Hypertension induced by prolonged intracoronary administration of dobutamine in conscious dogs

J.-F. LIARD

Institut National de la Santé et de la Recherche Médicale, Unité 25, Hôpital Necker, Paris, France

(Received 19 May 1977; accepted 10 August 1977)

Summary

1. In order to determine if a sustained increase in cardiac output can lead to hypertension, seven conscious dogs were given a continuous infusion of dobutamine, a powerful stimulant of cardiac inotropism, into the left coronary artery for a 7 day period while arterial pressure, cardiac output (electromagnetic flowmeter) and heart rate were measured.

2. The infusion technique (1-5 × 10⁻⁸ mol min⁻¹ kg⁻¹, intracoronary) was selected after short-term experiments showed that it increased cardiac output more effectively than intravenous infusion at the same rate.

3. The rise in cardiac output elicited by intracoronary infusion of dobutamine was largest during the first 6 h of the 7 days administration, at which time calculated peripheral resistance was decreased. Subsequently, cardiac output returned progressively toward its control value whereas mean arterial pressure remained elevated (by an average of 20–25 mmHg) and peripheral resistance increased significantly.

4. Measurements of blood and extracellular fluid volumes as well as plasma renin activity indicated that these factors were not involved in the blood pressure increase.

5. When the infusion was ended, arterial pressure fell rapidly but peripheral resistance remained elevated during the first 6 h. Cardiac output fell after 2 and 6 h to a value below that of the pre-infusion control. After 1 day and subsequently, blood pressure became normal, as did the peripheral resistance and cardiac output.

6. Both at the onset and offset transients of this model of hypertension, changes in cardiac output preceded changes in peripheral resistance. These experiments may give experimental support to the concept of cardiogenic hypertension.

Key words: arterial pressure, cardiac output, cardiogenic hypertension, dobutamine, heart rate, myocardial contractility, whole-body auto-regulation.

Introduction

The concept of cardiogenic hypertension is based upon the simple consideration that, as arterial pressure is determined by both cardiac output and peripheral resistance, the heart might play an active role in the development of some types of hypertension by increasing cardiac output. As pointed out by Tarazi (1975), there are theoretical objections to such a mechanism. First, under normal conditions the cardiac output is controlled primarily by peripheral factors, and the heart itself has little to do with cardiac output regulation (Guyton, Jones & Coleman, 1973). Even more important, the role of the kidneys in controlling blood pressure appears critical, and an increase in cardiac output alone would not be expected to sustain an increase in arterial pressure, as the urinary output would rise from the augmented perfusion pressure (Guyton, Coleman, Cowley, Liard, Norman & Manning, 1972).

It was attempted to create a model of cardiogenic hypertension by prolonged stimulation of the cardiac sympathetic nerves in conscious dogs (Liard, Tarazi, Ferrario & Manger, 1975). Although mean arterial pressure increased as a result of such stimulation, it was not clear whether this resulted from the transient increase in cardiac output at the start of stimulation, or from other
mechanisms such as stimulation of afferent fibres from the heart, which are known to induce pressor spinal reflexes (Peterson & Brown, 1971). More specific cardiac stimulation was therefore necessary. This was attempted in the experiments of this paper by a prolonged infusion of dobutamine directly into the left coronary artery of conscious dogs. Dobutamine, a synthetic catecholamine (Tuttle & Mills, 1975), was selected because it is a strong stimulant of cardiac inotropism with less chronotropic, arrhythmogenic and vascular effects than isoprenaline (Tuttle & Mills, 1975; Robie, Nutter, Moody & McNay, 1974; Vatner, McRitchie & Braunwald, 1974; Bolter & Ledsome, 1976; Jewitt, Birkhead, Mitchell & Dollery, 1974; Lumley, Broadley & Levy, 1977). Short-term intravenous and intracoronary infusions of dobutamine were given in preliminary experiments in order to select the proper rate to use for the prolonged infusions.

Methods

Animal preparation

Sixteen male mongrel dogs were used for these experiments (initial body weight 23.1 ± 0.7 kg, mean ± SEM). Under anaesthesia, left thoracotomy at the fourth intercostal space allowed insertion in sterile conditions of an electromagnetic flow transducer (Statham Instruments Inc.) on the root of the aorta, and insertion of a Tygon catheter in the left coronary artery by the technique of Herd & Barger (1964). The tip of the catheter was directed toward the aorta in such a way that both the left anterior descending and the left circumflex branches could be perfused. This was checked on chest radiographs after injection of radio-opaque material into the intracoronary catheter. Thus drugs infused through this catheter were expected to be distributed directly to the areas controlled by the left coronary artery, which contributes about 85% of myocardial blood flow in the dog (Gregg & Fisher, 1963). During the same operation, catheters were also inserted into the aorta and the inferior vena cava through iliac vessels.

Measurement of haemodynamics

All the measurements were performed in the conscious dogs (Cowley, Liard & Guyton, 1973). Two channels of a polygraph recorder were used for cardiac output; one recorded the pulsatile signal from the flowmeter to detect shifts of zero baseline, taken as the end-diastolic value of the signal. The other recorded an electronic mean value. The pulsatile frequency response was usually set at 20 Hz, but at regular intervals it was decreased to 1 Hz to obtain a more precise reading of the mean output. Mean arterial pressure and heart rate (triggered by the pulsatile arterial pressure signal) were also recorded.

Body fluid volumes and chemical measurements

Plasma volume was measured with Evans Blue dye by extrapolation to zero time from three samples collected 30, 45 and 60 min after injection. Blood volume was calculated from plasma volume and arterial packed cell volume obtained by microcentrifugation. Extracellular fluid volume was estimated from the volume of diffusion of radioactive sulphate after injection of a weighed amount of a solution containing 20 μCi of 35S/ml as carrier-free sodium sulphate and extrapolation to zero time from samples collected at 30, 45 and 60 min after the injection. The extracellular fluid volume value was calculated with a correction factor for plasma water and Donnan equilibrium. Plasma renin activity was measured by a radioimmunoassay for angiotensin I modified from the method of Haber, Koerner, Page, Kliman & Purnode (1969). Plasma sodium and potassium concentrations were obtained by flame photometry, osmolality by a freezing-point-depression osmometer, and plasma protein, glucose, urea and creatinine concentrations with a Technicon Auto-analyzer.

Experimental protocol

Training. The training procedures were started approximately 2 weeks after surgery. Both short-term and chronic experiments were performed after stable haemodynamic values had been obtained for several consecutive days.

Short-term experiments. The haemodynamic effects of 5 min intravenous and intracoronary infusions of dobutamine were compared in 16 dogs with infusion rates ranging from 1.86 × 10−6 to 1.35 × 10−7 mol min−1 kg−1 (0.56–40.7 μg min−1 kg−1).

Chronic dobutamine infusions. In seven dogs a continuous infusion of dobutamine into the left
coronary artery was given for 7 days with a small portable battery-operated pump attached to the dog. The dobutamine solution was prepared daily in a bag of sterile isotonic glucose solution containing heparin (50 units/ml). For each 24 h period the exact rate of infusion was determined from the weight of the bag, and ranged from 0-26 to 0-35 ml/min; this rate was selected to avoid excessive fluid loading (less than 500 ml/day) and yet obtain a smooth, continuous delivery of the solution and avoid clotting of the catheter. The average rate for the chronic infusion of dobutamine in the seven dogs was 1-505 ± SEM 0-073 x 10⁻⁸ mol min⁻¹ kg⁻¹ (4-54 ± 0-22 µg mm⁻¹ kg⁻¹).

Haemodynamic measurements were recorded every day for several hours before and during the infusion and at regular intervals after the end of the infusion. For each day a value for mean arterial pressure, cardiac output, heart rate, calculated total peripheral resistance and peak aortic blood flow was obtained by averaging about 10 periods of at least 5 min each, during which the dog was very quiet, with stable values. The pre-infusion control value was taken as the average for the 4 days preceding the infusion, and changes were calculated from that value. Conversely, the changes after the end of the infusion were calculated from the value measured after 7 days of infusion. Several blood samples were obtained before the start of the infusion on different days for chemical measurements. Plasma volume and extracellular fluid volume were measured at least twice in the control period. Chemical and volume measurements were repeated 1, 4 and 7 days after the start of the infusion, and again 1, 4 and 7 days after the end of the infusion.

In five control dogs isotonic glucose solution and heparin alone was infused (intracoronary) during 7 days, and the same haemodynamic variables were measured.

**Statistical analysis**

Results are given as mean values ± 1 SEM. Comparison between groups was made by unpaired t-tests, normal distribution being assumed. Paired differences were used for comparing intravenous and intracoronary infusions. Linear regressions were calculated with the least-squares method and their slopes compared with standard methods. Changes were considered significant for $P < 0.05$.

**Results**

**Short-term dobutamine infusions**

Fig. 1(a) depicts the changes in cardiac output with increasing doses of dobutamine. It shows the greater cardiac output change for a given infusion rate in the low range after intracoronary than intravenous administration. In order to obtain a given increase in cardiac output, the intravenous infusion had to be about five times the intracoronary infusion ($P < 0.05$). Fig. 1(b) shows that mean arterial pressure tended to increase with small rates of infusion and...
Fig. 2. Sustained increase in mean arterial pressure in response to prolonged infusion of dobutamine into the left coronary artery (at arrow: $1.52 \times 10^{-8}$ mol min$^{-1}$ kg$^{-1}$) in a chronically instrumented dog. Note the initial increase in cardiac output, followed by a progressive return toward control value. Pulsatile frequency response of the flowmeter was set at 20 Hz or at 1 Hz (control, third panel, and 7 days, second panel).

The increase in heart rate was less pronounced and tended to decrease with higher rates for both intracoronary and intravenous infusions.

**Seven-day dobutamine infusions**

Control, pre-infusion, values for the seven dogs subjected to the prolonged intracoronary infusion of dobutamine ($1.5 \times 10^{-8}$ mol min$^{-1}$ kg$^{-1}$) are given in Table 1.

Fig. 2 shows part of an original record in one dog. Two hours after the start of the infusion cardiac output was clearly increased above the control value; mean arterial pressure was also elevated and increased more over the next few days, whereas cardiac output returned toward control value.

Fig. 3 and Table 1 summarize the results obtained for all seven dogs. Cardiac output was significantly increased during the first 4 days, the largest increase taking place after 2 and 6 h. During the last 3 days of dobutamine infusion, cardiac output was slightly, but not significantly, elevated above control value.

Mean arterial pressure was increased during the whole infusion period, more so after several days, when the increase was between 20 and 25 mmHg. Total peripheral resistance decreased initially and then rose progressively. Heart rate increased markedly during the early phases, by $46.6 \pm 10.7$
TABLE 1. Mean arterial pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), heart rate (HR) and peak aortic blood flow (PABF) before and the last day of a 7 day infusion of dobutamine (1.5 x 10^-4 mol min^-1 kg^-1, n = 7), or vehicle alone (glucose, n = 5), into the left coronary artery in conscious dogs, and at 7 days after ending the infusion

Values are mean results ± SEM. * Value significantly different from control value before infusion.

<table>
<thead>
<tr>
<th></th>
<th>Control (before infusion)</th>
<th>After 7 days of infusion</th>
<th>7 days after end of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dobutamine</td>
<td>Glucose</td>
<td>Dobutamine</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>87.5 ± 2.9</td>
<td>93.6 ± 1.7</td>
<td>109.1 ± 3.6*</td>
</tr>
<tr>
<td>CO (ml min^-1 kg^-1)</td>
<td>88.7 ± 8.0</td>
<td>89.6 ± 7.5</td>
<td>92.7 ± 7.4</td>
</tr>
<tr>
<td>TPR (kPa l^-1 kg s)</td>
<td>8309 ± 711</td>
<td>8664 ± 594</td>
<td>9751 ± 706*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>78.2 ± 5.0</td>
<td>76.9 ± 4.1</td>
<td>86.3 ± 8.8</td>
</tr>
<tr>
<td>PABF (ml/s)</td>
<td>239.8 ± 26.2</td>
<td>228.2 ± 30.0</td>
<td>281.3 ± 35.0*</td>
</tr>
</tbody>
</table>

FIG. 4. Changes ± SEM in mean arterial pressure, cardiac output and peripheral resistance in seven dogs after cessation of a continuous infusion of dobutamine into the left coronary artery. * Significant change from the value reached after 7 days of infusion.

When the infusion was stopped, mean arterial pressure fell rapidly. Compared with the average value of day 7 of the infusion, the change in mean arterial pressure was -12.2 ± 2.4 mmHg 10 min after the end of the infusion and -16.6 ± 3.0 mmHg after 1 h. Changes measured later are given in Fig. 4, which shows that the blood pressure fell to normal values (Table 1). Corresponding to the initial fall in mean arterial pressure there was a decrease in cardiac output by 6.18 ± 1.95 ml min^-1 kg^-1 after 10 min and 10.54 ± 2.88 ml min^-1 kg^-1 after 1 h. After 2 and 6 h, cardiac output fell even more, as shown in Fig. 4, the value of cardiac output being significantly below that of the control, pre-infusion value. After that initial drop in cardiac output, the pre-infusion value was regained 1 day after the end of the infusion and remained stable thereafter (Fig. 4, Table 1). The changes in total peripheral resistance were not significantly different from zero during the first 55 h, indicating that peripheral resistance remained elevated as compared with the pre-infusion values, despite cessation of dobutamine administration (Fig. 4). The day after ending the infusion, however, peripheral resistance had decreased to its pre-infusion value and remained stable thereafter. Heart rate decreased somewhat when the infusion was stopped, by 7.8 ± 6.4 beats/min after 6 h and 16.8 ± 10.0 beats/min after 7 days. Peak aortic blood flow fell very rapidly to its control value.

In summary, the return of mean arterial pressure to its control value was rapid, but not immediate, and accompanied by a large initial decrease in cardiac output followed later by a fall in peripheral resistance.

In the five dogs subjected to a chronic infusion of isotonic glucose solution alone, changes from the pre-infusion control values (Table 1) were small and usually not statistically significant. For instance, 4 days after the start of the infusion, mean arterial pressure was decreased by 3.1 ± 1.5 mmHg, cardiac output increased by 1.4 ± 1.0 ml min^-1 kg^-1, peripheral resistance decreased by 501 ± 289 kPa 1^-1 kg s, heart rate increased by 6.8 ± 2.7
Table 2. Blood volume (BV), extracellular fluid volume (ECFV) and plasma renin activity (PRA) before, during and after a continuous, 7 day intracoronary infusion of dobutamine in seven conscious dogs

Values are mean results ± 1 SEM. * Value significantly different from control values.

<table>
<thead>
<tr>
<th></th>
<th>Control (before infusion)</th>
<th>During infusion</th>
<th>After infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>Day 4</td>
</tr>
<tr>
<td>BV (ml/kg)</td>
<td>92.1 ± 2.0</td>
<td>94.3 ± 4.5</td>
<td>87.2 ± 1.6</td>
</tr>
<tr>
<td>ECFV (ml/kg)</td>
<td>203.4 ± 5.3</td>
<td>208.4 ± 5.5</td>
<td>203.8 ± 6.8</td>
</tr>
<tr>
<td>PRA (pmol h⁻¹ ml⁻¹)</td>
<td>1.41 ± 0.49</td>
<td>0.76 ± 0.17*</td>
<td>0.84 ± 0.28*</td>
</tr>
</tbody>
</table>

beats/min and peak aortic blood flow decreased by 11.0 ± 10.3 ml/s (see also Table 1).

Table 2 summarizes blood volume, extracellular fluid volume and plasma renin activity measurements obtained before, during and after the 7 day dobutamine infusion. Blood volume and extracellular fluid volume did not show any significant change during the whole period of observation, nor was the ratio of plasma volume to extracellular fluid volume altered. A small decrease in plasma renin activity was observed after 1 and 4 days of infusion. The values for plasma osmolality and sodium, potassium, proteins and glucose concentrations did not change significantly throughout the experiment. Plasma urea and creatinine concentration tended to fall during the infusion, and for creatinine this fall was significant after 7 days.

Discussion

Our studies have shown that an increase in mean arterial pressure resulted from a continuous, 7 days infusion of dobutamine into the left coronary artery in conscious dogs. The sequence of haemodynamic events observed could indicate that a primary increase in cardiac output, originating from the heart, triggered a later rise in peripheral resistance. Conversely, on stopping the infusion, a fall in cardiac output preceded the return of the previously elevated peripheral resistance to its normal value. This study, then, appears to provide experimental support to the concept of cardiogenic hypertension.

The intracoronary infusion of dobutamine was an attempt to elicit an increase in cardiac output mainly due to the cardiac effects of the drug and to increase the overall perfusion of the body in excess of tissue needs. In the short-term experiments, we found cardiac output to increase significantly more after intracoronary than intravenous administration of dobutamine, at least with moderate infusion rates such as those used in the chronic infusions. This suggests that cardiac effects of the drug were responsible for the difference in cardiac output response.

Despite the use of intracoronary administration, it is possible that extracardiac effects did play some role in the development of the hypertension observed with the chronic infusions. Dobutamine possesses α-adrenergic activity, which could be important in the long run through its effects on peripheral resistance, renal function or capacitance vessels.

A recent analysis of blood pressure regulation (Guyton et al., 1972) suggests that raising arterial pressure without change in renal function or fluid intake will promote increased urinary output of salt and water, and so return the pressure to the control value. Thus increasing cardiac output without modifying the renal function curve relating urinary output to arterial pressure should not increase arterial pressure for more than a few hours or so. However, it is possible that the necessary shift of the renal function curve is a consequence, rather than the cause, of the rise in arterial pressure. It would then indicate adaptation of renal function to the increased perfusion pressure, from either functional or structural changes in the renal vasculature, hormonal adjustments, or response of the kidney to fluid depletion (Thompson & Dickinson, 1976). Such an adaptation does not need to occur very rapidly, since an increase in cardiac output elicits rather limited changes in arterial pressure when baroreceptor reflexes are intact (Cevese & Guyton, 1976). In any event, body fluid volumes did not change in our studies, suggesting that the kidneys did not correct the change in arterial pressure by the expected pressure diuresis. Whether this was due to progressive adaptation to the increased perfusion pressure, to the α-adrenergic or other properties of the drug infused or to other mechanisms such as changes in renal function resulting from the alteration in cardiac inotropism, i.e. through changes in intrathoracic
blood volume, cannot be decided on the basis of our experiments.

A final question arises as to whether the transition from the initial hyperkinetic circulation, with decreased peripheral resistance, to the final haemodynamic pattern, with almost normal cardiac output and elevated resistance, represents whole-body autoregulation. The same question applies to the transients observed on stopping the infusion after 7 days. Several types of experimental hypertension have been described where a phase of elevated cardiac output precedes an increase in peripheral resistance (Ledingham & Cohen, 1964; Coleman & Guyton, 1969; Bianchi, Tenconi & Lucca, 1970; Ferrario, Page & McCubbin, 1970; Ferrario, 1974). It has been suggested that the changes in resistance could reflect the response of peripheral vascular beds to an unwarranted increase in blood flow (for a review, see Guyton, Cowley, Young, Coleman, Hall & DeClue, 1976). However, in many of these conditions hypertension is associated with some degree of volume expansion, and humoral agents operating through the Na⁺—K⁺ pump in vascular smooth muscle could account for the rise in peripheral resistance (Haddy & Overbeck, 1976). There was no such volume expansion in our study. Thus the observed changes in resistance could reflect the combined effects of the baroreceptor reflex and the peripheral control of tissue perfusion, whereby the initial fall in resistance is due to baroreceptor activity, and the later rise to both baroreceptor adaptation (accounting at most for the return of resistance to its control value) and peripheral regulation. In turn, increased peripheral resistance decreases cardiac output.

Such an explanation, however, cannot apply to the fall in heart rate that followed the initial tachycardia. This suggests either independent control of heart rate or a reduction in the cardiac effects of dobutamine from prolonged exposure. A fall in the number of adrenoreceptors is known to occur when the agonist acts over a prolonged time (Lefkowitz, Limbird, Mukherjee & Caron, 1976; Haber & Wrenn, 1976). The persistence of an increased peak aortic blood flow throughout the chronic infusion argues against that possibility, if changes in this variable do reflect a direct action of dobutamine on the heart.

In a previous attempt to create cardiogenic hypertension (Liard et al., 1975) by electrical stimulation of the stellate ganglion in conscious dogs, it was thought that factors other than the initial increase in cardiac output were probably responsible for the maintenance of an increased arterial pressure. In the present study, the increased peripheral resistance might result from the systemic action of dobutamine. However, these two models of hypertension share several important haemodynamic characteristics, and their main common feature appears to be a primary increase in cardiac inotropism. It is therefore suggested that an increase in cardiac output, unrelated to fluid load, can lead to hypertension characterized by increased peripheral resistance.

Acknowledgments

The technical assistance of Miss L. Eloy, Miss M. de Cerval and Miss D. Pasques is gratefully acknowledged. I thank Dr Claude Mariel (Eli Lilly and Co.) for a generous supply of dobutamine, and Dr Richard Affre, from the Service de Radiologie du Professeur Michel, Hôpital Necker, Paris, who made all X-ray examinations. This work was supported by Grant ATP 32.76.64 from Institute National de la Santé et de la Recherche Médicale.

References


