in which the blood-pressure should be lowered to improve prognosis (Turner, 1962; Smirk, 1962). These patients are usually symptomless, so that treatment should be free of side-effects.

Many of these patients are treated with a combination of reserpine and a diuretic of the thiazide group. Such a combination is not free from side-effects, and it was thought that the addition of hydrochlorothiazide to the new hypotensive drug methyl dopa might lower the blood-pressure to the same extent with less side-effects. A double-blind trial on 18 patients with moderate hypertension comparing methyl dopa combined with hydrochlorothiazide and reserpine with hydrochlorothiazide has not supported this idea. Both combinations satisfactorily reduced the blood-pressure of all patients, but in every case the patient felt better on placebo than on either form of treatment. When comparing the two treatments in the 17 patients who completed the trial, nine preferred the reserpine with hydrochlorothiazide, three methyl dopa with hydrochlorothiazide, and five had no preference.

Methyl dopa is a potent hypotensive agent; the optimum daily dose for any patient can vary between 750 mg. and 3 g. (Irvine *et al.*, 1962). Because of this variable response it was thought necessary to have a preliminary phase to the trial to find the optimum dose of methyl dopa with hydrochlorothiazide for each patient. This dose of methyl dopa was compared with the maximum satisfactory dose of reserpine (0.5 mg. a day) (Smirk, 1957).

The ideal drug for the hypertensive patient without symptoms who needs treatment should be free from side-effects. Methyl dopa is an effective hypotensive drug, but often a large number of tablets are needed and minor side-effects are present. A combination of hydrochlorothiazide and methyl dopa produces good control of blood-pressure with a reduced number of tablets. This combination caused significant side-effects in 9 out of 18 patients.

The margin of difference between the two regimes of treatment was small, and related only to the incidence and severity of side-effects. The most striking finding in our patients was that they all felt much better on placebo. Neither methyl dopa with hydrochlorothiazide nor reserpine with hydrochlorothiazide is ideal treatment for moderate hypertension.

Summary

Eighteen patients were treated in a double-blind trial to compare methyl dopa with hydrochlorothiazide and reserpine with hydrochlorothiazide (one patient did not finish the trial). Both combinations satisfactorily reduced blood-pressure; the average falls were 45/23 mm. Hg standing and 32/18 mm. lying with methyl dopa and hydrochlorothiazide and 45/25 mm. Hg standing and 34/20 mm. lying with reserpine and hydrochlorothiazide.

Nine patients preferred reserpine with hydrochlorothiazide, three methyl dopa with hydrochlorothiazide, and five had no preference. All felt much better on placebo. Neither combination is ideal treatment for symptomless patients who require hypotensive drugs.

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HAEMODYNAMIC EFFECTS OF OCCLUSION OF ABDOMINAL AORTA DURING NITROGEN MUSTARD THERAPY

BY

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Alkylating agents have been used extensively in the chemotherapy of cancer. Occlusion of the abdominal aorta was developed in order to increase the tumour dose of nitrogen mustard (methyl-bis (β -chloroethyl) amine) (Duff *et al.*, 1961; Lawrence *et al.*, 1961; Miller *et al.*, 1962). By using this method the pelvic bone-marrow is adequately protected against the effects of the drug, and since approximately 45% of the body circulation is cut off (Duff *et al.*, 1961; Lawrence *et al.*, 1961) the drug is more concentrated in the remaining body area.

In our experience, after release of the occlusion of the aorta a profound fall in blood-pressure occurred which lasted for as long as two to three days. Since no studies of the haemodynamics of patients undergoing occlusions had been made, the present investigation was undertaken.

Methods

The investigation was carried out on 20 adult African patients with cancer of the head and neck. The main study

was made on 12 patients, in all of whom the femoral-artery pressures were ascertained. In eight of these patients the right atrial pressure was measured, in five measurement was made of the pulmonary-artery pressure, in one the pulmonary wedge pressure, and in six the cardiac output. The other investigations reported were undertaken in a further eight patients.

Anaesthesia.—All patients were anaesthetized with 0.5 g. of thiopentone, paralysed with 120 mg. of gallamine triethiodide, intubated, and then maintained on positive-pressure respiration by means of the Radcliffe pump. The duration of the anaesthesia was approximately 20 minutes.

Catheterization.—Before the patient was anaesthetized a cardiac catheter size 7 or 8 was passed under local analgesia through the right antecubital vein into the right side of the heart. The site of pressure recording was as stated above. Right atrial pressures were recorded on two separate occasions in two patients. All recordings were made with a Sanborn pressure-transducer, using a Sanborn

four-channel recorder. In all cases mean pressures were noted prior to, during, and after occlusion. The considerable fluctuations to be seen on the tracings coincide with the positive-pressure respirations. A narrow "polythene" catheter was introduced into the femoral artery and continuous recordings of the femoral-artery pressure were made.

Cardiac Outputs.—In six patients the effect of occlusion on the cardiac output was studied. Azovan blue, in a dosage that ranged from 17 to 20 mg., was injected through the cardiac catheter and the degree of dilution of the dye was measured by a photoelectric cell placed on the ear and connected to a Cambridge dye-dilution-curve recorder. A high input-resistance was used so that the response of the recorder was linear over the range of dye-concentration levels attained (Gabe and Shillingford, 1961). Dye curves were recorded before, during, and after occlusion. In order to exclude the effect of recirculation, the heights of the dye curves in millimetres at one-second intervals were plotted on semi-logarithmic paper and the first downslope was extrapolated to the abscissa. The heights of the curve so formed were read off from the semi-logarithmic paper. The area under this curve was then measured. The reciprocals of the area under the curves obtained before, during, and after occlusion were compared.

Endotracheal Pressures.—These were measured in two patients, using a water-filled tube to connect the Sanborn pressure-transducer to the endotracheal tube.

Peripheral Resistance in Arms.—Peripheral resistances were measured in six patients by means of a water-filled phlethysmograph fitted on to the index finger, and were recorded with a Sanborn pressure-transducer. An alteration in the size of the finger was assumed to indicate either an increase or a decrease in the volume of blood in the finger. A decrease in size was taken to indicate an increase in peripheral resistance and an increase to indicate a fall.

Blood Volumes.—The blood volume above a manual occlusion was compared with the volume above an occlusion produced by an inflatable cuff in one patient, using azovan blue. The concentration of dye in heparinized plasma was measured at 620 m μ , using standard dilutions of dye prepared in the patient's plasma. The blood volume was calculated by the correction factors recommended by Mollison *et al.* (1950).

Screening.—Four patients were screened before, during, and after occlusion and the outline of their hearts was drawn on the screen.

Aortic Occlusion.—In all cases, soon after the aorta was occluded, the nitrogen mustard was injected intravenously and the occlusion maintained for 10 minutes. In the first seven studies on six patients the aorta was occluded by means of a sandbag and Esmarch tourniquet as described by Duff *et al.* (1961). In the remaining eight studies an inflatable cuff was used (Miller *et al.*, 1962). The inflatable cuff takes about 30 seconds to occlude the aorta completely. The "onset of occlusion" is the time the cuff is inflating. Thereafter, pressures were taken continuously during the whole period of complete occlusion.

Blood-pressure.—Blood-pressures were measured at short intervals during the occlusion, using a mercury sphygmo-

manometer on the arm. Pulse rates were also recorded at frequent intervals.

Results

Right Atrial Pressures (Figs. 1 and 2, Table I).—The right atrial pressures measured before, at the onset of, during, and after occlusion are set out in the Table. In seven of the eight patients the right atrial pressure increased at the onset of occlusion and remained elevated during the occlusion. The mean pressure was 3.7 mm. Hg before occlusion, 8.9 mm. Hg at the onset of occlusion, and 8.2 mm. Hg during occlusion. After removal of the occlusion the pressure decreased to below the pre-occlusion

FIG. 1.—Comparison of manual and cuff occlusions: femoral artery and right atrial pressures. A, Manual occlusion. Arrows 1 and 2 indicate completion of occlusion. B, Cuff occlusion. Arrows 1 indicate beginning of occlusion. Arrows 2 indicate completion of occlusion. Arrows 3 indicate release of occlusion. The gap in the tracing is a time interval of approximately six minutes.

FIG. 2.—Femoral artery and right atrial pressures during cuff occlusion. Arrows 1 indicate onset of occlusion. Arrows 2 indicate completion of occlusion. Arrows 3 indicate release of occlusion. The gap in the tracing is a time interval of approximately six minutes.

level in six of the eight patients, the mean pressure being 2.4 mm. Hg. All these alterations from the pre-occlusion pressure attain statistical significance between the 1% and 5% levels. The high pre-occlusion mean pressure was thought to be due to the effect of positive-pressure respiration.

Pulmonary Artery Pressures (Fig. 3, Table II).—The mean pulmonary artery pressure before occlusion was

TABLE I.—Right Atrial Pressures

Patient	Pre-occlusion	Onset of Occlusion	During Occlusion	Post-occlusion
1	1.5	7.5	6.5	1.5
2	2.0	5.0	4.0	0.5
3	5.5	7.0	7.0	4.0
4	4.0	17.0	16.0	3.0
5	5.0	3.5	3.5	1.0
6	2.0	8.5	8.0	3.0
7	5.5	11.0	10.0	3.0
8	4.0	11.5	10.5	3.0
Mean	3.7	8.9	8.2	2.4

14.9 mm. Hg. At the onset of occlusion the pressure rose in five patients, the mean being 20.2 mm. Hg ($P=0.02$). It decreased to nearly the pre-occlusion level for the remainder of the period of occlusion (mean 15.5 mm. Hg) and decreased slightly more after the occlusion was released (mean 12.3 mm. Hg). Neither of the two latter differences from the pre-occlusion pressure attains statistical significance.

FIG. 3.—Femoral artery and pulmonary artery pressures during cuff occlusion. Arrows 1 indicate onset of occlusion. Arrows 2 indicate completion of occlusion. Arrows 3 indicate release of occlusion. The gap in the tracing is a time interval of approximately six minutes.

TABLE II.—Pulmonary Artery Pressure (mm. Hg)

Patient	Pre-occlusion	Onset of Occlusion	During Occlusion	Post-occlusion
2	12.0	16.0	12.0	9.0
8	8.0*	16.0*	13.0*	11.5*
9	14.5	18.5	17.0	12.5
10	12.0	17.0	14.0	15.0
11	25.0	25.0	19.0	19.0
12	18.0	29.0	18.0	7.0
Mean	14.9	20.2	15.5	12.3

* Pulmonary wedge pressure.

Femoral-artery Pressure (Table III).—The mean femoral-artery systolic pressure before occlusion was 107 mm. Hg. At the onset of occlusion it rose in 8 of the 10 patients; in the other two it was unchanged. The mean pressure at this time was 139 mm. Hg—a significant increase ($P<0.001$). There was no detectable pressure in the femoral arteries during occlusion. After occlusion the femoral-artery pressure increased suddenly to a mean of 82 mm. Hg and then more gradually over the next two minutes to 147 mm. Hg. The differences between the mean pre-occlusion pressure and the mean pressure after removal of the occlusion attain statistical significance. Similar changes were observed in the diastolic pressures.

Endotracheal Pressures.—In one of these two patients the endotracheal pressure rose by 0.5 mm. Hg and in the other by 1.5 mm. Hg during the occlusion.

Peripheral Resistance.—During occlusion there was a transient fall in peripheral resistance in the fingers in two patients, a transient rise in one, a maintained increase in one, and a maintained fall in two. After release of the occlusion the peripheral resistance rose to above the pre-occlusion level for 60–100 seconds in all four patients for whom readings were available.

TABLE III.—Femoral Artery Pressure (mm. Hg)

Patient	Pre-occlusion	Onset of Occlusion	Immediate Post-occlusion	2 Mins. Post-occlusion
<i>Systolic</i>				
1	70	70	120	175
2	120	170	75	150
3	80	135	80	155
4	135	165	125	160
5	105	140	100	200
6	100	135	70	115
8	120	155	85	150
9	120	155	65	140
10	135	180	65	160
11	80	80	30	60
Mean	107	139	82	147
<i>Diastolic</i>				
1	60	60	80	105
2	70	100	45	85
3	55	100	50	100
4	85	120	90	95
5	80	95	60	100
6	80	100	40	80
8	75	100	55	95
9	80	110	35	85
10	90	115	50	105
11	40	40	15	30
Mean	72	93	49	87

Cardiac Outputs (Table IV).—From the results obtained with the six patients in whom cardiac output was measured there was a suggestion that the cardiac output either remained unchanged or decreased during occlusion. After the release of the occlusion the cardiac output rose to 1.65 times that prior to occlusion ($P<0.005$).

TABLE IV.—Ratio of Cardiac Outputs

Patient	During Occlusion	Post-occlusion
1	1.0	1.57
2	1.0	1.57
8	0.57	1.75
9	0.57	1.32
11	1.08	2.06
12	0.53	—
Mean	0.78	1.65

Screening.—As the aortic occlusion proceeded, the diaphragmatic cupolae were markedly elevated and showed considerable diminution of range of movement on respiration. Diaphragmatic movement remained symmetrical and no abnormal appearance other than that due to basal compression was recognized in the lung fields. The cardiac outline showed marked changes. The first change was an emphasis of the left ventricle at the apex below the point of opposite pulsations on the left cardiac border. The whole heart then appeared to swing to the right, the displacement of the right cardiac border to the right being nearly double the displacement of the left border to the right. The right atrium and the right ventricle then appeared to enlarge. As the occlusion was released the diaphragmatic cupolae returned to their normal positions and the same sequence of events was seen in the heart outline, except that the changes were in a reverse order and slower.

Blood Volume.—In one patient comparison was made of the blood volume above the occlusion, using manual and inflatable-cuff occlusion. The pre-occlusion total blood volume was 5,250 ml. The blood volume above the manual occlusion was 2,580 ml. and above the cuff occlusion 2,710 ml.

Blood-pressure and pulse rates in the arms showed no significant changes during the procedure.

Discussion

During aortic occlusion there was a rise in right atrial, pulmonary artery, and pulmonary wedge pressures, which returned to normal on release of the occlusion. In three patients there was a fall in cardiac output during occlusion, but in three others the cardiac output was unchanged. In all of these six patients there was a significant rise in cardiac output on release of the tourniquet. Changes in peripheral resistance during occlusion were variable, but in four of the six patients there was a rise in resistance when the occlusion was released. The femoral-artery pressures rose as the occlusion was proceeding, were not measurable during the occlusion, and rose to a level higher than that prior to the occlusion shortly after the tourniquet was removed.

As there was often a fall in cardiac output during occlusion, the elevation of the pressures in the right heart and the wedge pressure suggest that the heart had temporarily failed. This hypothesis is supported by the appearance of the heart on screening, which suggested that it had dilated.

The cardiac output is the product of heart rate and stroke volume. As the pulse rate showed no significant change the stroke volume must have fallen. The reason for this failure is difficult to explain. There was no increase in blood-pressure in the arms causing the heart to fail in face of a sudden hypertension. Neither would the slight increase in endotracheal pressures be sufficient to cause interference with filling of the right heart. The nitrogen mustard was injected after the cardiac output curves were drawn during the occlusion, so this could not have been a contributing factor. In view of the high right atrial pressure a decrease in venous return can be ruled out. This leaves two possibilities: (1) a failure of contractility of the cardiac muscle due possibly to decreased coronary blood supply, or (2) diminution of distensibility of the heart due to constriction, as occurs in constrictive pericarditis. There was certainly considerable elevation of the diaphragm, and this may have been a constricting factor, especially when combined with an increase in the endotracheal pressure. The smaller elevation of right atrial pressure associated with manual aortic occlusion, which produced less elevation of the diaphragm, might support this hypothesis. However, both these mechanical factors might have compressed the coronary arteries.

The increase in cardiac output over the pre-occlusion levels on release of the tourniquet suggests that when the tourniquet was released all adverse factors that were acting on the heart were removed. The rapid increase in cardiac output after removal of the occlusion probably resulted from a high filling pressure, so that the heart was acting at the optimum part of the Starling curve.

Duff *et al.* (1961) showed that the occlusion is below the renal arteries. It would then be expected that the blood volume above the occlusion should be 70–75% of the total volume. However, since in this study the blood volume above the occlusion was approximately 50% of the total, it would seem that at the start of the occlusion the venous return was obstructed while the aorta continued to

pump blood into the lower limbs (I. Gabe, personal communication).

The low blood-pressure occurring immediately on release of the tourniquet may have been due to an overall decrease in peripheral resistance—probably mainly in the occluded limbs. This was almost immediately compensated for by an increase in peripheral resistance, as shown in the arms, with a consequent rise in systemic pressure. However, this was followed later by a profound fall in systemic pressure. This could have resulted from the release of substances such as histamine in the compressed gut and occluded lower limbs. In three white patients (not included in this study), on whom aortic occlusion has been performed, we have noted marked flushing of the skin in the lower half of the body after release of the tourniquet.

Summary

The haemodynamic changes during occlusion of the abdominal aorta were studied on 20 African patients suffering from anaplastic growths of the post-nasal space. These studies were carried out during the course of high-dosage nitrogen mustard therapy.

The following results were obtained during occlusion: (1) an elevation of pressures on the right side of the heart; (2) a fall in cardiac output in three of six patients, with no change in the remaining three; and (3) a rise in the femoral-artery pressures until the occlusion was completed.

On removal of the occlusion the pressures on the right side of the heart returned to normal, and both the cardiac output and the femoral-artery pressure rose to above the pre-occlusion levels.

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The United Kingdom National Branch of the Royal Life Saving Society has published a new *Handbook of Instruction* which brings up to date the basic principles of rescue from drowning used by the Society since it was founded in 1891. The new handbook will be used in the United Kingdom and in all parts of the Commonwealth outside the areas under the jurisdiction of the National Branches of the Society in Canada, Australia, and New Zealand. Artificial respiration is dealt with fully. The expired-air, Silvester-Brosch, and Holger Nielsen methods are described and there is a brief description of external cardiac massage, though this is not at present included in the Society's examinations. The price of the new handbook is 4s. 6d. (plus 8d. postage). It may be obtained from the headquarters of the Society, 14 Devonshire Street, London W.1, or from its branches, of which there are 23 in the United Kingdom.