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).
Plasma noradrenaline concentrations during isometric exercise

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</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Cor. angio</th>
<th>LV Cine</th>
<th>Cardiac index (l/min per m²)</th>
<th>Ejection fraction</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 1; C 1; RCA 1</td>
<td>Moderately good</td>
<td>2.9</td>
<td>0.67</td>
<td>R</td>
<td>71</td>
<td>161</td>
<td>405</td>
<td>—</td>
<td>0-3</td>
<td>None, chronic bronchitis</td>
</tr>
<tr>
<td>48/M</td>
<td>IHD</td>
<td>AD 1</td>
<td>General hypokinesia</td>
<td>3.2</td>
<td>0.65</td>
<td>R</td>
<td>69</td>
<td>112</td>
<td>389</td>
<td>437</td>
<td>0-3</td>
<td>Metoprolol</td>
</tr>
<tr>
<td>51/F</td>
<td>IHD</td>
<td>AD-patchy atheroma</td>
<td>Normal</td>
<td>4.0</td>
<td>0.90</td>
<td>R</td>
<td>72</td>
<td>181</td>
<td>448</td>
<td>425</td>
<td>0-3</td>
<td>Propranolol</td>
</tr>
<tr>
<td>52/M</td>
<td>IHD</td>
<td>AD 2</td>
<td>Ant. wall hypokinesia</td>
<td>2.3</td>
<td>0.56</td>
<td>R</td>
<td>86</td>
<td>131</td>
<td>1025</td>
<td>997</td>
<td>0-27</td>
<td>None, asthma</td>
</tr>
<tr>
<td>57/M</td>
<td>IHD, BP ↑</td>
<td>Main stem LCA 2; RCA 2</td>
<td>Large apical LV aneurysm</td>
<td>3.6</td>
<td>0.37</td>
<td>R</td>
<td>76</td>
<td>168</td>
<td>434</td>
<td>465</td>
<td>0-3</td>
<td>Propranolol</td>
</tr>
<tr>
<td>49/M</td>
<td>IHD</td>
<td>AD 3; C 2; RCA 1</td>
<td>Small ant. wall aneurysm; mild MR</td>
<td>3.5</td>
<td>0.86</td>
<td>R</td>
<td>63</td>
<td>106</td>
<td>327</td>
<td>331</td>
<td>0-28</td>
<td>Metoprolol</td>
</tr>
<tr>
<td>30/M</td>
<td>Normal</td>
<td>NAD</td>
<td>Normal</td>
<td>4.1</td>
<td>0.73</td>
<td>R</td>
<td>62</td>
<td>104</td>
<td>173</td>
<td>187</td>
<td>0-3</td>
<td>Metoprolol</td>
</tr>
<tr>
<td>52/M</td>
<td>COCM</td>
<td>NAD</td>
<td>Gross hypokinesia LVH; moderate contraction</td>
<td>2.4</td>
<td>0.32</td>
<td>R</td>
<td>88</td>
<td>169</td>
<td>765</td>
<td>697</td>
<td>0-3</td>
<td>None, asthma</td>
</tr>
<tr>
<td>44/M</td>
<td>Mild BP ↑</td>
<td>NAD</td>
<td>Moderate LVH; moderate contraction</td>
<td>3.2</td>
<td>0.74</td>
<td>R</td>
<td>63</td>
<td>95</td>
<td>150</td>
<td>164</td>
<td>0-3</td>
<td>Propranolol</td>
</tr>
<tr>
<td>55/M</td>
<td>IHD</td>
<td>AD 2; RCA 1; C 2</td>
<td>Good</td>
<td>3.7</td>
<td>0.86</td>
<td>R</td>
<td>67</td>
<td>151</td>
<td>314</td>
<td>383</td>
<td>0-3</td>
<td>Propranolol</td>
</tr>
<tr>
<td>54/M</td>
<td>Severe MR</td>
<td>NAD</td>
<td>Large LV; moderate contraction</td>
<td>1.9</td>
<td>(X)</td>
<td>R</td>
<td>91</td>
<td>114</td>
<td>984</td>
<td>1189</td>
<td>0-3</td>
<td>None, heart failure</td>
</tr>
<tr>
<td>47/M</td>
<td>IHD</td>
<td>AD 3; RCA 2</td>
<td>Good</td>
<td>3.0</td>
<td>0.71</td>
<td>R</td>
<td>84</td>
<td>133</td>
<td>120</td>
<td>140</td>
<td>0-3</td>
<td>Propranolol</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- COCM: Congestive cardiomyopathy
- MR: Mitral regurgitation
- LVH: Left ventricular hypertrophy
- n: Normal heart
- IHD: Ischaemic heart disease
- PNA: Plasma noradrenaline
- RCA: Right coronary artery
- AD: no abnormality detected.
- VSP: Left ventricular systolic pressure
- V: Left ventricle
- A: Pulmonary artery
- Circunf.: Circumflex
- D: Anterior descending
- abbreviations: C: Incalculable, severely reduced.
- *: On pranoprolol 120 mg/d.
- **: On pranoprolol 30 mg/d.
- P: Blood pressure
- **: On pranoprolol 30 mg/d.
- \*: On pranoprolol 120 mg/d.
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
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 pulmonary 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 ventricular 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 noradrenaline 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 associated with a greater rise in venous noradrenaline than that observed during dynamic work involving large muscle groups (Kozlowski et al., 1973).

In the present study, 12 patients with various cardiac pathologies requiring invasive investigations were found to have a significant rise in plasma noradrenaline in response to a limited moderate grip 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 contracting 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 significant 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 Dusntan, 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 underlying mechanism, however, remains obscure. A central effect or alternatively a peripheral antagonism 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 (Naylor 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 circulating noradrenaline levels which rose further during isometric stressing. These patients presumably required an increased sympathetic drive to maintain 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 extrasystoles (Zoll et al., 1955). It seems likely that the ventricular arrhythmias frequently encountered during hand-gripping are related to the concentration of circulating noradrenaline.

It, therefore, appears justifiable to plead for caution when subjecting patients suffering from ischaemic heart disease or left ventricular dysfunction 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 noradrenaline 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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