

## Impaired vagal heart rate control in coronary artery disease

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**SUMMARY** Heart rate variation in deep breathing, a sensitive non-invasive measure of cardiac parasympathetic activity, was measured in 63 patients with coronary artery disease, in 22 patients with atypical chest pain, and in 20 healthy symptom free volunteers. There was significantly less heart rate variation in deep breathing in the patients with coronary artery disease than in the healthy subjects. Twenty patients (32%) with coronary artery disease had lower than normal variation in heart rate. The patients with chest pain showed an intermediate heart rate response to deep breathing. Sinus arrhythmia in the patients with coronary artery disease was not related to the functional class, medication, number or location of narrowed vessels, or to the left ventricular ejection fraction, and end diastolic pressure.

These results suggest that impairment of the parasympathetic nervous function is common in coronary artery disease.

The harmful effects of increased sympathetic activity after myocardial infarction are well established and the beneficial effects of sympathetic blockade in reducing mortality in high-risk patients have been recognised.<sup>1-3</sup> Recently, attention has also been directed toward the electrophysiological effects of the parasympathetic nervous system. Reduced vagal activity is associated with an increased frequency of cardiac death,<sup>4-6</sup> and parasympathetic blockade may precipitate ventricular arrhythmias including ventricular fibrillation.<sup>7 8</sup>

The majority of patients with acute myocardial infarction show evidence of autonomic disturbances during the acute stage of the attack.<sup>9 10</sup> The suggestion that there is dysfunction of the parasympathetic nervous system in stable coronary artery disease<sup>11 12</sup> and after myocardial infarction<sup>13 14</sup> is, however, more controversial and based on relatively small series of patients. We have evaluated parasympathetic nervous function in coronary artery disease by standard non-invasive cardiovascular tests and have related our findings to the clinical and angiographic features of coronary artery disease.

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### Patients and methods

#### PATIENTS

We studied 63 patients (57 men, six women) with coronary artery disease. They were consecutive patients referred for elective cardiac catheterisation in our hospital and fulfilled the following inclusion criteria: age <60 years; no valvar heart disease, hypertension, manifest heart failure, or atrial fibrillation; not on antiarrhythmic medication or other medication known to have anticholinergic activity; and no diabetes mellitus or uraemia.

The mean age of the patients was 50 years (range 33-59) and 36 patients had had a myocardial infarction (eight anterior, 15 inferior, and 13 non-Q wave). None was in the acute stage of the attack. Seven patients were in New York Heart Association class IV, 36 patients in class III, and 20 patients in class II. Their medication included  $\beta$  blockers in 42 cases (67%), calcium antagonists in 29 cases (46%), nitrates in 47 cases (75%), digitalis in 11 cases (18%), and diuretics in nine cases (14%).

The control group of 20 healthy subjects (10 men, 10 women) of the same age group (mean age 46, range 36-55 years) was recruited among the employees of a nearby pulp mill and among hospital staff. None was taking any medication known to affect autonomic nervous function. They were healthy as

shown by history, physical examination, chest x rays, echocardiogram, and exercise electrocardiogram.

A group of 22 patients (10 men, 12 women) with atypical chest pain was also assessed to evaluate the potential effects of long term antianginal medication and reduced physical activity on the autonomic control of heart rate. They were consecutive patients catheterised because of disabling symptoms and fulfilling the inclusion criteria. Their mean age was 47 years (range 35–59 years) and all had normal electrocardiograms, chest x rays, echocardiograms, left ventricular cineangiograms, and coronary angiograms. Their medication included  $\beta$  blockers and nitrates in 14 cases (64%), calcium antagonists in 10 cases (45%), diuretics in three cases (13%), and digitalis in one case (5%). Informed consent was obtained from all the subjects.

#### CARDIAC CATHETERISATION

All patients underwent left-sided cardiac catheterisation, including selective coronary arteriography performed by the Judkins' technique. Biplane left ventricular cineangiography was performed in the 45° right anterior oblique position. The angiographic findings were interpreted by two independent observers who were unaware of the tests of the autonomic nervous function. A stenosis causing reduction of > 50% in the luminal diameter of a coronary artery was regarded as an important lesion. Left ventricular pressures were recorded with a Statham 2351a transducer, and a data acquisition system (Hewlett-Packard 5400B) was used for analysis of pressure.

#### TESTS OF AUTONOMIC NERVOUS FUNCTION

The tests of autonomic nervous function were performed by specially trained nurses in the cardiovascular laboratory on patients in a postabsorptive state during the morning of the day before cardiac catheterisation. The patients were on their regular medication. Smoking and coffee drinking were not allowed in the morning before the tests. The heart rate was recorded with an instantaneous beat to beat rate recorder (Hewlett-Packard 8812 A rate computer). After a demonstration of the procedures and 10 minutes of supine rest the patients were asked to take six deep breaths. The depth of respiration is not critical as long as it is more than 40% of the vital capacity, but the rate of breathing is important and was standardised at six per minute.<sup>15 16</sup> The difference between the maximum and minimum heart rate during each breath was measured and the mean was taken as the heart rate variation during deep breathing (fig 1).

About 1–2 minutes after forced breathing the

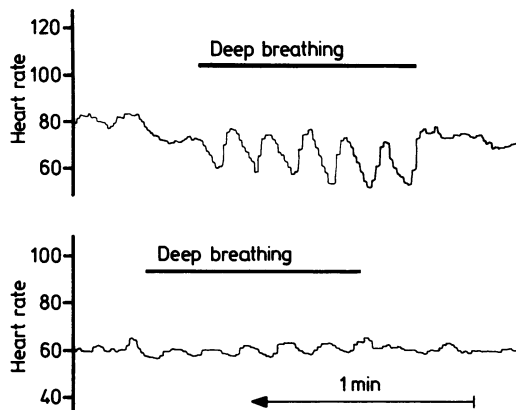


Fig 1 Normal heart rate variation during deep breathing in a healthy subject (above) and a blunted heart rate variation in a patient with coronary artery disease (below).

patients stood up quickly. The shortest RR interval at around the fifteenth beat after standing and the longest RR interval at around the thirtieth beat after standing were measured to show the response of the heart rate to standing (the 30:15 ratio).<sup>16</sup> Generally accepted normal values were used to evaluate these tests.<sup>16</sup>

Supine heart rate was determined as the mean rate over a 30 s period before standing up. The mean heart rate of the last 30 s during the two minutes' standing was taken as the standing heart rate. Blood pressure was measured with a sphygmomanometer while the patient was lying down and after 30–60 s of standing.

The reproducibility of the tests was assessed by examining 11 subjects (three with coronary artery disease) twice at an interval of at least two days. The mean (SD) difference in heart rate variation during deep breathing between test 1 and test 2 was 0 (4) (SD) beats/min (NS). The corresponding difference in the 30:15 ratio was +0.05 (0.19) (NS).

To assess ventricular parasympathetic reflexes,<sup>17</sup> we measured the degree of bradycardia induced by coronary arteriography—that is the shortest RR interval at the beginning of each coronary injection and the longest RR interval at around the end of each injection—and the induced maximum lengthening was expressed as a percentage. Only cases in which Urografin 76 was used as the contrast medium and who received no atropine as premedication were included in the analysis.

To assess the effects of cardiovascular medication on the tests of autonomic nervous function the drugs were gradually withdrawn at least two days (digitalis one week) before the tests in 12 patients with stable

Table 1 Heart rate and blood pressure changes evoked by standing up and the catheterisation data in the study groups (mean (SD))

Variable	CAD patients (n = 63)	Controls (n = 20)	Patients with chest pain (n = 22)
Heart rate, supine (beats/min)	67 (12)	69 (11)	73 (11)
Heart rate, standing (beats/min)	82 (14)†	83 (15)	93 (14)
The 30:15 ratio	1.21 (0.15)	1.27 (0.21)	1.24 (0.13)
Blood pressure, supine (mm Hg):			
Systolic	130 (18)	126 (14)	128 (15)
Diastolic	82 (10)	82 (11)	80 (13)
Blood pressure, standing (mm Hg):			
Systolic	122 (17)	121 (18)	118 (17)
Diastolic	85 (11)	80 (14)	85 (12)
LV end diastolic pressure (mm Hg)	12.9 (5.0)	—	14.7 (6.0)
LV end diastolic volume (ml)*	160 (34)§	—	126 (28)
LV ejection fraction (%)*	59 (10)§	—	70 (7)
RR interval change in response to coronary arteriography (%)*†	66 (67)	—	50 (42)

CAD, coronary artery disease; LV, left ventricular. \*Data on 35 patients with CAD and 12 patients with chest pain. †Data on 35 patients with CAD and nine with chest pain. Difference vs patients with chest pain: ‡ p < 0.05, § p < 0.01.

coronary artery disease and the tests were repeated one day after the treatment was resumed ( $\beta$  blockers in nine patients, nitrates in nine patients, calcium antagonists in seven patients, and digitalis in four patients).

#### STATISTICAL ANALYSIS

Differences between the three groups were evaluated by analysis of variance followed by the Bonferroni modification of *t* test. A paired or unpaired *t* test was used when appropriate and Fisher's test was used to evaluate the differences in frequencies. Standard formulas were used to calculate the linear correlations.

#### Results

##### CATHETERISATION DATA

Table 1 shows the catheterisation data in the patients. Five (8%) of the patients with coronary artery disease had an important stenosis of left main coronary artery; 34 patients (54%) had three vessel disease, 11 (17%) two vessel disease, and 13 (20%) one vessel disease.

##### PARASYMPATHETIC NERVOUS FUNCTION

There was less variation in heart rate during deep breathing in patients with coronary artery disease than in healthy subjects (difference between means 5, 95% confidence interval one to 10 beats/min), but not in patients with chest pain (fig 2). In the subgroup analysis of the patients, 40% of those with local akinesia or dyskinesia, 26% of the remaining patients with coronary artery disease, and 18% of the patients with chest pain had abnormal ( $\leq 10$  beats/min) heart rate variation in deep breathing. One healthy subject also had a heart rate variation just below the lower limit of normal (fig 2).

The number or location of affected vessels did not significantly affect the variation in heart rate during deep breathing. Nor was the variation related to New York Heart Association class, left ventricular ejection fraction, or end diastolic pressure in the patients with coronary artery disease. The medication taken by patients with abnormal heart rate vari-

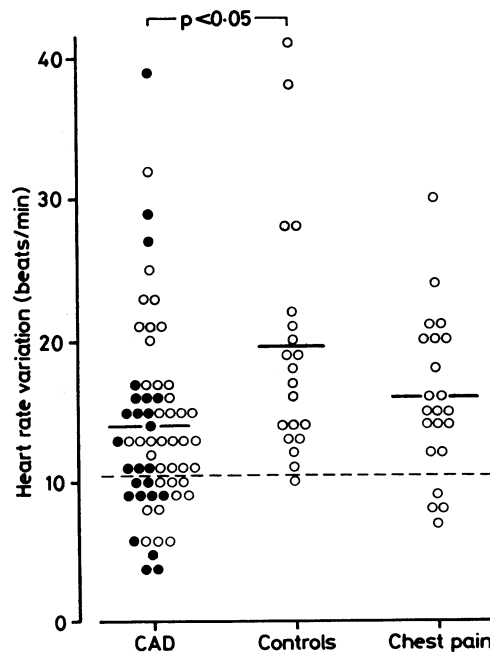


Fig 2 Heart rate variation in deep breathing in patients with coronary disease (CAD), healthy subjects, and patients with chest pain. Patients with transmural myocardial infarction (●). Broken line shows lower limit of normal.

Table 2 Clinical and catheterisation data on patients with coronary artery disease who had normal or abnormal heart rate variation during deep breathing (mean (SD))

Variable	Normal heart rate variation (n = 43)	Abnormal heart rate variation (n = 20)
Age	50 (6)	51 (5)
Mean NYHA class	2.8	2.9
Treatment:		
β Blockers	29 (67%)	13 (65%)
Calcium antagonists	23 (53%)	6 (30%)
Nitrates	30 (70%)	17 (85%)
Digitalis	9 (21%)	2 (10%)
Diuretics	8 (19%)	1 (5%)
Heart rate, supine (beats/min)	67 (10)	66 (16)
Heart rate, standing (beats/min)	83 (12)	79 (17)
The 30:15 ratio	1.23 (0.16)	1.15 (0.11)*
Blood pressure, supine (mm Hg):		
Systolic	131 (20)	126 (13)
Diastolic	82 (10)	81 (10)
Blood pressure, standing (mm Hg):		
Systolic	126 (17)	115 (17)*
Diastolic	86 (10)	83 (12)
Location of coronary stenosis:		
Left main coronary artery	4 (9%)	1 (5%)
Left anterior descending branch	38 (88%)	19 (95%)
Circumflex branch	32 (74%)	13 (65%)
Right coronary artery	32 (74%)	13 (65%)
LV end diastolic pressure (mm Hg)	12.8 (5.9)	13.3 (5.3)
LV end diastolic volume (ml)	158 (37)	166 (26)
LV ejection fraction (%)	60 (10)	57 (11)
RR interval change in response to coronary arteriography (%)	71 (72)	53 (48)

NYHA, New York Heart Association; LV, left ventricular. Difference between the groups: \* $p < 0.05$ .

ation did not differ significantly from that of the patients with normal heart rate variation (table 2) or of the patients with chest pain. Heart rate variation in deep breathing was not significantly related to age in the patients with coronary artery disease ( $r = -0.05$ ), but tended to diminish with age in the other subjects ( $r = -0.29$ ,  $n = 42$ ).

Changes in heart rate evoked by standing up (the 30:15 ratio) as well as supine and standing blood pressure were not significantly different in the three groups (table 1). In the subgroup analysis of patients with coronary artery disease, the standing systolic blood pressure and the 30:15 ratio of the patients with abnormal heart rate variation were, however, lower than those in the patients with normal heart rate variation ( $p < 0.05$ ) (table 2).

The mean (SD) heart rate variation in deep breathing was similar after withdrawal and reinstatement of the cardiovascular medication (13.8 (7.4) and 11.6 (7.1) beats/min, respectively, NS) in the 12 patients in which it is evaluated.

The bradycardia caused by coronary arteriography was not significantly different in patients with coronary artery disease and those with chest pain.

## Discussion

The variation in heart rate induced by deep breathing is the single most sensitive and reproducible

non-invasive test of cardiac parasympathetic activity.<sup>18,19</sup> It correlates closely with invasive measurement of parasympathetic heart rate control—for example, baroreflex sensitivity.<sup>18</sup> Several physiological mechanisms contribute to respiratory sinus arrhythmia. These include both reflex mechanisms (pulmonary stretch receptors, baroreceptors, Bainbridge reflex) and the direct interaction of the respiratory and cardiovascular medullary centres.<sup>20</sup> The fact that vagotomy and atropine abolish respiratory sinus arrhythmia and that recorded vagal efferent activity closely predicts the magnitude of heart rate variation shows that parasympathetic efferents are mainly responsible for mediating these effects.<sup>20,21</sup> Changes in heart rate induced by standing up also reflect mainly parasympathetic heart rate control, but are not so useful because they are less sensitive and have a wider range of normal responses, especially in older people.<sup>22,23</sup>

Our study suggests that cardiac vagal efferent activity is depressed in coronary artery disease. Earlier studies of autonomic nervous function in coronary artery disease have given somewhat divergent results. Ryan *et al* found impaired parasympathetic response to facial immersion, but normal sympathetic pressor responses in 27 patients three months after myocardial infarction.<sup>13</sup> On the other hand, Bennett *et al* found impaired sympathetic responses in a group of 18 asymptomatic patients studied at least one year after myocardial

infarction.<sup>14</sup> The difference in parasympathetic responses did not reach statistical significance, although the values were comparable to those in the present study. The heart rate response to the Valsalva manoeuvre has been reported to be abnormally low in patients with coronary artery disease,<sup>11</sup> although they may have an exaggerated heart rate response to carotid sinus massage.<sup>12</sup> The apparent discrepancies may result from the fact that various tests reflect different aspects of autonomic nervous function.

We cannot explain the impairment of vagal control of heart rate in coronary artery disease. Heart rate variation tends to decline with age in healthy subjects,<sup>23 24</sup> but heart rate variation in deep breathing was not affected by age in patients with coronary artery disease, so it seems that minor differences in age between the groups were not a crucial factor. Earlier observations suggest that medication was unlikely to have had any major impact on our findings.<sup>6 14 25</sup> This view is supported by the findings that the withdrawal of medication did not significantly alter the heart rate variation and that patients with abnormal and normal heart rate variation in deep breathing were on similar medication.

The level of physical activity may affect the parasympathetic tone and reflex heart rate control.<sup>26</sup> Interestingly, the patients with chest pain also had slightly diminished heart rate responses to deep breathing, which might suggest that reduced physical activity caused by disabling symptoms may contribute to the blunting of heart rate variation. The severity of the symptoms did not, however, correlate with the heart rate variation in deep breathing.

Earlier experimental studies have shown that transmural infarction can interrupt both the afferent and efferent limbs of the autonomic innervation of the myocardium apical to the infarction.<sup>27</sup> Heart rate variation in deep breathing or the degree of bradycardia caused by coronary arteriography, however, were not significantly reduced in patients with transmural myocardial infarction compared with other patients with coronary artery disease. Nor was heart rate variation in deep breathing related to the location or number of diseased vessels or to left ventricular function. So it seems that reduced vagal efferent activity in coronary artery disease cannot be predicted by any specific feature of the disease.

The role of the parasympathetic nervous system in protecting the heart against serious ventricular arrhythmias and sudden death has recently attracted attention. The interaction of the parasympathetic nervous system with the sympathetic nervous system can buffer the deleterious effect of sympathetic storm on the threshold for ventricular fibrillation.<sup>28 29</sup> Experimental studies have shown

that dogs with a healed myocardial infarction and reduced levels of cardiac vagal activity are liable to exercise-induced ventricular fibrillation and that subsequent increases in vagal activity protect against ventricular fibrillation.<sup>26</sup> In accordance with this, reduced respiration-related variation in heart rate is associated with an increased frequency of cardiac death both in middle aged men<sup>5</sup> and after myocardial infarction.<sup>6 30</sup> These studies suggest that a diminished heart rate variation in deep breathing, a simple bedside measure of cardiac vagal activity, might identify a subpopulation of patients with coronary artery disease who are at an increased risk of sudden death. It is not yet known whether interventions known to augment the vagal activity—for example pharmacological ones,<sup>31</sup> and exercise programmes, or on the other hand blocking of sympathetic activity, might be of particular value in this group of patients.

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