HEART FAILURE AND CARDIOMYOPATHY

Prediction of sudden death in patients with mild-to-moderate chronic heart failure by using cardiac iodine-123 metaiodobenzylguanidine imaging

Hidetaka Kioka, Takahisa Yamada, Takanao Mine, Takashi Morita, Yasumasa Tsukamoto, Shunsuke Tamaki, Masaharu Masuda, Keiji Okuda, Masatsugu Hori, Masatake Fukunami

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See end of article for authors' affiliations

Correspondence to: Dr H Kioka, Division of Cardiology, Osaka General Medical Centre, 3-1-56, Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan; hidetaka-k@umin.ac.jp

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Objective: To evaluate the usefulness of cardiac iodine-123 (^{123}I) metaiodobenzylguanidine (MIBG) imaging as a predictor of sudden death in patients with chronic heart failure (CHF).

Design and setting: Prospective cohort study in a tertiary referral centre.

Patients: 97 outpatients with CHF with a radionuclide left ventricular ejection fraction $<40\%$ (mean (SD) 29% (7.5%)).

Interventions: At study entry, cardiac I-123 MIBG imaging was performed. The cardiac MIBG heart-to-mediastinum ratio (H/M) and washout rate (WR) were obtained from MIBG imaging.

Main outcome measures: Patients were assigned to two groups based upon 27% of WR, which was the mean (2SD) control WR. 48 of 97 patients with CHF had abnormal WR ($\geq 27\%$), whereas the remaining 49 patients had normal WR ($<27\%$). All the study patients were then followed up.

Results: During the mean (SD) follow-up period of 65 (29) months, 12 (25%) patients in the abnormal WR group and 2 (4%) patients in the normal WR group died suddenly. Kaplan–Meier analysis revealed that sudden death was more often observed in patients with abnormal WR than those with normal WR ($p=0.001$). On Cox regression analysis, MIBG WR, H/M on the delayed image and H/M on the early image were significantly associated with sudden death.

Conclusion: Cardiac MIBG imaging would be useful for predicting sudden death in patients with CHF.

Sudden death contributes up to one-third to one-half of total mortality in patients with chronic heart failure (CHF).¹ Identification of patients who are at increased risk of sudden death is of clinical significance for the management of patients with CHF. However, it remains unclear as to what kind of patients with CHF have increased risk of sudden death.

It has been reported that abnormalities of the autonomic nervous system are involved in sudden death.² In patients with CHF, cardiac autonomic dysfunction, characterised by sympathetic overactivity and parasympathetic withdrawal, contributes to the progression of the disease and is associated with an unfavourable prognosis.^{3–4} Cardiac adrenergic nerve activity has been estimated using iodine-123 (I-123) metaiodobenzylguanidine (MIBG) as a norepinephrine analogue.^{5–6} It has been reported that cardiac MIBG imaging provides prognostic information in patients with CHF.^{7–11} Brain natriuretic peptide (BNP), heart rate variability, and peak oxygen uptake, other known prognostic markers, have been shown to provide useful information in combination with cardiac MIBG imaging.^{8–9–11} Of these prognostic markers, BNP and heart rate variability could predict sudden death in patients with CHF.^{12–14} However, no information is available on the usefulness of cardiac MIBG imaging in the prediction of sudden death in patients with CHF. In this study, we prospectively tested the hypothesis that cardiac MIBG imaging would be useful for predicting sudden death in patients with CHF.

METHODS

Study patients

We studied 97 consecutive outpatients with CHF, whose radionuclide left ventricular ejection fraction (LVEF) was

$<40\%$. Their mean (SD) age was 64 (12) years. Of the 97 patients, 77 (79%) were men and 20 (21%) were women. Radionuclide LVEF was 29% (7.5%). In all, 16 (16%) patients were in New York Heart Association (NYHA) functional class I, 57 (59%) patients were in class II, and 24 (25%) patients were in class III. Heart failure was due to ischaemic heart disease in 51 (53%) patients and to idiopathic dilated cardiomyopathy in 46 (47%) patients. Idiopathic dilated cardiomyopathy was defined as left ventricular systolic dysfunction associated with dilatation without known aetiologies such as significant coronary artery stenosis ($<75\%$ of the lumen) on the coronary angiogram and acute myocarditis proven by endomyocardial biopsy. Twenty-one patients in ischaemic aetiology had a history of coronary intervention or bypass surgery. To be included in the study, all patients who had experienced at least one episode of decompensated heart failure were required to be stable for at least 3 months with the conventional therapy of ACE inhibitors, diuretics and digoxin. Patients were excluded for the presence of significant renal dysfunction, insulin-dependent diabetes mellitus or autonomic neuropathy. None of the patients were receiving β blockers, calcium antagonists or arrhythmia drugs except for mexiletine ($n=20$) and amiodarone ($n=6$) at study enrolment. At study entry, all patients had cardiac MIBG imaging, 24-h ambulatory ECG monitoring, echocardiography and a plasma norepinephrine assay within a

Abbreviations: BNP, brain natriuretic peptide; CHF, chronic heart failure; H/M, heart-to-mediastinum ratio; I-123, iodine-123; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MIBG, metaiodobenzylguanidine; NYHA, New York Heart Association; ROI, region of interest; VT, ventricular tachycardia; WR, washout rate

month. All patients gave written informed consent for their participation in this study, which was approved by the review committee of Osaka General Medical Centre, Osaka, Japan.

Radionuclide angiography for entry criteria

Before entering this study, patients underwent ECG-gated blood pool scintigraphy at rest in the supine position, using a conventional rotating γ camera (Prism 2000, Picker, Bedford, Ohio, USA) equipped with a low-energy, high-resolution parallel hole collimator. Patients were given 740 MBq of ^{99m}Tc -labelled human serum albumin (Nihon Medi-Physics, Nishinomia, Japan). The camera was positioned in the modified left anterior oblique projection to isolate the left ventricle from other cardiac structures, and data acquisition was then completed. LVEF was calculated using a standard program.¹⁵

Cardiac MIBG imaging

No patients were taking tricyclic antidepressant drugs, sympathomimetic agents or other drugs known to interfere with MIBG uptake for a month preceding the cardiac MIBG imaging.

Cardiac MIBG acquisition

All patients underwent myocardial imaging with I-123MIBG (Daiichi Radioisotope Laboratory, Tokyo, Japan) using the same γ camera as for the radionuclide angiography. Patients were placed in the supine position. A 111 MBq dose of I-123 MIBG was injected intravenously at rest after an overnight fast. Initial and delayed image acquisitions were performed in the anterior chest view 20 and 200 min after the isotope injection.

Image analysis

Two independent observers, unaware of the clinical status of patients, assessed cardiac MIBG uptake. Left ventricular activity was recorded using a manually drawn region of interest (ROI) over the whole left ventricular myocardium, and the mean heart counts per pixel were calculated. Another 7×7 pixel ROI was recorded over the upper mediastinal area, and the mean counts per pixel were calculated. Background subtraction was performed using the upper mediastinal ROI. The heart-to-mediastinum ratio (H/M) was then determined by dividing the mean counts per pixel in the left ventricle by the mean counts per pixel in the mediastinum. After taking radioactive decay of I-123 into consideration, the cardiac MIBG washout rate (WR) was calculated from initial and delayed images, as reported previously.^{10–11} Based on our previous study, abnormal WR was defined as $\geq 27\%$, which was the mean (2SD) control WR.^{10–11}

Echocardiography

Two-dimensional echocardiography was performed with a Toshiba (Tokyo, Japan) SSH-380A recorder equipped with 2.5 MHz or 3.75 MHz transducers. The standard technique was used for sizing the left ventricle and atrium.¹⁶ Left ventricular dimension was measured at end diastole on the R wave of the electrocardiogram-derived QRS complex just below the level of the mitral leaflets through the standard left parasternal window. The left atrial dimension (LAD) was measured as the distance from the leading edge of the posterior aortic wall to the leading edge of the posterior left atrial wall at end systole.

24-h ambulatory ECG monitoring

Patients underwent 24-h dual-channel ambulatory ECG recording with a Marquette Electronics (Milwaukee, Wisconsin, USA) 8000 Holter monitoring system. Recordings were analysed by two independent observers who were blinded to the clinical status of the patients. Ventricular arrhythmias were classified according to Lown's grade, and non-sustained ventricular

Table 1 Baseline clinical and study characteristics of patients in abnormal and normal metaiodobenzyleguanidine washout rate groups

	Abnormal WR group	Normal WR group	p Value
n	48	49	
Age (years)	65 (11)	62 (12)	NS
Gender (male)	79%	80%	NS
NYHA	2.1 (0.7)	2.1 (0.6)	NS
Ischaemic heart disease	50%	55%	NS
Systolic pressure (mm Hg)	127 (15)	127 (18)	NS
Diastolic pressure (mm Hg)	72 (10)	73 (9)	NS
Heart rate (bpm)	74 (10)	75 (13)	NS
Radionuclide LVEF (%)	28 (8)	30 (7)	NS
Lown's grade	3.9 (1.0)	3.1 (1.6)	0.006
Non-sustained VT	19%	16%	NS
LVEDD (mm)	65 (9)	61 (7)	0.01
LAD (mm)	45 (9)	41 (6)	0.03
Norepinephrine (pg/ml)	534 (279)	366 (167)	<0.001
Medications			
ACE inhibitors	83%	77%	NS
Digitalis	94%	82%	NS
β blocker*	60%	63%	NS
Aldosterone antagonist	73%	54%	NS
Arrhythmia drug (class Ib/III)†	29% (11/6)	18% (9/0)	NS

LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NS, not significant; NYHA, New York Heart Association; VT, ventricular tachycardia; WR, washout rate. Data are presented as the mean (SD) or as percentage of patients. *The use of β blocker (carvedilol) as recorded at the last follow-up visit. †Class Ib anti-arrhythmia drug, mexiletine; class III, amiodarone.

tachycardia (VT) was defined as ≥ 5 consecutive premature ventricular beats, each lasting < 30 s.

Plasma norepinephrine concentration

Blood sampling for the determination of the plasma norepinephrine concentration was done from an intravenous cannula after resting for at least 30 min in the supine position. Plasma norepinephrine concentration was determined in EDTA plasma by high-performance liquid chromatography at Shionogi Biomedical Laboratories (Osaka, Japan). Duplicate determination in the laboratory had a coefficient of variation of 0.4–5.5%.

Follow-up

At study entry, patients were assigned to two groups based on the value of MIBG WR: abnormal WR group and normal WR group. All the study patients were then followed up at Osaka General Medical Centre, Osaka, Japan, at least once a month by clinicians who did not know the results of the cardiac MIBG imaging. Sudden death was defined as witnessed cardiac arrest or death within an hour of the onset of acute symptoms or unexpected, or unwitnessed death in a patient known to have been well in the previous 24 h.

Table 2 Follow-up outcome of patients in the abnormal and normal washout rate (WR) groups

Mode of death	Abnormal WR (n = 48)	Normal WR (n = 49)
Sudden death	12 (25)	2 (4)
Death from pump failure	7 (15)	1 (2)
Non-cardiac death	6 (13)	2 (4)

Values are n (%).

Table 3 Baseline clinical and study characteristics in patients who had and who did not have a sudden death

	Had sudden death	Did not have sudden death	p Value
n	14	83	
Age (years)	64 (14)	64 (11)	NS
Gender (male)	79%	80%	NS
NYHA	2.1 (0.6)	2.0 (0.6)	NS
Ischaemic heart disease	50%	53%	NS
Systolic pressure (mm Hg)	125 (12)	128 (17)	NS
Diastolic pressure (mm Hg)	74 (12)	73 (9)	NS
Heart rate (bpm)	73 (9)	75 (12)	NS
Radionuclide LVEF (%)	25 (9)	30 (7)	0.038
Lown's grade	3.7 (1.2)	3.5 (1.4)	NS
Non-sustained VT	21%	17%	NS
LVEDD (mm)	65 (5)	62 (9)	NS
LAD (mm)	45 (8)	42 (8)	NS
Norepinephrine (pg/ml)	594 (270)	427 (233)	0.021
H/M (e)	1.72 (0.32)	1.88 (0.26)	NS
H/M (d)	1.54 (0.27)	1.77 (0.30)	0.006
WR	41 (16)	27 (14)	<0.001
Medications			
ACE inhibitors	79%	81%	NS
Digitalis	93%	87%	NS
β blocker*	57%	64%	NS
Aldosterone antagonist	71%	62%	NS
Antiarrhythmia drug (class Ib/III)†	29% (2/5)	23% (18/2)	NS

H/M (d), the heart-to-mediastinum metaiodobenzylguanidine (MIBG) uptake ratio on the delayed images; H/M (e), the heart-to-mediastinum MIBG uptake ratio on the early images; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NS, not significant; NYHA, New York Heart Association; VT, ventricular tachycardia; WR, washout rate.

Data are presented as the mean value (SD) or as percentage of patients.

*The use of β blocker (carvedilol) as recorded at the last follow-up visit.

†Class Ib anti-arrhythmia drug, mexiletine; class III, amiodarone.

Statistical analysis

Data are presented as mean (SD); Student's t test and Fisher's exact test were used to compare differences in continuous and discrete variables, respectively. The sudden-death-free survival rate and the total mortality-free survival rate in the two groups were calculated using the Kaplan–Meier method, and the difference between them was detected using the log rank test. The Cox proportional hazards regression model was used to determine the significance of variables, which is predictive of outcome by univariate analysis ($p < 0.05$), as an independent predictor of sudden death and total mortality. However, WR and H/Ms on the early and delayed images were thought to be

inter-related. Thus, only WR of the MIBG indices was included in the multivariate analysis. All statistical analyses were carried out using the StatView statistical package, V.4.5. A p value < 0.05 was considered significant.

RESULTS

Baseline characteristics of patients

In all, 48 of 97 study patients had abnormal WR (42% (10%)), whereas the remaining 49 patients had normal WR (17% (7%)). Table 1 lists the baseline clinical and study characteristics of the patients. There were no significant differences in age, gender, proportion of ischaemic heart disease, NYHA functional classification, radionuclide LVEF, the presence of non-sustained VT or drug use between the two groups. The abnormal WR group had significantly higher Lown's grade, left ventricular end-diastolic dimension (LVEDD), LAD and plasma concentration of norepinephrine than the normal WR group. Incidentally, H/M on the early and delayed images was significantly lower in the abnormal WR group than in the normal WR group (early image: 1.78 (0.29) vs 1.93 (0.24); $p = 0.007$, delayed image: 1.53 (0.23) vs 1.93 (0.25); $p < 0.001$, respectively).

Follow-up outcome

All patients were completely followed up. During the mean (SD) follow-up period of 65 (29) months, 12 (25%) patients died suddenly, 7 (15%) patients died from progressive pump failure and 6 (13%) patients died from non-cardiac causes in the abnormal WR group, whereas 2 (4%) patients died suddenly and 1 (2%) patient died from progressive heart failure and 2 (4%) from non-cardiac causes in the normal WR group (table 2). Sudden death-free rate curves of the two groups based on WR abnormality are shown in fig 1. Sudden death was significantly ($p = 0.001$) more often observed in the abnormal WR group than in the normal WR group. The risk ratio of sudden death in patients with abnormal WR was 6.13 (95% CI 1.53 to 24.5, $p < 0.05$). In addition, the two total mortality-free rate curves are similarly shown in fig 2. Total mortality was significantly ($p < 0.001$) higher in the abnormal WR group than in the normal WR group. The risk ratio of total mortality in patients with abnormal WR was 5.10 (95% CI 2.13 to 12.2, $p < 0.05$).

Comparison of baseline characteristics between patients who had and who did not have a sudden death

Table 3 lists the baseline characteristics of patients who had and who did not have a sudden death. There were no differences in age, gender, NYHA functional class, the proportion of ischaemic

Table 4 Univariate and multivariate Cox regression analysis of the identification of patients with chronic heart failure at increased risk of sudden death

	Univariate analysis		Multivariate analysis	
	p Value	HR (95% CI)	p Value	HR (95% CI)
WR	0.001	1.057 (1.023 to 1.091)	0.007	1.052 (1.014 to 1.091)
H/M (d)	0.004	0.065 (0.010 to 0.426)	—	—
Plasma norepinephrine level	0.018	1.002 (1.000 to 1.004)	0.43	1.001 (0.999 to 1.003)
Radionuclide LVEF	0.036	0.929 (0.867 to 0.995)	0.086	0.933 (0.861 to 1.010)
H/M (e)	0.049	0.135 (0.018 to 0.991)	—	—
LVEDD	0.099	1.054 (0.990 to 1.122)	—	—
LAD	0.15	1.051 (0.983 to 1.124)	—	—
Lown's grade	0.34	1.238 (0.797 to 1.923)	—	—

—, Not included in the multivariate analysis; H/M (d), the heart-to-mediastinum metaiodobenzylguanidine (MIBG) uptake ratio on the delayed images; H/M (e), the heart-to-mediastinum MIBG uptake ratio on the early images; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; WR, washout rate.

Figure 1 The sudden-death-free survival rate curves according to Kaplan-Meier analysis in patients with chronic heart failure with and without an abnormal washout rate (WR). The sudden-death-free rate was significantly lower in patients with abnormal WR ($\geq 27\%$) than in those with normal WR ($< 27\%$).

heart disease, blood pressure, heart rate, LVEDD, LAD, Lown's grade or the presence of non-sustained VT between the two groups. Patients with sudden death had significantly lower ($p = 0.038$) radionuclide LVEF and higher ($p = 0.021$) plasma concentration of norepinephrine than those without sudden death. Furthermore, patients with sudden death had significantly ($p = 0.006$) lower H/M on the delayed image and significantly ($p < 0.001$) higher WR than those without sudden death, although there was no significant difference in H/M on the early image between the two groups.

Prognostic analysis

On univariate Cox regression analysis, MIBG WR, H/M on the delayed image, H/M on the early image, radionuclide LVEF and plasma norepinephrine level were significantly associated with sudden death, whereas LVEDD, LAD and Lown's grade were not (table 4). Multivariate Cox analysis revealed that MIBG WR was the only independent predictor of sudden death. In addition, MIBG WR, H/M on the delayed image, H/M on the early image, radionuclide LVEF, LVEDD and LAD were significantly associated with an all-cause mortality, whereas plasma norepinephrine level, Lown's grade and H/M on the

Figure 2 Total mortality-free survival rate curves according to Kaplan-Meier analysis in patients with chronic heart failure with and without an abnormal washout rate (WR). The total mortality-free rate was significantly lower in patients with abnormal WR ($\geq 27\%$) than in those with normal WR ($< 27\%$).

early image were not (table 5). On multivariate analysis, MIBG WR was the only independent predictor of total mortality.

DISCUSSION

In patients with CHF, cardiac adrenergic function is characterised by a reduction in norepinephrine uptake and acceleration of spillover in the myocardial adrenergic terminals.¹⁷ Imaging of MIBG, an analogue of norepinephrine that shares the same uptake pathway in the myocardial adrenergic synapse, should reflect cardiac adrenergic nerve activity.¹⁸ It has been shown that cardiac MIBG imaging had prognostic value in patients with CHF.⁷⁻¹¹ However, its potential as a predictor of sudden death in patients with CHF has not been evaluated. Therefore, we attempted to prospectively investigate whether cardiac MIBG imaging could predict sudden death in patients with mild-to-moderate CHF. This study demonstrates that it would be a predictor.

Pathophysiological relation between cardiac sympathetic nerve activity assessed by cardiac MIBG imaging and sudden death

An accurate non-invasive assessment of cardiac sympathetic nerve activity would be particularly important in the setting of

Table 5 Univariate and multivariate Cox regression analysis of the identification of patients with chronic heart failure at increased risk of total mortality

	Univariate analysis		Multivariate analysis	
	p Value	HR (95% CI)	p Value	HR (95% CI)
WR	<0.001	1.049 (1.026 to 1.027)	0.002	1.044 (1.015 to 1.074)
H/M (d)	0.001	0.112 (0.032 to 0.396)	—	—
Radionuclide LVEF	0.015	0.943 (0.899 to 0.989)	0.054	0.946 (0.895 to 1.001)
LVEDD	0.031	1.047 (1.004 to 1.091)	0.44	1.022 (0.946 to 1.063)
LAD	0.035	1.050 (1.003 to 1.098)	0.93	1.003 (0.946 to 1.063)
Plasma norepinephrine level	0.051	1.001 (1.000 to 1.002)	—	—
Lown's grade	0.107	1.301 (0.945 to 1.791)	—	—
H/M (e)	0.18	0.404 (0.106 to 1.533)	—	—

—, Not included in the multivariate analysis; H/M (d), the heart-to-mediastinum metaiodobenzylguanidine (MIBG) uptake ratio on the delayed images; H/M (e), the heart-to-mediastinum MIBG uptake ratio on the early images; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; WR, washout rate.

CHF because of the association between high sympathetic activity in this condition and an adverse prognosis.³ Cardiac MIBG imaging provides direct information on the function and integrity of the presynaptic sympathetic nerve endings.^{5 18 19} The present study shows that patients with CHF with higher cardiac MIBG WR are at increased risk of sudden death. This result is consistent with the finding that increased sympathetic activity can modulate basic arrhythmia mechanisms of re-entry, automaticity and triggered activity to provoke lethal arrhythmias.^{20–22} MIBG WR may reflect adrenergic activity (norepinephrine spillover) more directly in patients with CHF, in whom denervation is suspected, because WR is independent of the amount of adrenergic neurones, whereas H/M might be mainly dependent on denervated status. This would be the reason why MIBG WR was a more potent predictor of sudden death than H/M from the statistical viewpoint.

Previous studies identifying patients at increased risk of sudden death in CHF

In the present study, as reported previously in some studies,^{23–25} non-sustained VT was not a predictor of sudden death in patients with CHF, whereas it was reported that non-sustained VT would predict sudden death in other studies.^{26 27} The discrepancy between these studies might be due to the severity of CHF and the reproducibility of non-sustained VT in 24-h Holter ECG monitoring. The prognostic value of other non-invasive electrophysiological tests, such as heart rate variability,^{12 13} signal-averaged ECG,²⁸ and T-wave alternans²⁹ are not conclusive. These non-invasive tests based on the ECG recordings are not interpretable in 20–30% of patients with CHF because of atrial fibrillation or limitations peculiar to the test. BNP, one of the important prognostic biomarkers in patients with heart failure, was also shown to predict sudden death in patients with CHF, although we did not measure BNP in this study.

Study limitations

There are several limitations of this study. First, it was a substudy of our placebo-controlled prospective study (unpublished). Furthermore, the small number of patients included in this study is the major limitation. In this respect, a large-scale, completely prospective study is needed. Second, the medications used during the follow-up period may affect MIBG uptake and clinical outcome. However, the proportion of the patients treated with β blockers was not significantly different between the two groups. Third, there may be a problem in quantifying the cardiac MIBG images. A large decrease in cardiac MIBG activity is known to occur in patients with heart failure. This may introduce errors when drawing ROIs manually on cardiac MIBG images of patients with CHF. In the present study, two independent observers drew the ROI. The interobserver variation in counts per pixel was within 1.2%. Thus, errors introduced by drawing the ROI manually on the cardiac MIBG images are likely to be small. Fourth, in this study, we studied only stable outpatients who had mild-to-moderate CHF. The results of our study should not be generalised to inpatients with severe CHF.

CONCLUSIONS

To the best of our knowledge, this is the first study to show the usefulness of cardiac MIBG imaging in the prediction of sudden death in patients with mild-to-moderate CHF.

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Authors' affiliations

Hidetaka Kioka, Takahisa Yamada, Takanao Mine, Takashi Morita, Yasumasa Tsukamoto, Shunsuke Tamaki, Masaharu Masuda, Keiji Okuda, Masatake Fukunami, Division of Cardiology, Osaka General Medical Centre, Osaka, Japan
Masatsugu Hori, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

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Atrial infarction in a premature infant

Atrial infarction is rarely diagnosed, usually being recognised only when associated with ventricular infarction. The most common ECG sign of atrial infarction is elevation or depression of the P-Ta segment, reflected by the P-R segment; this pattern, however, is usually mild (<1 mm), and is difficult to observe unless an accurate search is made.

We report the case of a premature infant with respiratory distress syndrome (RDS) and patent ductus arteriosus (PDA), in whom atrial infarction was diagnosed on the basis of a typical ECG pattern.

A female preterm infant, born at 28 weeks with a birth weight of 790 g, was referred to the neonatal intensive care unit at 2 months, after surgical ligation of PDA, performed at another institution. On admission, the baby

weighed 720 g and was mechanically ventilated. The admission ECG showed a pattern of left ventricular hypertrophy (deep S waves in lead V1, tall R waves and negative T waves in lead V6). There was, in addition, a striking P-R segment elevation (up to 2 mm) in leads I, II, III, aVF, V4, and V6 (panel A). The echocardiogram confirmed the left ventricular hypertrophy, and disclosed two hyper-echogenic left atrial masses, one located close to the posterior mitral valve leaflet and the other in correspondence of the atrial roof; these were interpreted as atrial thrombi. Laboratory tests showed raised creatine kinase MB (143 U/l), aspartate aminotransferase (201 U/l), lactic dehydrogenase (3230 U/l), and T-troponin (0.96 ng/ml) values. Seven days later, the P-R interval elevation had disappeared

(panel B), the T waves were less abnormal, the markers of cardiac necrosis had returned to normal, and intracardiac thrombi were markedly reduced in size.

Myocardial ischaemia is a common phenomenon in preterm newborn infants with PDA and RDS: myocardial infarction, as shown by the T-troponin and creatine kinase MB increase, has been reported in these patients. The occurrence of apparently isolated atrial infarction, however, has not been hitherto reported in this clinical setting. In our case, transient P-R segment elevation associated with left atrial thrombi strongly suggested such a diagnosis.

M P Calabrò, F L De Luca, I Barberi, G Oretò
oretomp@tin.it

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