

Cardiac and whole body [³H]noradrenaline kinetics in ischaemic heart disease: contrast between unstable anginal syndromes and pacing induced ischaemia

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SUMMARY Radiotracer kinetics were used to evaluate the activity of the sympathetic nervous system in 10 patients who had had unstable ischaemic symptoms within the previous 12 weeks and 10 with stable angina. Patients with recent unstable angina or angina after recent acute myocardial infarction had higher basal cardiac noradrenaline spillover than patients with stable angina. This represents a selective increase in cardiac sympathetic tone because whole body noradrenaline spillover was not significantly increased in the patients with recent unstable angina. Atrial pacing in 15 patients caused angina in 13 but did not significantly alter cardiac noradrenaline spillover in either patients with stable or unstable angina. The flow of plasma in the coronary sinus increased during pacing but because cardiac noradrenaline extraction decreased cardiac noradrenaline clearance was not significantly altered. Both whole body noradrenaline spillover and clearance were modestly increased by pacing, and arterial noradrenaline concentration was unchanged.

Patients with recent symptoms of unstable ischaemia had a sustained and selective increase in cardiac efferent sympathetic tone compared with patients with stable angina, and angina induced by atrial pacing did not cause important cardiac sympathetic activation.

The sympathetic nervous system has a profound effect on the susceptibility of the ischaemic myocardium to serious ventricular arrhythmias,^{1,2} and the cardiac autonomic nervous system has been implicated in sudden cardiac death.³ Experimental coronary occlusion, however, does not increase coronary venous overflow of noradrenaline^{4,5} but sympathetic responsiveness was temporarily related to vulnerability to arrhythmia in open chest anaesthetised dogs.⁶ Coronary occlusion increases local concentrations of cyclic adenosine monophosphate, possibly because of an increase in sympathetic activity.⁷ In addition to local exocytotic catecholamine release via reflex mechanisms or local nerve terminal depolarisation, ischaemia itself may result in the direct release of noradrenaline via outward transport from the nerve terminal mediated by a carrier.⁸ Little is known about the response of the sympathetic nervous system to myocardial ischaemia in human beings.

Assessment of sympathetic tone in clinical research has often been based on the measurement of concentrations of noradrenaline in the venous plasma for overall sympathetic tone and of the venoarterial difference in noradrenaline concentration for sympathetic tone to individual organs. These methods, however, disregard the influence of noradrenaline clearance. Recently developed radiotracer kinetic techniques, with infusions of [³H]noradrenaline, can simultaneously assess noradrenaline spillover to plasma and noradrenaline clearance.⁹ These radiotracer techniques assume that a steady state has been reached, that infused [³H]noradrenaline is not re-released to an appreciable degree, and that alumina extractable [³H]metabolites do not accumulate during infusion. Our own studies¹⁰ and those of Esler *et al*¹¹ have shown these assumptions to be valid. Although this technique measures noradrenaline spillover to plasma and not noradrenaline release, it has been shown for several organs, including the heart,¹² that regional noradrenaline spillover correlates well with the rate of direct sympathetic nerve stimulation.¹³ Thus these techniques allow a better assessment of cardiac sympathetic activity than was possible before.

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The aim of this study was to evaluate the effects on cardiac and overall sympathetic activity in patients with coronary artery disease of recent unstable ischaemic symptoms and of a short period of myocardial ischaemia induced by atrial pacing.

Patients and methods

PATIENTS

We studied 20 patients (table 1) while they were supine and in the fasting state one hour after diagnostic cardiac catheterisation. Nineteen were male and all had coronary arterial disease (> 50% stenosis of the diameter of at least one major coronary artery). All patients were stabilised on medical treatment at the time of study. Ten patients had unstable ischaemic symptoms (sudden deterioration of previously stable angina, onset of angina at rest, or angina after acute myocardial infarction) within the previous 12 weeks (group 1) and 10 had angina which had been stable for at least 12 weeks (group 2). Four of group 2 and three of group 1 had systemic hypertension and none was on a sodium restricted diet. The resting left ventricular ejection fraction was

determined from the right anterior oblique cine-angiogram.¹⁴ The two groups were well matched for age, extent and severity of coronary disease, and for medical treatment. Blood pressure and left ventricular end diastolic pressure were higher in group 2 but the left ventricular ejection fraction was not significantly different. All subjects gave informed consent to the study, which was approved by the Central Oxford Research Ethics Committee.

PROTOCOL

After left ventricular and coronary angiography, performed by the standard femoral approach, a sampling catheter was left in the artery and a Baim flow catheter (Electro-catheter Corporation, New Jersey) was inserted under fluoroscopic control via the right subclavian vein into the distal coronary sinus. Correct placement was confirmed by injection of a small quantity of contrast material. This catheter permitted repeated sampling of blood from the coronary sinus and measurement of blood flow in the coronary sinus by thermodilution.¹⁵ For measurement of blood flow in the coronary sinus we infused 0.9% saline at room temperature via a

Table 1 Clinical data and results of cardiac catheterisation for 20 patients with ischaemic heart disease

| Case No | Age (yr) | BP (mm Hg) | LVEF (%) | LVEDP (mm Hg) | CAD | Drugs | ETT |
|--|----------|-----------------|----------|---------------|---------------|--------------------|---------------------|
| Group 1 (n = 10) (recent unstable ischaemic symptoms): | | | | | | | |
| 1 | 58 | 110/68 | 70 | 11 | LAD,Cx,RCA | Met,nif,ISDN | St 2, 3 mm, ant-lat |
| 2 | 58 | 155/82 | 64 | 10 | LAD,Cx | Frus,amil,ISDN | — |
| 3 | 61 | 120/72 | 52 | 12 | LAD,Cx,RCA | Met,ISDN,asp | St 2, 2 mm, inf-lat |
| 4 | 58 | 125/85 | 36 | 18 | Cx,RCA | Met,frus,amil,ISDN | St 3, ST↑, inf |
| 5 | 56 | 110/70 | 54 | 10 | LAD,RCA | At,cap,thiaz | — |
| 6 | 51 | 174/92 | 71 | 14 | RCA | At,thiaz | St 2, 2 mm, inf-lat |
| 7 | 68 | 155/94 | 74 | 11 | LAD,Cx,RCA | At,dilt,GTN | St 2, 3 mm, lat |
| 8 | 48 | 105/70 | 55 | 16 | Cx,RCA | At,asp | St 3, 2 mm, lat |
| 9 | 57 | 160/85 | 60 | 10 | LAD,Cx,RCA | At,nif,asp | St 1, 5 mm, lat |
| 10 | 58 | 148/88 | 62 | 10 | LAD,Cx | At,ISDN,asp | St 2, no ST↓ |
| Mean (SEM) | 57 (2) | 136/81 (8/3) | 60 (4) | 12 (0.9) | | | |
| Group 2 (n = 10) (stable angina): | | | | | | | |
| 11 | 57 | 100/62 | 46 | 10 | LAD,Cx,RCA | Aceb,ISDN | St 3, 6 mm, inf-lat |
| 12 | 57 | 122/70 | 64 | 10 | LM,Cx,RCA | Prop,asp | St 3, 3 mm, ant-lat |
| 13 | 60 | 115/55 | 52 | 8 | LAD,Cx,RCA | At,nif,ISDN | St 2, 3 mm, inf-lat |
| 14 | 72 | 135/58 | 70 | 8 | LAD,Cx,RCA | At,nif,ISDN | St 1, 3 mm, inf-lat |
| 15 | 53 | 112/65 | 61 | 12 | LAD,Cx,RCA | At,nif,ISDN,asp | St 3, 2 mm, lat |
| 16 | 53 | 115/82 | 64 | 8 | LAD,Cx,RCA | Dilt,ISDN,asp | St 2, 2 mm, inf-lat |
| 17 | 54 | 100/55 | 67 | 10 | LAD | At,nif | St 2, 2 mm, lat |
| 18 | 61 | 92/50 | 71 | 8 | LM,LAD,Cx,RCA | Prop,asp | St 1, 2 mm, inf-lat |
| 19 | 55 | 135/85 | 75 | 9 | LAD,RCA | At,nif,thiaz | St 3, no ST↓ |
| 20 | 58 | 105/70 | 70 | 8 | LAD,Cx,RCA | At,nif,ISDN | St 3, 1 mm, inf-lat |
| Mean (SEM) | 58 (2) | 113*/65** (5/4) | 65 (3) | 9* (0.4) | | | |

*p < 0.05, **p < 0.01 group 1 versus group 2 (non-paired *t* test).

Aceb, acebutolol; amil, amiloride; ant-lat, anterolateral (V2-V6); asp, aspirin; at, atenolol; BP, blood pressure; CAD, extent of coronary artery disease; cap, captopril; Cx, circumflex coronary artery; dilt, diltiazem; ETT, result of exercise tolerance test (stage reached, amount and localisation of ST segment depression); frus, frusemide; GTN, glyceryl trinitrate; inf, inferior (2,3, aVF); inf-lat, inferolateral (2,3,aVF,V5,V6); ISDN, isosorbide dinitrate; LAD, left anterior descending artery; lat, lateral (V5,V6 ± 1, aVL); LM, left main coronary artery; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end diastolic pressure; met, metoprolol; nif, nifedipine; prop, propranolol; RCA, right coronary artery; St, stage (standard Bruce protocol) reached on exercise testing; ST↓, ST segment depression, ST↑, ST segment elevation; thiaz, thiazide diuretic.

Harvard pump at 28 ml/min until equilibrium was reached (15–30 seconds). Measurements were made in quiet held respiration to minimise respiratory movement of the catheter. The output from the Baim Coronary Sinus Flow Analyser (Electro-catheter Corporation) was linked to a Hewlett-Packard 9000 217 computer to give on line measurement of blood flow in the coronary sinus by use of the standard equation to determine flow from the temperature drop, integrated over a five second period. The system gave reproducible measurements of coronary sinus flow, which were made in duplicate. The coefficient of variation between repeated single measurements at rest was 3%. Plasma flow in the coronary sinus was calculated by correction for the arterial haematocrit. Cardiac catheterisation was uncomplicated in all patients and none developed symptomatic myocardial ischaemia during the procedure.

After insertion of the Baim catheter subjects were transferred to the research laboratory, where the [³H]noradrenaline infusion was started. Samples of arterial blood and blood from the coronary sinus were taken 30 minutes after the start of the infusion. In 10 subjects with stable angina and five subjects with unstable symptoms atrial pacing via the Baim catheter was then started and the rate was increased to the maximum sustainable rate (the fastest rate not causing severe angina or Wenckebach atrioventricular block). Pacing increased the heart rate from 62 beats/minute at rest (range 48–70) to 110 (94–123) beats/minute. In 13 patients angina developed during pacing. In nine of these ST segment depression on the standard 12 lead surface electrocardiogram was ≥ 1 mm. Arterial and coronary sinus blood samples (10 ml each) were taken after 10 and 20 minutes pacing and again 10 minutes after the end of pacing. Coronary sinus blood flow was measured immediately before each sampling time.

NORADRENALINE KINETICS

Noradrenaline kinetics were measured according to the techniques of Esler *et al.*¹¹ 1-[2,5,6-³H]noradrenaline (New England Nuclear) was given intravenously as a bolus (12 μ Ci (0.44 MBq) followed by constant infusion (0.7 μ Ci (0.026 MBq) $\text{min}^{-1}\text{m}^{-2}$) for up to 80 minutes. Blood samples were collected into chilled lithium heparin tubes, centrifuged at 4°C, and the plasma was frozen on dry ice and stored at -20°C for up to three months. Sodium metabisulphite at a final concentration of 1 mmol/l was used as an antioxidant. Plasma noradrenaline was measured by high performance liquid chromatography.¹⁶ The normal range in our laboratory is 120–300 pg/ml and the within day coefficient of variation is 4%. Plasma [³H]noradrenaline was measured by liquid scintillation counting of

alumina extracts with correction for recovery of a non-radioactive internal standard (dihydroxybenzylamine).¹⁰ The within day coefficient of variation for the estimation of [³H]noradrenaline is 7%. Each sample was assayed in duplicate, with half of each alumina extract being used for estimation of [³H]noradrenaline and half for estimation of noradrenaline and dihydroxybenzylamine.

Noradrenaline (NA) plasma clearance and noradrenaline spillover to plasma for the heart and whole body were measured according to the following relations, which hold under steady state conditions¹¹:

$$\text{Whole body NA clearance} = \frac{\text{Infusion rate (dpm/min)}}{\text{Plasma } [^3\text{H}] \text{ NA (dpm/ml)}}$$

$$\text{Whole body NA spillover} = \frac{\text{Infusion rate (dpm/min)}}{\text{Specific radioactivity of plasma NA (dpm/pg)}}$$

$$\text{Cardiac NA clearance} = \text{CSPF} \times \text{NA}_E$$

$$\text{Cardiac NA spillover} = \text{CSPF} \times [(\text{NA}_{\text{CS}} - \text{NA}_A) + (\text{NA}_A \times \text{NA}_E)]$$

where CSPF = coronary sinus plasma flow; NA_E = fractional extraction of [³H]noradrenaline by the coronary circulation; NA_{CS} = coronary sinus noradrenaline concentration; NA_A = arterial noradrenaline concentration; and dpm = disintegrations per minute of [³H]noradrenaline.

STATISTICAL ANALYSIS

Analysis of variance was used to assess the differences between the data at the four time points of the pacing protocol. The data on noradrenaline kinetics were log transformed because their distribution was skewed. Differences between patients with stable and unstable symptoms were analysed by a two tailed Mann-Whitney U test. Results were deemed to be significant at the 5% level. Results are expressed as the mean (1 SEM).

Results

BASAL NORADRENALINE KINETICS IN PATIENTS WITH STABLE AND RECENT UNSTABLE SYMPTOMS (table 2, figs 1 and 2)

The ranges of basal concentrations of noradrenaline in the coronary sinus (62–1438 pg/ml) and of basal cardiac noradrenaline spillover (2–76 ng/min) were large. Patients with chronic stable angina had much lower concentrations of noradrenaline in the coronary sinus and much lower cardiac noradrenaline spillover than did patients with recent unstable ischaemic symptoms. Values were highest in a man

Table 2 Basal noradrenaline kinetics in patients with recent unstable or stable symptoms

| Case No and history | Cardiac NA spillover (ng/min) | Cardiac NA clearance (ml/min) | CS NA (pg/ml) | Art NA (pg/ml) | Total NA spillover (ng/min) | Total NA clearance (ml/min) |
|---|-------------------------------|-------------------------------|---------------|----------------|-----------------------------|-----------------------------|
| Group 1 (n = 10) (recent unstable ischaemic symptoms): | | | | | | |
| (1) 8/52 unstable AP | 10 | 49 | 210 | 214 | 197 | 919 |
| (2) 2/52 unstable AP → pulmonary oedema | 76 | 35 | 1438 | 814 | 649 | 797 |
| (3) 6/52 unstable AP | 14 | 47 | 470 | 274 | 335 | 1222 |
| (4) AMI 6/52 previously → ventricular aneurysm | 49 | 24 | 839 | 271 | 335 | 783 |
| (5) HT, non Q-wave AMI 8/7 previously → continued AP | 26 | 52 | 449 | 271 | 483 | 1784 |
| (6) HT, 12/52 unstable AP | 20 | 41 | 387 | 207 | 386 | 1866 |
| (7) 2/12 unstable AP | 6 | 29 | 222 | 267 | 374 | 1401 |
| (8) Non Q-wave AMI 2/52 previously → continued AP | 12 | 23 | 380 | 158 | 236 | 1494 |
| (9) HT, 2/12 unstable AP | 17 | 44 | 296 | 132 | 168 | 1296 |
| (10) Non Q-wave AMI 10/52 previously → continued AP | 15 | 33 | 456 | 408 | 686 | 1680 |
| (1-10) Mean (SEM) | 24 (7) | 38 (3) | 515 (117) | 317 (63) | 385 (56) | 1325 (125) |
| Group 2 (n = 10) (stable angina): | | | | | | |
| (11) Previous AMI, 10 yr class II AP | 9 | 31 | 331 | 452 | 380 | 820 |
| (12) HT, previous AMI, MR, 1 yr class II AP | 4 | 27 | 179 | 208 | 182 | 875 |
| (13) 1 yr class III AP | 2 | 32 | 62 | 114 | 315 | 2766 |
| (14) HT, 6/12 class IV AP | 14 | 64 | 202 | 178 | 246 | 1406 |
| (15) Previous AMI and CABG, 1 yr class III AP | 2 | 25 | 94 | 179 | 248 | 1387 |
| (16) Previous AMI, 5/12 class III AP, unstable AP 5/12 ago | 12 | 49 | 226 | 200 | 93 | 467 |
| (17) 18/12 class II AP | 2 | 47 | 84 | 98 | 156 | 1598 |
| (18) HT, previous CABG, 4/12 class III AP | 8 | 45 | 180 | 218 | 317 | 1455 |
| (19) HT, 18/12 class III AP | 5 | 33 | 163 | 197 | 346 | 1757 |
| (20) 4/12 class II AP | 4 | 23 | 194 | 248 | 310 | 1249 |
| (11-20) Mean (SEM) | 6 (1)* | 38 (4) | 171 (24)* | 210 (30) | 257 (25) | 1416 (182) |

*p < 0.001, group 1 v group 2, Mann-Whitney U test.

AMI, acute myocardial infarction; AP, angina pectoris; Art, arterial; CABG, coronary artery bypass grafts; class, New York Heart Association class; CS, coronary sinus; HT, systemic hypertension; MR, mitral regurgitation; NA, noradrenaline. Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

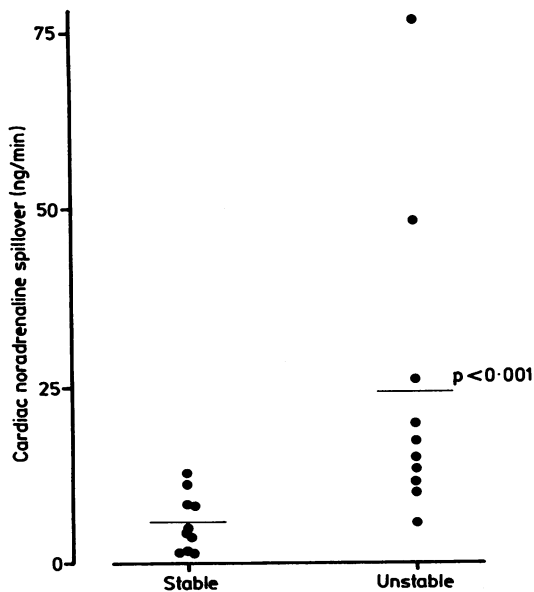


Fig 1 Cardiac noradrenaline spillover in patients with stable and unstable symptoms. Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

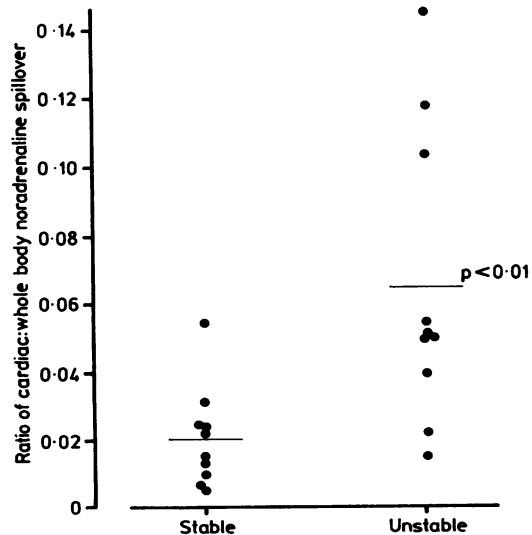


Fig 2 Cardiac to whole body noradrenaline spillover ratio in patients with stable and unstable symptoms.

with a two week history of unstable angina, culminating in severe pulmonary oedema (patient 2, table 2). Myocardial infarction was excluded and when cardiac catheterisation was performed a week later, after the resolution of the pulmonary oedema, severe three vessel coronary artery disease was found. There was some anteroapical hypokinesis but left ventricular contraction was good overall (left ventricular ejection fraction = 64%). Mean cardiac noradrenaline spillover in the 10 patients with recent unstable ischaemic symptoms was 24 (7) ng/min compared with 6 (1) ng/min for the 10 patients with stable angina ($p < 0.001$, fig 1). Coronary sinus noradrenaline concentration was also significantly greater in the patients with recent unstable angina ($p < 0.001$, table 2).

In contrast with coronary venous noradrenaline concentration and spillover, arterial noradrenaline concentration was not significantly higher in the group with recent unstable angina (317 (63) pg/ml versus 210 (30) pg/ml). Similarly, whole body noradrenaline spillover was not significantly higher in this group (385 (56) ng/min versus 257 (25) ng/min). Whole body noradrenaline clearance was similar in both groups (table 2).

The ratio of cardiac noradrenaline spillover in the group with recent unstable angina compared with that in the patients with stable angina was 4.0:1. For whole body spillover the ratio between the same two groups was only 1.5:1. Similarly the ratio of cardiac to whole body noradrenaline spillover was greater in the group with recent unstable angina (0.065 (0.013)) than in the group with stable angina (0.021 (0.005)) ($p < 0.01$, fig 2), so there was evidence of a selective increase in cardiac sympathetic activity in patients with recent unstable angina.

There was no significant correlation between left ventricular ejection fraction and cardiac noradrenaline spillover ($r = -0.30$, $p = \text{NS}$). Similarly there was no significant correlation between left ventricular end diastolic pressure and cardiac noradrenaline spillover ($r = 0.36$, $p = \text{NS}$).

NORADRENALINE KINETICS DURING ATRIAL PACING (figs 3, 4, 5, and 6)

Atrial pacing increased coronary sinus plasma flow from 55 (5) ml/min to 78 (7) ml/min but, as a result of a decline in the fractional extraction of noradrenaline by the coronary circulation from 71 (3)% to 59 (4)%, cardiac noradrenaline clearance was not significantly altered by pacing (fig 3). Despite the development of myocardial ischaemia in most of the subjects there was a trend towards a decline in coronary sinus noradrenaline concentration during atrial pacing and cardiac noradrenaline spillover was unchanged (fig 4). No consistent trend in cardiac noradrenaline

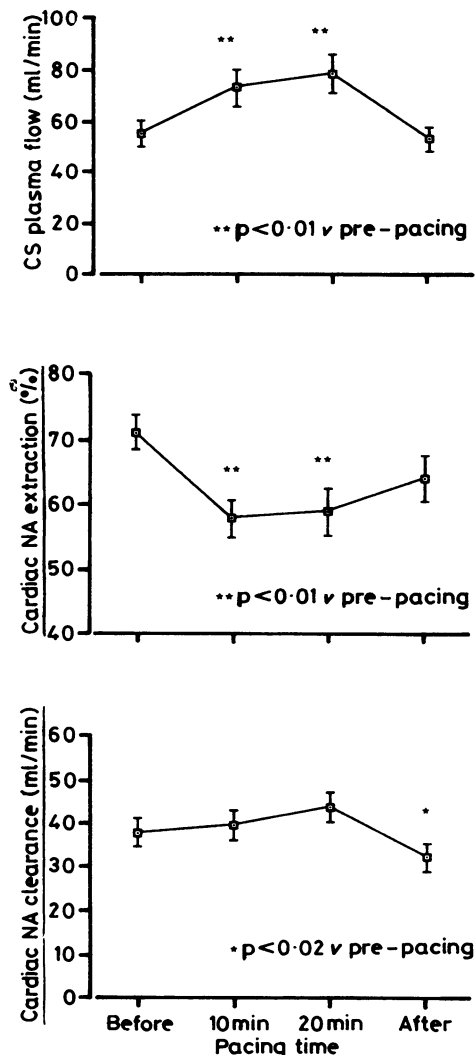


Fig 3 Coronary sinus (CS) plasma flow, cardiac noradrenaline (NA) extraction, and cardiac noradrenaline clearance in response to atrial pacing.

spillover was seen in response to atrial pacing in either groups (stable $n = 10$, unstable $n = 5$) (fig 5).

Atrial pacing resulted in a modest rise in whole body noradrenaline clearance, from 1311 (138) ml/min to 1508 (213) ml/min. This was associated with a small rise in noradrenaline spillover to plasma and no change in arterial noradrenaline concentration (fig 6). There was no difference in the cardiac or whole body noradrenaline kinetics between 10 and 20 minutes pacing, confirming that a new steady state had been reached.

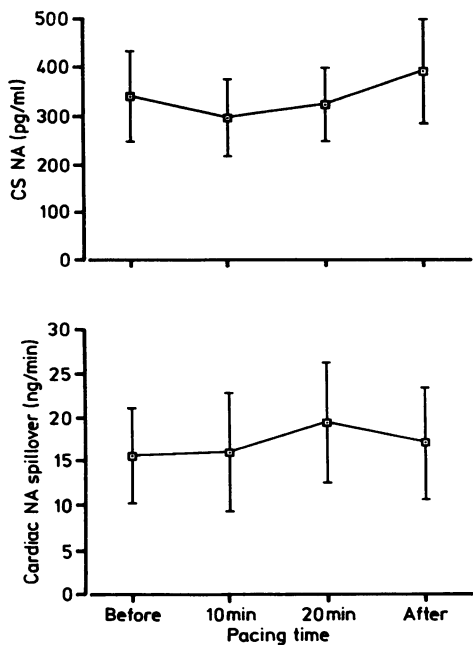


Fig 4 Coronary sinus (CS) noradrenaline (NA) concentration and cardiac noradrenaline spillover in response to atrial pacing to ischaemia. Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

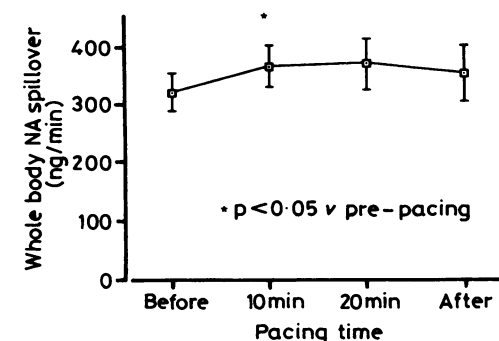
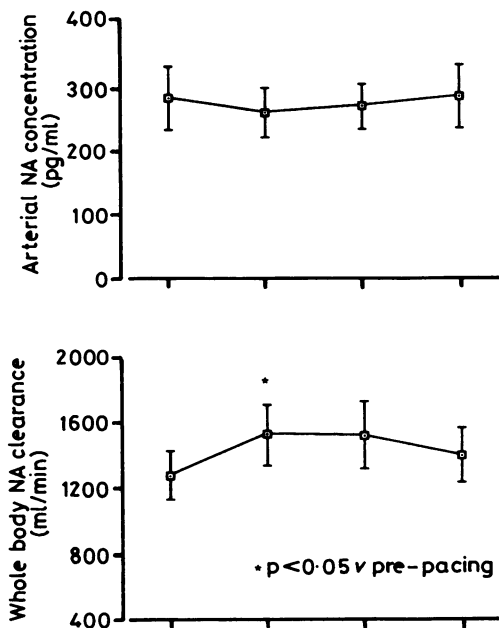


Fig 6 Whole body noradrenaline (NA) kinetics in response to atrial pacing. Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

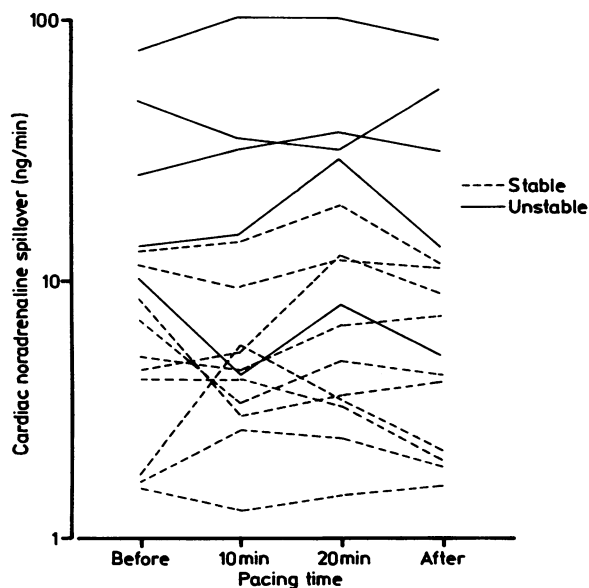


Fig 5 Cardiac noradrenaline spillover during atrial pacing in 15 patients—10 with stable angina and five with recent unstable ischaemic symptoms. Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

Discussion

SYMPATHETIC ACTIVITY IN ISCHAEMIC HEART DISEASE

It is widely believed that angina and myocardial ischaemia give rise to a generalised increase in sympathetic tone.¹⁷ Few studies have, however, investigated this belief or attempted to define cardiac sympathetic tone during myocardial ischaemia. Those studies which have measured catecholamine concentrations in ischaemic heart disease have not taken into account the influence of noradrenaline clearance. All organs both extract noradrenaline from and secrete noradrenaline into the circulation,

and at rest the heart, with its rich sympathetic innervation, extracts about 70% of the noradrenaline entering the coronary circulation. Because, as this study shows, cardiac noradrenaline uptake may be profoundly altered by manoeuvres that alter blood flow, it is not possible to come to meaningful conclusions about the sympathetic tone to a given organ simply by measuring venoarterial differences in noradrenaline concentration and organ blood flow. The use of steady state radiotracer methods overcomes this difficulty and allows sympathetic tone to be more reliably estimated.

Two previous studies have evaluated concentrations of catecholamine in the coronary sinus during atrial pacing to ischaemia in man. One found that "myocardial noradrenaline release" increased in response to atrial pacing but to a greater extent in normal controls than in patients with ischaemic heart disease.¹⁸ A modest increase in concentration of noradrenaline in the coronary sinus was shown during atrial pacing to angina but there was no significant increase in arterial noradrenaline concentration. The second, conversely, reported a decrease in "myocardial noradrenaline overflow" during atrial pacing to angina, and showed a modest increase in arterial noradrenaline concentration but no significant change in coronary sinus noradrenaline.¹⁹ In anaesthetised dogs epicardial pacing did not increase cardiac noradrenaline spillover.¹² Robertson *et al* measured coronary sinus and arterial noradrenaline concentrations during the course of spontaneous coronary artery spasm.²⁰ No changes were seen early during ischaemia. Towards the end of ischaemia both arterial and coronary sinus concentrations of noradrenaline were increased, although venoarterial difference in concentration was little changed and coronary sinus blood flow was not measured.

Hasking *et al* measured resting cardiac noradrenaline spillover using radiotracer techniques in 15 subjects with normal left ventricular function, of whom five had ischaemic heart disease, and found mean cardiac noradrenaline spillover to be 5 ng/min¹³; this accorded with the findings in the present study, but no previous study has used radiotracers to assess the response of the sympathetic nervous system to myocardial ischaemia in man.

BASAL NORADRENALINE KINETICS IN ISCHAEMIC HEART DISEASE

In subjects with stable angina cardiac and whole body noradrenaline spillover were similar to those previously reported for normal subjects²¹ and to our patients with normal coronary arteries undergoing coronary arteriography (unpublished data). There is, therefore, no evidence of either generalised or cardiac sympathetic overactivity in stable angina, even when

the angina is severe and the underlying coronary disease extensive. Those with similar severity of underlying disease but with unstable ischaemic symptoms within the previous 12 weeks had much higher basal cardiac noradrenaline spillover than patients with stable angina, although whole body noradrenaline spillover was not significantly different. This represents a selective and sustained increase in cardiac efferent sympathetic tone in these high risk patients.

Although systemic hypertension was diagnosed in similar numbers of patients in each group, blood pressure was significantly higher in the group with recent unstable angina. Transient hypertension has been used as a marker of sympathetic overactivity²² and it is not unexpected that blood pressure was higher in the group of patients in whom considerable cardiac sympathetic activation was shown.

Unstable angina, acute myocardial infarction, and sudden ischaemic cardiac death are all believed to be initiated by a rapid increase in luminal narrowing of a coronary artery by an unstable atherosclerotic plaque. This change in luminal narrowing is believed to be caused by the pathological process of plaque rupture and haemorrhage and thus unstable angina, myocardial infarction, and sudden cardiac death are probably a range of clinical manifestations of one pathological process.²³ Which clinical path an individual patient will follow depends partly upon the severity, duration, and extent of the resulting myocardial ischaemia, but the occurrence of sudden death depends also on the susceptibility of the ischaemic myocardium to serious ventricular arrhythmias, and here the sympathetic nervous system may have a pivotal role. Although sudden cardiac death is usually associated at necropsy with an acute coronary arterial lesion,²⁴ survivors resuscitated from out of hospital ventricular fibrillation ("failed sudden death") do not usually sustain a myocardial infarction.²⁵

This study has shown increased cardiac sympathetic activity in patients with recent unstable ischaemic symptoms. This suggests that acute coronary arterial lesions, causing unstable angina or acute myocardial infarction and carrying an increased risk of sudden death,²⁶ are associated with pronounced cardiac sympathetic activation.

NORADRENALINE KINETICS DURING ATRIAL PACING

We found no consistent changes in arterial or coronary sinus noradrenaline concentration in response to atrial pacing and indeed the trend was for coronary sinus noradrenaline to decrease. Cardiac noradrenaline spillover to plasma was not increased by atrial pacing in either stable or unstable angina (fig 6)

despite the development of angina in most patients. There is thus no evidence that myocardial ischaemia per se, at least of the degree induced in this study, causes cardiac or generalised sympathetic activation.

LIMITATIONS OF THE STUDY

Regional heterogeneity within the heart

Sampling from the coronary sinus does have certain theoretical disadvantages. Samples taken from this site during angina will inevitably contain venous effluent from both ischaemic and non-ischaemic areas and the relative contribution of each is not assessable. In the dog model it is possible to cannulate local veins from ischaemic and non-ischaemic territories⁶ but this cannot be done in man. However, the severity and distribution of the coronary disease in our subjects make it highly likely that, when they developed myocardial ischaemia, the coronary sinus samples contained a substantial proportion of venous effluent from ischaemic myocardium (14 of the 15 paced patients had significant disease of the left anterior descending artery and 12 had significant disease of the circumflex artery). Thus any important increase in cardiac sympathetic activity, whether or not it was localised to the ischaemic area, should have been detectable.

Medications

All the patients in the study were on antianginal medication, which we and our ethics committee felt should not be withdrawn. The possibility that this may have modified the sympathetic response to myocardial ischaemia cannot be excluded. Although β adrenoreceptor antagonists (the most likely drugs to alter sympathetic activity) decrease noradrenaline clearance, at least in the short term, they do not change total noradrenaline spillover.²⁷ It therefore seems unlikely that the patients' drug treatment was responsible for the observed lack of increase in cardiac noradrenaline spillover when myocardial ischaemia was induced by atrial pacing.

Variation between patient groups

All patients had been stabilised on medical treatment before study and at the time of study showed no evidence of myocardial ischaemia. Left ventricular function was slightly worse in the patients with recent unstable ischaemic symptoms than the patients with stable angina, as shown by higher left ventricular end diastolic pressure and slightly but not significantly lower resting left ventricular ejection fraction. However, overall left ventricular function was good in both groups and there was no significant correlation between left ventricular ejection fraction or left ventricular end diastolic pressure and cardiac noradrenaline spillover. Thus the substantial cardiac sympathetic overactivity shown in the unstable

group was not the result of impaired left ventricular function.

Four of the patients in the unstable group were receiving diuretic drugs (patients 2, 4, 5, and 6, table 1)—two for pulmonary congestion and two for hypertension. All four had high cardiac noradrenaline spillover. Only one patient in the stable group (patient 19) was receiving diuretics and he did not have high cardiac noradrenaline spillover. Diuretics were associated with a 40% increase in whole body noradrenaline spillover in the only study in which this has been assessed,⁹ so diuretics may have contributed to the cardiac sympathetic activation seen in some of our patients. However, the magnitude of the increases in cardiac noradrenaline spillover makes it unlikely that they were caused solely by diuretics and even if the two patients on loop diuretics for pulmonary congestion are excluded from the analysis the difference between the stable and the unstable groups remains significant at the 1% level. The observed differences between the groups are, therefore, not the result of a diuretic effect. In other respects the stable and unstable groups were well matched (table 1).

CLINICAL RELEVANCE OF THE STUDY

Many experimental studies have shown that the combination of myocardial ischaemia and sympathetic stimulation is a powerful cause of ventricular arrhythmias, which are responsible for sudden cardiac death in most cases.^{3,7} It is likely that the arrhythmogenic action of sympathetic stimulation operates at several levels and sensitises the myocardium to the arrhythmogenic effects of myocardial ischaemia through various mechanisms, including coronary blood flow regulation, myocardial oxygen demand, and promotion of automatic and re-entrant pathways and triggered activity.²⁸

The demonstration in this study of increased cardiac sympathetic tone in unstable ischaemic syndromes is therefore of considerable importance in view of the increased risk of sudden death in such patients. The benefit in terms of mortality that is associated with the use of β blockers after myocardial infarction is due to a reduction in sudden death,²⁹ and a reduction in the response of the target organ to sympathetic stimulation may be the mechanism for this protective effect.

The cause of the cardiac sympathetic activation in unstable ischaemic syndromes is not clear. An excitatory cardio-cardiac sympathetic reflex elicited by myocardial ischaemia exists³⁰ and such reflexes may have a role, albeit that at the time of these studies there was no evidence of continuing myocardial ischaemia at rest. Some aspect of the unstable ischaemic syndromes seems to give rise to a sustained activation of the cardiac sympathetic nerves but

whether this relates to the length and severity of myocardial ischaemia or to some more basic response to the process of plaque rupture and haemorrhage or to the presence of intracoronary platelet emboli²⁴ cannot, at present, be ascertained. Differential organ-specific activation of the sympathetic nerves to the heart and kidneys has been shown in patients with cardiac failure¹³ and such patients are also known to be at high risk of sudden death secondary to ventricular arrhythmias.³¹ Sustained cardiac sympathetic overactivity persisting six months after acute myocardial infarction has also recently been shown by power spectrum analysis of heart rate variability.³²

This study shows that patients with recent unstable ischaemic symptoms suggestive of an acute coronary arterial lesion have evidence of a sustained increase in cardiac efferent sympathetic tone, whereas moderate myocardial ischaemia induced by atrial pacing does not cause important cardiac sympathetic activation. These data may in part explain the worse prognosis and increased risk of sudden death in unstable angina and support the theory that sympathetic overactivity and myocardial ischaemia are important interacting factors in the pathogenesis of serious ventricular arrhythmias and sudden cardiac death in ischaemic heart disease.

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