Clinical research

Presence of sympathetically denervated but viable myocardium and its electrophysiologic correlates after early revascularised, acute myocardial infarction

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Aims After acute myocardial infarction (AMI), regional denervation exceeding the scar area has been described. We sought to define the electrophysiologic correlates of denervated, but viable, myocardium by combining scintigraphic imaging with extensive electrocardiographic evaluation in AMI patients treated with early reperfusion therapy.

Methods and results Within 14 days after AMI, 67 consecutive patients underwent radionuclide imaging of myocardial resting perfusion using 201thallium and of presynaptic sympathetic innervation using 123I-metaiodobenzylguanidine (MIBG). The mean left ventricular ejection fraction was 58 ± 15%. Electrophysiologic studies included evaluation of ventricular repolarisation (resting ECG), depolarisation (signal-averaged ECG), and 24-h Holter monitoring. The perfusion defect, innervation defect, and perfusion/innervation mismatch size of the left ventricle were 14 ± 15%, 39 ± 22%, and 26 ± 16%, respectively. Mismatch was present in 60/67 patients (90%) and correlated with prolonged repolarisation defined by QTc interval \( r = 0.40; P < 0.001 \), and with indexes of delayed depolarisation from signal-averaged ECG \( r = -0.32; P = 0.014 \). Other electrophysiologic parameters did not correlate. During follow-up (4.3 ± 1 years) event rates were low, with two cardiac deaths and no severe ventricular arrhythmia causing hospitalisation.

Conclusions After early reperfusion for myocardial infarction, viable but denervated myocardium is frequent and correlates with slow depolarisation and repolarisation. However, in patients with small infarct size and preserved left ventricular function, these findings seem to have little influence on outcome.

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Introduction

Myocardial scintigraphy using iodine-123-metaiodobenzylguanidine (123I-MIBG) has been used extensively for non-invasive assessment of global and regional cardiac function.
sympathetic innervation in many cardiac diseases.\textsuperscript{1,2} Studies in patients after acute myocardial infarction consistently demonstrated areas of sympathetic denervation exceeding the limits of myocardial necrosis, suggesting that viable but sympathetically denervated myocardium is a common finding in this clinical context.\textsuperscript{3–4} In early studies, infarct patients with large areas of sympathetic denervation showed an increased frequency of ventricular arrhythmias compared to patients with no or small defects in some studies, suggesting that cardiac sympathetic denervation may be related to the genesis of ventricular arrhythmias after acute myocardial infarction.\textsuperscript{5,6} Additionally, in experimental models, a topographic correlation between regions of viable denervated myocardium and disturbances of ventricular depolarisation/repolarisation has been demonstrated using \textsuperscript{125}I-MIBG scintigraphy.\textsuperscript{7,9}

In humans, few studies have investigated the correlation between electrophysiologic abnormalities and cardiac denervation. Study groups were generally small and only specific electrophysiologic aspects were evaluated.\textsuperscript{10} Additionally, conflicting results were reported, for example, regarding a potential association between heart rate variability abnormalities and the extent of denervated viable myocardium in infarct patients.\textsuperscript{11–13} Several of the aforementioned studies were performed when early reperfusion using thrombolysis and/or angioplasty/stenting was not yet a standard therapy for myocardial infarction, so results are difficult to extrapolate to the present situation.

Thus, we sought to perform a prospective correlative study in patients after early reperfusion therapy for acute myocardial infarction. Scintigraphic imaging of the sympathetic nervous system was employed to define the incidence and extent of denervated but viable myocardium, and multiple electrophysiologic methods were applied in the same patient population to permit global evaluation of repolarisation and depolarisation processes and their association with scintigraphic findings. In addition, the study group, which is, to our knowledge, the largest group of infarct patients having undergone scintigraphic assessment of denervation to date, were followed up over a longer time period to get insight into the potential impact of the results on patient outcome.

\section*{Methods}

\subsection*{Study population}

Sixty-seven consecutive stable patients presenting with acute myocardial infarction (AMI), confirmed by resting ECG and enzymatic elevation, that survived the acute coronary care unit hospitalisation phase were recruited prospectively. None of the patients had a history of coexistent significant valvular disease, pulmonary disease, or other chronic diseases. The mean left ventricular ejection fraction (LVEF) was 58 ± 15\%, ranging from 17\% to 85\%. Additional clinical and angiographic characteristics of the study population are summarised in Table 1.

Prior to inclusion, all patients signed written informed consent forms that had been approved by the ethics committee of the medical faculty of the Technische Universität München.

\begin{table}[h]
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\begin{tabular}{|l|c|}
\hline
\textbf{Table 1} Clinical, laboratory, and demographic characteristics of the study population (\textit{n} = 67) \\
\hline
\textbf{Age} & 58.3 ± 11.2 \\
\textbf{Male (\%)} & 73\% \\
\textbf{Previous myocardial infarction} & 13 (19\%) \\
\textbf{Previous CABG} & 3 (5\%) \\
\textbf{Myocardial infarction topography} & \\
\textbf{Anterior} & 30 (45\%) \\
\textbf{Inferior} & 24 (36\%) \\
\textbf{Lateral/posterior} & 13 (19\%) \\
\textbf{Reperfusion therapy} & \\
\textbf{Primary PTCA with stent} & 47 (70\%) \\
\textbf{Thrombolysis + PTCA} & 18 (26\%) \\
\textbf{Primary PTCA alone} & 1 (1\%) \\
\textbf{Thrombolysis alone} & 1 (1\%) \\
\textbf{Time to reperfusion (h)} & 9.3 ± 7.6 \\
\textbf{Peak CKP (U/l)} & 962 ± 1035 \\
\textbf{Left ventricular ejection fraction} & 58 ± 15\% \\
\textbf{Extension of coronary artery disease} & \\
\textbf{One vessel} & 31 (46\%) \\
\textbf{Two vessels} & 16 (24\%) \\
\textbf{Multivessel disease} & 20 (30\%) \\
\textbf{Risk factors for coronary artery disease} & \\
\textbf{Arterial hypertension} & 49 (73\%) \\
\textbf{Dyslipidaemia} & 47 (70\%) \\
\textbf{Cigarette smoking} & 34 (51\%) \\
\textbf{Family history} & 18 (27\%) \\
\textbf{Diabetes mellitus} & 8 (12\%) \\
\textbf{Cardiovascular drugs used during hospital stay} & \\
\textbf{Beta-blockers} & 60 (90\%) \\
\textbf{ACE inhibitors} & 58 (87\%) \\
\textbf{Diuretics} & 19 (28\%) \\
\textbf{Calcium channel blockers} & 2 (3\%) \\
\textbf{Digital} & 1 (1\%) \\
\hline
\end{tabular}
\caption{Clinical, laboratory, and demographic characteristics of the study population (\textit{n} = 67).}
\end{table}

ACE, angiotensin converting enzyme; CABG, coronary artery bypass surgery; CPK, serum level of creatine kinase.

\section*{Study design}

\textsuperscript{125}I-MIBG myocardial scintigraphy was performed within 14 days of infarct onset. Two to four days later, myocardial perfusion scintigraphy was performed at rest using \textsuperscript{201}thallium. Electrophysiologic studies were performed within 4 weeks after infarct onset. All studies were performed without discontinuing the medication routinely used after AMI (Table 1). No patient was taking antiarrhythmic drugs or other drugs known to interfere with the presynaptic sympathetic nervous system, such as antidepressants, chloridone, or reserpine.

Follow-up data were prospectively collected every 6 months by phone or mail. Endpoints were death and cardiac death.

\section*{Electrophysiologic tests}

\subsection*{Rest electrocardiogram}

A simultaneous 12-lead rest electrocardiogram was acquired 12.6 ± 4.6 days after AMI onset using a Max 1 Stress System (Marquette Electronics, Paris, France). The duration of the QT interval, heart rate-corrected QT interval (QTc) and QT-interval dispersion were automatically calculated by the system according to accepted standards.
Signal-averaged electrocardiogram
The signal-averaged ECG was acquired with a Predictor I System (Dr. Kaiser Medizintechnik, GmbH, Bad Hersfeld, Germany) using a digital sampling rate of 2 kHz, with application of a band-pass filter with cutoff frequencies of 40 and 250 Hz. Patients presenting with bundle-branch block or not amenable to obtaining an acceptable recording noise level (<0.3 μV) were excluded. The automatically calculated parameters were: (1) duration of filtered QRS complex; (2) root mean square of the amplitude (μV) of the filtered QRS complex in the terminal 40 ms (RMS40), and (3) duration of the low amplitude signal (below 40 μV) in the terminal portion of the filtered QRS complex (LAS40).

Holter monitoring
Twenty-four-hour continuous ECG recordings were obtained in a SpaceLabs Holter Recorder System. The data were analysed in a Medilog Excel version 7.1 (Oxford Instruments GmbH, Wiesbaden, Germany). After an initial automatic processing of the data, an experienced observer reviewed the classification of abnormal beats; the number of ventricular ectopic beats per hour (VEB/h), total number of VEB occurring in couplets, and total number of VEB in runs of three or more beats were computed.

Heart rate variability analysis was performed in the time domain using SDNN (standard deviation of normal RR [NN] intervals) and RMSSD (square root of the mean squared differences of successive NN intervals).

Scintigraphic studies

Data acquisition

**123I-MIBG-SPECT.** Resting intravenous injection of 185 MBq of 123I-MIBG was performed 30 min after oral thyroid blockade with 600 mg perchlorate. Five hours later, SPECT imaging was performed using a large-field-of-view gamma camera (DIACAM, Siemens AG, Erlangen, Germany) equipped with a medium-energy parallel-hole collimator.

**201Thallium-SPECT.** Twenty minutes after resting intravenous injection of 110 MBq of 201thallium, SPECT images were acquired using the same camera, now equipped with a low-energy general-purpose collimator.

Scintigraphy analysis

Transaxial SPECT images were reconstructed by filtered back-projection. Further image processing involved a polar mapping approach developed in our laboratory, including interactive LV axis definition in three dimensions and an automatic volumetric radial search for maximal myocardial activity in 460 segments of the left ventricle. Polar maps were generated separately for 123I-MIBG and 201thallium and normalised to their maximum. Regions of reduced tracer uptake were defined using a threshold of 50% of the maximum and defect sizes were expressed as the percentage of the total left ventricle. Mismatch size, corresponding to the extent of viable but denervated myocardial tissue, was defined by 123I-MIBG defect size minus 201thallium defect size, again expressed as a percentage of left ventricle surface area.

Statistical analysis

This was a prospective, cross-sectional study focusing on the correlational analysis of several scintigraphic and electrophysiologic variables. Accordingly, the sample size was planned to be large enough to allow for testing the correlations, initially more than 50 patients. Data presenting normal distributions were expressed as means ± standard deviation. The many variables presenting non-Gaussian distributions, demonstrated by using the method of Kolmogorov and Smirnov, were expressed as median and range values, and non-parametric, distribution-free statistical methods were used. The association between variables was tested by the Spearman rank-correlation test and the difference between means was tested using the Mann–Whitney test for unpaired data and the Wilcoxon matched-pair test for paired data. Statistical significance was set to P < 0.05.

Results

Scintigraphic findings

The 201thallium defect size was 26 ± 8%, ranging from 0.2% to 89%, and correlated significantly with left ventricular ejection fraction (r = −0.4682; P < 0.0001) and peak serum creatine kinase (r = 0.534; P = 0.0002). Significantly larger 201thallium defect sizes were found in the subgroup of patients with Q-wave infarct in comparison with the non-Q-wave infarct patients, while anterior infarcts in comparison to non-anterior infarcts presented similar thallium defect sizes (Table 2).

The 123I-MIBG defect size was 37 ± 26% (range 0–95%), being significantly larger than the 201thallium defect size (P < 0.0001). This resulted in mismatch sizes ranging from 0% to 59% with a mean value of 10 ± 18%. Overall, 60 of the 67 patients (90%) had a mismatch, and 56 (83%) had a mismatch in >10% of the LV. The mismatch defect size was significantly correlated to the total 123I-MIBG defect extent (r = 0.7191; P < 0.0001). Conversely, no significant correlation was found between the mismatch and thallium defect sizes (r = 0.03; P = 0.864) or peak CK value (r = 0.1489; P = 0.248). A weak but significant negative correlation between mismatch and LVEF was obtained (r = −0.2897; P = 0.0192). Patients with anterior infarct in comparison to those with non-anterior infarct presented larger areas of mismatch (Table 2), but the mismatch size did not differ significantly between

<table>
<thead>
<tr>
<th>Infarct location</th>
<th>P</th>
<th>Q-wave development</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td></td>
<td>20 ± 17</td>
<td>3 ± 4</td>
</tr>
<tr>
<td>Non-anterior</td>
<td></td>
<td>44 ± 20</td>
<td>27 ± 22</td>
</tr>
<tr>
<td>201Thallium</td>
<td>0.03</td>
<td>26 ± 14</td>
<td>26 ± 20</td>
</tr>
<tr>
<td>123I-MIBG</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mismatch</td>
<td>0.87</td>
<td></td>
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</tr>
</tbody>
</table>

Table 2 Scintigraphic variables according to myocardial infarction topography and the presence of a Q-wave in the resting ECG
Q-wave and non-Q-wave infarcts. An example of a patient with posterior wall AMI and a large mismatch defect is shown in Fig. 1.

Electrophysiologic parameters and correlation with scintigraphic results

The results of electrophysiologic studies and correlation with scintigraphic mismatch size are summarised in Table 3.

Repolarisation (resting ECG; $n = 67$)
A significant prolongation of the QTc interval (>480 ms) was present in six patients and increased QT dispersion (>60 ms) was found in 24 patients. QTc duration presented a significant correlation with mismatch size (Table 3, Fig. 2) while no significant correlation was found with QT dispersion.

Depolarisation (signal-averaged ECG; $n = 60$)
Using previously established criteria to define abnormal values for each variable (filtered QRS duration >114 ms, RMS40 <20 $\mu$V, and LAS40 >38 ms), prolongation of ventricular depolarisation was present in only six patients. Overall, however, RMS40 had a significant inverse correlation with mismatch size (Fig. 3).

Frequency of arrhythmia/heart rate variability (Holter monitoring; $n = 66$)
The overall incidence of ventricular arrhythmia was low and no patient showed sustained ventricular tachycardia during the 24-h recording period. Sixty patients had isolated VEB during the study and couplets of VEB were detected in 14 patients, while runs of VEB were present in nine patients. No significant correlation was found between the presence and frequency of ventricular arrhythmias and the extent of the mismatch defect, although there was a trend towards larger mismatch size in the case of more frequent runs (Table 3).

At heart rate variability analysis, nine patients showed reduction of SDNN (<80 ms); reduced RMSSD <27 ms was seen in 17 patients. A significant correlation was found between SDNN and the $^{201}$Thallium defect size ($r = -0.354$; $P = 0.0041$), but no significant correlation was found between heart rate variability indexes and mismatch size.

Clinical follow-up
During the follow-up period (median of 4.7 years, ranging from 0.7 to 5.5 years), four patients died and cardiac death occurred in only two patients, in which large mismatch defect sizes were observed (47% and 37%). No hospitalisation related to severe symptomatic ventricular arrhythmia was recorded. Detailed survival analysis correlating the mismatch size and patient outcome was precluded by the low event rate observed.

Discussion

In summary, our study included patients submitted to early reperfusion therapy for acute myocardial infarction and characterised by a small infarct size, preserved global ventricular function, very low frequency of arrhythmia, and excellent outcome. Even in these early reperfused patients, scintigraphic investigation demonstrated a high incidence of regional myocardial denervation exceeding the area of necrosis. A combination of nuclear imaging with multiple electrophysiologic tests revealed that the extent of viable, but denervated myocardium correlated with a prolongation of ventricular repolarisation and late potentials in the depolarisation phase. However, although this study comprises the largest group of infarct patients assessed for scintigraphic evidence of denervation and multiple electrophysiologic abnormalities to date, no major impact of the observed correlations of frequency of ventricular arrhythmias and patient outcome could be identified.

Various previous studies have demonstrated that myocardial uptake of $^{123}$I-MIBG after acute myocardial infarction is not only reduced in the central infarct zone (topographically correlated to the area of predominant necrotic tissue and concordant with severe reduction of perfusion tracer uptake), but also in the surrounding zone of still viable myocardium, as confirmed by preserved uptake of perfusion tracers. A similar pattern has been observed in humans using quantitative positron emission tomography with $^{11}$C-hydroxyephedrine, an-
other radiolabeled catecholamine analogue. Experimental studies have demonstrated that areas with reduced $^{123}$I-MIBG uptake are characterised by reduced catecholamine content and abnormal electrical activity consistent with regional sympathetic denervation. The results of the present study confirm previous observations in a larger patient group and also confirm that denervated but viable myocardium is present when patients undergo early reperfusion therapy, which was not a standard treatment at the time that several previous studies were made.

We recently demonstrated that the myocardial area with reduced $^{123}$I-MIBG uptake is closely related to the area of myocardium-at-risk exposed to transitory severe ischaemia due to coronary occlusion prior to reperfusion therapy. Consistently larger areas of adrenergic nerve disruption were found in anterior wall myocardial infarctions in comparison with non-anterior infarctions in the present study, most likely reflecting larger areas of myocardium at risk and of myocardial salvage. The mechanism of sympathetic denervation in viable cardiac tissue after reperfused acute myocardial infarction thus seems to involve an increased sensitivity of the neural tissue to hypoxia as compared to myocardial fibres.

Because the sympathetic nervous system is thought to play a role in the regulation of myocardial electrophysiology, we made a detailed analysis of electrophysiologic correlates of denervated, but viable, myocardium. First, evidence suggesting that myocardial denervation can be an important determinant for the genesis of abnormal cardiac electrophysiologic properties arose from animal models using phenol application and experimental

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Summary of the electrophysiologic tests results and correlation analysis with mismatch defect size (Spearman rank test)</th>
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<tbody>
<tr>
<td>Parameter</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Resting ECG</td>
<td></td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>424 ± 42</td>
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<tr>
<td>QT dispersion (ms)</td>
<td>–</td>
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<tr>
<td>Signal-averaged ECG</td>
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</tr>
<tr>
<td>QRS duration (ms)</td>
<td>102.2 ± 1.4</td>
</tr>
<tr>
<td>RMS40 (µV)</td>
<td>36.1 ± 2.7</td>
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<tr>
<td>LAS40 (ms)</td>
<td>33.1 ± 1.0</td>
</tr>
<tr>
<td>Holter monitoring</td>
<td></td>
</tr>
<tr>
<td>VEB/h</td>
<td>–</td>
</tr>
<tr>
<td>Couplets/24 h</td>
<td>–</td>
</tr>
<tr>
<td>Runs/24 h</td>
<td>–</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>111.9 ± 31.6</td>
</tr>
<tr>
<td>RMSSD</td>
<td>–</td>
</tr>
</tbody>
</table>

Fig. 2 Scatter plot illustrating the positive correlation between mismatch defect size (% of left ventricle surface) and QTc interval duration (ms).

Fig. 3 Scatter plot illustrating the negative correlation between mismatch defect size (% of left ventricle surface) and RMS40 (root mean square of the amplitude (µV) of the terminal 40 ms of the filtered QRS). Reduced values of this variable indicate the presence of ventricular late potentials.
myocardial infarction. In these studies, regions with myocardial denervation showed a non-homogeneous decrease in repolarisation time and abnormally increased shortening of repolarisation during catecholamine stimulation. This denervation supersensitivity in conjunction with marked dispersion of the refractoriness has been considered a substrate for ventricular tachycardia and fibrillation.8 9 19 21 In addition, a topographic correlation between ventricular refractoriness and disturbances of sympathetic denervation was also demonstrated by Calkins et al.22 using 11C-hydroxyephedrine positron emission tomography and invasive electrophysiology in patients with sustained ventricular tachycardia referred for implantable defibrillator placement.

Our findings of a significant correlation between the extent of sympathetically denervated, but viable, myocardium and electrophysiologic parameters characterising repolarisation and depolarisation give further evidence of a link between autonomic nervous system abnormalities and myocardial electrophysiology in the clinical setting. This is consistent with the results of some previous studies using 123I-MIBG scintigraphy in smaller patient groups, combined with more limited electrophysiologic information. Yukinaka et al.,10 for example, found that a subgroup of patients with prolonged ventricular depolarisation (characterised by the finding of late potentials in the signal-averaged ECG) exhibited larger 123I-MIBG and mismatch defect scores as compared to patients without this abnormality. However, a correlation analysis on a continuous scale was not performed and ventricular repolarisation was not assessed.

Heart rate variability is also thought to be under the control of the autonomic nervous system, and impairments have been shown to be a predictor of outcome after myocardial infarction.23 24 Some previous clinical investigations have focused on the relationship between heart rate variability and scintigraphic evidence of denervation, but yielded conflicting results. Livanis et al.12 investigated 25 patients 15 days after acute infarction and encountered significant correlations between reduced heart rate variability and innervation/perfusion mismatch size. Conversely, Spinnler et al.11 studied 10 patients 5–10 days after AMI with spectral analysis of RR intervals and late potentials, which correlated with denervated but viable myocardium in the present study, have previously been shown to be clinical predictors of an increased risk of arrhythmias.25 26 Our results, however, could not reproduce a significant correlation between the extent of denervation and presence of ventricular arrhythmias. This is most likely due to the markedly reduced incidence of arrhythmic events in our study population. This could be related to early reperfusion, and the resulting preservation of left ventricular function, and also to the potential anti-arrhythmic effects of drugs like beta-blockers and ACE inhibitors, which were taken by most of the patients. Patients with impaired ventricular function, which are known to be at higher risk for arrhythmic events, were excluded from this study. Heart failure per se has been demonstrated to impair the sympathetic nervous system and results would have been more difficult to interpret because of interferences between adverse effects of ischaemia/infarction and of heart failure on innervation.

The observed clinical outcome in the 4-year follow-up period was excellent despite documented ischaemia-induced abnormalities of the sympathetic nervous system. Only two patients died because of cardiac events and no hospital admission related to severe arrhythmias was recorded. Because of the very low event rate, a more detailed analysis of the prognostic implications of regional denervation cannot be performed, but our results suggest little effect despite the observed interrelation with ventricular electrophysiology. Prospective trials in infarct patients with ventricular dysfunction and a higher risk of arrhythmia may be useful for a more detailed evaluation of the prognostic value of cardiac neurotransmitter imaging in ischaemic heart disease.

Study limitations

This investigation did not include Holter monitoring evaluations during the follow-up. Therefore, the incidence of asymptomatic arrhythmia and its correlation with the extent of myocardial denervation could not be assessed. This was a cross-sectional correlative study and follow-up analysis was not a primary objective. The very low event rate obtained precluded any detailed survival analysis.

In summary, although regional sympathetic denervation exceeding the scar area is present in most patients with preserved ventricular function after reperfusion therapy for acute myocardial infarction, and although there are electrophysiologic correlates in the depolarisation and repolarisation phases, it does not seems to influence the patient’s course very much. This is probably because the incidence of arrhythmia remains low. In patients without myocardial infarction, the integrity of myocardial sympathetic innervation has been shown to have effects on tissue characteristics other than electrophysiology and arrhythmogenesis, such as microc-
culation, metabolism, and contractile performance. These interrelations may be evaluated in more detail in the future to further enhance the understanding of physiologic effects and the clinical role of denervated but viable myocardium.

References