Kinetics of ^{123}I-MIBG After Acute Myocardial Infarction and Reperfusion Therapy

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Metaiodobenzylguanidine (MIBG) washout from the myocardium has been thought to reflect sympathetic nerve tone. After acute myocardial infarction, however, little is known about this parameter. The aim of this study was to determine the significance of cardiac washout after myocardial infarction and early reperfusion by investigating MIBG kinetics and correlating those kinetics to clinical parameters. **Methods:** Sixty patients with acute myocardial infarction underwent planar MIBG and thallium imaging within 14 d of early reperfusion therapy. Global uptake and washout in myocardium, lungs and liver were calculated from early and delayed images. A regional analysis of myocardial kinetics in normal and infarcted myocardium and in an infarct border zone was also performed. Scintigraphic data were correlated with heart-rate variability as an electrophysiologic marker for autonomic tone and prevalence of arrhythmia in 52 patients. Heart-rate variability was described by time-domain indices from long-term electrocardiogram recordings. An age-matched normal control group for MIBG consisted of 10 individuals without heart disease. **Results:** The infarct patients had preserved left-ventricular ejection fraction (LVEF) (56% ± 17%). Although late myocardial uptake was expectedly lower in infarct patients compared with healthy volunteers (2.36 ± 0.66 versus 2.80 ± 0.55; $P = 0.04$), global myocardial MIBG washout was faster (11.6% ± 7.9% versus 0.2% ± 10.2%, respectively; $P = 0.002$). Lung and liver kinetics did not differ in patients and healthy volunteers. Global MIBG washout showed a weak but significant positive correlation with the baseline heart rate ($r = 0.28$, $P = 0.03$) and an inverse correlation with LVEF ($r = -0.28$, $P = 0.04$). Washout was faster in a subgroup of 8 patients with reduced heart-rate variability (16.5% ± 9.9% versus 10.3% ± 8.3%; $P = 0.04$). Regional analysis revealed similar degrees of enhanced MIBG washout for infarcted (low perfusion, low MIBG uptake) and remote myocardium (normal perfusion, high MIBG uptake), whereas the border zone (normal perfusion, low MIBG uptake) showed a nonsignificant trend toward higher washout. **Conclusion:** After myocardial infarction, changes in MIBG kinetics occur specifically in the myocardium, whereas kinetics in lung and liver remain unchanged. Even in patients with left-ventricular function preserved by reperfusion therapy, MIBG washout is abnormal and globally increased. Enhanced washout may reflect increased sympathetic nerve tone and represent increased catecholamine turnover or impaired reuptake in the subacute phase of myocardial infarction.

Key Words: ^{123}I-metaiodobenzylguanidine; washout; myocardial infarction; reperfusion therapy; heart-rate variability

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Using the catecholamine analog ^{123}I-metaiodobenzylguanidine (MIBG) and nuclear imaging techniques, regional denervation exceeding the area of necrosis has been reported after acute myocardial infarction (*1–8*). In these studies, integrity of presynaptic sympathetic nerve terminals was described by MIBG uptake that was derived from a single data acquisition. Repeated measurements at different time points after injection, on the other hand, allow for the calculation of tracer clearance. Increased myocardial MIBG washout has been reported for a variety of diseases (*9–13*). This additional parameter of MIBG kinetics has been thought to reflect sympathetic nerve tone (*10,14*). However, little is known about the significance or clinical relevance of MIBG washout from the heart.

Cardiac kinetics of MIBG may be influenced by alterations of kinetics in organs surrounding the myocardium, either methodologically by scatter contamination or physiologically by competition for the radiotracer. Little data are available defining MIBG uptake and washout in lungs and liver after myocardial infarction.

Thus, the aim of this study was to investigate kinetics of MIBG after myocardial infarction and reperfusion therapy. Myocardial MIBG parameters were compared with clinical data and electrophysiological findings to determine the relevance of MIBG washout from the heart. In addition, kinetics in the surrounding organs, which potentially interfere with myocardial kinetics, were studied.

MATERIALS AND METHODS

Study Population

Sixty patients (18 women, 42 men; mean age 58 ± 12 y) were included in the study after reperfusion therapy for acute myocardial infarction. None of the patients had a history of diabetes mellitus, coexistent significant valvular disease, pulmonary disease or other severe chronic diseases. Diagnosis of myocardial infarction was based on electrocardiographic findings and enzymatic changes. Reperfusion therapy consisted of either coronary angioplasty alone (n = 44) or a combination of thrombolysis and coronary angioplasty (n = 16). Intracoronary stents were placed in all but 1 patient. The median time interval between onset of symptoms and reperfusion was 13.5 h. Twenty-six patients had an occlusion of the left anterior descending artery, 12 patients had an occluded left circumflex artery and 22 patients had an occluded right coronary artery. A Q-wave infarction was found in 31 patients, and a non–Q-wave infarction was present in 29 patients. Peak creatine

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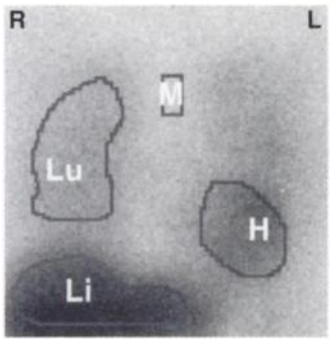

FIGURE 1. Global parameters derived from planar MIBG images. ROIs are placed over heart (H), mediastinum (M), right lung (Lu) and liver (Li) in early and delayed MIBG images to calculate uptake ratios and washout rates. Early/delayed images: H/M = myocardial uptake; Lu/M = pulmonary uptake; Li/M = liver uptake.

kinase levels were 1070 ± 1134 U/L. Left-ventricular ejection fraction (LVEF) measured by left ventriculography at control cardiac catheterization 2 wk after reperfusion was 56% ± 17% (range 14%–85%). Of the 60 patients, 29 had underlying one-vessel coronary artery disease and 31 had multivessel disease.

Medical treatment based on β-blockers, angiotensin converting enzyme inhibitors, ticlopidine and aspirin (*15*) was continued during the study. None of the patients was taking medication known to interfere with the presynaptic sympathetic nervous system.

An age-matched normal control group for MIBG (mean age 55 ± 11 y) consisted of 10 individuals with no evidence of heart disease.

The study protocol was approved by the ethical committee of our hospital. Written informed consent was given by all patients.

Scintigraphic Studies

Planar MIBG imaging was performed within 14 d of the onset of myocardial infarction. Before imaging, patients had a baseline heart rate of 64 ± 13 bpm and a systolic blood pressure of 128 ± 23 mm Hg. The rate pressure product at rest was 8219 ± 1894.

Before the MIBG study, 600 mg sodium perchlorate were administered orally to block iodine uptake by the thyroid. Thirty minutes later, approximately 185 MBq ^{123}I-MIBG were injected intravenously. Fifty minutes and 5.5 h after tracer administration, static planar images of the chest in anterior view were acquired for 10 min in a 128 × 128 matrix using a gamma camera with a large field of view (Siemens Diacam, Erlangen, Germany) and a medium-energy collimator.

Myocardial perfusion was studied 2–4 d after MIBG imaging. Fifteen minutes after intravenous injection of 75–110 MBq ^{201}Tl-chloride at rest, a 10-min anterior planar image was obtained using the same gamma camera but equipped with a low-energy, all-purpose collimator.

Global MIBG Analysis

The planar MIBG images were analyzed by a region-of-interest (ROI) technique to obtain semiquantitative parameters for tracer distribution.

To assess global myocardial kinetics of MIBG, an ROI was drawn manually over the left ventricle. A second, rectangular ROI over the upper mediastinum was used as a reference background region. According to previous studies (*16,17*), the heart-to-mediastinum (H/M) ratio of average counts per pixel was calculated for the early and delayed images. Global myocardial MIBG uptake was described by the H/M ratio (*16*). Early and delayed H/M values were then used to compute the myocardial washout rate (WR) of MIBG (*17*):

$$WR = (H/M[50\ min] - H/M[5.5\ h]) \times 100 / H/M[50\ min]$$

In addition, MIBG kinetics in lung and liver tissue were investigated. ROIs were placed over the right lung and the liver. Using the mediastinum as reference, uptake ratios and washout rates were calculated using a method similar to that used for the myocardium.

The global semiquantitative parameters calculated by ROI analysis are summarized in Figure 1. Washout rates for heart, lung and liver were calculated with the following equation:

$$WR = \frac{uptake(early) - uptake(delayed)}{uptake(early)} \times 100.$$

Regional Myocardial Analysis

To assess regional differences, three small square ROIs were placed manually on the planar perfusion images over normally perfused remote myocardium, hypoperfused infarct territory and over a normally perfused border zone of the infarct. These three ROIs were then copied to identical positions in early and delayed MIBG images to investigate regional myocardial MIBG kinetics (Fig. 2). Uptake and washout were calculated as described above for global analysis.

Six patients had to be excluded from regional analysis because substantially reduced global cardiac MIBG uptake did not allow accurate placement of ROIs over the myocardium.

Holter Electrocardiography

Fifty-three of the 60 patients underwent long-term, 24-h, electrocardiographic monitoring within 14 d of the onset of myocardial infarction. The Holter data were subsequently analyzed to assess heart-rate variability and the presence of arrhythmia.

As time-domain indices of heart-rate variability, the SD of

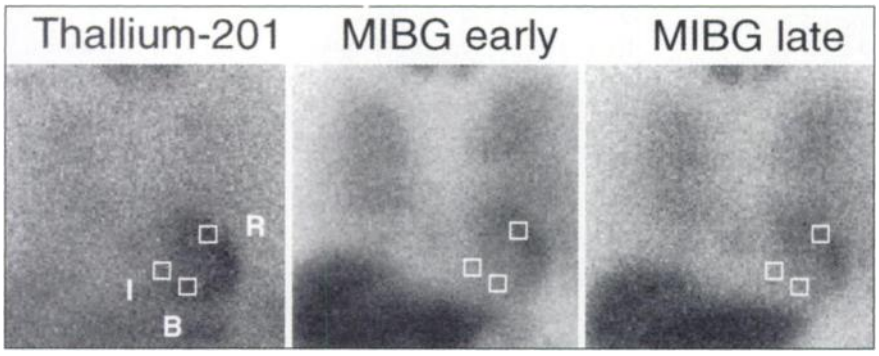

FIGURE 2. Regional analysis. ROIs for infarct area (I), border zone (B) and remote area (R) are defined using thallium scan and then copied to identical positions on early and late MIBG images.

heart-rate variability (SDNN), a broad-band measure of autonomic balance, and the root-mean-square of successive differences (RMSSD), a continuous measure of vagal tone, were calculated. Ventricular arrhythmia was described by the number of premature ventricular complexes (PVCs) per hour and presence of ventricular tachycardia during the 24-h monitoring period.

Statistical Analysis

Data were expressed as mean ± SD. The Mann-Whitney Wilcoxon U test was used to compare scintigraphic findings in patients with normal control subjects and to compare subgroups of infarct patients. One-way factorial analysis of variances and the posthoc *t* test according to Bonferroni-Dunn were used to compare results of regional myocardial analysis. Linear regression analysis was performed to study correlations between continuous variables. $P < 0.05$ was considered significant. For the *t* test according to Bonferroni-Dunn, $P < 0.0167$ was considered significant.

RESULTS

Global MIBG Kinetics

Scintigraphic results for patients and normal control subjects are shown in Table 1. Global myocardial washout of MIBG was significantly faster in patients than in normal control subjects. Although early global MIBG uptake was not significantly different between groups, late myocardial uptake in infarct patients was significantly lower. The washout rate was weakly negatively correlated to early myocardial MIBG uptake ($r = -0.27$, $P < 0.04$), whereas the correlation to late myocardial MIBG uptake was stronger ($r = -0.55$, $P < 0.01$).

No difference was found between the groups for pulmonary or liver uptake and washout. In both groups, lung and liver washout were faster than myocardial washout. Liver uptake was generally the highest, whereas pulmonary uptake was lower than myocardial uptake in normal control subjects. In patients, pulmonary uptake was almost equal to myocardial uptake in the delayed images.

TABLE 1
Comparison of Scintigraphic Parameters of ^{123}I-MIBG

Parameter	Patients	Normals	*P*
Early myocardial uptake	2.65 ± 0.64	2.84 ± 0.54	ns
Late myocardial uptake	2.36 ± 0.66	2.80 ± 0.55	0.04
WR myocardium	11.6% ± 7.9%	0.2% ± 10.2%	0.002
Early lung uptake	3.03 ± 0.70	2.82 ± 0.50	ns
Late lung uptake	2.37 ± 0.51	2.19 ± 0.37	ns
WR lung	20.9% ± 9.6%	21.4% ± 8.6%	ns
Early liver uptake	6.69 ± 1.47	6.00 ± 1.46	ns
Late liver uptake	5.50 ± 1.23	5.06 ± 1.36	ns
WR liver	16.7% ± 14.2%	15.6% ± 14.9%	ns

MIBG = metaiodobenzylguanidine; ns = not significant; WR = washout rate.

Data expressed as mean ± SD. Uptake measured by ratio of organ-to-mediastinum.

TABLE 2
Regional Results in Different Myocardial Areas

Parameter	Remote area	Border zone	Infarct area
Uptake of ^{201}Tl	2.53 ± 0.30*	2.47 ± 0.34*	2.09 ± 0.34
Early MIBG uptake	3.47 ± 0.81*†	2.74 ± 0.67*	2.34 ± 0.63
Late MIBG uptake	3.02 ± 0.82*†	2.30 ± 0.67	2.03 ± 0.62
Washout rate (%)	13.0 ± 9.2	16.1 ± 9.4‡	13.3 ± 8.1

*$P < 0.0167$ vs. infarct area.

†$P < 0.0167$ vs. border zone.

‡$P = 0.07$ vs. remote and infarct areas.

Data expressed as mean ± SD. Uptake measured by ratio of area-to-mediastinum.

Regional Myocardial MIBG Kinetics

To better understand myocardial MIBG kinetics, we performed a regional analysis for infarct area, remote area and border zone. Results are shown in Table 2.

The infarct area was characterized by significantly lower myocardial perfusion, expressed by the uptake of ^{201}Tl, compared with remote area and border zone. Additionally, early and late MIBG uptake were significantly lower compared with remote area.

In the border zone, myocardial perfusion was not different compared with remote area, but early and late MIBG uptake were significantly lower. Compared with the infarct area, early MIBG uptake was higher, but late uptake was not different.

No significant difference among the three areas was found for washout of MIBG. However, in the border zone, a nonsignificant trend toward higher washout ($P = 0.07$) was observed.

Heart-Rate Variability and Ventricular Arrhythmia

Because of atrial fibrillation, 1 patient was excluded from heart-rate variability analysis. In the remaining 52 patients, SDNN was 109.8 ± 29.8 ms, and RMSSD was 52.3 ± 39.1 ms. A reduced SDNN of less than 80 ms was present in 8 patients, and 12 had a reduced RMSSD below 27 ms.

Overall, the incidence of ventricular arrhythmia was low. The median of PVCs was 0.4/h (range 0–1060/h). Seven patients had frequent PVCs (more than 8/h). Six patients had episodes of ventricular tachycardia.

Correlations of Clinical, Electrocardiographic and Scintigraphic Findings

Early global myocardial uptake of MIBG showed a weak but significant negative correlation to peak creatine kinase levels ($r = -0.27$, $P = 0.04$). Also, myocardial MIBG uptake was higher in non–Q-wave infarct patients than in Q-wave infarct patients (Fig. 3). MIBG uptake was significantly lower in patients with decreased SDNN (Table 3). Also, there was a trend of lower uptake values for patients with ventricular tachycardia, but significance was not reached (Table 4). No differences in uptake were found for subgroups of RMSSD and frequency of PVCs.

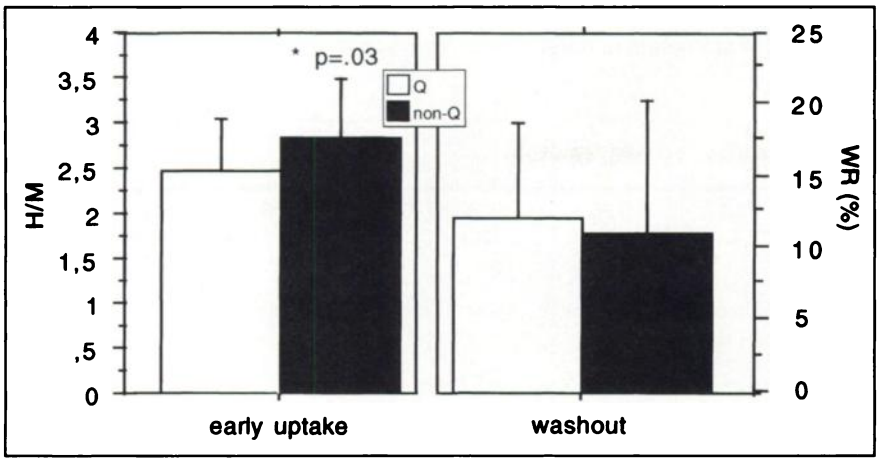

FIGURE 3. Early myocardial uptake and washout of MIBG in patient with Q-wave and non–Q-wave infarcts. There is significant difference for MIBG uptake (2.48 ± 0.58 for patients versus 2.83 ± 0.66 for normal control subjects; $P = 0.03$), whereas washout was not different between patients and normal control subjects (12.1% ± 6.6% versus 11.1% ± 9.2%; $P = 0.63$).

Global myocardial washout rate of MIBG was weakly but significantly correlated to baseline heart rate (Fig. 4). Also, MIBG washout showed a weak but significant inverse correlation with LVEF ($r = -0.28$, $P = 0.04$). The subgroup of patients with low SDNN had significantly higher myocardial washout rates compared with those with normal SDNN (Table 3). In this subgroup, LVEF was significantly lower compared with patients with normal SDNN (41% ± 21% versus 58% ± 14%, respectively; $P < 0.04$), whereas there was only a nonsignificant trend toward a higher baseline heart rate (72 ± 16 bpm versus 63 ± 13 bpm for normal SDNN; $P = 0.12$). Subgroups with low RMSSD, frequent PVCs or episodes of ventricular tachycardia showed no differences in washout rates (Tables 3 and 4). No correlation was found for washout and peak creatine kinase levels ($r = 0.14$, $P = 0.29$). In addition, there was no difference between Q-wave and non–Q-wave infarcts (Fig. 3). The time interval from onset of symptoms to revascularization was not correlated to any MIBG parameter ($r = -0.21$, $P = 0.12$ for early uptake and $r = 0.07$, $P = 0.64$ for washout).

Lung and liver kinetics of MIBG were not correlated to any of the clinical cardiologic parameters.

DISCUSSION

This study demonstrates that changes in MIBG kinetics after myocardial infarction occur specifically in the heart. Lung and liver kinetics remain unchanged. As expected, myocardial MIBG uptake is reduced in the hypoperfused infarct area and a normally perfused border zone. Cardiac washout of MIBG is enhanced globally even for patients with left-ventricular function preserved by reperfusion therapy.

MIBG Kinetics in Tissue Surrounding Myocardium

MIBG, an analog of guanethidine, is thought to share uptake and storage mechanisms in the sympathetic nerve terminal with norepinephrine (*18*). Although liver activity of MIBG represents nonspecific uptake and metabolism of the tracer, MIBG is actively taken up by lung endothelium. Pulmonary uptake and washout may thus be useful for determining endothelial cell function in the lung (*19*). However, in this study, both lung and liver kinetics of MIBG in the infarct patients were similar to normal control subjects, supporting the notion that changes in MIBG kinetics after myocardial infarction occur specifically in the myocardium.

Myocardial MIBG Kinetics

The mechanisms underlying MIBG washout from myocardial tissue are controversial. Experimental studies suggested that release from extraneuronal tissue may be one of the potential factors (*20,21*). In the denervated human heart, on the other hand, low nonspecific MIBG uptake has been described in patients after transplantation (*22*). Therefore, MIBG washout in humans should be closely related to

TABLE 3
Global Myocardial MIBG Parameters and Heart-Rate Variability

	SDNN			RMSSD		
MIBG	>80 ms (n = 44)	≤80 ms (n = 8)	*P*	>27 ms (n = 40)	≤27 ms (n = 12)	*P*
Early uptake (H/M)	2.80 ± 0.63	2.25 ± 0.39	0.02	2.71 ± 0.61	2.75 ± 0.70	0.91
Washout (%)	10.3 ± 8.3	16.6 ± 9.9	0.04	10.5 ± 9.0	13.6 ± 7.8	0.26

MIBG = metaiodobenzylguanidine; SDNN = standard deviation of heart-rate variability; RMSSD = root mean square of successive differences; H/M = heart-to-mediastinum ratio.
Values expressed as mean ± SD.

TABLE 4
Global Myocardial MIBG Parameters and Ventricular Arrhythmia

MIBG	PVC >8/h (n = 7)	PVC ≤8/h (n = 46)	P	VTach Present (n = 6)	VTach Absent (n = 47)	P
Early uptake (H/M)	2.61 ± 0.47	2.73 ± 0.63	0.56	2.36 ± 0.66	2.76 ± 0.60	0.17
Washout (%)	11.4 ± 12.5	11.3 ± 7.4	0.61	13.0 ± 12.8	11.1 ± 7.9	0.35

MIBG = metaiodobenzylguanidine; PVC = premature ventricular complex; VTach = ventricular tachycardia; H/M = heart-to-mediastinum ratio.
Values expressed as mean ± SD.

release from the sympathetic nerve terminal. Efflux from extravesicular cytosolic sites and specific exocytosis of MIBG from storage vesicles may account for tracer washout (*10,23*). Additionally, it has recently been shown that MIBG washout in a variety of patients with different diseases is correlated to heart-rate variability (*14*). Clearance of MIBG from the myocardium is thus believed to be at least partially determined by sympathetic nerve tone.

Nakajima et al. (*13*) described increased global myocardial MIBG washout in a small group of patients with myocardial infarction, but detailed analysis was not performed. In this study, unlike global myocardial uptake, global MIBG washout was not correlated to parameters related to infarct size, such as peak creatine kinase levels or presence of Q-waves. Moreover, myocardial washout correlated with left ventricular ejection fraction and the baseline heart rate despite β-blockade. These findings support the notion that washout may reflect autonomic nerve tone, whereas MIBG uptake describes integrity of the nerve terminal (*24*).

Regional analysis in this study confirms previous work describing reduced regional MIBG uptake in the infarct area and in a normally perfused border zone of the infarct (*1–3,5,25*). Global myocardial uptake of MIBG early after injection, on the other hand, showed only a nonsigificant trend toward lower values compared with normal control subjects, suggesting little denervation caused by early reperfusion therapy after myocardial infarction. Moreover, myocardial washout was globally enhanced in the infarct patients and regionally pronounced in the infarct border zone especially. Reduced late myocardial uptake may thus represent damage to the sympathetic nerve terminals (reflected by initial MIBG uptake) and increased sympathetic tone (reflected by MIBG washout).

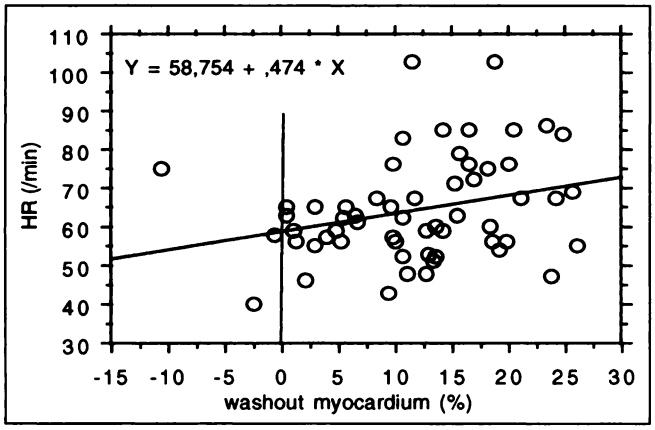

FIGURE 4. Regression plot for myocardial MIBG washout and baseline heart rate (HR) shows weak but significant correlation ($r = 0.28$, $P = 0.03$).

MIBG Parameters and Electrophysiologic Data

Mantysaari et al. (*3*), using regional assessment of late MIBG uptake, described a larger area of denervated but viable myocardium in patients with low heart-rate variability. As a measure of heart-rate variability, they obtained a ratio of maximum-to-minimum RR intervals during a short-term period of deep breathing. In a study by Livanis et al. (*26*), late MIBG defect after myocardial infarction was compared with well-established long-term parameters of heart-rate variability, and a significant correlation was reported. This study confirms the findings of Livanis et al. in a larger patient group and extends them by a detailed analysis not only of MIBG uptake but of MIBG washout.

SDNN is known as a broad-band measure of autonomic balance (*27*). Enhanced MIBG washout, indicating increased sympathetic tone and lower MIBG uptake, reflecting more extensive damage to nerve terminals, were found in infarct patients with reduced SDNN. This again confirms the functional relevance of MIBG findings in the infarct patients, and shows that reduced heart-rate variability after myocardial infarction may be associated not only with cardiac denervation, as suggested by Livanis et al. (*26*), but also with increased sympathetic tone. Not surprisingly, no differences in MIBG parameters were found for subgroups with low and normal RMSSD, because this index reflects a continuous measure of vagal tone (*27*) and thus should be less dependent on changes of the sympathetic system.

An association between ventricular ectopic activity and MIBG defect size after myocardial infarction was found by McGhie et al. (*5*). Stanton et al. (*8*), on the other hand, did not find a correlation between MIBG results and sustained ventricular tachycardia induced by electrophysiologic study. No association between ventricular ectopic activity and

MIBG parameters was found in this study. The overall frequency of arrhythmia, however, was low because of early reperfusion therapy, and the subgroup of patients may have been too small to yield significant results.

Potential Clinical Relevance of MIBG Washout from the Heart

In addition to the low frequency of arrhythmia, reperfusion therapy early after the onset of myocardial infarction resulted in preserved LVEF in our patients. Nevertheless, myocardial MIBG washout was impaired globally. Washout was higher for lower LVEF and was higher in patients with low SDNN as a parameter of heart-rate variability. LVEF is a powerful parameter of global left-ventricular performance and frequently used for risk stratification. Also, time-domain indices of heart-rate variability are known as independent predictors of outcome after myocardial infarction (*28,29*). The data in this study suggest that it may be worthwhile to test myocardial MIBG washout as an independent prognostic parameter after myocardial infarction. Further studies including follow-up data are warranted.

Limitations

Using a SPECT technique, regional changes in MIBG uptake after myocardial infarction have been well described in previous studies (*1–3,5,25*). This study, however, focused on the investigation of MIBG kinetics not only in myocardium but in surrounding organs and aimed at an improved understanding of the significance of cardiac MIBG kinetics. Using planar images, washout of MIBG was examined on a global basis, similar to washout of ^{201}T1. A regional analysis was performed but was limited by the projection of several overlying structures in a planar image. The infarct area may therefore contain some amounts of normally perfused myocardium, which may in part explain the presence of increased MIBG washout in this area. Additionally, the border zone can only be estimated, and a clear-cut definition is difficult to provide. It may be speculated that the nonsignificant trend toward highest MIBG washout in this area may be confirmed as significant, if a clear regional definition is possible.

SPECT imaging definitely offers advantages for regional analysis. However, assessment of regional tracer washout by SPECT is more susceptible to methodological influences derived from reconstruction, reangulation and calculation of relative uptake. If tracer uptake is globally decreased, relative regional uptake of segments in SPECT images may be overestimated. To calculate MIBG washout, information from two image sets is needed. This further increases the susceptibility to methodological influences. To avoid such problems, parameters in this study were derived from planar MIBG imaging as a more stable and reliable method.

The data in this study demonstrate the significance of myocardial washout of MIBG derived from planar images. These results may serve as a background for more detailed and sophisticated approaches to assess regional differences of MIBG washout as an additional parameter of MIBG uptake using a SPECT technique.

CONCLUSION

After acute myocardial infarction, changes in MIBG kinetics occur specifically in the myocardium. Washout of MIBG from the myocardium is enhanced globally in remote as well as infarcted areas and is especially pronounced in the infarct border zone and may reflect an increase of sympathetic nerve tone even in patients with ventricular function preserved by early reperfusion therapy. Additionally, the association of enhanced washout with low heart-rate variability demonstrates the functional significance of MIBG findings.

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