Total Cardiac Denervation in Diabetic Autonomic Neuropathy

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SUMMARY

Total loss of the autonomic regulation of heart rate is described in a 28-year-old diabetic with extensive autonomic neuropathy. The patient had an almost fixed heart rate that barely responded to any of the tests that stimulate or inhibit the autonomic nerves. Its behavior was similar to that of the transplanted heart. DIABETES *25*:748-51, September, 1976.

Abnormalities of cardiovascular reflexes are well recognized in patients with diabetic neuropathy.[1] Sympathetic and parasympathetic control of the heart may both be impaired,[2] but the loss is rarely complete.

This report describes a diabetic patient whose heart behaved as if totally denervated. The physiology of the denervated heart has been extensively studied in animals, as well as in humans with transplanted hearts,[3-5] but similar findings due to neuropathy have not been previously described.

CASE HISTORY

The patient was a married woman aged 28 years who had been diabetic for 16 years. She had always been difficult to manage and by 1973 had had approximately 67 hospital admissions. At the age of 22 she developed episodes of diabetic diarrhea and vomiting, and absence of knee and ankle reflexes was noted at the time. She also developed bilateral iritis with subsequent corneal opacification, leading to deterioration of vision and making observation of the retinas almost impossible. In 1971, aged 26 years, she began to have feelings of faintness on standing (blood pressure 140/80 lying, 90/70 standing). Treatment with 9-alpha fluorohydrocortisone gave little relief and caused edema. Ephedrine did not help; it caused the further complication of urinary retention. Elastic stockings were no help, and a space suit was unacceptable. Diarrhea and disabling postural symptoms persisted during 1972 and 1973, and she was often confined to a chair. She thought that the warning symptoms of hypoglycemia had diminished during the previous year, and she now had few premonitory symptoms. Recently she had had frequent episodes of unconsciousness, sometimes suffering minor injuries, which she attributed to hypoglycemia. She had never experienced angina, ankle swelling, or undue dyspnea.

She was of short stature and almost blind from corneal opacities. There were no signs of cardiac failure, and the heart size and electrocardiogram were normal. Details of pulse and blood pressure are given below. There was evidence of mild peripheral neuropathy in the legs (all sensory modalities were impaired in the toes, and knee and ankle jerks were absent), and lateral popliteal motor-nerve conduction was somewhat impaired at 44 meters per second. The hands were neurologically normal, and perception was so well preserved that she could read Braille. The bladder was sometimes distended to the umbilicus. On rectal examination anal tone was poor.

There was evidence of nephropathy (urine protein of 200-600 mg./24 hours), but renal function was normal (serum creatinine 0.9 mg./100 ml.). There was no steatorrhea or malabsorption, and barium meal and follow-through examination were normal.

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She left hospital having rejected most of her treatments. She was taking only bethanechol, with which bladder function was clinically satisfactory. Later she begged for treatment with vasopressin injections, and for several weeks her husband gave her Pitressin tannate in oil, 5 units intramuscularly daily. Her standing systolic blood pressure levels varied between 60 and 100 mm. Hg, and she slowly regained confidence, and could again manage housework and short walks. After cessation of vasopressin injections the general improvement was maintained, although she still has bad days when she suffers symptoms of hypotension.

METHODS

Investigations of sympathetic and parasympathetic function were carried out with continuous recordings of the electrocardiogram for the accurate measurement of heart rate. Blood pressure was recorded simultaneously from a small indwelling catheter in a radial artery by use of an Elema-Schönander pressure transducer and Mingograph recorder.

The following tests were performed:

Mental calculation—Subtraction tasks were rapidly performed aloud under harassment.

Valsalva's maneuver—The patient blew into a modified mercury sphygmomanometer. A pressure of 40 mm. Hg was reached as soon as possible and maintained for 15 seconds. Pressure was then released abruptly and recordings were continued for at least another 20 seconds.

Carotid sinus pressure—Firm pressure was applied for 10 seconds to each carotid sinus in turn.

Amyl nitrite—Transient hypotension was induced by inhalation of one ampule of amyl nitrite.

Tilting—The patient was tilted to vertical for three minutes.

Phenylephrine—Transient hypertension was induced by the intravenous injection of 50 μg. of phenylephrine given as a bolus to test baroreceptor reflexes.

After each of these tests the pulse rate and blood pressure were allowed to return as near to control levels as possible before the next test was carried out.

Propranolol—A 10-mg. dose of propranolol was given slowly intravenously to block sympathetic stimulation of the heart.

Atropine—Atropine, 1.8 mg., was given intravenously about 30 minutes after propranolol to block vagal stimulation of the heart.

On separate occasions the effects of repeated tilting, 10 mg. vasopressin given by subcutaneous injection, and exercise were also investigated.

Variation of heart rate on deep breathing was also recorded by a cardiotachometer, as previously described.[6]

RESULTS

Heart Rate

Results are shown in table 1. The heart rate was almost constant at 86 per minute and beat-to-beat variation on deep breathing was two beats per minute. There was no detectable effect of mental calculation, carotid sinus pressure, or a fall in systolic pressure of 54 mm. Hg after amyl nitrite. Heart rate changes of about one beat per minute occurred with propranolol and atropine (change of R-R interval +10 milliseconds to −6 milliseconds, respectively). Small paradoxical heart rate responses were seen with phenylephrine, Valsalva's maneuver, and tilting.

Phenylephrine—50 μg. of phenylephrine increased the systolic blood pressure by 54 mm. Hg but caused heart rate to increase by three beats per minute (change of R-R interval 24 milliseconds).

Valsalva's maneuver—The pulse rate fell by about three beats per minute during the Valsalva strain and rose by about one beat per minute following the release (changes of R-R interval 28 and 12 milliseconds, respectively). Almost identical results were obtained

TABLE 1

Responses of heart rate to tests of autonomic function

Test	Control pulse interval (msec.)	Change of pulse interval (msec.)
Calculation	694	−4
Valsalva	698	+30/−10*
Valsalva (repeated)	700	+24/−12*
Right carotid sinus pressure	704	0
Left carotid sinus pressure	702	0
Amyl nitrite (B.P. decrease 54 mm. Hg)	702	−4
Tilting	706	+14
Phenylephrine (B.P. increase 54 mm. Hg)	692	−24
Propranolol	690	+10
Valsalva†	704	+24/−6*
Valsalva† (repeated)	700	+28/−8*
Tilting†	700	+20
Atropine†	700	−6

*The two figures given for each Valsalva's maneuver show the changes in pulse interval during the strain phase and following release of pressure.

†Autonomic tests performed after beta-blockade with propranolol.

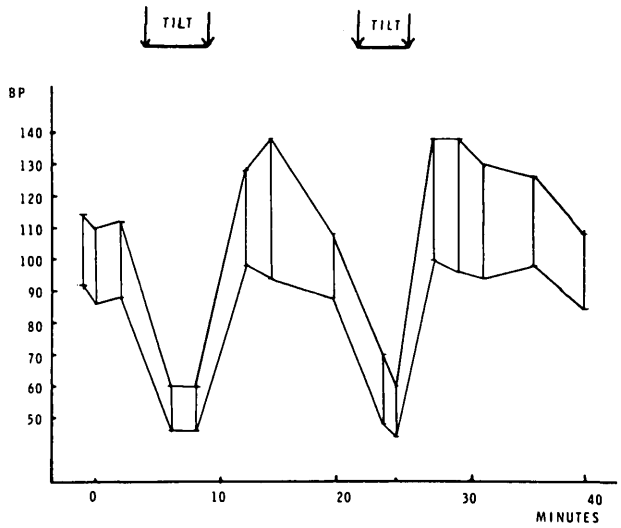

FIG. 1. Blood pressure levels in mm. Hg showing the effect of tilting to 90°.

when the test was repeated both before and after β-blockade.

Tilting—The response to vertical tilting varied slightly on different occasions. A fall in pulse rate of two to three beats per minute occurred initially. This was followed by a return to control levels or even a small increase of two to three beats per minute after five minutes.

Vasopressin—10 mg. of vasopressin given subcutaneously had no effect on the supine heart rate in spite of an increase of blood pressure. However, after vasopressin, vertical tilting caused a fall in pulse rate of eight beats per minute (68 milliseconds), which persisted until the patient was returned to the supine position 10 minutes later.

Exercise—The patient was unable to exercise satisfactorily in the erect posture because of dizziness. After two minutes on a treadmill at 3 k.p.h. the pulse rate increased by only four beats per minute. Supine exercise for 10 minutes with the arms and legs raised the heart rate by 11 beats per minute, but she was unable to exercise maximally.

Blood Pressure

Tilting—Postural hypotension was always present, although variable in severity. Blood pressure reached higher than control levels on return to the supine position. This hypertensive response lasted for five to 10 minutes (figure 1).

Valsalva's maneuver—The blood pressure continued to fall throughout the strain, and there was no overshoot following the release, the pressure slowly returning to control levels.

Vasopressin—The response to 10 mg. vasopressin given subcutaneously is shown in figure 2. Supine hypertension developed, and on tilting, although blood pressure fell, the actual levels reached initially were not as low as those usually attained without vasopressin. However, blood pressure continued to fall during the 10-minute period of tilting and reached levels low enough to cause hypotensive symptoms.

DISCUSSION

The patient described here had exceptionally severe autonomic neuropathy, exhibiting most of its known clinical manifestations in the presence of relatively mild peripheral neuropathy.

Several recent studies[2,6-8] have shown abnormal cardiac responses in diabetic autonomic neuropathy, but some autonomic control of the heart is usually retained.[2] The behavior of the heart rate in this patient indicated that her heart was devoid of all autonomic influence. There was no change in heart rate that could be attributed to attempts to stimulate, inhibit, or pharmacologically block autonomic nerves to the heart.

These findings are best explained by neuropathy affecting efferent cardiac nerves, and it is most likely that this patient had a totally denervated heart. Postural hypotension and abnormal Valsalva responses in diabetics have previously been attributed to lesions on the afferent pathway.[1] Afferent or central lesions

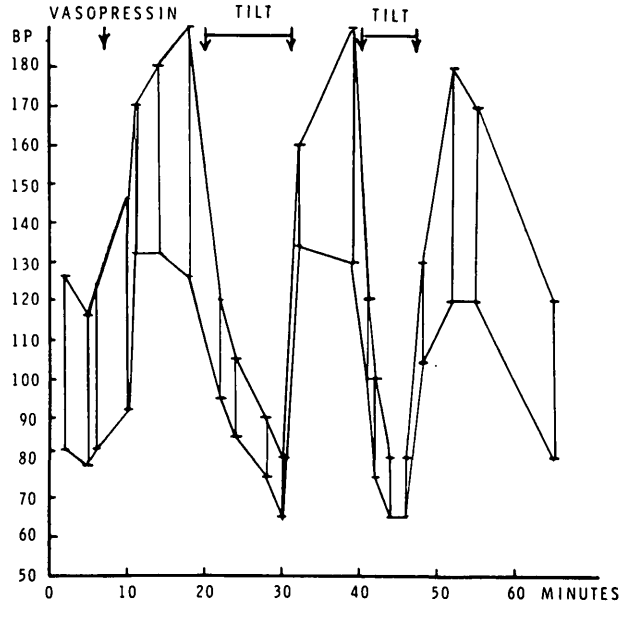

FIG. 2. Blood pressure levels, showing the effects of 10 mg. vasopressin given subcutaneously and subsequent tilting.

could account for lack of response to reflex testing in our patient but would hardly expalin the apparent total absence of resting autonomic tone in the cardiac efferent nerves. Our observations could also be attributed to failure of the sinus node to respond to autonomic stimulation. Pharmacologic tests to assess responsiveness of the sinus node were not carried out, but there was no other evidence of heart disease, and patients with disordered function of the sinus node tend to have bradycardia and an unstable heart rate and rhythm.[9]

Phenylephrine, tilting, and Valsalva's maneuver altered the heart rate very slightly but paradoxically. A positive chronotropic effect of phenylephrine has previously been described in atropinized and transplanted hearts,[10] the usual reflex response to the drug having been blocked. Mechanical effects on the sinus node might explain the responses to tilting and Valsalva's maneuver.[4]

Exercise to the maximum levels possible in our patient increased heart rate by 11 beats per minute. In the transplanted human heart the rate is barely affected by mild exercise, but during prolonged exercise the rate may increase almost as much as in the normal heart.[5] However, in autonomic neuropathy, cardiac response to exercise might also be reduced through failure of blood catecholamine levels to rise.[11]

Postural hypotension due to autonomic neuropathy may be dangerous, and treatment is notoriously difficult. It may become worse after insulin administration, and episodes of unconsciousness attributed to hypoglycemia are sometimes due to hypotension.[12] Nine-alpha fluorohydrocortisone was not effective in this patient, and ephedrine could not be used because it caused retention of urine. She found a space-suit intolerable. Subcutaneous vasopressin, which is known to increase the blood pressure of subjects with postural hypotension,[13] was partially effective, and there was some symptomatic improvement with daily intramuscular injections for several weeks. The improvement was, however, maintained after she had stopped this treatment: this observation illustrates difficulties encountered in assessing treatment both because of the variability of the blood pressure changes and also because of the inconsistency of symptoms in relation to the actual blood pressure readings.

Total cardiac denervation must be a rare diabetic complication: the inability to alter heart rate and therefore cardiac output would tend to aggravate postural hypotension and impair the capacity to undertake strenuous exercise.

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