PAPERS AND ORIGINALS

Hypotension in Tetanus

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Summary

Three patients with severe tetanus had episodes of profound arterial hypotension lasting from minutes to hours. The blood pressure was recorded continuously for 13, 19, and six days respectively by an intra-arterial catheter, and other measurements included heart rate, central venous pressure, cardiac output, and blood gases.

The hypotension was distinguished from that of "shock", for there was no clinical evidence of peripheral vasoconstriction and no tachycardia. It could not be attributed to disturbances of salt and water balance. During episodes of hypotension the blood pressure fell as low as 32/16 mm Hg, the heart rate fell from a mild tachycardia to normal values or a mild bradycardia, and the central venous pressure did not rise. The onset and the end of such episodes was often abrupt and the hypotension was often produced in response to a stimulus. In one patient extreme hypotension followed the aspiration of secretions from the trachea. These changes may represent another effect of tetanus on autonomic nervous activity, including impairment of baroreceptor reflexes.

Introduction

There have been reports of hypotension in patients with tetanus (Alhady *et al.*, 1960; Clifton, 1964; Adams *et al.*, 1966; Macrae, 1967), but they have not included detailed cardiovascular investigations and the hypotension has usually been regarded as a preterminal episode. This paper describes measurements of intra-arterial blood pressure and related variables in three patients who survived severe tetanus but developed

extreme hypotension during their illness. Various approaches to the clinical management of the condition are considered.

Methods

All patients were treated in the respiration unit of the Churchill Hospital, Oxford, with antibiotics, human antitetanus serum, tracheostomy, anticoagulation, curarization sufficient to prevent muscle spasms, and intermittent positive pressure ventilation. In case 2 the patient also received phenobarbitone by intragastric tube.

Intra-arterial blood pressure was measured continuously from days 4 to 16 in case 1, days 2 to 20 in case 2, and days 2 to 7 in case 3 (day 1 = first day of trismus) from a Teflon catheter introduced percutaneously into the brachial artery and connected by a device for slow continuous perfusion and series mechanical damping (Macmillan and Stott, 1968) to a strain-gauge electromanometer. The central venous pressure was measured with a similar technique from days 4 to 9 and 12 to 15 in case 1, and days 7 to 12 in case 2. In all patients the airway pressure was measured from another electromanometer and the electrocardiogram was derived from standard chest and arm leads. A Neilson cardi tachometer (Devices Instruments Ltd.) was triggered from the electrocardiogram or blood pressure signal to enable the instantaneous heart rate to be derived. The blood pressure, central venous pressure, heart rate, and airway pressure were recorded continuously on a multichannel recorder (Devices Instruments Ltd.) and on an instrumentation F.M. magnetic tape recorder in parallel.

During periods of hypotension the blood pressure was also taken by auscultation and palpation, except when it was too low to be measured with this method.

Cardiac output was measured repeatedly on day 8 in case 1 and day 7 in case 2 by an indicator-dilution method using indocyanine green. About 1 ml of dye was injected through the central venous pressure catheter and the arterial dye concentration was detected with a Gilford cuvette densitometer and amplifier. Dye curves were analysed at the time with an analogue computer (Gilford) and later checked by numerical techniques (Kelman and Prys-Roberts, 1967). Stroke volume and systemic vascular resistance were derived from the measured data by conventional formulae. Arterial blood samples were taken intermittently, and PaO_2 , PaCO_2 , and pH were measured at 37°C in Radiometer polarographic, CO_2 sensitive, and capillary glass electrodes respectively.

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Case Histories and Results

CASE 1

A male patient aged 75 years developed tetanus after a motor vehicle accident in which he sustained minor abrasions and mild concussion. He had almost recovered by the morning eight days later when trismus developed. Severe generalized tetanus was present within 24 hours and curarization and intermittent positive pressure ventilation were instituted, sometimes with added oxygen.

A summary of the cardiovascular and other measurements for the period up to day 16, when intra-arterial pressure measurements were discontinued, is given in table I. The average daily oral temperature was 36.6-38.0°C (overall average 37.4°C). There was no consistent electrolyte abnormality (Na^+ , 128-139 mEq/l.; K^+ , 3.3-5.2 mEq/l.; Cl^- , 94-106 mEq/l.; HCO_3^- , 24-34 mEq/l.), the daily urine output ranged from 1,430-3,280 ml (average 1,976 ml), and the average daily urinary specific gravity ranged from 1.001-1.019 (average 1.012). The patient was weighed daily by transferring him to a lever-type weighing machine. A weight loss of 3.3 kg occurred in spite of well-balanced

TABLE I—Summary of Cardiovascular Data in Case 1 from Days 1 to 16

Day of Illness	Maximum Systolic B.P. (mm Hg)*	Heart Rate with Maximum Systolic B.P. (beats/min)	Minimum Systolic B.P. (mm Hg)	Heart Rate with Minimum Systolic B.P. (beats/min)	Average Systolic B.P. (mm Hg)
1	130		105		120
2	125		100		112
3	195		100		144
4	216	128	92	116	160
5	228	108	32	82	155
6	245	108	38	76	135
7	242	128	40	90	160
8	240	124	42	92	125
9	250	98	38	85	130
10	250	100	48	80	150
11	248	96	50	90	150
12	265	112	52	68	110
13	235	120	58	76	130
14	250	114	48	84	145
15	265	110	72	76	145
16	245	110	52	96	150

*B.P. and heart rate on days 1-3 by clinical methods and on days 4-16 from arterial catheter and heart rate meter.

feeding of adequate caloric value given by nasogastric tube, and the haemoglobin fell from 90% to 75% of normal in spite of a transfusion on day 6 of one unit of fresh blood. Blood urea increased from 51 mg/100 ml on admission, when mild dehydration was present, to a maximum for the total period in hospital of 106 mg/100 ml on day 9, falling by day 10 to 70 mg/100 ml. Plasma albumin levels were between 2.7 and 3.5 g/100 ml. Blood gases were measured often during the acute stage of the illness and values obtained in eight measurements from days 2 to 16 were as follows: PaO_2 69-470 mm Hg (average 193 mm Hg); Paco_2 25-57 mm Hg (average 38 mm Hg); pH 7.38-7.55 (average 7.46). Repeated blood cultures were negative.

On days 1 and 2 the blood pressure and heart rate appeared normal at 100-130/75-80 mm Hg and 75-112 (average 85/min) respectively, but the blood pressure subsequently became highly variable, as indicated by the wide interval between the maximum and minimum systolic blood pressure values (table I) as previously described for other patients in this unit (Kerr *et al.*, 1968; Corbett *et al.*, 1969; Kerr *et al.*, 1969; Prys-Roberts *et al.*, 1969). From day 4 onwards, apparently spontaneous episodes of acute hypotension developed on many occasions. The degree and duration of hypotension, the frequency of the episodes, the interval between them, and the blood pressure, heart rate, and central venous pressure levels during the intervals were all extremely variable and the blood pressure for a nine-hour period is indicated in fig. 1, in which the time base has been compressed during subsequent replay from an instrumentation magnetic tape recorder. The highest blood pressure in fig. 1 was

FIG. 1—Blood pressure (B.P.) during a nine-hour period from 00.05 hours on day 6 in case 1. Upper and lower records are continuous. They were obtained by time base compression during replay from an instrumentation tape recorder. In 12-hour period preceding record patient received D-tubocurarine 15 mg intramuscularly at 12.45, 13.45, 14.40, 18.40, 21.50, and 23.55 hours, and penicillin 1 megaunit intramuscularly at 12.45, 18.00, and 23.58 hours.

200/112 mm Hg and the lowest was 44/36 mm Hg, the latter being associated with a heart rate of 70/min and central venous pressure of 1 mm Hg. Despite extreme hypotension on this and subsequent occasions the patient did not appear shocked, since his skin remained warm, veins were not constricted, and there was no excessive sweating, though later in the disease there was some skin oedema. He was curarized throughout, with only occasional muscle twitches. The hypotension could not be corrected by putting the patient head-down or by using a negative-pressure phase on the ventilator, and at this time muscle spasms and tracheal suction also had little effect. The pupil diameter was 3-5 mm and both pupils reacted briskly to light.

The patient's level of consciousness was difficult to assess owing to curarization, but it was not seen to be different during hypotensive and hypertensive episodes. No motor or vasomotor response occurred when he was spoken to until day 14.

During days 5-10 the lowest blood pressure was 32/16 mm Hg, and typical concurrent values for blood pressure, central venous pressure, and heart rate respectively at various blood pressure levels were: 180/100 mm Hg, 5 mm Hg, and 115/min (day 5); 134/70 mm Hg, 4 mm Hg, 118/min (day 5); 52/30 mm Hg, 5 mm Hg, 84/min (day 5); 40/20 mm Hg, 4 mm Hg, 90/min (day 6). These figures reflect the fact that during periods of hypotension the heart rate always decreased and central venous pressure almost always decreased. The electrocardiogram, which was displayed throughout most of this period and often recorded in addition, was unremarkable. It has been observed above that in the hypotensive episodes early on day 6 there was little cardiovascular response to stimuli. This was not always the case as such responses were sometimes obvious (fig. 2), sometimes slight, and sometimes absent. As shown in fig. 2 there was no cardiovascular response to the firing of a starting gun on this or on

FIG. 2—Variations of heart rate (H.R.), blood pressure (B.P.) and central venous pressure (C.V.P.) in case 1 from 23.50 hours on day 7, and occasional effect of stimuli (gun = firing of starting pistol, twitch = spontaneous twitch, T.S. = aspiration of tracheal secretions, pinch = pinching of patient's skin, S.E. = painful stimulation of patient's ear). Vertical lines on heart rate record are artifacts. In 12 hours preceding record patient received D-tubocurarine 15 mg intramuscularly at 12.00, 13.00, 13.50, 15.30, 16.30, 17.40, and 19.45 hours, and 15 mg intravenously at 20.35 hours on day 7. In addition he received digoxin 0.25 mg by nasogastric tube at 17.30 hours and penicillin 1 megaunit intramuscularly at 17.30 hours on day 7.

most other occasions, though late in the second week slight responses to this stimulus did occur. Hypertensive responses to aspiration of tracheal secretions and painful stimuli to the skin were present and some cardiovascular changes appeared to be spontaneous, the direction of blood pressure, heart rate, and central venous pressure changes being in the same direction throughout. Increases in P_{aCO_2} produced by temporarily adding a dead space to the airway were usually followed by a rise of blood pressure from previously hypotensive levels. There was little blood pressure recovery when the foot of the bed was raised by 15° and when the bed was kept in this position for long periods the frequency and severity of the hypotensive episodes were unaltered.

Drugs were used at different times in attempts to overcome the hypotension or investigate its cause. *Propranolol* was used on day 5 only and when given intravenously in 0.1 mg increments to a total of 1 mg produced a fall in heart rate of 20 beats/min, but no other apparent change, and did not prevent or worsen subsequent blood pressure falls. *Phentolamine* was given intravenously on three occasions (1.0, 1.2, and 2.0 mg doses) without obvious effect. *Trimetaphan* (8 mg intravenously) on two occasions also had no apparent effect, but *hexamethonium* (2.0 mg intravenously on one occasion) was followed by a blood pressure fall in which the systolic blood pressure remained below 80 mm Hg for most of the subsequent 150 min and the lowest blood pressure level was 45/24 mm Hg. In addition to the usual intramuscular doses, *D-tubocurarine* was administered intravenously on a number of occasions in doses of 10 and 15 mg, and *alcuronium chloride* 10 mg on other occasions, both without obvious effect. "Single shot" injections of 8–20 μ g of *noradrenaline* via the central venous pressure catheter typically produced rises in mean blood pressure of 13–16 mm Hg from a resting level of 30–40 mm Hg, associated with small increases in heart rate and central venous pressure. These changes passed off in less than one minute.

During a hypotensive period on day 8, 16 measurements of cardiac output were made. The blood pressure, heart rate, and central venous pressure records for some of this period are shown in fig. 3 with the time of the cardiac output measurements. Decreases in blood pressure

FIG. 4—Parallel variations of blood pressure (B.P.), heart rate (H.R.), central venous pressure (C.V.P.), cardiac output (C.O.), stroke volume (S.V.), and systemic vascular resistance (S.V.R.) from 15.20 hours in case 1 on day 8. Drugs given to this patient on day 8 are indicated in legend for fig. 3.

average level of blood pressure "troughs" was 76/30 mm Hg, corresponding to an average heart rate of 90 beats/min. On days 12 and 13 the lowest blood pressure was 52/20 mm Hg, with a heart rate of

FIG. 3—Heart rate, blood pressure, central venous pressure (H.R., B.P., C.V.P.) from 15.20 hours on day 8 in case 1 during a period of cardiac output measurements (each marked by a dark band). Records 1 and 2 are continuous with one another. Up to 18.00 hours on day 8 he received *D-tubocurarine* 15 mg intramuscularly at 03.35, 05.00, 06.00, 07.20, 09.00, 11.00, 13.30, 14.35, 15.50, and 18.00 hours, digoxin 0.25 mg by nasogastric tube at 06.00 hours, and penicillin 1 megaunit intramuscularly at 06.00 and 12.00 hours.

were associated with decreases in heart rate, cardiac output, and stroke volume (fig. 4). Blood gas measurements made at 14.30 hours on the same day were as follows: P_{aO_2} = 114 mm Hg, P_{aCO_2} = 44 mm Hg, and pH = 7.38. On a number of occasions injection of the dye (about 1 ml) was followed by blood pressure increases (fig. 3) and the relationship appeared causal. Simple manipulation of the taps and connexions had no effect and the response seemed only to follow the rapid intravenous injection of a small volume of fluid, which usually produced some movement of the catheter in the vein.

From day 10 to day 16, when the arterial catheter was removed, the pattern of hypotensive episodes was similar except that the episodes became less frequent and somewhat less severe towards the end of the period. The blood pressure in the interval between episodes of hypotension also increased in comparison to the earlier records. On day 11 the lowest blood pressure was 50/30 mm Hg, but the

84 beats/min, and the highest systolic blood pressure was 265 mm Hg. Throughout these three days (11–13) cardiovascular responses to tracheal suction, muscle spasms, and other stimuli gradually increased in magnitude. On day 14 the patient's level of consciousness became gradually lighter and for the first time the blood pressure increased when he was spoken to. On this day the blood pressure and heart rate ranged from 48/20 mm Hg and 84 beats/min to 250/126 mm Hg and 114 beats/min respectively, and blood pressure increases, rather than decreases, tended to dominate the record. On day 15 the blood pressure ranged from 72/40 mm Hg (heart rate 76 beats/min) to 265/142 mm Hg (heart rate 110 beats/min), and the patient began to obey simple commands if curare was allowed partially to wear off. Responses to oral and tracheal stimulation and muscular activity continued to be obvious but some changes still occurred without apparent stimuli. On day 16 the existing tendency to increased

responses to stimuli continued, and the lowest blood pressure was 52/26 mm Hg (heart rate 96 beats/min). The arterial catheter was removed on this day and the heart rate and electrocardiogram alone were monitored until day 19, by which time hypotensive episodes (judged by the nursing charts) were very infrequent, and the patient was readily responsive.

The principal drugs administered on days 1-16 were D-tubocurarine 45-300 mg/day (average 152 mg) given intramuscularly, except on days 7-11 when alcuronium chloride 30-160 mg/day (average 88 mg/day) was substituted. The patient also received diazepam 60 mg on day 1, diazepam 20 mg and quinal barbitone 500 mg on day 2, and quinal barbitone 500 mg on day 3. Digoxin 0.25-0.5 mg was given from days 5-16 (average 0.43 mg/day) and frusemide 20-40 mg was given on three occasions. All drugs except D-tubocurarine and alcuronium chloride were given by nasogastric tube. From day 16 there was a gradual return to normality and the major problems in managing the patient were incidental to tetanus. Intermittent positive pressure ventilation was discontinued on day 30 and the patient was subsequently discharged in good health. He could walk two miles (three kilometres) without difficulty and though he still felt weaker than before his admission to hospital he was fully independent and able to cerebrate well.

CASE 2

A 65-year-old woman contracted tetanus after scratching her skin while gardening. The incubation period was eight days, generalized spasms began one day later, and curarization and intermittent positive pressure ventilation were instituted soon after her admission to hospital on day 2.

The blood pressure, heart rate, and central venous pressure were labile and there were some pronounced responses to stimuli. For instance, tracheal suction on day 3 produced mean blood pressure rises of up to 50 mm Hg, paralleled by heart rate increases of 5-20 beats/min, while other stimuli produced somewhat smaller parallel increases. From day 4 onwards cardiovascular lability increased and episodes of severe hypotension occurred which were similar to those described in case 1 and were again not associated with clinical appearances of shock or abnormalities of the electrocardiogram. The maximum and minimum blood pressure measured each day are shown in table II together with the simultaneously measured heart rate. On most days the systolic pressure fell below 90 mm Hg, and on day 12 was as low as 55/32 mm Hg. As in case 1 the blood pressure falls were usually not associated with obvious stimuli, the recovery of a normal blood pressure following a period of hypotension was often also

apparently spontaneous, and the duration of hypotension varied similarly. The blood pressure, heart rate, and central venous pressure almost always varied in parallel, the central venous pressure range being 4-14 mm Hg. The average cardiac output from 11 estimations on day 7 was 4.5 l./min (range 3.6-5.1 l./min) and the mean blood pressure during this time was 92-157 mm Hg. Repeated estimations of blood gases produced values which were normal or indicative of over-ventilation (P_{aCO_2} range 19-34 mm Hg, average 27 mm Hg). The principal drugs administered from days 4 to 20 were tubocurarine intramuscularly 120-300 mg/day (average 170 mg/day) and pentobarbitone 300-400 mg/day (average 365 mg/day), while bethanidine was given from days 7 to 20 in a dose of 30-100 mg/day (average 66 mg/day) and propranolol was given from days 17 to 20 in a dose of 10-30 mg/day (average 15 mg/day). The last three drugs were given via a nasogastric tube.

Usually the hypotension had no obvious cause, but occasionally it appeared to result from a stimulus. On day 14 there was a brief episode of severe hypotension and extreme bradycardia associated with aspiration of secretions from the trachea (fig. 5). A resting blood pressure of 125/52 mm Hg (heart rate 68 beats/min) fell within a minute to 30/14 mm Hg (heart rate 25 beats/min), remained at or near this level for three minutes, and then rose within the next

FIG. 5—Acute hypotension and bradycardia associated with tracheal suction (T.S.) on day 14 in case 2. On this day patient received D-tubocurarine 15 mg intramuscularly every four hours, pentobarbitone 100 mg by nasogastric tube every six hours, and bethanidine 10 mg by nasogastric tube every two hours.

minute to a maximum diastolic pressure of 110 mm Hg (heart rate 72 beats/min) and a maximum systolic pressure in excess of 265 mm Hg (off-scale on the recorder), thereafter settling at a new level of 170/70 mm Hg (heart rate 68 beats/min) within 10 minutes. On day 15 aspiration of the trachea was associated with a sudden fall of blood pressure from 185/72 to 100/24 mm Hg rising to 260/100 mm Hg within two minutes. The hypotension was accompanied by a fall in heart rate from 80 to 40 beats/min followed by a rise to 88 beats/min. On day 19 there was another episode of transitory hypotension (55/22 mm Hg) while the tracheotomy was being dressed. On day 20 the arterial catheter was removed but it appeared from nurses' blood pressure measurements with auscultation that blood pressure variability continued to be high until about day 28.

Gradual recovery occurred thereafter and the patient was discharged on day 59 with a stiff right shoulder as her only residual disability.

CASE 3

This 77-year-old man developed tetanus with an incubation period of 12 days, and generalized spasms began within 24 hours. An arterial catheter was inserted on day 2. During days 2-4 his blood pressure was fairly stable at about 170/85 mm Hg and there was little response to muscular spasms or the aspiration of respiratory tract secretions. During days 5-7 the blood pressure was much more labile and there were frequent hypotensive episodes of variable duration. The maximum blood pressure during the period was 285/130 mm Hg and the greatest variation during a 30-minute period was from 240/120 to 46/38 mm Hg. The hypotension was always associated with a relative bradycardia. The electrocardiogram was not remarkable throughout this period, and there was a low serum sodium level (119-122 mEq/l.). No other consistent electrolyte abnormality was noted, the blood urea

TABLE II—Summary of Cardiovascular Data in Case 2 from Days 2 to 20

Day of illness	Maximum Systolic B.P. (mm Hg)*	Heart Rate with Maximum Systolic B.P. (beats/min)	Minimum Systolic B.P. (mm Hg)	Heart Rate with Minimum Systolic B.P. (beats/min)	Average Systolic B.P. (mm Hg)
2	256	92	150	94	175
3	300	100	130	80	185
4	250	92	102	80	150
5	285	104	84	74	140
6	300	100	70	74	170
7	320	120	80	78	200
8	260	88	70	70	150
9	290	74	90	65	170
10	320	80	85	75	205
11	245	72	80	70	135
12	230	88	56	72	105
13	246	82	105	72	145
14	275	72	28	62	150
15	260	76	82	65	135
16	225	70	80	58	125
17	220	82	82	70	115
18	335	90	80	70	150
19	232	78	55	66	130
20	250	80	74	72	130

*B.P. and heart rate on day 2 partly by auscultation. Remaining data from arterial catheter and heart rate meter recordings.

was 25-44 mg/100 ml, and the temperature was 36.4-37.8°C. The principal drugs administered in days 5-7 were tubocurarine 105-180 mg/day (average 135 mg/day) by intramuscular injection, and digoxin 0.25 mg on day 5 and 0.5 mg on days 6 and 7 by nasogastric tube. The arterial catheter was removed on day 7 but measurements made by auscultation indicated that the blood pressure continued to be labile for a further two weeks and thereafter resumed a normal pattern. The tetanus was no longer severe after the first 30 days and the patient returned home in good health.

Discussion

Hypotension has been reported elsewhere in tetanus (Alhady *et al.*, 1960; Clifton, 1964; Adams *et al.*, 1966; Macrae, 1967), and body fluid and electrolyte disturbances, episodes of hypoxia, and over-indulgent drug therapy have been suggested as possible causes (Adams *et al.*, 1966; Ablett, 1967; Glossop, 1967). Some hyponatraemia was present in two of our patients but neither hyponatraemia of this degree nor its possible causes have been reported to produce episodic severe hypotension in supine patients. Blood gas estimations indicate that our patients were generally normally ventilated or somewhat over-ventilated, and over-ventilation of this degree does not appear to produce similar effects (Richards, 1965). The doses of barbiturates and diazepam used are unlikely to have caused hypotension, but the effects of D-tubocurarine must be considered since it can cause partial autonomic blockade and release of histamine (Alam *et al.*, 1939; Shild and Gregory, 1947; Foldes, 1960). The former effect is mild and should not cause such hypotension in a recumbent patient but histamine may produce hypotension through arteriolar and capillary dilatation and increased permeability of capillaries. However, such hypotension was not related in time to injections of D-tubocurarine. The absence of hypotensive episodes in other tetanus patients receiving D-tubocurarine (Alhady *et al.*, 1960; Clifton, 1964; Adams *et al.*, 1966; Macrae, 1967), and in the present patients at earlier and later stages of the disease when treatment was identical, also suggests that D-tubocurarine or other drug therapy is unlikely to be the major cause of this hypotension. Furthermore, repeated injections of D-tubocurarine given during periods of hypotension did not lower the blood pressure further, and substitution of alcuronium chloride (which has no histamine-releasing effect) (Waser and Harbeck, 1962) did not prevent hypotension from occurring. For similar reasons the hypotension cannot be attributed to effect on venous return of D-tubocurarine in abolishing the muscle pump, and raising the foot of the bed—a method commonly used to increase venous return—did not overcome the hypotension. Haemoglobin, packed cell volume, daily body weight, daily urinary output, and urinary specific gravity estimations suggest that the patients were not dehydrated and did not have a consistent disturbance of body fluids.

Septicaemia may present a similar clinical picture, but organisms have not been recovered from the blood in cultures from these patients and treatment with antibiotics did not prevent the hypotension. Similar experiences and poor responses to treatment with antibiotics and steroids have been reported from other centres (Clifton, 1964; Adams *et al.*, 1966; Clark and Taylor, 1966; Macrae, 1967). It has also been suggested that toxic myocarditis could be a cause of hypotension in tetanus (Lassen *et al.*, 1954; Alhady *et al.*, 1960; Stirnemann, 1966; Macrae, 1967). There was no evidence from the electrocardiograms of our patients to suggest myocarditis and the central venous pressure did not rise as in heart failure. In addition, the hypotension which might occur with septicaemia and myocarditis would be expected to occur as part of a picture of shock, which is not the picture displayed by our patients. They did not appear to have peripheral vasoconstriction, sweating was not pronounced, urinary output was maintained throughout, the hypotension was accompanied by a relative bradycardia rather than tachycardia, and the blood pressure often recovered rapidly with or without external stimuli. These are not normal clinical features of shock.

Prolonged sympathetic overactivity has also been suggested as the cause of hypotension in tetanus (Clifton, 1964). Sustained nervous or humoral sympathetic stimulation may itself be noxious to the heart (Szakacs and Mehlerman, 1960; Melville, 1966; Raab, 1966; Northfield, 1967) and may force the heart to work at too fast a rate against too high a blood pressure (Corbett *et al.*, 1969). It may also produce sufficient systemic vasoconstriction to cause local hypoxia, capillary damage, and increased cell permeability, resulting in a decreased circulating fluid volume and venous return (Freeman, 1933; Mollaret *et al.*, 1958) again contributing to hypotension. We believe that we have seen this sequence of events in other patients and that it is essential to prevent it by giving sympatholytic drugs during the hypertensive phase. If hypotension develops in this way, however, the clinical picture is one of severe shock, often leading to death. The possibility of sympathetic overactivity, however, was investigated in case 1. Beta-adrenergic, alpha-adrenergic, and ganglionic neurogenic blockade with propranolol, phentolamine, trimetaphan, and hexamethonium respectively did not alleviate the hypotension, and increased sympathetic activity produced by small doses of noradrenaline produced a rise in blood pressure, heart rate, and central venous pressure. We conclude that the hypotension described here and shown in fig. 1 was not due to sustained sympathetic nervous overactivity.

The rapid, irregular, spontaneous transitions from hypotension to hypertension, and the parallel changes of heart rate, stroke volume, and cardiac output (fig. 4) indicate that the myocardium and other cardiovascular structures remained capable of maintaining the arterial pressure and cardiac output. The fact that when the blood pressure and heart rate decreased the central venous pressure also usually decreased again suggests that heart failure was not the cause of the arterial hypotension. A decrease of heart rate rather than an increase with the hypotension suggests impairment of baroreceptor reflexes. It therefore seems possible that the various disturbances may have been produced by tetanus toxin impairing the neural integration of cardiovascular control. This would accord with our previous findings of sympathetic nervous dysfunction in tetanus (Kerr *et al.*, 1968; Corbett *et al.*, 1969; Kerr *et al.*, 1969; Prys-Roberts *et al.*, 1969) and could explain the abnormal response to tracheal stimulation during aspiration of secretions shown in fig. 5, an excessive depressor response being followed by excessive compensation.

Though our patients have survived, this condition is alarming. We have been reluctant to depend on catecholamines for treatment, as hypotension is liable to recur intermittently over many days, and prolonged catecholamine infusions may be harmful. Catecholamines would also worsen episodes of hypertension occurring between periods of hypotension. We have therefore used physiological stimuli to raise the blood pressure when severe hypotension has persisted—for instance, if the systolic pressure has remained below 60 mm Hg for 15-20 min. Such stimuli included muscle spasms, minor painful stimuli to the skin, increasing the arterial carbon dioxide level, and head-down tilt. They are harmless, easy to control, and easily reversed. None has been universally effective but the most useful appeared to be increasing the arterial carbon dioxide level by temporarily adding a dead space to the patient's airway.

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Oral Contraceptives and Myocardial Infarction

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Summary

Between January 1970 and December 1972 22 women aged between 31 and 45 years were admitted to the coronary care unit with acute myocardial infarction and six of these (27%) had been taking oral contraceptives. There were nine women aged 40 or less and five of them (55%) had been on oral contraceptives while three of the other four had been sterilized by tubal interruption.

Both these figures of prevalence of oral contraceptive use are significantly greater than estimates for the general population of women of similar age. For those aged 30-44 years, current estimates suggest that it is between 8 and 11%.

All the women in this study had risk factors recognized as being associated with the premature development of ischaemic heart disease, and the prevalence of these risk factors was similar in those taking oral contraceptives as in those not doing so. Oral contraceptives probably enhance the chance of developing myocardial infarction in women whose risk is increased for other reasons.

Introduction

A direct relation between acute myocardial infarction in young women and the use of oral contraceptives has not been statistically proved, but continued reporting of the association (Boyce *et al.*, 1963; Hartveit, 1965; Naysmith, 1965; Scharf *et al.*, 1968; Oliver, 1970; Dear and Jones, 1971; Waxler *et al.*, 1971; Weiss, 1972) suggests the need for caution in prescribing contraceptives to individual patients.

This paper reports the experience of the coronary care unit of the Royal Infirmary of Edinburgh over a three-year period, 1970-2, and is a sequel to a previous report (Oliver, 1970).

Method

From January 1970 to December 1972 22 women aged between 31 and 45 years were admitted to the coronary care unit in the Royal Infirmary of Edinburgh with clinical features of acute myocardial infarction. The diagnosis was substantiated by classical electrocardiographic changes classifiable according to the Minnesota code (Rose and Blackburn, 1968) or by raised serum creatine phosphokinase levels or by both methods.

All of the women were asked specifically about the use of oral contraceptive pills, and details of the type and duration of such therapy were confirmed with their general practitioners. All were assessed for risk factors known to be associated with the early development of ischaemic heart disease and a scoring system was used with one point being given for the presence of each of the following features: (1) hypertension—a diastolic blood pressure >100 mm Hg recorded before the acute event or six weeks or more after the acute myocardial infarction; (2) hypercholesterolaemia—a fasting serum cholesterol value >270 mg/100 ml found at an interval of at least six weeks after the acute event; (3) smoking—20 or more cigarettes daily at the time of infarction; (4) an abnormal glucose tolerance test of the diabetic type using a 50 g oral glucose load more than six weeks after the acute event; (5) family history—a myocardial infarct or known ischaemic heart disease under the age of 55 years in one or more near relatives; (6) obesity—weight greater than 10% above the standard for height and age; and (7) a premature menopause or bilateral oophorectomy.

The number of risk factors for each patient was totalled and is quoted as the risk score.

Results

Of the 22 women aged between 31 and 45 years admitted with acute myocardial infarction six were found to have been using oral contraceptives at or just before the time of their infarct. There were nine women aged between 31 and 40 years, and five of these had been using the pill. The sixth oral contraceptive user was aged 45 and she died of an extensive anterior acute myocardial infarction. Attention has been focused primarily on the group of younger women, aged 40 years or less, documented in the table. Their risk scores averaged 2.6.

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