Abnormalities of Cardiac Sympathetic Function in Pacing-Induced Heart Failure as Assessed by [123I]Metaiodobenzylguanidine Scintigraphy

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Background  Increased activity of the sympathetic nervous system contributes significantly to the pathophysiology of heart failure. However, cardiac efferent sympathetic function has not been well characterized in this disorder. In this study, we evaluated cardiac sympathetic innervation using [123I]metaiodobenzylguanidine (MIBG) and compared this with left ventricular (LV) tissue norepinephrine concentration and myocardial perfusion, assessed by 201TI, in a canine model of heart failure.

Methods and Results  Planar and tomographic cardiac imaging was performed for MIBG and 201TI in 23 dogs: 8 normal dogs (group 1) and 15 dogs with heart failure induced by right ventricular pacing at 250 beats per minute either continuously for 3 weeks (group 2) or intermittently for 7 weeks (group 3). Plasma and LV tissue norepinephrine concentrations were also measured. Scintigraphic studies in group 2 demonstrated reduced cardiac MIBG activity at heart failure (0.17±0.04 versus 0.29±0.05 counts per megabecquerel per pixel at baseline, mean±SD; \( P = .0001 \)), whereas thallium activity was unchanged from baseline. This reduction in cardiac MIBG activity with heart failure was associated with increased intramural variability in the distribution of MIBG activity (21±8% versus 13±7% at baseline, mean±SD; \( P = .0001 \)). The MIBG heart-to-lung ratio was calculated for all groups to control for the inhibitory effect that plasma norepinephrine has on the neuronal uptake of MIBG. There was a positive correlation between LV tissue norepinephrine and the MIBG heart-to-lung ratio (\( r = .67; P < .001; n = 22 \)), for which the group 2 heart failure animals had the lowest values. No relation existed between plasma norepinephrine concentration and the MIBG heart-to-lung ratio. In addition, regional LV tissue norepinephrine concentration and MIBG activity were both lowest at the apex in normal (group 1) and heart failure (group 2) dogs. The MIBG heart-to-lung ratio also correlated inversely with cardiac filling pressure (\( r = -.59; P < .05 \)) and heart rate (\( r = -.65; P < .01 \)) and positively with cardiac output (\( r = .53; P < .05 \)).

Conclusions  Heart failure is associated with severe cardiac adrenergic dysfunction manifested by reduced MIBG activity and increased heterogeneity in the LV distribution of MIBG. Furthermore, MIBG scintigraphy is a simple noninvasive method for assessing global and regional LV tissue norepinephrine levels. (Circulation. 1994;89:2843-2851.)

Key Words  •  heart failure, congestive  •  nervous system  •  metaiodobenzylguanidine  •  norepinephrine

There is general agreement that activation of the sympathetic nervous system is important in the pathophysiology of congestive heart failure, and recent studies demonstrate that this activation precedes the clinical manifestations of heart failure. Impairment of baroreflex sensory mechanisms with diminished activity of inhibitory autonomic afferent regulation may contribute to this state of sympathoexcitation. Acutely, this enhanced adrenergic activity may have a salutary effect in supporting cardiac output through its positive inotropic effect on the heart. However, chronic heart failure is marked by an attenuation in cardiac responsiveness to p-adrenergic stimuli, and prolonged sympathetic activation may ultimately contribute to the progression of heart failure and arrhythmias.

In an attempt to understand the mechanism by which sympathetic neural overactivity may adversely affect the course of heart failure, much attention has been directed toward the possible detrimental effects of elevated levels of circulating norepinephrine. However, plasma norepinephrine is derived from adrenergic activity throughout the body and is therefore not a specific index of cardiac adrenergic activity. Knowledge of cardiac adrenergic activity could be of greater potential pathogenetic and prognostic significance in heart failure, but assessment of cardiac sympathoneural function is limited by presently available techniques, which require complex invasive procedures that are impractical and insensitive for detecting regional changes in cardiac sympathetic function. Therefore, development of a noninvasive means of assessing global and regional cardiac adrenergic function is a high priority.

Noninvasive scintigraphy with [123I]metaiodobenzylguanidine (MIBG), an analogue of guanethidine that shares many neuronal transport and storage mechanisms with norepinephrine, can image efferent adrenergic nerve terminals in the heart. MIBG competes with norepinephrine for neuronal uptake (uptake-1) and is also taken up by a low-affinity nonneuronal mechanism (uptake-2). Moreover, its potential for future use in clinical settings is facilitated by the ability to acquire images with a standard gamma camera. In the
present study, this technique was applied to an experimental canine model of heart failure produced by rapid ventricular pacing. This model is characterized by the predictable development of biventricular dilatation without hypertrophy and hemodynamic changes similar to human heart failure.25-27 As in human heart failure, plasma norepinephrine levels are elevated, and left ventricular tissue norepinephrine and baroreceptor sensitivity are reduced.4,25,28,29

To assess a spectrum of severity of pacing-induced heart failure, we examined three groups of animals, a group of normal dogs and two groups that were paced to heart failure of various hemodynamic severities. Accordingly, the hypotheses tested in this study were that (1) pacing-induced heart failure produces cardiac sympathetic neuronal dysfunction as manifested by reduced myocardial MIBG activity and (2) myocardial MIBG activity would correlate with left ventricular tissue norepinephrine concentration.

Methods

Studies were performed in 23 adult mongrel dogs weighing 19 to 30 kg. All dogs were acclimatized to the laboratory and taught to lie quietly in the right decubitus position to permit conscious hemodynamic and echocardiographic assessment. Eight normal dogs (group 1) were used as controls for left ventricular volume and were housed and cared for similarly to the paced dogs. In 9 dogs, heart failure was induced by continuous rapid ventricular pacing at 250 beats per minute for 3 weeks (group 2). In another group of 6 animals, heart failure of intermediate severity was produced by a novel intermittent pacing regimen in which the dogs were paced at 250 beats per minute with alternating periods of 48 hours of pacing and 24 hours of sinus rhythm for 7 weeks (group 3). Experiments on animals were conducted in accordance with the guidelines of the Canadian Council on Animal Care (1984).

Under thiopental sodium general anesthesia, a unipolar pacemaker lead was advanced via the external jugular vein to the right ventricular apex under fluoroscopic guidance. A programmable pulse generator (Medtronic SX-5985, Medtronic Inc) was inserted into a subcutaneous cervical pocket. All animals were allowed to recover from surgery for 1 week before asynchronous rapid ventricular pacing at 250 beats per minute was initiated.

Hemodynamics and Echocardiography

All paced dogs underwent echocardiographic and hemodynamic assessment in sinus rhythm immediately before initiation of pacing. Echocardiographic studies were performed with an ultrasonograph (ATL Mark 600, Advanced Technology Laboratory) with a 5-MHz transducer with the dogs fully awake, lying quietly in the right decubitus position. Images were recorded on 0.5-inch videotape with a VHS video recorder (Panasonic NV8200) for later analysis. Standard left ventricular cross-sectional views were taken at the level of the papillary muscles, and internal left ventricular dimensions were obtained for the purposes of calculating ejection fraction as

\[(\text{diastolic} - \text{systolic area}) / \text{diastolic area} \times 100\]

After the echocardiographic assessment, dogs were weighed, and the hemodynamic studies were conducted with lidocaine local anesthesia with the dogs in the conscious state. A thermodilution Swan-Ganz catheter was introduced via the femoral vein for measurement of cardiac output and pulmonary wedge pressure. Mean arterial pressure was obtained with a micromanometer-tipped catheter (Mikro-Tip SPC-480, Millar Instruments) introduced into the descending aorta via the femoral artery. Catheters were removed after completion of the hemodynamic studies.

Echocardiographic and hemodynamic studies were repeated at 3 weeks in group 2 and at 7 weeks in group 3. These measurements were obtained in sinus rhythm according to the above protocol after a 15-minute stabilization period subsequent to deactivation of pacing. Paired echocardiographic data were available for all paced dogs, and hemodynamic studies were completed for 11 dogs.

Imaging Protocol

The dogs were injected while in sinus rhythm with 5 mCi IV 123I-MIBG and 4 hours later received 2 mCi 201Tl to simultaneously assess myocardial perfusion.20 Thirty minutes later, dual-isotope imaging was commenced with the dogs in sinus rhythm. The 5-hour delay in imaging was selected to maximize the amount of MIBG in the neuronal versus the extraneuronal compartment.24 Dual-isotope imaging was performed at baseline in the group 1 dogs; at both the baseline and 3-week time points for group 2; and in group 3 at 7 weeks.

In preparation for dual-isotope imaging, the dogs were fasted for 12 hours before receiving 2 to 4 mg IV of morphine sulfate, titrated to produce mild sedation, and then were suspended in a sling. An Elscint tomographic system with a general all-purpose collimator was used with 20% windows around the 72-keV and 159-keV photopeaks of 201Tl and 123I, respectively. Five-minute planar acquisition was performed in the anterior projection in a 256 x 256 matrix. A tomographic study was then performed over a 15-minute period with 180° continuous circular acquisition in 3° increments starting from the 45° right anterior oblique position. Sixty images were acquired and stored in a 64 x 64 matrix. Tomographic reconstruction was performed with a Butterworth filter with a cutoff of 0.35 in the fifth order. Horizontal short-axis, vertical, and horizontal long-axis slices, each 1 pixel thick, were generated (Fig 1).

Image Processing and Analysis

For all data processing, 123I-MIBG and 201Tl counts per minute were corrected for decay, and both were normalized to a 1-MBq (0.027-mCi) dose.

Planar Images

123I-MIBG activity in the heart and lung were measured in regions of interest (ROIs), 89 pixels in size, obtained from the anterior view. The means of two ROIs were used to calculate a ratio of heart-to-lung 123I-MIBG activity (Fig 2). Pulmonary MIBG activity was used in this way as an internal control for the negative competitive effect that an elevated plasma norepinephrine level may have on the uptake of MIBG (uptake-1).21-23 We assessed the interobserver variability of the MIBG heart-to-lung ratio in 22 dogs and found an excellent correlation (r = .85, P = .0001) with a low SEE (0.106). Similarly, ROIs were created over the liver and mediastinum, and 123I-MIBG activity in these areas was compared with cardiac activity. Since the lung and liver are sympathetically innervated, the MIBG activity in these organs was also examined to exclude a generalized effect of heart failure on sympathetic function as opposed to a specific effect on cardiac adrenergic function.

Tomographic Images

An ROI was drawn around the left ventricular MIBG and 201Tl images, and both radionuclides were quantified (counts per megabecquerel per pixel) separately. Quantification of regional left ventricular MIBG and 201Tl counts was performed for the lateral, inferior, and anterior walls and septum from the midventricular horizontal short-axis slice, and global left ventricular activity was calculated from a mean of these four regions. Apical counts were quantified from a mean of the midventricular vertical and horizontal long-axis slices. The ratio of MIBG to 201Tl was determined for the separate left
ventricular regions and for the mean of the midventricular horizontal short-axis slice (Fig 3) to account for the potential effect that perfusion could have on MIBG uptake. We assessed the interobserver variability of the MIBG-to-\(^{201}\text{TI}\) ratio in 20 dogs and found an excellent correlation \((r=.94, P=.0001)\) with a low SEE \((0.081)\). Intraimage regional variability in MIBG activity was calculated from the midventricular horizontal short-axis slice as the difference in the maximum and minimum regional counts divided by the maximum regional counts and expressed as a percentage.\(^{30}\)

After completion of the final scintigraphic study, dogs were killed with a lethal dose of KCl. Myocardial tissue from the lateral free wall of the left ventricle was removed and stored at \(-80^\circ\text{C}\). In addition, for the purposes of regional left ventricular analysis, myocardium from the septum, anterior wall, and apex was obtained from four dogs in group 1 and seven dogs in group 2.

Plasma and left ventricular tissue norepinephrine contents were determined by high-performance liquid chromatography with electrochemical detection.\(^{31}\) The results are expressed as picograms per milliliter of plasma and nanograms per gram of left ventricle.

**Statistical Analysis**

Intragroup comparisons were performed by paired \(t\) tests. Comparisons between groups of dogs were made with ANOVA and Tukey’s test. To study the regional variations in left ventricular MIBG activity and norepinephrine content, two-way ANOVA with repeated measures and Tukey’s test were used. Associations between tissue and plasma norepinephrine versus MIBG heart-to-lung ratio; and heart rate, pulmonary capillary wedge pressure, and cardiac output versus tissue norepinephrine were studied with regression analysis. Data are expressed as mean±SD, and a probability of \(P<.05\) was considered to be significant.

**Results**

**Continuous Pacing Regimen (Group 2)**

Since the principal study objective was to examine the effect of pacing-induced heart failure on cardiac sympathetic function as assessed by MIBG scintigraphy, group 2 data are presented here because these were the only animals with paired MIBG studies. Hemodynamic indexes and echocardiographically derived ejection fraction demonstrated the development of heart failure after 3 weeks of pacing with significant increases in heart rate \((83±22\text{ to } 161±9\text{ beats per minute, } P<.005)\)
and pulmonary wedge pressure (10±2 to 38±7 mm Hg, 
P<.005). This was accompanied by a decrease in cardiac output (131±28 to 76±9 mL · min⁻¹ · kg⁻¹, P<.05) and ejection fraction (52.7% to 22.5%, P<.005).

Left ventricular MIBG activity for group 2 is displayed in Table 1. There was a reduction in global cardiac MIBG activity at heart failure (from 0.29±0.05 to 0.17±0.04 counts per megabecquerel per pixel at baseline and heart failure, respectively; P=.0001), with MIBG activity decreasing significantly in all regions of the left ventricle. There was also regional variation in left ventricular MIBG activity, with the apex having the least and the anterior wall having the greatest activity both at baseline and after 3 weeks of pacing (Table 1). There was no change in global (0.50±0.11 versus 0.46±0.08 counts per megabecquerel per pixel at baseline and heart failure, respectively; P=NS) or regional left ventricular perfusion, as assessed by ²⁰¹Tl, associated with 3 weeks of pacing. Hence, the global MIBG-to-²⁰¹Tl ratio was reduced with the development of pacing-induced heart failure (0.58±0.07 to 0.39±0.04, P<.005).

There was greater intramural variability in the distribution of left ventricular MIBG activity with the development of pacing-induced heart failure (13±7% for baseline versus 21±8% for 3-week pacing, P=.0001; Fig 1).

In Table 2, cardiac MIBG activity is compared with that of other organs for the group 2 animals. Left ventricular MIBG activity was reduced from the baseline value with the development of heart failure (18.91±2.84 to 14.28±2.79 counts per megabecquerel, P<.005). Notably, the reduction in MIBG activity was selective for the heart, since pulmonary, mediastinal, and hepatic activity remained unchanged with the development of heart failure. The MIBG heart-to-lung ratio decreased significantly with 3 weeks of pacing (1.92±0.16 to 1.48±0.25, P=.0001), and similar changes (P<.005) were observed in the MIBG heart-to-mediastinum and heart-to-liver ratios.

Intermittent Pacing Regimen (Group 3)

The intermittent pacing regimen in group 3 produced a significant increase in the pulmonary capillary wedge pressure (8±2 to 23±8 mm Hg, P<.005) and decreases in cardiac output (205±77 to 118±23 mL · min⁻¹ · kg⁻¹, P<.05) and left ventricular ejection fraction (50±8% to 23±5%, P<.005) compared with baseline. With the development of heart failure, both group 2 and group 3 had similar decreases in ejection fraction. However, the intermittently paced animals had hemodynamically less severe heart failure, with both a lower pulmonary capillary wedge pressure (23±8 mm Hg for group 3 versus 38±7 mm Hg for group 2, P<.01) and heart rate (126±20 beats per minute for group 3 and 161±9 beats per minute for group 2, P<.01). There was also a trend (P=.057) for a higher cardiac output at heart failure in

![](image)

Fig 3. Dual-isotope emission computed tomograms for thallium (TL201, left) and [¹²³I]metaiodobenzylguanidine (123I-MIBG, right) in the horizontal short-axis (HSA) view at control. Quantification of regional and mean left ventricular thallium and MIBG activity was performed separately for each radionuclide, and the ratio of MIBG to thallium was determined. In this example, the mean left ventricular MIBG-to-thallium ratio is 0.68.

**TABLE 1. Impact of Pacing on Global and Regional Left Ventricular MIBG Activity in Group 2**

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Septum</th>
<th>Anterior</th>
<th>Lateral</th>
<th>Apex</th>
<th>Inferior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.29±0.05</td>
<td>0.27±0.06</td>
<td>0.30±0.05</td>
<td>0.29±0.05</td>
<td>0.24±0.05(1)</td>
<td>0.28±0.05</td>
</tr>
<tr>
<td>3-Wk HF</td>
<td>0.17±0.04*</td>
<td>0.16±0.05*</td>
<td>0.19±0.04*</td>
<td>0.18±0.04*</td>
<td>0.15±0.03*</td>
<td>0.16±0.03*</td>
</tr>
</tbody>
</table>

¹²³I-MIBG indicates [¹²³I]metaiodobenzylguanidine; HF, heart failure. n=9.

*P<.001 versus baseline; †P=.0001 for (1) apex vs all other regions at baseline; (2) anterior wall vs septum at baseline; (3) apex vs anterior and lateral walls at 3-wk HF; and (4) anterior wall vs septum and inferior wall at 3-wk HF.
Table 2. Cardiac and Other Organ 123I-MIBG Activity of Group 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline (Mean±SD)</th>
<th>3-Wk Heart Failure (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>18.91±2.84</td>
<td>14.28±2.79*</td>
</tr>
<tr>
<td>Lung</td>
<td>9.87±1.49</td>
<td>9.71±1.42</td>
</tr>
<tr>
<td>Heart/lung</td>
<td>1.92±0.16</td>
<td>1.48±0.25†</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>10.35±1.34</td>
<td>10.46±1.30</td>
</tr>
<tr>
<td>Heart/mediastinum</td>
<td>1.83±0.14</td>
<td>1.36±0.23*</td>
</tr>
<tr>
<td>Liver</td>
<td>13.29±1.15</td>
<td>12.98±1.40</td>
</tr>
<tr>
<td>Heart/liver</td>
<td>1.42±0.19</td>
<td>1.10±0.20*</td>
</tr>
</tbody>
</table>

MIBG indicates [123I]metaiodobenzylguanidine. n=9.

*P<.05 compared with baseline; †P=.0001 compared with baseline.

Fig 4 summarizes the left ventricular and other organ MIBG data for all three groups studied. Myocardial MIBG activity was lower in group 2 than in group 1 and 3 animals (P<.05). The MIBG heart-to-lung ratio was significantly reduced in group 2 compared with the other two groups (1.48±0.25 for group 2 versus 1.98±0.21 for group 1 and 1.80±0.24 for group 3, P=.001). The group 2 animals also had lower MIBG heart-to-mediastinum (P<.005) and heart-to-liver (P<.05) ratios.

Plasma and left ventricular tissue norepinephrine data for the three groups are shown in Fig 5. The plasma norepinephrine level for the group 2 dogs at heart failure was elevated compared with the other groups (879±363 for group 2 versus 400±164 for group 3 and 252±98 pg/mL for group 1; P<.0001), whereas the groups 1 and 3 dogs were not significantly different from each other. Left ventricular tissue norepinephrine concentrations were significantly (P=.0001) distinct for each of the three groups for which the group 2 animals had the lowest level (145±42 ng/g for group 2 versus 502±42 ng/g for group 1), and the group 3 animals had an intermediate concentration (299±76 ng/g).

There was a positive correlation between left ventricular tissue norepinephrine and the MIBG heart-to-lung ratio for all animals (r=.67, P<.001, n=22) (Fig 6). Normal dogs (group 1) had the highest MIBG and tissue norepinephrine levels, group 2 animals with the most severe heart failure had the lowest values, and group 3 dogs had intermediate values. Both the pulmonary capillary wedge pressure (r=-.59, P<.05, n=16) and heart rate (r=-.65, P<.01, n=16) for the groups 2 and 3 animals were negatively correlated with the MIBG heart-to-lung ratio. For these two groups, there was also a positive correlation between cardiac output and the MIBG heart-to-lung ratio (r=.53, P<.05, n=16). No correlation was found between plasma norepinephrine and the MIBG heart-to-lung ratio. Modest correlations also existed between left ventricular tissue norepinephrine and the MIBG heart-to-mediastinum ratio (r=.56, P<.01, n=22) and the heart-to-liver ratio (r=.43, P<.05, n=22) for all animals.

Regional left ventricular MIBG activity on the tomographic study and tissue norepinephrine levels for the
groups 1 and 2 animals are shown in Fig 7. A marked reduction in norepinephrine content, accompanied by a more modest reduction in MIBG activity, is present in all regions of the left ventricle of the group 2 animals at heart failure compared with group 1. In the group 2 animals, MIBG activity in the septum (0.16±0.05 counts per megabecquerel per pixel) is less than that of the anterior wall (0.19±0.04 counts per megabecquerel per pixel, P<.001), whereas the norepinephrine contents of these regions are similar. However, both groups demonstrate a matched reduction in apical MIBG activity and norepinephrine content compared with other regions of the left ventricle of the same group.

Discussion

The principal novel findings of the present study are that (1) pacing-induced heart failure is associated with a reduction in left ventricular MIBG activity, which is independent of any change in myocardial perfusion as assessed by thallium imaging; (2) there is greater heterogeneity in the distribution of MIBG in the left ventricle with the development of heart failure; (3) the MIBG heart-to-lung ratio is positively correlated with left ventricular tissue norepinephrine content, and MIBG scintigraphy detected the regional variation in tissue norepinephrine levels; and (4) the MIBG heart-to-lung ratio is positively correlated with cardiac output and inversely correlated with pulmonary capillary wedge pressure and heart rate.

Previous investigations have shown enhanced early washout of MIBG30,32 with reduced myocardial MIBG activity on delayed images in patients with dilated cardiomyopathy.30,32-34 Similar results were reported in a canine model of left ventricular hypertrophy and failure.35 Hemodynamics were not reported in these studies; thus, an assessment of the interaction between the hemodynamic severity of heart failure and MIBG activity cannot be made. Moreover, it is important to note that a concomitant assessment of myocardial perfusion to ensure the adequate delivery of MIBG to the myocardium was not made in these studies; this is a particularly important caveat in the canine study,35 given the presence of left ventricular hypertrophy.36 Our data demonstrate that pacing-induced heart failure is associated with a reduction in left ventricular myocardial MIBG activity, whereas perfusion, as assessed by thallium, remains unchanged. This latter finding is consistent with previous studies in this model that have demonstrated increased left ventricular myocardial blood flow without any change in its overall transmural distribution and the absence of myocardial lactate production.37,38 These data corroborate the use of MIBG in this model as a surrogate for cardiac sympathetic neuronal function without the requirement for a simultaneous assessment of myocardial perfusion.

As mentioned, studies in patients with dilated cardiomyopathy30,32 and in a canine model of heart failure35 have reported an enhanced early washout of myocardial MIBG. However, a general limitation of MIBG imaging is that it is less than ideal for performing kinetic analyses of cardiac sympathetic function because of its significant early nonneuronal uptake, which is minimized with delayed imaging 3 to 5 hours after injection.29,34 Recent studies suggest, however, that the non-
neuronal uptake of MIBG in the human heart may be considerably less than in the dog\(^{32,39}\); thus, MIBG kinetics may better approximate norepinephrine kinetics in the human heart. Interpretation of the previous studies in dilated cardiomyopathy\(^{30,32,33}\) is also limited by the concurrent use of digoxin and angiotensin-converting enzyme inhibitors, which can alter sympathetic activity\(^{40-42}\) and possibly myocardial MIBG activity.\(^{22,43}\) Norepinephrine competes with MIBG for neuronal uptake (uptake-1) and can inhibit MIBG accumulation.\(^{21-23}\) Therefore, we compared myocardial with pulmonary MIBG activity to control for any negative competitive effect that an elevated plasma norepinephrine level might have on MIBG uptake, since both of these organs would be exposed to circulating norepinephrine. Previous studies examining the potential for an elevation in pulmonary arterial pressure to affect norepinephrine extraction by the lungs have revealed conflicting results.\(^{44,45}\) In the present study, there was not a significant change in pulmonary MIBG activity.

Our rationale for selecting the lungs as an internal control for this potential effect of circulating norepinephrine was that (1) although they are anatomically extraneuronal, pulmonary endothelial cells actively take up MIBG and norepinephrine by the uptake-1 process\(^{46,47}\); (2) pulmonary MIBG accumulation can be competitively reduced by norepinephrine and by the uptake-1 inhibitor imipramine\(^{17,21}\); and (3) pulmonary sympathetic activity, as assessed by norepinephrine spillover, remains unchanged in heart failure.\(^{12}\)

We found a positive correlation between left ventricular tissue norepinephrine concentration and the MIBG heart-to-lung ratio across a spectrum of physiological circumstances. One other study\(^{29}\) reported a positive correlation between myocardial norepinephrine content and the ratio of myocardial-to mediastial MIBG activity; this association was found in the present study but was less significant than the correlation between tissue norepinephrine and the MIBG heart-to-lung ratio. The mediastinum is a heterogeneous structure that has not been demonstrated to possess uptake-1. Thus, it may be inferior to the lungs when used for comparison with cardiac MIBG activity in the setting of elevated circulating norepinephrine levels for the reasons previously outlined.

Assessment of the normal pattern of sympathetic innervation in dogs has previously demonstrated reduced levels of norepinephrine at the apex compared with the base.\(^{47,49}\) The findings of the present study demonstrate that myocardial MIBG activity can map the normal regional variation in canine myocardial norepinephrine levels by showing a matched reduction in apical MIBG activity and norepinephrine content. This pattern of reduced apical MIBG activity and norepinephrine content was also present at heart failure. Therefore, the regional distribution of MIBG in the heart appears to correspond to that of the adrenergic nervous system.

Pacing-induced heart failure was associated with increased heterogeneity in the left ventricular distribution of MIBG; this may correspond to alterations in cardiac innervation during heart failure. This finding has previously been reported in patients with dilated cardiomyopathy.\(^{30}\) The mechanism underlying this pattern of MIBG distribution with pacing-induced heart failure is unknown, but destruction of adrenergic nerve terminals or increased myocardial fibrosis is unlikely, given the paucity of histological findings in this model and also the potential for functional recovery, which is accompanied and may in part be mediated by the restoration of tissue norepinephrine levels.\(^{50,51}\) However, the ability to noninvasively detect global and regional differences in cardiac adrenergic activity may eventually prove to be of prognostic value in heart failure, since heterogeneous catecholamine stimulation by itself can cause nonuniformity of both systolic and diastolic function and lead to a deterioration of overall ventricular function.\(^{52,53}\) Moreover, heterogeneity of sympathetic innervation may increase the dispersion of electrical refractoriness and thereby promote reentry arrhythmias.\(^{54}\) Therefore, cardiac MIBG scintigraphy may be useful as a prognostic indicator in heart failure, as recently suggested by Merlet et al.\(^{55}\)

The mechanism for the reduction in left ventricular tissue norepinephrine and MIBG activity in pacing-induced heart failure was not evaluated in the present study. Studies in a variety of other heart failure models have revealed often conflicting results and attributed the decrease in cardiac norepinephrine content to decreased neuronal uptake, or release of norepinephrine\(^{56,57}\) and release\(^{58,59}\) of norepinephrine, increased turnover or release of norepinephrine\(^{24-26}\) with preserved neuronal reuptake, or decreased synthesis of norepinephrine.\(^{60}\) Further studies in the pacing model are needed to address this issue.

In the present study, tissue norepinephrine concentrations distinguished the three groups of dogs, whereas plasma levels were of less discriminatory value and did not correlate with the MIBG heart-to-lung ratio. These findings are not surprising, given that plasma norepinephrine is derived from total body adrenergic activity and its subsequent clearance. The latter is dependent on hemodynamic factors and has been reported to be reduced in heart failure.\(^{21,62}\) Thus, plasma norepinephrine is not an accurate index of cardiac adrenergic activity, and perhaps this may account for its relatively low prognostic value in heart failure when it is assessed as a continuum.\(^{63}\) Furthermore, the hypothesis that dysfunction of the efferent limb of the sympathetic nervous system may be predominantly localized to the failing heart is supported by the selective reduction in myocardial MIBG activity compared with other organs, reported in this study and others.\(^{30,32}\)

In summary, this report demonstrates that pacing-induced heart failure is associated with severe cardiac adrenergic dysfunction manifested by reduced MIBG activity and increased heterogeneity in the left ventricular distribution of MIBG. Furthermore, we have provided evidence that cardiac MIBG scintigraphy is a simple noninvasive method for assessing global and regional myocardial norepinephrine levels.

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