Haemodynamic Effects of Intravenous Adrenaline Sulphate Following Aortic Valvar Homograft Replacement

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Intravenous adrenaline sulphate is commonly used in the treatment of low cardiac output states following heart operations. Although its cardiovascular effects have been studied in animals and in normal man (Aviado, 1959; Eckstein and Abboud, 1962), its precise effects immediately following open-heart operations have received little attention. This paper reports the haemodynamic effects of intravenous adrenaline when used in the early post-operative period following homograft replacement of the aortic valve.

SUBJECTS AND METHODS

Six men aged 27–64 years (Table I) were studied 16–20 hours after homograft replacement of the aortic valve under cardiopulmonary bypass. Continuous normothermic perfusion of both coronary arteries was maintained during the time that the aorta was open. Three patients had mixed aortic valvar stenosis and regurgitation, two had dominant aortic valvar stenosis, and one had dominant aortic regurgitation with mitral stenosis. All six were in sinus rhythm before operation, and clinical, electrocardiographic, haemodynamic, and angiographic studies confirmed the severity of the aortic valvar lesion. Patient 6 had been in severe left ventricular failure, and in addition had survived two episodes of cardiac arrest. At the time of the post-operative study all six patients were considered to be in a satisfactory clinical condition, though Patient 6, referred to above, showed arterial oxygen desaturation (81%) and Patient 3 had developed left bundle-branch block. All except Patient 4 showed clinical peripheral vasoconstriction. The individual clinical data are shown in Table I.

During the operation Portex FG3 tubing was positioned in the right atrium, pulmonary artery, and, in one patient, the left atrium; teflon tubing (TF11) was introduced into the brachial artery by the Seldinger (1953) technique. Systemic and pulmonary arterial pressures

were recorded using a strain gauge (Statham P23G) and oscillographic recording system (Sanborn Model 296) and mean right and left atrial pressures were recorded via a saline manometer. All pressures were referred to a point in the anterior axillary line at the level of the fourth chondrosternal junction. Adrenaline sulphate, 10 $\mu\text{g./min.}$, was injected into a peripheral vein for a period of 10 minutes before each study and during the collection of data, using a constant rate infusion pump (C. F. Palmer, London Ltd.). All patients were sedated with intravenous papaveretum (5 mg.) before the investigation, and were studied in the supine position, with the upper part of the body tilted head up by 15–30°. Control data were collected before the adrenaline infusion and were repeated during the infusion once a steady state had been reached. Pressure from the brachial and pulmonary arteries was recorded at each stage with the electrocardiogram and mean right and left atrial pressures noted. Blood samples were withdrawn at each stage from the pulmonary and brachial arterial catheters during a two- or three-minute collection of expired air, into siliconized syringes, the dead spaces of which had been filled with heparin. Expired air was analysed using a Lloyd-Haldane gas analysis apparatus (Lloyd, 1958) and passed through a calibrated Parkinson-Cowan dry gas meter to obtain its volume which was expressed at STPD. Blood samples were analysed for oxygen content from the values of percentage saturation as measured on a Kipp and Zonen haemoreflexor (Brinkman and Zylstra, 1949) and haemoglobin as measured by a spectrophotometer, a correction being made for dissolved oxygen. This method has been found, in our laboratory, to agree to within ± 2 per cent with values for oxygen content as measured by the Van Slyke manometric technique (J. Manders and R. Sillett, 1966, personal communication).

Cardiac output was calculated by the direct Fick method. Mean left atrial pressure, when not measured directly, was assumed to be equal to the mean right atrial pressure +3 mm. Hg (R. M. M. Fordham, 1966, unpublished observations); left ventricular stroke and minute work indices and the total peripheral resistance

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TABLE I
CLINICAL DETAILS OF THE PATIENTS STUDIED

Patient No.	Body surface area (m. ²)	Sex	Age (yr.)	Disease	Operation	Condition during study	Rhythm
1	1.92	M	57	Aortic valvar stenosis	Aortic valve homograft	Good; tachycardia	Sinus
2	1.77	M	32	Aortic valvar stenosis; mitral stenosis	Aortic valve homograft; mitral valvotomy	Good; tachycardia	Sinus
3	1.71	M	64	Aortic valvar stenosis	Aortic valve homograft	Good	Sinus left bundle-branch block
4	1.77	M	27	Aortic valvar stenosis and regurgitation	Aortic valve homograft	Good	Sinus
5	1.78	M	62	Aortic valvar stenosis and regurgitation	Aortic valve homograft	Good	Sinus
6	1.64	M	64	Aortic valvar stenosis and regurgitation; severe left ventricular failure	Aortic valve homograft	Good; arterial hypoxaemia	Sinus

were calculated from standard formulae as previously described (Resnekov, Fordham, and Ross, 1968).

RESULTS

The values as measured and calculated in the six patients, the mean values, standard deviations, and the statistical significance of changes from the control findings are shown in Table II. As previously reported (Fordham and Resnekov, 1967), the cardiac index during the control period was once more found to be abnormally low and averaged 1.67 l./min./m.²; similar low control values were obtained for stroke index (18 ml./m.²), left ventricular stroke work index (19.3 g.m./m.²) and mixed venous oxygen content (9.31 vol. %). These values were associated with a raised arteriovenous oxygen difference which averaged 7.95 vol. per cent and total peripheral resistance (average 2232 dynes. sec. cm.⁻⁵). The intravenous infusion of adrenaline resulted in a rise in the average value for cardiac index (+48%), stroke index (+33%), heart rate (+14%), left ventricular stroke work index (+46%), left ventricular minute work index (+64%), oxygen consumption (+20%), mixed venous oxygen content (+10%), systemic systolic arterial pressure (+30 mm. Hg), and pulse pressure (+31%). The arteriovenous oxygen difference fell by an average of 20 per cent and the total peripheral resistance by 26 per cent. Variable changes, which were not statistically significant, were recorded in the systemic arterial diastolic pressure and in the mean systemic arterial pressure which rose by an average of 7 mm. Hg. The arterial oxygen content fell by an average

of 0.44 vol. per cent and the mean right atrial pressure by 1.6 mm. Hg; the average mean pulmonary arterial pressure rose by 1.9 mm. Hg, but all three values were not significant at the 5 per cent level. The pulmonary vascular resistance fell from 295 to 213 dynes sec. cm.⁻⁵ in Patient 3 during the adrenaline infusion.

Cardiac dysrhythmias developed during the adrenaline infusion in 3 patients. Patient 1 developed ventricular ectopic beats; Patient 6 nodal ectopic beats. Nodal rhythm supervened in Patient 5, with the start of the adrenaline infusion, but sinus rhythm recurred before the collection of data. Facial pallor was noted in three patients during the infusion.

DISCUSSION

The circulatory effects of an intravenous infusion of adrenaline in normal man occur in two phases (Barcroft and Swan, 1953; Allwood *et al.*, 1962). The initial transitory phase is characterized by a large increase in muscle blood flow, a rise in cardiac output and stroke volume, tachycardia, and a small fall in blood pressure. During the second phase which is sustained, a decrease in the muscle blood flow to about twice the control levels is found; slight slowing of the heart rate occurs, the stroke volume increases still further, but there is only slight additional change in the cardiac output, and this may vary from subject to subject; the systolic blood pressure rises.

The measurements in the present series were made 10 minutes after beginning the infusion of

TABLE

RESULTS BEFORE AND DURING INFUSION OF ADRENALINE SULPHATE IN PATIENTS STUDIED,

Patient No.	Dose ($\mu\text{g./min.}$)	O ₂ uptake (ml./min.)	O ₂ Content of arterial blood (vol. %)	O ₂ Content of mixed venous blood (vol. %)	Arterio-venous O ₂ diff. (vol. %)	Cardiac index (l./min./m. ²)	Heart rate (beats/min.)	Stroke index (ml./m. ²)
1	Control 10	206 241	16.5 16.5	9.8 10.2	6.7 6.3	1.6 2.0	120 125	13 16
2	Control 10	282 329	17.1 16.3	7.8 9.8	9.3 6.5	1.7 2.9	115 134	15 21
3	Control 10	213 307	18.7 17.5	9.4 10.1	9.3 7.4	1.3 2.4	73 86	18 28
4	Control 10	220 251	19.7 19.6	12.4 14.4	7.3 5.3	1.7 2.7	95 113	18 24
5	Control 10	226 265	19.1 18.5	9.9 10.9	9.2 7.6	1.4 1.9	73 78	19 25
6	Control 10	225 258	12.5 12.5	6.6 7.3	5.9 5.2	2.3 3.0	86 104	27 29
Mean (SD)	Control 10	229 (27.2) 275 (34.8)	17.3 (2.64) 16.8 (2.47)	9.3 (1.99) 10.5 (2.30)	7.95 (1.51) 6.38 (1.01)	1.67 (0.35) 2.48 (0.46)	93.7 (20.3) 106.7 (21.8)	18.3 (4.8) 23.8 (4.8)
p	—	<0.01	N.S.	<0.01	<0.01	<0.01	<0.01	<0.01

adrenaline and correspond to the second sustained phase. Previous studies during this phase have shown a mean rise in cardiac output of 40 per cent above the control values (range +28 to +98%) (Goldenberg *et al.*, 1948; Barcroft and Starr, 1951; Witham and Fleming, 1951; Cyvin *et al.*, 1955), an increase of about 25 per cent in stroke volume (Allwood *et al.*, 1962; Witham and Fleming, 1951), an increase in heart rate of about 20 per cent (Barcroft and Starr, 1951; Witham and Fleming, 1951), and an increase of about 15 per cent in the systemic systolic and pulse pressures (Allwood *et al.*, 1962; Barcroft and Starr, 1951); an increase in myocardial contractile force has also been reported (Goldberg *et al.*, 1960). A rise in the pulmonary artery "wedge" pressure gradient and variable changes in the pulmonary vascular resistance may occur (Witham and Fleming, 1951).

The results of the present series (Table II) are qualitatively similar to those described above and are compared in Table III with those of Allwood *et al.* (1962) who investigated the circulatory effects of an infusion of 10 $\mu\text{g./min.}$ adrenaline in normal subjects. Although the average percentage increase in cardiac output is the same in the two series the absolute increase in the present series is less than half that found in normal subjects, for control values were abnormally low in our patients. Furthermore a much smaller absolute increase was found in the

stroke volume though the percentage increase was found to be higher in our series. Similar changes in heart rate were noted in both series.

The dominant action of adrenaline in the present series was inotropic, for the increase in cardiac output with the increased heart rate was always associated with an increased stroke volume (Fig. 1). Furthermore an increase in left ventricular stroke work index accompanied the rise in left ventricular minute work index (Fig. 2). The rise in cardiac output was associated with a significant decrease in the total peripheral vascular resistance (Fig. 3); despite the increased systolic brachial arterial pressure, only non-significant changes in the mean arterial and mean right atrial pressures were noted during the administration of the drug (Table II). A linear correlation was found between the percentage changes in stroke index and percentage changes in systemic pulse pressure ($r=0.8423$; $p<0.01$). The increase in oxygen consumption (+20%) which was found during the administration of adrenaline was associated with an even greater rise in the cardiac output (+48%); the arteriovenous oxygen difference fell by 20 per cent and the mixed venous oxygen content rose by 10 per cent, indicating an improvement in oxygen supply to the body in relation to demand.

The mean left atrial pressure which was measured in Patient 3 rose by 3 mm. Hg and was associated

II

MEAN VALUES, AND STATISTICAL SIGNIFICANCE OF CHANGES FROM CONTROL LEVELS

Brachial artery				Mean pulm. arterial pressure (mm. Hg)	Mean right atrial pressure (mm. Hg)	Mean left atrial pressure (mm. Hg)	Left ventr. stroke work index (g.m./m. ²)	Left ventr. minute work index (kg. m./min./m. ²)	Total periph. resist. (dynes. sec. cm. ⁻⁵)
Systolic pressure (mm. Hg)	Diastolic pressure (mm. Hg)	Mean pressure (mm. Hg)	Pulse pressure (mm. Hg)						
127	74	84	53	15.0	5.0		13.7	1.65	2045
134	67	80	67	15.0	3.5		16.0	2.00	1617
118	85	88	33	16.5	6.5		15.9	1.83	2152
135	72	78	63	15.5	4.0		20.6	2.76	1172
98	59	75	39	18.0	5.0	9.5	16.3	1.20	2434
158	72	103	86	23.5	5.0	12.5	34.4	2.98	1898
138	95	108	43	11.0	3.5		24.8	2.37	2758
195	99	117	96	12.5	3.5		35.8	4.06	1903
120	73	77	47	11.5	4.3		17.8	1.31	2364
145	64	85	81	12.0	3.2		26.9	2.09	1886
131	77	85	54	28.5	7.0		27.5	2.37	1638
143	80	95	63	33.0	2.5		35.4	3.70	1483
122 (13.9)	77 (12.1)	86 (11.8)	45 (8.2)	16.6 (6.4)	5.2 (1.33)		19.3 (5.5)	1.79 (0.506)	2232 (381.9)
152 (22.9)	76 (12.6)	93 (15.1)	76 (13.7)	18.6 (8.2)	3.6 (0.85)		28.2 (8.4)	2.93 (0.833)	1660 (296.0)
<0.05	N.S.	N.S.	<0.01	N.S.	N.S.		<0.05	<0.01	<0.01

Note: All pressures in mm. Hg with reference to the anterior axillary line at the level of the fourth chondrosternal junction.
N.S.—Not significant at the 5 per cent level.

with an increase of 2.5 mm. Hg in the (PA_m-LA_m) pressure gradient and a fall in the pulmonary vascular resistance as described by Witham and Fleming (1951). Right atrial pressure, however, fell in 4 of the 6 patients and remained unchanged in the other 2, which is contrary to the findings of Ranges and Bradley (1943) who reported a rise in right atrial pressure in two patients following the administration of adrenaline. The fall in right atrial pressure was unexpected in view of the known constrictor action of adrenaline on peripheral veins (Sharpey-Schafer and Ginsburg, 1962; Glover *et al.*, 1958), and the suggestion by Eckstein and Hamilton (1957) that a significant volume of blood is moved centrally following the administration of adrenaline, though

Witham and Fleming (1951) could find no evidence for a central shift of blood. Control studies in our patients indicated a considerable degree of peripheral constriction (Table II), so that the fall in right atrial

TABLE III

AVERAGE CHANGES IN CARDIAC OUTPUT (ΔCO), STROKE VOLUME (ΔSV), AND HEART RATE (ΔHR) DURING INFUSION OF ADRENALINE SULPHATE, 10 μ g./min. (DATA FROM ALLWOOD *ET AL.* (1962) AND PRESENT SERIES)

	ΔCO		ΔSV		ΔHR	
	l./min.	Per cent	ml.	Per cent	beats/min.	Per cent
Allwood <i>et al.</i> (1962) (7 normals)	+3.2	+47	+28	+25	+13	+21
Present series (6 patients)	+1.42	+48	+10	+31	+13	+14

FIG. 1.—The relation between cardiac index, stroke index, and heart rate (HR) before and during the adrenaline infusion in six patients. ● control; ○ adrenaline.

FIG. 2.—The relation between left ventricular minute work index (LVMWI), left ventricular stroke work index (LVS WI), and heart rate (HR), before and during the infusion of adrenaline. (Symbols as in Fig. 1.)

pressure might have resulted from the improved cardiac output during the adrenaline infusion and from the associated fall in total peripheral resistance (Fig. 3).

The smallest increase in stroke volume during the adrenaline infusion occurred in Patient 6 who had

been in severe left ventricular failure before operation and whose arterial oxygen saturation was low (81%) during the investigation. His control values for cardiac output and stroke output were the highest in the series possibly due to the effects of the anoxia (Asmussen and Nielsen, 1955). An increased

FIG. 3.—The relation between cardiac output, total peripheral resistance, and the pressure difference ($BA_m - RA_m$). (Symbols as in Fig. 1.)

BA_m —Mean brachial arterial pressure. RA_m —Mean right atrial pressure.

amount of circulating adrenaline and noradrenaline was almost certainly present before and during the investigation (Greene and Phillips, 1957) and would explain the absence of an inotropic effect during the adrenaline infusion; the circulatory changes recorded were almost entirely rate dependent.

SUMMARY

The cardiovascular effects of an intravenous infusion of adrenaline sulphate were studied in 6 patients in a dose of 10 µg./min., in the early post-operative period following homograft replacement of the aortic valve. In 5 patients, increases in cardiac output above the control values which were all abnormally low resulted from increases in stroke volume, and changes in heart rate were less important; a significant rise in left ventricular stroke work index accompanied an increase in left ventricular minute work index; there was an associated fall in the total peripheral resistance and in the arterio-venous oxygen difference, and an improvement noted in the oxygen supply to the body in relation to demand. The haemodynamic changes in the remaining patient who had been in severe left ventricular failure just before operation and in whom the arterial oxygen saturation was reduced at the time of the investigation were entirely rate dependent, and a possible cause relating to the anoxia and an increased amount of circulating catecholamines is suggested. In all 6 patients the right atrial mean pressure fell or remained unchanged during the adrenaline infusion and the mechanism for this finding is discussed. Cardiac dysrhythmias developed in 3 patients during the adrenaline infusion. It is concluded that the circulatory effects of adrenaline sulphate following homograft replacement of the aortic valve, in the absence of anoxia, are inotropic as well as being chronotropic, the former being dominant.

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