients and control subjects (norepinephrine, 2.84±2.9 versus 1.77±1.2 nmol/L, \(P=.28\); epinephrine, 0.22±0.1 versus 0.31±0.2 nmol/L, \(P=.26\)). There were no significant changes in the plasma catecholamine levels measured in the samples obtained after injection of either \[^{11}\text{C}]\text{HED or} \[^{11}\text{C}]\text{CGP}. \n
Myocardial Blood Flow

Average left ventricular blood flow was comparable in patients and control subjects (0.92±0.19 versus 1.00±0.21 mL·min\(^{-1}\)·g\(^{-1}\)), respectively, \(P=.26\), and there were no differ-
ences in the different cardiac regions in patients or control subjects.

**Volume of Distribution of [11C]HED**

In patients with HCM, the myocardial V_d of [11C]HED was 33.4±14.3 compared with 71.0±18.8 mL/g (P<.001) in control subjects (Fig 1). The COV of the regional V_d over the 14-segment bull’s-eye scheme was not significantly different between HCM patients and control subjects (COV, 21.8±7.3% versus 17.0±4.1%, respectively; P=.09). In HCM there was a significant correlation (r=.76, P=.017) between left ventricular shortening and myocardial V_d of [11C]HED.

**Myocardial βAR Density**

Global βAR density was significantly lower in the patients (7.3±2.6 pmol/g tissue) compared with the control subjects (10.2±2.9 pmol/g tissue, P=.008) (Fig 2). Regional analysis showed no significant difference in tracer distribution throughout the 14 ROIs both in HCM patients and in control subjects (COV, 17.1±6.6% versus 18.7±7.1%; P=.51). In the six HCM patients studied with both [11C]HED and [11C]CGP, there was no significant correlation between myocardial V_d of [11C]HED and βAR density (r=.34, P=NS).

**Discussion**

The results of the present study confirm and extend previous observations that suggest a dysfunction of the myocardial autonomic nervous system in patients with HCM. As reported earlier, myocardial βAR density is significantly reduced in HCM patients compared with control subjects.9,10 The degree of βAR downregulation observed in the present study (≈32%) is in good agreement with previously reported results (≈35%) in patients with preserved left ventricular function.7

The second and major finding of the present study is significant impairment of transporter-mediated neuronal uptake via the uptake-1 mechanism in patients with HCM. This is consistent with previous reports using single-photon emission tomography, where reduced myocardial fixation of an iodine-123–labeled marker, [123I]-metaiodobenzylguanidine, was demonstrated in HCM patients, who experienced increased washout of the catecholamine analogue from the myocardium.17–22 Furthermore, using labeled norepinephrine,
with aortic and coronary sinus sampling, Brush et al\(^3\) found significantly reduced myocardial norepinephrine uptake in patients with HCM compared with control subjects (59±17\% versus 79±13\%).

The analysis of \(^{[1]}\text{C}\)HED kinetics was extended beyond the simple assessment of tracer uptake to improve the accuracy and sensitivity of the measurement.\(^{24-26}\) A simple uptake measurement is time dependent because of the constantly changing myocardial concentration of \(^{[1]}\text{C}\)HED after injection, and the rapid sequestration of the tracer by the uptake-1 transporter is flow-limited except for the most severe cases of uptake-1 malfunction.\(^7\) The \(V_d\) of the tracer (which is independent of time and blood flow) was therefore measured to overcome these limitations. The technique was additionally modified by including (1) subtraction of tracer spillover from the myocardium into the ventricular ROI in the estimation of arterial blood time-activity function, (2) correction for the substantial "grow in" of radioactive metabolites of \(^{[1]}\text{C}\)HED in the circulating plasma, and (3) partial volume correction of the \(V_d\) using the measurement of tissue fraction.

An alternative interpretation of the reduced values of the \(V_d\) of the ligand could be that the hypertrophy and abnormal structure of the myocardium in HCM results in a relative reduction of the number of sympathetic nerve terminals per gram of tissue. We do not consider this explanation to be tenable because the reduction in \(V_d\) was associated with a much greater increase in the clearance of the tracer from the tissue in HCM patients compared with normal subjects. A reduction in nerve terminals alone would not result in an increase in the clearance of the tracer from tissue. In addition, the perfusable tissue index was similar in the patients and control subjects, and the changes in the \(V_d\) were not confined to the regions of maximal myocardial hypertrophy.

Previous clinical studies of catecholamine reuptake using \(^{[1]}\text{C}\)HED have relied on a relatively crude kinetic analysis of the studies with terms such as retention, retention fraction, and retention index being used to describe the regional myocardial concentration of this tracer after normalization to the area under the arterial blood time-activity curve (derived from an ROI over the left ventricle). This analysis is sufficient for clinical studies in which there is gross disturbance or loss of sympathetic nerve terminals, but because we anticipated relatively subtle changes in HCM, a new analysis was developed. Animal models\(^{13,28}\) and studies in the isolated rat heart\(^7\) have defined the behavior of \(^{[1]}\text{C}\)HED, particularly in response to blockade of the uptake-1 transporter with desipramine and differing concentrations of norepinephrine. Similar studies are not feasible in humans, but we feel that the sympathomimetic \(^{[1]}\text{C}\)HED provides a surrogate model of norepinephrine reuptake by the sympathetic nerve terminal.

The regional analysis performed in the present study indicates that the abnormalities of sympathetic innervation are relatively homogeneous throughout the left ventricular myocardium. This observation is in keeping with the demonstration that other key features of this disease, eg, the distribution of some pathological changes,\(^29\) diastolic function abnormalities,\(^30\) and coronary vasodilator reserve,\(^31\) do not necessarily match the geography of macroscopic hypertrophy. From a pathophysiological point of view, these studies strengthen the hypothesis that the increased local neurotransmitter concentration in the synaptic cleft is associated with a chronic reduction in catecholamine reuptake and contributes to myocardial \(\beta\)AR downregulation in HCM, although we could not find any relationship between \(\beta\)AR and \(^{[1]}\text{C}\)HED \(V_d\) in the 6 patients who underwent both studies. Similar results have been reported in idiopathic dilated cardiomyopathy, in which myocardial \(\beta\)AR downregulation has been demonstrated using \(^{[1]}\text{C}\)CGP and PET.\(^3\) However, studies of myocardial norepinephrine concentration in biopsy specimens have yielded conflicting results; the mean norepinephrine concentration in HCM was normal although substantially elevated in 2 patients, whereas in patients with dilated cardiomyopathy, myocardial norepinephrine concentration was reduced.\(^33\) Although the arteriovenous difference of norepinephrine is significantly higher in HCM patients than in control subjects, cardiac production of dihydroxyphenylglycol is reduced for a given amount of norepinephrine spillover, suggesting reduced neuronal uptake of norepinephrine.\(^25\) Furthermore, inhibition of neuronal uptake by desipramine augmented the cardiac response to administered norepinephrine and prolonged the response to sympathetic stimulation.

Unlike patients with congestive heart failure, no significant increase in circulating catecholamines was found in patients with HCM in this or other studies,\(^9,10,32\) despite the demonstration of myocardial \(\beta\)AR downregulation. This supports the model proposed by Bristow et al,\(^34\) suggesting that increases in local neurotransmitter concentrations rather than circulating catecholamine levels are probably responsible for myocardial \(\beta\)AR downregulation in HCM.

The ligand used for quantification of \(\beta\)ARs in the present study is a radiolabeled nonselective \(\beta\) blocker, \(^{[1]}\text{C}\)CGP. Human myocardium contains a relatively high proportion of the \(\beta_1\) \(\beta\)AR subtype (14\% to 40\% of the total \(\beta\)AR population), with the downregulation that occurs in the failing ventricle being almost entirely due to reduction in the \(\beta_1\) subtype. Although we did not perform selective measurements, we consider it reasonable to assume that the reduction in \(\beta\)AR density as indicated by \(^{[1]}\text{C}\)CGP binding reflects a reduction in the number of available receptors of the \(\beta_1\) subtype. The relative importance of the \(\beta\)AR subtypes in HCM is unknown, but we\(^27\) have previously demonstrated a significant positive correlation between left ventricular function (as assessed by echocardiography) and myocardial \(\beta\)AR density in a group of HCM patients with and without heart failure. In addition, only those patients with HCM undergoing no treatment or treatment with verapamil alone were eligible for the present study, and they represent those with less symptomatic limitation. Because no relationship has been demonstrated between symptoms, phenotype, and prognosis, it is unlikely that the present study describes an abnormality that is not present in those patients receiving treatment for more significant symptomatic limitations or dysrhythmias.

Conclusions
The present study is the first to show noninvasively and quantitatively that norepinephrine reuptake by the cardiac sympathetic neurons is abnormal in HCM. These findings offer an explanation for the global reduction in \(\beta\)AR, with
insufficient spillover of norepinephrine to elevate the plasma norepinephrine concentration. Further studies are needed to ascertain whether these changes in the cardiac sympathetic system relate to the variable phenotype and prognosis seen within pedigrees with the same mutation.

Acknowledgments

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References

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