CARDIOVASCULAR MEDICINE

Assessment of myocardial adrenergic innervation in patients with sick sinus syndrome: effect of asynchronous ventricular activation from ventricular apical stimulation

M E Marketou, E N Simantirakis, V K Prassopoulos, S I Chrysostomakis, A A Velidaki, N S Karkavitsas, P E Vardas

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Objective: To investigate ventricular sympathetic innervation in patients with sick sinus syndrome and to detect regional deterioration of adrenergic innervation caused by asynchronous ventricular activation from right ventricular pacing.

Design: Prospective controlled study.

Setting: Tertiary cardiac referral centre.

Patients: 22 patients with sick sinus syndrome and indications for permanent dual chamber pacing; 20 healthy individuals as controls.

Interventions: All patients underwent myocardial imaging with planar and single photon emission computed tomography (SPECT) after an intravenous infusion of 5 mCi ^{123}I -meta-iodobenzylguanidine (^{123}I -MIBG) before and after pacemaker implantation. A SPECT thallium 201 myocardial study was done during the same week as the ^{123}I -MIBG study in all patients.

Main outcome measures: The heart to mediastinum (H/M) ratio and washout rate were calculated during the ^{123}I -MIBG study to assess the global cardiac sympathetic activity; the aim of the SPECT study was to investigate the regional distribution of adrenergic innervation.

Results: The H/M ratio was significantly smaller in the patients with sick sinus syndrome than in the controls ($p < 0.001$). In sick sinus syndrome there were regional adrenergic innervation defects, mostly in the inferior and apical walls. After a medium term pacing period, a redistribution of ^{123}I -MIBG uptake was detected, with deterioration of adrenergic innervation in the inferior, apical, and posterior walls. The thallium 201 myocardial perfusion study showed no change after three months of permanent pacing.

Conclusions: Patients with sick sinus syndrome have global and regional disturbances of the adrenergic innervation of the left ventricular myocardium. These seem to deteriorate as a result of asynchronous electrical activation. The clinical significance of this finding requires further investigation.

See end of article for authors' affiliations

Correspondence to:
Professor P E Vardas,
Cardiology Department,
University Hospital of
Heraklion, PO Box 1352,
Stavrakia, Heraklion,
Crete, Greece;
cardio@med.uoc.gr

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Sick sinus syndrome, in which there is progressive dysfunction of the sinus node, is one of the most common indications for a permanent pacemaker. The sites that are normally used for electrode implantation in permanent cardiac pacing are the high right atrium and the apex of the right ventricle. However, it has been shown that pacing through the right ventricular apex is associated with alterations in the contraction and relaxation pattern of the left ventricle,¹⁻³ remodelling, and histological abnormalities in the left ventricular myocardium.⁴⁻⁷ Recently, there have been indications that long term permanent pacing is related to abnormalities of regional perfusion and adrenergic innervation.^{8,9} However, there is a lack of comparable data on these perfusion and innervation disturbances before and after pacemaker implantation, so the net real effect of pacing has not been clarified. Patients with sick sinus syndrome have rhythm disturbances that may be associated with alterations in cardiac autonomic tone affecting myocardial adrenergic innervation, so it is important to know whether any adrenergic innervation defects found in paced patients were present before the start of pacing.

In our study, we evaluated the adrenergic innervation of the left ventricle in patients with sick sinus syndrome using the radioiodinated noradrenaline (norepinephrine) analogue, ^{123}I -meta-iodobenzylguanidine (^{123}I -MIBG) as an imaging marker.¹⁰ We also assessed the alterations in regional myocardial adrenergic innervation in these patients after the implantation of a permanent dual chamber pacemaker, in order to

examine the effect of the asynchronous ventricular activation stimulus.

METHODS

Patient population

We studied 22 consecutive patients (12 men, 10 women; mean (SD) age, 65.05 (6.11) years) with sick sinus syndrome and indications for dual chamber, rate adaptive (DDDR) pacemaker implantation. The diagnosis was suggested by the presence of the following:

- symptomatic persistent spontaneous sinus bradycardia not caused by drugs
- sinus arrest or exit block
- combinations of sinoatrial and atrioventricular conduction disturbances
- alteration between paroxysms of atrial tachyarrhythmias and periods of slow atrial and ventricular rates, documented by ECG or 24 hour Holter recordings.

Patients with diabetes mellitus and arterial hypertension, a history of coronary artery disease, or clinical indications of

Abbreviations: H/M ratio, heart to mediastinum ratio; ^{123}I -MIBG, ^{123}I -meta-iodobenzylguanidine; SPECT, single photon emission computed tomography

organic heart disease or heart failure of any type were excluded.

As controls, we also studied 20 healthy individuals with a similar sex and age distribution. They had no signs of heart disease and their clinical, echocardiographic, and thallium²⁰¹ scintigraphic findings were normal.

A dual chamber permanent pacemaker with a Holter recording system was implanted in each patient, with the atrial lead placed in the right atrial appendage and the ventricular lead in the right ventricular apex. All pacemakers were capable of rate adaptation of atrioventricular delay, and they were programmed to achieve the longest delay that maintained the maximum QRS duration observed under VVI pacing, so that ventricular activation would be fully paced. The patients underwent pacemaker interrogation to determine the proportion of paced ventricular systoles three months after the implantation, and 24 hour Holter monitoring (Elatec V3.03B; Ela Medical, La Boursidiere, Le Plessis-Robinson, France) for assessment of ventricular activation patterns. They also underwent an echocardiographic examination (Sonos 2500; Hewlett Packard Inc, Andover, Massachusetts, USA) to evaluate left ventricular structure and function.

Before and three months after pacemaker implantation, all patients completed a myocardial thallium²⁰¹ scintigraphic perfusion study and an ¹²³I-MIBG myocardial scintigraphic study during the same week to assess adrenergic innervation. The control group also underwent thallium²⁰¹ and ¹²³I-MIBG myocardial scintigraphic examinations. None of the subjects was receiving drug treatment or had any clinical condition that has been shown to affect ¹²³I-MIBG uptake. Subjects with thallium²⁰¹ perfusion defects were referred for coronary angiography. Patients with coronary artery stenosis of more than 50% were excluded from the study. We also excluded obese patients and women with large breasts.

All subjects provided their written informed consent for inclusion in the study. The hospital's ethics committee approved the protocol.

Imaging protocols

Dipyridamole-thallium²⁰¹ myocardial scintigraphy

All subjects were fasted overnight. They had a four minute intravenous infusion of dipyridamole, 0.56 mg/kg body weight, and three minutes later 3 mCi of thallium²⁰¹ was injected intravenously. A 12 lead ECG was recorded before testing and at one minute intervals for a minimum of 10 minutes after the dipyridamole infusion was started.

Any therapeutic agents containing methylxanthine were discontinued for a minimum of 48 hours before dipyridamole administration; no caffeine containing beverages were consumed within the 24 hours of the test.

Imaging was achieved with a rotating, dual head gamma camera (GE Medical Systems, Milwaukee, Wisconsin, USA) 10 minutes and four hours after the injection. Thirty two projections (40 seconds each) were obtained over a 180° arc, beginning with the 45° left posterior oblique and finishing with the 45° right anterior oblique view. All images were stored using a 64 × 64 matrix. Transaxial, sagittal, and oblique tomograms were obtained using a nuclear medicine computer (software: GENIE v. 2.5H, 99224, rev. 137).

¹²³I-MIBG scintigraphy

On the day of the ¹²³I-MIBG scintigraphy all patients and controls were instructed to fast for six hours. Lugol's solution (1 ml) was given orally two hours before a slow intravenous injection of 5 mCi ¹²³I-MIBG (Mallinckrodt Inc, St Louis, Missouri, USA; specific activity 74 MBq/mg).

At 10 minutes, one hour, and four hours after the tracer injection, a 10 minute static acquisition was performed in the anterior view of the chest, using a General Electric (GE Medical Systems) large field of view, single head gamma camera

fitted with a low energy, all purpose, parallel hole collimator. A 20% energy window centred on 157 keV and a 128 × 128 matrix size were used. After the delay planar image, single photon emission computed tomography (SPECT) was done using a dual head gamma camera (GE Medical Systems). Thirty two projections (50 seconds each) were obtained over a 180° arc, from left posterior oblique to right anterior oblique, and the images were stored using a 64 × 64 matrix. Transaxial, sagittal, and oblique tomograms were obtained using a nuclear medicine computer (software: GENIE v. 2.5H, 99224, rev. 137).

Cardiac uptake was quantified in all planar views. A 7 × 7 pixel region of interest was drawn over the cardiac region and another 7 × 7 region of interest over the upper mediastinum area. The heart to mediastinum (H/M) activity ratio, introduced by Merlet and colleagues,¹¹ was then computed to quantify cardiac ¹²³I-MIBG accumulation. Two independent observers measured the H/M ratio, and the average of the two measurements was taken as the datum. The clearance rate from the myocardium (washout rate) was calculated as follows:

$$[\text{initial myocardial } ^{123}\text{I-MIBG uptake} - \text{delayed myocardial } ^{123}\text{I-MIBG uptake}] / [\text{initial } ^{123}\text{I-MIBG uptake}] \times 100.$$

In SPECT imaging the left ventricular myocardium was divided into six segments. ¹²³I-MIBG scintigrams were examined by two independent experts—with no knowledge of the patients' clinical and angiographic status—for the presence of any abnormalities. A four point scoring system was used to provide a defect score for visual interpretation of the ¹²³I-MIBG and thallium²⁰¹ scintigraphy in the six segments of left ventricular myocardium, as follows: 3, absence of detectable tracer in a segment, or severe reduction of radioisotope uptake; 2, moderately reduced uptake; 1, mildly reduced uptake; 0, normal radioisotope uptake.

Statistical analysis

Continuous data are summarised as mean (SD). Continuous variables were compared between the two groups with an independent samples *t* test. Changes in ¹²³I-MIBG scores before and after pacing were evaluated using paired samples *t* tests. Changes in the time course of the ratio between the two groups were assessed with a repeated measures analysis of variance (ANOVA) model with two repeated and one between factors. One of the repeated factors had three levels (at 10 minutes, 60 minutes, and four hours) and the other had two (before–after). Bonferroni adjustments were made in multiple comparisons. The criterion for significance was set at 5%.

The interobserver variability for the H/M ratio was very low, the 95% confidence interval for difference being –0.043 to 0.043 for prepacing values, and –0.108 to 0.123 for values after pacing.

RESULTS

Five of the 22 patients initially included in the study, and none of the control group, had perfusion defects on thallium²⁰¹ myocardial scintigraphy. Two of the patients had significant coronary artery stenosis (more than 50%) in one or more vessels and were excluded from the study. The clinical characteristics of the remaining patients and controls are shown in table 1, together with the main results. All patients had ventricular pacing throughout most of the 24 hour monitoring period (completely paced ventricular beats in 96.5 (18.5%); the interrogation of the pacemakers revealed ventricular pacing in 95.9 (19.8)%, with a mean programmed atrioventricular interval of 80 (30) ms. The mean interval between the dipyridamole SPECT thallium²⁰¹ and the ¹²³I-MIBG was 5.1 (1.7) days before the pacing period and 4.8 (1.3) days afterwards (NS).

Table 1 Characteristics and main findings from patients and controls

	Patients (n=20)	Controls (n=20)	p Value
Sex (M/F)	10/10	11/9	NS
Age (years)	65.1 (6.1)	64.9 (8.6)	NS
Echocardiographic findings			
EDD (mm)	47.4 (9.2)	46.9 (8.6)	NS
ESD (mm)	35.0 (7.9)	33.9 (6.5)	NS
IVS (mm)	9.8 (1.4)	9.5 (1.3)	NS
PW (mm)	9.6 (1.6)	9.7 (0.9)	NS
EF (%)	56.8 (9.9)	57.8 (4.6)	NS
¹²³I-MIBG H/M ratio			
10 min	1.79 (0.14)	2.07 (0.19)	<0.001
1 h	1.74 (0.15)	2.06 (0.16)	<0.001
4 h	1.69 (0.17)	2.00 (0.19)	<0.001
Washout (%)	5.46 (4.52)	3.41 (2.22)	NS

Values are mean (SD) or n.

EDD, end diastolic diameter; EF, left ventricular ejection fraction; ESD, end systolic diameter; F, female; H/M ratio, heart to mediastinum ratio; IVS, intraventricular septum; M, male; PW, posterior left ventricular wall; ¹²³I-MIBG, ¹²³I-meta-iodobenzylguanidine.

Figure 1 Time course of heart to mediastinum ratio in patients with sick sinus syndrome (SSS) and controls. Open symbols: pre-pacing data. Solid symbols: after three months of permanent pacing. Squares, 10 minutes; circles, 60 minutes; diamonds, 4 hours. CI, confidence interval.

Thallium²⁰¹ dipyridamole scintigraphy

In three of the 20 patients with sick sinus syndrome who were finally included in the study, thallium²⁰¹ dipyridamole scintigraphy showed a reversible perfusion defect in the inferior wall which remained unchanged after the three month pacing period.

¹²³I-MIBG scintigraphy

The H/M ratio was significantly lower both in early and delayed images (fig 1), while the washout rate tended to be increased in patients with sick sinus syndrome but not enough to differ significantly from the controls (fig 2). Most of the patients with sick sinus syndrome had adrenergic innervation defects in the inferior wall (16 patients) and the apical wall (12 patients); some had defects in the anterior wall (five patients) and the lateral wall (four patients), but there were fewer with defects in the posterior and septal walls (three patients each). Only one of the control group had a mild adrenergic innervation defect in the inferior wall.

The quantitative analysis showed no significant change in the H/M ratio at 10 minutes, one hour, and four hours before and after the pacemaker implantation (fig 1). Similarly, the washout rate was unchanged during the three month pacing period. Although our results did not reveal alterations in the

Figure 2 There was no significant difference in the washout rate between patients with sick sinus syndrome (SSS) and controls. Likewise, in the SSS group there was no significant change before and after permanent pacing. Open symbols: pre-pacing data. Solid symbols: after three months of permanent pacing.

global sympathetic activity of the left ventricular myocardium, they indicated significant regional redistribution in ¹²³I-MIBG uptake. Specifically, aggravations of the innervation defects were noted in the inferior wall (mean defect score 1.5 (0.8) before pacing v 2.1 (0.91) after pacing; $p = 0.044$), in the apical wall (mean defect score 0.9 (0.9) before pacing v 1.45 (0.14) after pacing; $p = 0.047$), and in the posterior wall (mean defect score 0.35 (0.81) before pacing v 1.0 (1.16) after pacing; $p = 0.01$).

DISCUSSION

We found that patients with the sick sinus syndrome had disturbances of global and regional cardiac ¹²³I-MIBG uptake, indicating abnormal adrenergic nerve function. We also showed that asynchronous activation induced by permanent pacing in such patients leads to regional redistribution of the myocardial ¹²³I-MIBG uptake after a three month pacing period. These adrenergic disturbances were not associated with myocardial perfusion defects in this medium term pacing period.

Myocardial adrenergic innervation in the sick sinus syndrome group

An important finding of our study was that cardiac ¹²³I-MIBG imaging showed significant disturbances of adrenergic innervation in the patients with sick sinus syndrome compared with the normal controls. To our knowledge only one other published report, by Matsumura and colleagues,¹² has examined myocardial perfusion and innervation in the sick sinus syndrome. Those investigators suggested that impairment of the coronary microcirculation, coronary vasospasm, and cardiac sympathetic nerve dysfunction may all play a part in the pathophysiology of the syndrome. Our results also showed a significant sympathetic nervous impairment of the left ventricular myocardium, the cause of which cannot definitely be identified as anatomical or functional. The decreased H/M on delayed images may represent anatomical disturbances in nerve fibres. Though not reaching significance, washout of ¹²³I-MIBG appeared to be increased in the patients with sick sinus syndrome compared with the controls, so we cannot exclude a contribution of functional disorders to our findings. A possible relation with the pathophysiology of bradyarrhythmic or tachyarrhythmic presentations of the syndrome needs to be explored.

Myocardial adrenergic innervation after medium term pacing period

As far as we know, this study is the first to examine the effect of permanent dual chamber pacing on myocardial perfusion and adrenergic innervation before and after pacemaker implantation in humans.

Ventricular pacing through the right ventricular apex—although the site is easily accessible and traditionally used for electrode implantation—results in asynchronous ventricular activation.¹³ During the last few years, “normalisation” of ventricular electrical stimulation in paced patients has acquired considerable importance. Other researchers have suggested that ventricular pacing decreases fibre shortening, contractile work, and myocardial blood flow in early activated regions and increases these indices in late activated regions.¹⁴ It is also known that long term asynchronous electrical activation leads to asymmetrical changes of left ventricular wall mass induced by regional changes of mechanical load, with the early activated regions having a lower preload than the late activated regions. Local cardiac workload regulates local cardiac mass of both myocytes and collagen, so the early activated regions become thinner while the late activated regions become thicker.¹⁵ Previous reports have also suggested that the early activated regions show functional and histological changes, reduced oxygen consumption, and disturbances of fatty acid metabolism.^{4, 6, 16}

There is evidence that long term permanent right ventricular apical pacing leads to thallium²⁰¹ perfusion defects,⁸ while it has been shown that these disturbances in regional myocardial perfusion are associated with abnormalities of myocardial blood flow,¹⁷ even in the absence of coronary artery disease.¹⁸ A recent study from our department⁹ examined chronically paced patients with complete heart block and revealed disturbances of the adrenergic innervation of the left ventricle, as assessed by myocardial perfusion defects shown by ¹²³I-MIBG scintigraphy. These disturbances are described to be regional, affecting specific walls—mainly the inferior and apical—that are activated early on following right apical stimulation. However, the effect of permanent dual chamber pacing on cardiac perfusion and sympathetic activity is not entirely clear, because the studies cited above did not examine the perfusion and adrenergic innervation before pacemaker implantation. As a result the investigators cannot exclude the possibility that their findings reflect factors other than pacing. Most of the above studies examined the acute effects of right ventricular pacing or its long term results, without considering the preimplantation data.

Our results indicate that patients who are continuously paced from the right ventricular apex have a redistribution of the adrenergic innervation of the left ventricle caused by the alteration in the activation sequence. More precisely, they showed significant regional differences in early activated regions of the inferior, apical, and posterior walls after the medium term pacing period. Taking into account that global ¹²³I-MIBG uptake does not change significantly, we postulate that our findings suggest a functional rather than an anatomical alteration of sympathetic activity. Also, given the fact that the disturbances we observed were regional in nature, it seems unlikely that they could have been caused by systemic alterations of sympathetic nerve activity. The most probable explanation is that the decline in segmental contractility in early activated regions leads to a compensatory increase in sympathetic activity in the regions in question. This results in increased competition between ¹²³I-MIBG and noradrenaline for its uptake by the nerve terminals in the above mentioned segments, which leads to the defects in ¹²³I-MIBG uptake.

Although regional myocardial adrenergic function has not been studied in AAI versus DDD pacing, previous investigators found accelerated global cardiac sympathetic activity in dual chamber pacing compared with atrial pacing with normal

ventricular excitation,¹⁹ and increased cardiac tissue noradrenaline in paced animals,²⁰ supporting this explanation for the abnormalities in adrenergic activation. Additionally, in a small study by Nakata and colleagues,²¹ more prominent ¹²³I-MIBG scintigraphic defects were observed in patients with VVI as compared with DDD permanent pacemakers. It remains to be determined whether the abnormalities described above imply that inhomogeneity of myocardial adrenergic innervation can lead to increased dispersion of repolarisation,²² which may be related to the high incidence of sudden cardiac death in paced patients.^{23, 24}

Although previous reports have mentioned myocardial perfusion defects on thallium²⁰¹ scintigraphy in patients undergoing dual chamber pacing,^{8, 9, 18, 20} we did not find deterioration in left ventricular perfusion after this medium term pacing period. However, those reports examined the long term effects of pacing on myocardial perfusion. Although it is difficult to prove, we presume that perfusion defects appear after a longer period of asynchronous ventricular activation—which is necessary before the haemodynamically compromised left ventricular function leads to histological and anatomical alterations of myocardial tissue, and in particular of the microvascular system.

Study limitations

The anatomy of the coronary vessels was not known in all our patients; for ethical reasons, coronary angiography was only undertaken in those with perfusion defects on thallium²⁰¹ scintigraphy. Thus we cannot rule out the possibility that mild coronary lesions were the cause of an ¹²³I-MIBG defect. However, the fact that our patients neither had any clinical symptoms nor any risk factors for coronary disease persuaded us that the ¹²³I-MIBG abnormalities were not caused by coronary artery disease.

Additionally, it is possible that the higher prevalence of inferior and apical ¹²³I-MIBG defects derived in part from artefacts occurring in these ventricular segments. However, apart from the fact that the deterioration of these defects observed in individual patients after pacing makes it unlikely that they were artefacts, our findings from patients with sick sinus syndrome were also compared with those from the controls and were found to differ significantly. Furthermore, the image quality of ¹²³iodine is similar to that of technetium-99m and generally superior to that of thallium²⁰¹,²⁵ which is more likely to produce false positive findings as a result of attenuation of its energy in the inferior wall.

It should also be noted that we could not rule out the possibility that a proportion of the ventricular systoles during the patients' daily activity were not fully paced, even though 24 hour continuous ECG recordings showed mostly fully paced beats. As a result, we cannot be certain that the left ventricular excitation always followed the same contraction pattern. In addition, we were obliged to program the pacemakers with a short atrioventricular interval which could influence global ventricular function. However, it is very unlikely that these factors would have caused the disturbances of regional adrenergic innervation that we observed.

Conclusions

Patients with sick sinus syndrome have significant abnormalities of adrenergic innervation of the left ventricular myocardium in comparison with normal individuals. After a medium term pacing period with asynchronous ventricular electrical stimulation there is a regional redistribution of these innervation disturbances, with deterioration in the early activated regions of myocardium.

Although our findings from patients with sick sinus syndrome need further research to evaluate their clinical significance, our results derived from permanent pacing emphasise the importance of physiological synchronous ventricular electrical activation of the left ventricle, and the need for

pacing techniques that ensure a normal activation–contraction sequence.

Authors' affiliations

M E Marketou, E N Simantirakis, S I Chrysostomakis, P E Vardas, Cardiology Department, University Hospital of Heraklion, Crete, Greece
V K Prassopoulos, A A Velidaki, N S Karkavitsas, Department of Nuclear Medicine, University Hospital of Heraklion

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