Comparison of haemodynamic effects of intravenous isoprenaline and adrenaline after aortic valvar homograft replacement

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The cardiovascular effects of an intravenous infusion of adrenaline (10 µg./min.) and isoprenaline (0.75 µg./min.) have been compared in two groups of six patients in the early post-operative period following aortic valvar homograft replacement. These doses were chosen to produce obvious haemodynamic effects without precipitating dysrhythmias. Though both drugs have been shown to improve the circulatory state, adrenaline caused a greater change in stroke volume and in arterial pulse pressure, and for any given rise in heart rate a greater increase in the cardiac index. In addition, adrenaline caused a greater improvement in the relation between oxygen demand and oxygen supply of the body. Isoprenaline did not cause an increase in systolic and pulse pressure and always aggravated hypoxaemia. It is concluded from this study that adrenaline is the more satisfactory drug to use in the early post-operative phase following aortic valvar homograft replacement.

The haemodynamic effects of intravenous adrenaline and isoprenaline have been studied in normal subjects (Gorten *et al.*, 1961; Weissler, Leonard, and Warren, 1959; Harrison *et al.*, 1964; Allwood *et al.*, 1962; Barcroft and Starr, 1951; Cyvin *et al.*, 1955; Goldberg *et al.*, 1960; Dodge, Lord, and Sandler, 1960) and in diseased states (Bruce *et al.*, 1961; Benchimol, Lucena, and Dimond, 1965; Cox, Cobb, and Bruce, 1963; Witham and Fleming, 1951), including congestive heart failure (Dodge *et al.*, 1960; Dodge and Murdaugh, 1957). The results of these studies have been used to predict the haemodynamic changes that will follow their administration when used to treat low cardiac output states in the post-operative period after open-heart surgery (Moffitt, Sessler, and Kirklin, 1967). In this paper we wish to document the cardiovascular effects during an intravenous infusion of adrenaline and isoprenaline after aortic valvar homograft replacement and to compare the effects of the two drugs in detail to determine which is preferable in the post-operative period.

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Subjects and methods

Twelve patients were studied 16 to 20 hours after aortic valvar homograft replacement, 6 of whom were given intravenous isoprenaline and 6 intravenous adrenaline. The clinical details of the patients studied are listed in Table 1. One patient

TABLE 1 Clinical details of patients studied

Case No.	Age (yr.) and sex	Disease	Operation
<i>Isoprenaline</i>			
1	39, M	Aortic stenosis and regurgitation	Aortic valvar homograft
2	49, M	Aortic regurgitation	Aortic valvar homograft
3	56, F	Aortic stenosis and regurgitation, mitral stenosis	Aortic valvar homograft, closed mitral valvotomy
4	54, M	Aortic stenosis and regurgitation	Aortic valvar homograft
5	44, M	Aortic stenosis and regurgitation	Aortic valvar homograft
6	41, M	Aortic regurgitation, mitral stenosis and regurgitation	Aortic valvar homograft, mitral valvar decalcification
<i>Adrenaline</i>			
7	57, M	Aortic stenosis	Aortic valvar homograft
8	32, M	Aortic stenosis, mitral stenosis	Aortic valvar homograft, closed mitral valvotomy
9	64, M	Aortic stenosis	Aortic valvar homograft
10	27, M	Aortic stenosis and regurgitation	Aortic valvar homograft
11	62, M	Aortic stenosis and regurgitation	Aortic valvar homograft
12	64, M	Aortic stenosis and regurgitation	Aortic valvar homograft

TABLE 2 Mean control values and changes in measured and calculated parameters following 10 minutes adrenaline and isoprenaline infusion while continuing infusion

	O ₂ consump. (ml./min.)	Art. O ₂ content (vol. %)	Pulm. art. O ₂ content (vol. %)	AVO ₂ diff. (vol. %)	Cardiac index (l./min./m. ²)	Heart rate (beats/min.)	Stroke index (ml./m. ²)
<i>Isoprenaline (6)</i>							
Control	255 (33)	16.8 (1.3)	9.4 (1.31)	7.4 (0.78)	2.03 (0.20)	90 (18.9)	23 (4.5)
0.75 (µg./min.)	273 (23)	16.1 (1.6)	9.9 (1.31)	6.2 (0.92)	2.63 (0.44)	109 (14.3)	24 (4.7)
Change	+18	-0.7	+0.5	-1.2	+0.60	+19	+1
% Change	+7	-4	+6	-16	+30	+21	+4
p	N.S.	<0.01	<0.01	<0.01	<0.01	<0.01	N.S.
<i>Adrenaline (6)</i>							
Control	229 (27)	17.3 (2.64)	9.3 (1.99)	7.9 (1.51)	1.67 (0.35)	93.7 (20.3)	18.3 4.8
10 µg./min.	275 (35)	16.8 (2.47)	10.5 (2.30)	6.4 (1.01)	2.48 (0.46)	106.7 (21.8)	23.8 (4.8)
Change	+46	-0.5	+1.2	-1.5	+0.81	+13	+5.5
% change	+20	-3	+10	-20	+48	+14	+33
p	<0.01	N.S.	<0.01	<0.01	<0.01	<0.01	<0.01

(Case 12, adrenaline series) had been in a worse condition before operation than the others; he had been in severe left ventricular failure, had survived two episodes of cardiac arrest, and was hypoxaemic at the time of study. All the patients, however (including Case 12), were in a satisfactory clinical condition during this study, and none required additional supportive measures other than routine post-operative care. All were in sinus rhythm before and during the drug infusions.

Details of the methods of study have been previously described (Resnekov, Fordham, and Ross, 1968; Fordham, Resnekov, and Paddle, 1968). In brief, the following measurements were made before and during the drug infusion: oxygen consumption, arterial (ascending aorta) and mixed venous blood oxygen content (pulmonary artery), heart rate, systemic arterial, pulmonary arterial, and right atrial pressures. The arterio-venous oxygen difference, cardiac output (Fick principle), left ventricular stroke work, left ventricular minute work, and their indices, and the total peripheral resistance were calculated from the measurements as listed using standard formulae. The effects of an infusion of adrenaline (10 µg./min.) and isoprenaline (0.75 µg./min.) were compared after 10 minutes of administration of each drug and while the infusion continued, and the results were analysed for statistical significance using the Student's 't' test (Bradford Hill, 1966).

Results

The mean control values, mean values during infusions of isoprenaline and adrenaline, and the mean changes in the measured and

calculated parameters for each drug, as well as their statistical significance, are shown in Table 2. The changes from the control values during the infusion of the two drugs are compared in Fig. 1, in which the statistical significance of the differences between the effects of the two drugs is also given.

Despite the small numbers of the patients in each group, a statistically significant difference ($p < 0.01$) was found between the two drugs for changes in the stroke index (isoprenaline +1.0 ml./m.², adrenaline +5.5 ml./m.²) and arterial pulse pressure (isoprenaline +3 mm. Hg, adrenaline +31 mm. Hg). Probable significant differences ($p < 0.05$) were found for mean changes in arterial systolic pressure (isoprenaline +3 mm. Hg, adrenaline +30 mm. Hg), total peripheral resistance (isoprenaline -223 dynes sec. cm.⁻⁵, adrenaline -572 dynes sec. cm.⁻⁵) and left ventricular stroke work index (isoprenaline +2.4 g.m./m.², adrenaline +8.9 g.m./m.²). Variable increases were found in the heart rate in the two groups, though during infusion of isoprenaline the increase in heart rate was found to be inversely related to the control value (Resnekov *et al.*, 1968), a relation that did not occur during the infusion of adrenaline. The mean heart rate increase was slightly greater during infusion of isoprenaline (+19 beats/min.), than during infusion of adrenaline (+13 beats/min.) at the doses employed. Greater mean changes in cardiac index, oxygen

Brachial artery pressure (mm. Hg)			Pulse pressure (mm. Hg)	Mean pulm. art. pressure (mm. Hg)	Mean right atrial pressure (mm. Hg)	LV stroke work index (g.m./m. ²)	LV minute work index (g.m./m. ²)	Total periph. resist. (dynes. sec. cm. ⁻⁵)	
Systolic	Diastolic	Mean							
115 (27)	64.5 (10)	77 (12.5)	50 (18.5)	17.5 (4.7)	6.6 (2.8)	21.5 (5.4)	1.91 (0.45)	1586 (388)	Isoprenaline (6) Control
118 (27)	65.5	80 (13.8)	53 (18.0)	17.0 (4.8)	4.0 (2.5)	23.9 (5.1)	2.56 (0.52)	1363 (416)	0.75 (µg./min.)
+3 +2 N.S.	+1 +1 N.S.	+3 +4 N.S.	+3 +6 N.S.	-0.5 -3 N.S.	-2.6 -39 N.S.	+2.4 +11 N.S.	0.55 +34 <0.01	-223 -14 <0.05	Change % change p
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 (0.51)	2232 (382)	Adrenaline (6) Control
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 (0.83)	1660 (296)	10 µg./min.
+30 +25 <0.05	-1 -1 N.S.	+7 +8 N.S.	+31 +69 <0.01	+2.0 +12 N.S.	-1.6 -31 N.S.	+8.9 +46 <0.05	+1.14 +64 <0.01	-572 -26 <0.01	Change % change p

consumption, arteriovenous oxygen difference, mixed venous oxygen content, and left ventricular minute work were found during adrenaline than during isoprenaline infusion, though the differences between these changes were not statistically significant. Isoprenaline had very little effect on the arterial systolic, diastolic, mean, or pulse pressures.

Discussion

The two groups of patients studied were comparable (Table 1), though the mean age-group was slightly higher in the adrenaline series (51 years as compared with 47 years) and the average control cardiac index lower in the adrenaline series (1.67 l./min./m.² versus 2.03 l./min./m.²). All 12 patients were considered to be in a satisfactory condition before the study started and none required additional supportive therapy. Both adrenaline and isoprenaline caused a rise in the cardiac index (Table 2), but the difference between the effects of the two drugs failed to achieve statistical significance (Fig. 1). Infusion of both drugs caused feelings of anxiety in the patients studied, and in addition repeated collections of expired air were not conducive to maintaining the steady state. For these reasons, it was decided not to attempt to compare the effects of both drugs on each patient, but to use two groups of comparable patients studied in an identical fashion at a similar period of time following

aortic valvar homograft replacement, except that in the one group adrenaline would be used and in the other isoprenaline. Furthermore, the effects of an infusion of either isoprenaline or adrenaline often persist for a longer time than is immediately apparent (Cyvin *et al.*, 1955), making a true comparison difficult if the drugs are infused consecutively in the same patient. Another point of considerable importance is whether the doses of the two drugs used were strictly comparable. In previous reports where the effects of serial increases in the dosages of adrenaline and isoprenaline were studied (Resnekov *et al.*, 1968; Fordham *et al.*, 1968), it was found that higher doses often precipitated potentially dangerous dysrhythmias. A dose of isoprenaline of 0.75 µg./min. and of adrenaline of 10 µg./min. was therefore being used in this study, for it was shown that these doses produced consistent haemodynamic changes without precipitating any rhythm disturbance. Both isoprenaline and adrenaline caused tachycardia, and we have, therefore, compared the haemodynamic effects produced by the two drugs in respect of changes in heart rate. This approach has the additional practical advantage of indicating which drug is likely to improve the cardiovascular status of these patients most without causing too large an increase in heart rate.

The main distinction between the action of the two drugs depends on their different

FIG. 1 Individual and mean changes in measured and calculated parameters during adrenaline (●) and isoprenaline (○) infusion. Mean values are indicated by short horizontal lines. 'P' values indicate the statistical significance of the difference between the effects of the two drugs. ♦ Case 12, adrenaline series. His response differed from the other five in all respects and could relate to hypoxaemia (arterial oxygen saturation 81%) reducing the effects of circulatory catecholamines (Greene and Phillips, 1957). Case 12 has been identified in all the figures by this symbol. HR, heart rate; CI, cardiac index; SI, stroke index; $\dot{V}O_2$, oxygen consumption; $a-\bar{v}DO_2$, arteriovenous oxygen difference; BA, brachial arterial pressure; S, systolic; d, diastolic; m, mean; p, pulse pressure; $\bar{C}VO_2$, oxygen content mixed venous blood; TPR, total peripheral resistance; LVSWI, left ventricular stroke work index; LVMWI, left ventricular minute work index; NS, not significant at 5 per cent level.

effects on stroke volume. Individual changes in cardiac index plotted against changes in heart rate are shown in Fig. 2. As can be seen, for any given rise in heart rate there was generally a greater increase in cardiac index produced by adrenaline than by isoprenaline (except for Case 12). This finding is explained by the increase in stroke index induced by adrenaline, but not by isoprenaline. We have previously shown that a given dose of isoprenaline will produce a larger rise in heart rate and cardiac index when the control heart rate is slow than when it is rapid (Resnekov *et al.*, 1968), whereas no such relation was found with adrenaline. Furthermore, adrenaline seems the more effective drug in increasing the cardiac output when reduced. This is especially true when the control heart rate is high and the cardiac output low; a satisfactory increase in cardiac output may require higher doses of isoprenaline than used in this study and precipitate dysrhythmias.

The greater increase in cardiac output for a given rise in heart rate produced by adrenaline is reflected in the changes in the arteriovenous oxygen difference. From Fig. 3a it can be seen that, when compared to changes in heart rate, adrenaline produces a greater fall in arteriovenous oxygen difference than does isoprenaline, and that the magnitude of this fall is related to the change in cardiac index (Fig. 3b), irrespective of the drug used. Since the arteriovenous oxygen difference is an index of the relation between supply and

demand of oxygen in the tissues, adrenaline causes a greater improvement in oxygen supply to the body, in relation to demand, for any given increase in heart rate.

Differences were found in the effects of the two drugs on brachial artery systolic and pulse pressures (Fig. 4). Adrenaline caused a rise in these parameters, with no associated changes in diastolic or mean pressures. No consistent changes were caused by isoprenaline. In Fig. 4 it can be seen that increases in pulse pressure are linearly related to increases in stroke index, which suggests that the absence of any change in pulse pressure during isoprenaline infusion is secondary to its lack of effect on the stroke volume.

The relation between changes in total peripheral resistance and changes in heart

FIG. 2 Changes in cardiac index (l./min./m.^2) plotted against changes in heart rate (beats/min.) during adrenaline and isoprenaline infusion. Symbols as in Fig. 1. A linear relation was found between the two parameters during isoprenaline infusion ($r = 0.7697$; $t = 2.411$; $p < 0.05$).

FIG. 4 Changes in brachial arterial pulse pressure (mm. Hg) plotted against changes in stroke volume (ml.) during infusion of adrenaline and isoprenaline. Symbols as in Fig. 1. A linear relation was found between the two parameters (for all points plotted, $r = 0.9086$; $t = 6.879$; $p < 0.001$).

FIG. 3a and 3b Changes in arteriovenous oxygen difference ($a-v\bar{D}O_2$; vol. %) plotted against changes in heart rate (beats/min.) (Fig. 3a) and cardiac index (l./min./m.^2) (Fig. 3b) during adrenaline and isoprenaline infusion. Symbols as in Fig. 1. (For all points plotted in Fig. 3b, $r = 0.8060$; $t = 4.305$; $p < 0.01$.)

FIG. 5a and b Changes in total peripheral resistance (TPR dynes. sec. cm.^{-5}) plotted against changes in heart rate (beats/min.) (Fig. 5a) and per cent changes in cardiac index (l./min./m.^2) (Fig. 5b) during adrenaline and isoprenaline infusion. Symbols as in Fig. 1. (For all points plotted in Fig. 5b, $r = -0.7441$; $t = 3.491$; $p < 0.01$.)

rate are shown in Fig. 5a. For a given change in heart rate a greater fall in total peripheral resistance occurs with adrenaline, though no difference between the two drugs was shown when changes in total peripheral resistance were compared with changes in cardiac output (Fig. 5b).

From the data we have obtained, adrenaline appears to be the more effective drug in raising the stroke volume, cardiac output, and brachial arterial systolic and pulse pressures, and in reducing the arteriovenous oxygen difference and total peripheral resistance, especially when these changes are related to increases in heart rate. One disadvantage of isoprenaline was found, namely, it consistently aggravated arterial hypoxaemia (Fordham and Resnekov, 1968). From the information obtained in this study, therefore, adrenaline appears to be preferable to isoprenaline in the treatment of low cardiac output states after aortic valvar replacement.

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