Plasma noradrenaline concentrations during isometric exercise

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SUMMARY Blood was collected simultaneously from the left ventricle and pulmonary artery in 12 patients undergoing routine cardiac catheterisation and was analysed for noradrenaline concentrations at rest, during, and after isometric stress (hand grip).

Moderate isometric exercise resulted in a significant rise in plasma noradrenaline with a return to basal values 10 minutes after discontinuing the grip test.

There were no significant differences in noradrenaline levels between the left ventricular and pulmonary arterial samples either at rest or during exercise.

Three patients with evident left ventricular dysfunction had the highest plasma noradrenaline concentrations, in contrast to the much lower levels in 2 patients on beta-blockers and in 1 patient with a normal heart.

As moderate isometric effort results in an important increase in noradrenaline level, this form of exercise could be dangerous in subjects suffering from ischaemic heart disease or in those with impaired left ventricular function since these patients are particularly susceptible to arrhythmias.

Isometric or static exercise exerts profound haemodynamic changes. An important arterial pressure rise is generated against a moderate rise only in heart rate and cardiac output, with little alteration in stroke volume (Lind and McNicol, 1967; Lind, 1970). This pressure response results from the combined effects of an increase in heart rate resulting from a release from vagal tone, a positive inotropic mechanism (Grossman et al., 1973; Krayenbuehl et al., 1973; Stefadouros et al., 1974), and some peripheral vasoconstriction (Macdonald et al., 1966; Freyschuss, 1970). It has been claimed that changes in plasma noradrenaline concentrations reflect the activity of the sympathetic nervous system (Lake et al., 1976). The purpose of the current study was to investigate whether plasma noradrenaline levels were altered by isometric exercise and, if so, whether pulmonary arterial and left ventricular levels were different.

Subjects and method

Twelve consecutive patients (11 male, 1 female), with a mean age of 49-6 years (range 30-57 ± SD 7-3 years), had routine cardiac catheterisation. All patients gave their informed consent. All were fasting, in sinus rhythm, and premedicated with intramuscular diazepam 10 mg and promethazine hydrochloride 25 mg.

Resting heart rate and left ventricular systolic and diastolic pressures were recorded using Hewlett-Packard 120 series transducers and 350 series multichannel recording system at a paper speed of 25 mm/s. The zero reference point was taken at the mid chest position. The patient then performed a standardised hand-grip as described previously (Vecht, 1976). They were asked to squeeze a balloon dynamometer with their left hand to a level of 0-3 kg/cm² for a period of between 2 and 3 minutes while breathing normally. This degree of isometric effort can be comfortably performed by most patients and corresponds to a maximal voluntary capacity of approximately 30 per cent. The method has been fully described elsewhere (Krayenbuehl et al., 1972). Recordings were again obtained at 1-5 and 3 minutes hand-grip and repeated 5 and 10 minutes after discontinuing the isometric effort. At equal time intervals, left ventricular and pulmonary arterial blood samples (10 ml) were collected simultaneously into lithium heparin tubes, centrifuged for 5 minutes, and the plasma immediately frozen at −20°C until assayed (within 21 days of collection).
An average hand-grip of 0.29 kg/cm² ± SD 0.01 for a mean duration of 3 minutes 6 s ± SD 13 s was performed.

Patients on Beta-antagonists were taken off these drugs 3 days before the study, except in 2 cases.

Cardiac indices at rest were derived from arteriovenous samples collected simultaneously; the oxygen uptake was estimated from tables (Robertson and Reid, 1952).

Ejection fractions at rest were calculated planimetrically from left ventricular angiograms using the area-length method (Kasser and Kennedy, 1969).

The plasma noradrenaline levels were estimated by a radio-enzymatic method (Henry et al., 1975).

**Results**

Table 1 summarises the resting haemodynamic and angiographic data and the changes in plasma noradrenaline levels observed during maximal exercise.

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>Cor. angio</th>
<th>LV Cine</th>
<th>Cardiac index (l/min per m²)</th>
<th>Heart rate (b/min)</th>
<th>LVSP (mmHg)</th>
<th>LV PNA (pg/ml)</th>
<th>PA PNA (pg/ml)</th>
<th>Hand-grip (kg/cm²)</th>
<th>Beta-blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>57/M</td>
<td>IHD</td>
<td>AD; C; C;</td>
<td>Moderately good</td>
<td>2.9 0.67</td>
<td>R</td>
<td>71</td>
<td>161</td>
<td>405</td>
<td>—</td>
<td>0.3</td>
</tr>
<tr>
<td>48/M</td>
<td>IHD</td>
<td>AD 1; RCA</td>
<td>General hypothesis</td>
<td>3.2 0.65</td>
<td>R</td>
<td>69</td>
<td>112</td>
<td>389</td>
<td>437</td>
<td>0.3</td>
</tr>
<tr>
<td>51/F</td>
<td>IHD</td>
<td>AD-patchy</td>
<td>Normal</td>
<td>Aneurysm; mild MR</td>
<td>4.0 0.90</td>
<td>R</td>
<td>86</td>
<td>131</td>
<td>1025</td>
<td>997</td>
</tr>
<tr>
<td>52/M</td>
<td>IHD</td>
<td>AD 2</td>
<td>Ant. wall; hypotension</td>
<td>2.3 0.36</td>
<td>R</td>
<td>80</td>
<td>191</td>
<td>656</td>
<td>608</td>
<td>0.3</td>
</tr>
<tr>
<td>57/M</td>
<td>IHD, BP</td>
<td>Main stem LCA 2; RCA 2</td>
<td>Large apical aneurysm</td>
<td>3.6 0.37</td>
<td>R</td>
<td>76</td>
<td>168</td>
<td>434</td>
<td>465</td>
<td>0.3</td>
</tr>
<tr>
<td>49/M</td>
<td>IHD</td>
<td>AD 3; C 2; RCA</td>
<td>Small ant. wall aneurysm; mild MR</td>
<td>3.5 0.86</td>
<td>R</td>
<td>63</td>
<td>106</td>
<td>327</td>
<td>331</td>
<td>0.28</td>
</tr>
<tr>
<td>30/M</td>
<td>Normal</td>
<td>NAD</td>
<td>Normal</td>
<td>LVH; moderate contraction</td>
<td>4.1 0.73</td>
<td>R</td>
<td>72</td>
<td>135</td>
<td>227</td>
<td>185</td>
</tr>
<tr>
<td>52/M</td>
<td>COCM</td>
<td>NAD</td>
<td>Gross hypotension</td>
<td>2.4 0.32</td>
<td>R</td>
<td>88</td>
<td>169</td>
<td>765</td>
<td>697</td>
<td>0.3</td>
</tr>
<tr>
<td>44/M</td>
<td>Mild BP</td>
<td>NAD</td>
<td>LVH; moderate contraction</td>
<td>3.2 0.74</td>
<td>R</td>
<td>86</td>
<td>167</td>
<td>943</td>
<td>341</td>
<td>0.3</td>
</tr>
<tr>
<td>55/M</td>
<td>IHD</td>
<td>AD 2; RCA 1; C 2</td>
<td>Large LV; moderate contraction</td>
<td>3.7 0.86</td>
<td>R</td>
<td>67</td>
<td>151</td>
<td>314</td>
<td>383</td>
<td>0.3</td>
</tr>
<tr>
<td>54/M</td>
<td>Severe MR</td>
<td>NAD</td>
<td>Large LV; moderate contraction (X)</td>
<td>1.9 0.71</td>
<td>R</td>
<td>91</td>
<td>114</td>
<td>984</td>
<td>1189</td>
<td>0.3</td>
</tr>
<tr>
<td>47/M</td>
<td>IHD</td>
<td>AD 3; RCA 2</td>
<td>Large LV; moderate contraction</td>
<td>3.0 0.71</td>
<td>R</td>
<td>84</td>
<td>149</td>
<td>135</td>
<td>170</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- IHD: Ischaemic heart disease
- COCM: Congestive cardiomyopathy
- BP: Blood pressure
- LVH: Left ventricular hypertrophy
- NAD: Normal heart
- MR: Mitral regurgitation
- RCA: Right coronary artery
- AD: Anterior descending artery
- MR: Mitral regurgitation
- LV: Left ventricle
- RV: Right ventricle
- V: Pulmonary artery
- A: Aorta
- D: Right coronary artery
- P: Plasma noradrenaline
- Beta-blocker: Beta-blocker treatment
- Hand-grip: Hand-grip measurement
- Heart rate: Heart rate measurement
- LVSP: Left ventricular systolic pressure
- LV: Left ventricle
- RCA: Right coronary artery
- LH: Left heart
- RV: Right heart
- LVH: Left ventricular hypertrophy
- RVH: Right ventricular hypertrophy
- LV: Left ventricle
- RV: Right ventricle
- LV: Left ventricle
- RV: Right ventricle
- LV: Left ventricle
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- LV: Left ventricle
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- RV: Right ventricle
Table 2  Mean resting and hand-grip haemodynamics and plasma noradrenaline concentrations

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (b/min)</th>
<th>LVSP (mmHg)</th>
<th>LV PNA (pg/ml)</th>
<th>PA PNA (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>74</td>
<td>135</td>
<td>461</td>
<td>492</td>
</tr>
<tr>
<td>SE</td>
<td>3</td>
<td>8</td>
<td>88</td>
<td>102</td>
</tr>
<tr>
<td>Maximum hand-grip</td>
<td>89</td>
<td>174</td>
<td>630</td>
<td>655</td>
</tr>
<tr>
<td>SE</td>
<td>2</td>
<td>9</td>
<td>125</td>
<td>134</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Difference</td>
<td>+15</td>
<td>+39</td>
<td>+169</td>
<td>+163</td>
</tr>
</tbody>
</table>

Abbreviations:
PA, pulmonary artery; PNA, plasma noradrenaline; LVSP, left ventricular systolic pressure; LV, left ventricle.

Table 2 compares the mean resting and maximal hand-grip heart rates, left ventricular systolic pressures, and left ventricular and pulmonary arterial noradrenaline concentrations.

During hand-grip there was a significant rise in mean heart rate (from 74 ± SE 3.0 beats/min at rest to 89 ± 2.4 beats/min at maximum hand-grip; P < 0.005).

There was an equally significant rise in mean left ventricular systolic pressure (from 135 ± SE 8.5 mmHg at rest to 174 ± 9.6 mmHg at maximum hand-grip; P < 0.005) (Fig. 1). The mean resting left ventricular plasma noradrenaline level was 461.0 ± SE 88.3 pg/ml, rising significantly to 630.0 ± 125.0 pg/ml at maximum hand-grip; P < 0.01. This represented a 36.6 per cent rise. The mean resting pulmonary arterial plasma noradrenaline was 492.0 ± SE 102.4 pg/ml, which rose significantly to 655.0 ± 134.7 pg/ml at maximum hand-grip (P < 0.05), a percentage rise of 33.1 (Fig. 2).

Neither resting nor hand-grip pulmonary arterial noradrenaline was significantly different from left

Fig. 1  Resting (R) and maximal hand-grip (HG) heart rates on the left; left ventricular systolic pressures on the right. Patient marked N considered to have normal heart.

Fig. 2  Resting left ventricular and pulmonary arterial plasma noradrenaline levels on left and during maximal hand-grip on right. Patient marked N considered to have normal heart.

Fig. 3  Mean plasma noradrenaline percentage changes in left ventricle on left and pulmonary artery on right. HG1 represents samples taken at 1 min of hand-grip; HG2 equals maximal hand-grip at 3 minutes. R5 and R10; samples at 5 and 10 minutes after discontinuing hand-grip.
ventricular concentrations. These levels returned to
basal values 10 minutes after stopping the isometric
exercise. Fig. 3 shows the mean percentage rise in
plasma noradrenaline left ventricular and pulmona-
ry arterial samples.

Three patients in this series had cardiac indices
below 2-5 l/min per m² and poor ejection fractions
with severe radiological abnormalities of left ventri-
cular wall motion. These patients had the highest
resting and exercise noradrenaline levels.

The 2 patients studied while still on beta-blockers
and the one patient considered to have a normal
heart had the lowest resting and exercise noradrena-
line levels (Fig. 2).

Discussion

Emotional stress (Passon and Peuler, 1973), noise
(Aronow et al., 1973), posture (Lake et al., 1976),
and dynamic and isometric exercise (Kozlowski
et al., 1973; Lake et al., 1976) are known to stimulate
the release of noradrenaline from sympathetic post-
ganglionic nerve terminals.

In healthy subjects, isometric effort was asso-
ciated with a greater rise in venous noradrenaline
than that observed during dynamic work involv-
ing large muscle groups (Kozlowski et al., 1973).

In the present study, 12 patients with various
cardiac pathologies requiring invasive investiga-
tions were found to have a significant rise in plasma
noradrenaline in response to a limited moderate
grit test. The increase in plasma noradrenaline was
of the same magnitude and not significantly different
when comparing samples obtained from within the
left ventricular cavity or from the pulmonary
arterial lumen. This suggested that the pressor
response resulting from isometric stressing was
accompanied by an overall increase in sympathetic
tone rather than an isolated discharge from cardiac
nerve endings.

Others have shown in a group of postoperative
patients that venous noradrenaline levels were
significantly higher than arterial samples (Lake
et al., 1976) and this has been attributed to the
removal of noradrenaline during lung passage
(Gillis et al., 1972). This was not the case in the
current study since left ventricular and pulmonary
arterial noradrenaline concentrations were not
significantly different when compared at rest or
during hand-grip.

It has been suggested that the pressor response
induced by isometric effort is a reflex (initiated by
an accumulation of metabolites within the muscles)
designed to maintain adequately perfused con-
tracting muscles (Coote et al., 1971).

We have shown an appreciable rise in plasma
noradrenaline at 1-5 minutes of sustained muscular
contraction, whereas others have shown a signi-
ficant rise within 30 seconds only (Kozlowski et al.,
1973).

The dimension of the pressor response is not
related to the mass of the contracting musculature
but to the tension developed by a single group of
muscles, however small (Lind, 1970). So forceful is
this vasopressor reflex that it is not abolished by
beta-receptor antagonists (Macdonald et al., 1966;
Shaver et al., 1972; Vecht et al., 1972), the rise in
pressure in this situation being dependent on an
increase in peripheral resistance (Tarazi and
Dustan, 1971).

Two patients in this series who were on beta-
adrenergic blocking agents at the time of cardiac
catheterisation had very low resting as well as hand-
grip noradrenaline levels. It appears that beta-
adrenergic antagonists may reduce circulating
catecholamines in patients with cardiac disorders
and in some way attenuate the vasopressor response
to isometric stress (Vecht et al., 1972). The under-
lying mechanism, however, remains obscure. A
central effect or alternatively a peripheral anta-
gonism of presynaptic beta-receptors could explain
these observations. It is noteworthy that Naylor
reported diminished release of noradrenaline from
the coronary sinus after beta-blockade when dog
hearts were stimulated electrically (Nayler and
Chang, 1973). One man in this series, with a normal
heart, also had low noradrenaline levels compared
with the other patients investigated. At the other
extreme, 3 patients with impaired left ventricular
performance were found to have very high circu-
lating noradrenaline levels which rose further during
isometric stressing. These patients presumably
required an increased sympathetic drive to main-
tain an adequate cardiac output.

Isometric exercise is also known to induce
ventricular ectopy (Matthews et al., 1971). In
patients with complete atrioventricular block, small
doses of noradrenaline (as opposed to adrenaline
infusions) were associated with ventricular extrasy-
stoles (Zoll et al., 1955). It seems likely that the
ventricular arrhythmias frequently encountered
during hand-gripping are related to the concentra-
tion of circulating noradrenaline.

It, therefore, appears justifiable to plead for
care when subjecting patients suffering from
ischaemic heart disease or left ventricular dys-
function to isometric exercise and perhaps even
proscribe its use from cardiac rehabilitating centres.

We thank Dr E. M. M. Besterman for permission
to study his patients.
References


Addendum

Six additional patients have been studied in a similar way. One of these patients was in heart failure and very high resting and hand-grip plasma noradrenalineline levels were found.

In all 6 patients left ventricular and pulmonary arterial noradrenaline levels were again of similar magnitude both at rest and during hand-grip.

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