Localization of lesion in patients with idiopathic orthostatic hypotension

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The different components of the baroreceptor reflex were studied in 8 patients with idiopathic orthostatic hypotension. The reflex arc was interrupted in all patients and the lesion was most probably localized to the efferent sympathetic fibres. This was suggested by the negative cold pressor test, the absence of pressor response to mental arithmetic, and loss of reflex sweating. Selective sparing of sympathetic vasodilator fibres was probable in 2 patients. Cardiac acceleration after atropine injection was less than in normal subjects suggesting some degree of cardiac denervation.

The present study indicates that lesions in efferent sympathetic fibres are a common cause of idiopathic orthostatic hypotension. Other components of the reflex arc were intact in this series of patients.

The adjustments of the circulation to changes of body posture depend upon several mechanisms directed to defend homeostasis of arterial pressure. The autonomic nervous system plays a dominant role. The initial fall in blood pressure after assuming the upright position leads to a decrease of baroreceptor impulses from the carotid sinuses and aortic arch to the vasomotor centre; an increase in tone of the adrenergic sympathetic nerves should then occur, with consequent effects on peripheral blood vessels and heart function. In idiopathic orthostatic hypotension, this baroreceptor reflex arc is interrupted (Verel, 1951; Wagner, 1959). Impairment of afferent autonomic and of efferent adrenergic pathways has been described (Lewis and Dunn, 1967; Love et al., 1971). The present study was planned to test the integrity of each of the individual components of the baroreceptor reflex arc in 8 patients with idiopathic orthostatic hypotension.

Patients

Eight patients, 5 men and 3 women, with idiopathic orthostatic hypotension were investigated; their clinical picture has been described in two previous studies (Ibrahim et al., 1974, 1975). Their ages ranged from 52 to 75 years with a median age of 62.

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1 This work was part of a thesis which gained the William Lower Prize for Clinical Research.

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The diagnosis of idiopathic orthostatic hypotension was based on the presence of reproducible orthostatic hypotension, with anhidrosis, and impotence in men, in the absence of any obvious cause. The duration of postural hypotension was variable, ranging from 2 months to 5 years (median 24 months). All the patients complained of loss of consciousness associated with a documented fall in arterial pressure when upright: fainting spells occurred only on standing, often with dramatic suddenness, and were not preceded by symptoms of autonomic dysfunction, such as nausea, pallor, or sweating.

All patients were admitted to hospital but were encouraged to be as active as possible; neither their activity nor diet was restricted. All medications were discontinued for at least a week before the studies. A careful history ensured that none of them had had any long acting vasoactive, antidepressant, or sedative medication for at least the preceding 6 months.

Methods

The following physiological studies were carried out while intra-arterial pressure and electrocardiogram were continuously monitored. The sweat tests were performed by the Department of Physiotherapy.

Tests were classified according to the part of the reflex circuit investigated (Fig. 1) and they were carried out in the following order.

1) Integrity of baroreceptor reflex

The tilt-table and the Valsalva manoeuvre were used to test the overall integrity of the reflex circuit. After the patients had been recumbent on a tilt-table for 15 minutes, the responses of arterial pressure and heart rate
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Tests of autonomic function. Components of baroreflex arc and methods of their investigation.

- Hyperventilation
- Mental arithmetic
- Effferent sympathetic fibres
- Atropine test
- Cold pressor test
- Sweat test
- Baroreceptors
- VMC: Vasomotor centre.
- Adrenergic nerve ending
- Tyreine test
- Whole reflex arch
- Valsalva manoeuvre
- Postural head up tilt
- Baroreceptors sites in vascular smooth muscle

FIG. 1 Tests of autonomic function. Components of baroreflex arc and methods of their investigation. PE: Phenylephrine. VMC: Vasomotor centre.

to various degrees of head-up tilt were noted. After a rest period of 15 minutes, Valsalva manoeuvres were made in triplicate; the patients were asked to blow into a mercury manometer to a level of 40 mmHg (5.3 kPa) for a period of 15 to 20 seconds. Changes of arterial pressure during the four phases (Sharpey-Schafer, 1955) were continuously recorded.

2) Vasomotor centre responsiveness
Reduction of arterial pressure after hyperventilation indicates intact vasomotor centre responsiveness. Cerebral vasoconstriction that follows washing out carbon dioxide depresses vasomotor centre responsiveness and results in a decrease in arterial pressure (Sharpey-Schafer and Taylor, 1960). The test was made by asking the patients to breathe as deeply and as fast as possible for a period of 15 seconds.

3) Testing efferent sympathetic fibres
a) Cold pressor test The response of the arterial pressure to the painful cold stimulus is observed. Pain impulses are carried by the lateral spinothalamic tracts, while the motor impulses to the arterioles are in the efferent sympathetic fibres. The patient’s right hands were completely immersed in iced cold water (4°C) for 1 minute.

b) Mental arithmetic Mental stress raises arterial pressure. Serial subtractions of seven from 100 were made by the patients. During the test the patients were harassed and confused.

c) Reflex sweat test Motor impulses to the sweat glands are carried by the efferent sympathetic fibres. Reflex sweating in response to exposure to hot environ-

mental temperature was used to test the integrity of these fibres.

4) Responsiveness of arteriolar wall receptors
Phenylephrine – an alpha-receptor agonist – when given intravenously produces vasoconstriction and a rise in systemic pressure if arteriolar smooth muscle receptors are intact. The drug was given as one bolus in doses of 25 and 50 μg.

5) Afferent autonomic fibres
Cardiac slowing after phenylephrine injection indicates that both afferent autonomic fibres from the baroreceptor areas and efferent cardiac vagal fibres are intact.

6) Efferent vagal cardiac fibres
In addition to heart rate responses to a rise in arterial pressure, the atropine test was used, to test the efferent vagal fibres to the heart, and was given intravenously in a dose of 0.03 mg/kg. Changes in heart rate in patients with idiopathic orthostatic hypotension were compared to the previously reported results of the effect of atropine in normal subjects (Heimbach and Crout, 1972).

7) Extra-adrenal stores of norepinephrine
Tyramine – a sympathomimetic amine – produces its vasopressor effect through the release of norepinephrine from sympathetic nerve endings. The test has been described in detail in a previous study (Ibrahim et al., 1975). The drug was given intravenously in doses of 1, 2, and 3 mg.

8) Direct sweat test
Although not a test of the baroreceptor reflex arc, it was used here to verify that lack of reflex sweating, if present, was not caused by local absence or disease of sweat glands. The test was done in 4 patients by direct electrical stimulation of sweat glands (iontophoresis).

Results

1) Integrity of baroreceptor reflex
In all patients responses of arterial pressure and cardiac rate to tilt-table studies and Valsalva manoeuvre indicated interruption of the baroreceptor reflex. Arterial pressure decreased sharply in response to head-up tilt (Fig. 2). The severity of hypotension corresponded to the degree of tilting. Cardiac rate showed variable degrees of acceleration. The Table shows the results of tilt-table studies. During the straining phase of Valsalva (phase 2) in spite of a drop in arterial pressure, heart rate did not change. No overshoot in systemic pressure followed the release of straining (phase 4), and pressure recovered gradually to the control level (Fig. 3 and 4).
### TABLE Effect of head-up tilt on arterial pressure in patients with idiopathic orthostatic hypotension

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Degree of tilt</th>
<th>Supine blood pressure</th>
<th>Tilt blood pressure</th>
<th>Reduction of mean arterial pressure</th>
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Conversion factor from Traditional to SI units: 1 mmHg ≈ 0.133 kPa.

FIG. 2 Effect of head-up tilt on arterial pressure in a patient with idiopathic orthostatic hypotension. AP: arterial pressure. Interval between time markers = 30s.

2) Hyperventilation
Arterial pressure decreased after hyperventilation, and then gradually recovered to the control level (Fig. 3). Reduction in arterial pressure ranged from 16 to 55 mmHg (2.1 to 7.3 kPa), with an average of 32 mmHg (4.3 kPa).

3) Cold pressor test
In 6 patients there was little (4 to 8 mmHg rise (0.5 to 1.1 kPa)) or no change in arterial pressure at the end of the test. In 2 patients systolic pressure rose by 30 mmHg (4.0 kPa).

4) Mental arithmetic
Five patients had no change in arterial pressure in response to mental stress, while 2 patients responded paradoxically by a decrease of arterial pressure by 15 and 20 mmHg (2 and 2.7 kPa).

FIG. 3 Response to the Valsalva manoeuvre in a normal subject. The different phases are numbered. (Ibrahim et al., 1974.)

FIG. 4 Response to the Valsalva manoeuvre in a patient with idiopathic orthostatic hypotension. The overshoot in phase 4 is absent. (Ibrahim et al., 1974.)
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5) Sweat tests
In all patients studied reflex sweating was impaired over diffuse areas of the skin. However, the direct sweat test, when done, indicated functioning sweat glands in areas which had failed to sweat when tested through the reflex arc.

6) Phenylephrine test
A rise of arterial pressure ranging from 10 to 63 mmHg (1.3 to 8.4 kPa) followed phenylephrine injection (50 μg i.v.). In all patients there was reflex cardiac slowing in response to rise in arterial pressure.

7) Atropine test
Cardiac acceleration followed atropine injection. Increase in heart rate ranged between 3 and 87 per cent of the control rate, with an average of 21 per cent.

8) Tyramine test
The results of this test were described in a previous study (Ibrahim et al., 1975). Patients varied widely in their pressor response to tyramine. After a 2 mg dose the rise of arterial pressure ranged from 4 to 56 mmHg (0.5 to 7.4 kPa).

Discussion
The study was planned to investigate in a systematic way the different components of the baroreceptor reflex arc in patients with idiopathic orthostatic hypotension. Interruption of the reflex arc was demonstrated in all patients by the absence of the normal pressor response to Valsalva manoeuvre (Sharpey-Schafer and Taylor, 1960) and by the inability to maintain arterial pressure in the upright position. The lesion in the reflex circuit was most probably localized to the efferent sympathetic fibres. This was suggested by the negative cold pressor test, the absence of pressor response to mental arithmetic, and loss of reflex sweating. Two patients did respond to cold with a rise in blood pressure but their lesion was still localized to the efferent sympathetic limb by the documented integrity of both the afferent and the central part of the baroreceptor reflex and the absence of reflex sweating. In all patients, other components of the reflex arc were intact as shown by: a) pressor response to phenylephrine, indicating intact receptor sites in arteriolar smooth muscles; the varying degrees of that response might be related to varying degrees of denervation hypersensitivity; b) cardiac slowing in response to rise in blood pressure, proving an adequate afferent limb and efferent vagal mechanism; and c) vasomotor centre responsiveness as demonstrated by the hypotensive effect of hyperventilation (Sharpey-Schafer and Taylor, 1960); further, reflex cardiac slowing was an evidence that the central part of the reflex was intact. In 2 patients selective sparing of sympathetic vasodilator pathways (Abboud and Eckstein, 1966) was suggested by the reduction of arterial pressure with mental arithmetic. The degree of cardiac acceleration by atropine suggested some involvement of efferent cardiac vagal fibres. Acceleration of the heart was less in our patients than in normal subjects studied by Heimbach and Crout (21 and 49%). The results of the tyramine test indicated varying degrees of availability of extra-adrenal catecholamine stores in patients studied.

One cannot conclude from this study that lesions of efferent sympathetic pathways are the sole mechanism of failure of the reflex circuit, since other studies have described lesions in the afferent fibres or other parts of the reflex arc (Lewis and Dunn, 1967; Love et al., 1971). However, lesions in the efferent sympathetic pathways were the predominant findings in these patients and it seems these are a common cause of the disease.

These physiological studies in patients with postural hypotension are far from being only of academic interest. The presence of a normal response to the Valsalva manoeuvre rules out idiopathic orthostatic hypotension or any disturbance of the reflex circuit caused by diabetes mellitus, tabes dorsalis, adrenergic blocking drugs, or lesions of the vasomotor centre. Application of the above
tests in a systematic way as described can help to localize the site of the lesion in other diseases of the autonomic nervous system.

At present little is known about the aetiology of idiopathic orthostatic hypotension and treatment is only symptomatic; further studies may shed more light on the disease.

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References

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