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LEFT VENTRICULAR CONTRACTILITY AND DEVELOPED TENSION IN THE INTACT DOG SUBMITTED TO AN INTRACORONARY INFUSION OF ADENOSINE

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SUMMARY

1. The effect of adenosine on left ventricular contractility and developed tension was studied in the anaesthetized intact dog. Normal and propranolol-treated animals were used. Adenosine was infused through a catheter into one of the two main branches of the left coronary artery, usually the circumflex branch. The rate of infusion was 150×10^{-9} M/min. The infusion was maintained during 50 min.

2. In both series of animals, no change was observed in the heart rate, aortic pressure, left ventricular end-diastolic pressure, time from onset of left ventricular contraction to peak dP/dt, peak dP/dt and left ventricular tension–time index. It is concluded that a regional increase in adenosine concentration in the left ventricular wall has no inotropic effect when the adrenergic mechanisms are normal or depressed.

3. The myocardial blood flow response to adenosine was determined at the 10th, 30th and 50th min of the infusion by the radioactive inert gas method. At the 10th min of the infusion, the myocardial blood flow averaged three times the control value in both series of dogs. Thereafter, the flow response remained stable in the normal dogs but declined at the 50th min of the infusion in the propranolol-treated animals. It is suggested that autoregulation of the coronary circulation in response to overperfusion of the myocardium at constant cardiac work may be enhanced at the lower myocardial oxygen requirements of the propranolol-treated dogs while, in the normal animals, it was insufficient to overcome the potent coronary dilator action of adenosine.

INTRODUCTION

Since the initial report of Drury & Szent-Györgyi (1929), the effect of adenosine on the cardiac muscle has been repeatedly investigated on isolated preparations. An increase in the rate of repolarization and a reduction of the strength of contraction have been demonstrated on rat, guinea-pig and human atrial muscle (Johnson & McKinnon, 1956; Hollander & Webb, 1957; de Gubareff & Sleator, 1965). By contrast, no effect on the membrane resting or action potential has been found in guinea-pig ventricular fibres exposed to concentrations up to 185×10^{-6} M (Johnson & McKinnon, 1956) and, when a constant heart rate was maintained, no change in the amplitude of the ventricular myogram could be detected in the earlier studies on isolated rabbit hearts submitted to injections of doses up to $7{\cdot}4 \times 10^{-6}$ moles (2·0 mg) into the perfusion fluid (Wedd, 1931; Drury, 1932). Recently, however, Buckley (1970*a*, *b*) reported that adenosine increased the left ventricular contractile force in Langendorff preparations of rabbit hearts perfused with a 20×10^{-6} M solution and reduced this force in propranolol-treated or noradrenaline-depleted preparations. This author inferred that adenosine exerts a positive inotropic effect secondary to the release of myocardial noradrenaline.

It thus appears of interest to examine the effect of adenosine on the functional state of the left ventricle in the intact animal. Indeed, adenosine is continuously released by the myocardial cells into the surrounding interstitial fluid and its release is enhanced by coronary occlusion or hypoxaemia (Katori & Berne, 1966; Rubio & Berne, 1969; Rubio, Berne & Katori, 1969; Olsson, 1970). However, other than during hypoxaemia, the whole heart is not likely to be exposed to high adenosine concentrations as in experiments on isolated hearts or in animals submitted to an I.V. infusion of this substance. Moreover, an I.V. infusion of adenosine would introduce additional effects due to arterial hypotension and adrenergic discharge (Lammerant, Becsei, Mertens-Strijthagen & De Schryver, 1970). In the present study, therefore, adenosine was infused through a catheter into one of the two main branches of the left coronary artery in anaesthetized intact dogs. Normal and propranolol-treated animals were used.

METHODS

Mongrel dogs, weighing between 19 and 36 kg, were used. They were premedicated with morphine hydrochloride (2 mg/kg, I.M.) and anaesthetized 30 min later with sodium pentobarbitone (30 mg/kg, I.V.). The trachea was cannulated and artificial ventilation was initiated by means of a Starling pump, using room air. No curariform drugs were used. The rate of the pump was 12/min in all experiments and tidal volume was adjusted to stabilize the arterial blood pH before starting the first

measurements. The mean value ± S.D. of the control arterial blood pH was 7·41 ± 0·04 (Instrumentation Laboratory Inc., Boston, Mass., model 113 pH and blood gas analyser). A standard dose of 50 mg of heparin was given I.V. at 30 min intervals. The animals were studied in the right lateral position. Zero reference for pressure measurements was at the mid-chest level. Thomson Medical Telco (Saint Cloud, France) pressure transducers, multichannel oscillograph and photographic recorder were used.

Catheters were placed fluoroscopically into the aortic root, left ventricle and left coronary artery. The left ventricular pressure was sensed with a No. 8 micro-manometer catheter (MSD 8) inserted *via* a brachial or a femoral artery. The first derivative of left ventricular pressure with regard to time (dP/dt) was recorded by means of a differentiator (DE 53) connected to the output from the pressure channel. An electrocardiogram and the ventilatory pressure cycles in the tracheal cannula were simultaneously obtained. Left ventricular end-diastolic pressure, time from onset of left ventricular contraction to peak dP/dt, peak dP/dt and left ventricular tension–time index (Sarnoff, Braunwald, Welch, Case, Stainsby & Macruz, 1958) were averaged during the post-expiratory resting phase over several ventilatory cycles, using high speed recordings. Zero reference for the micro-manometer pressure curve was determined on the record by superimposing another ventricular pressure curve obtained from the lumen of the micro-manometer catheter and an external transducer (RA 9). An expanded scale of calibration was used for end-diastolic pressure measurements.

The left coronary artery was catheterized with a no. 6·5 double lumen catheter (Rashkind septostomy catheter with balloon removed) to allow tracer injections without interrupting the intracoronary infusion of adenosine. This catheter was advanced *via* the left common carotid artery and positioned 1·5–2·0 cm into the coronary artery with a minimal pressure drop (0–6 mm Hg) between the aorta and the tip of the catheter. To prevent displacement, it was fastened in the neck of the animal. Its position was reconfirmed at autopsy. The myocardial blood flow was determined with the radioactive inert gas method by using precordial counting of the myocardial clearance rate of ^{85}Kr after intracoronary injection of the tracer (Herd, Hollenberg, Thorburn, Kopald & Barger, 1962; Ross, Ueda, Lichtlen & Rees, 1964). Details of instrumentation and procedure have been described previously (Lammerant *et al.* 1970). The flow value (ml./100 g.min) was derived from the initial linear portion of the semi-logarithmic slope of the clearance curve without 'curve peeling', the actual flow being more accurately measured by the initial slope method than by curve peeling (Bassingthwaighte, Strandell & Donald, 1968).

The pressure and flow measurements were performed 10 min before starting the infusion of adenosine (control period) and at the 10th, 30th and 50th min of the infusion. Adenosine dissolved in isotonic saline solution was infused into the coronary artery at a rate of 150×10^{-9} M/min. In four experiments, adenosine dissolved in distilled water was used without modifying the results. The solution was delivered at a rate of 0·5 ml./min by means of a Braun pump. In the control period, isotonic saline solution was infused into the coronary artery at an identical rate. Two series of animals were studied, ten normal dogs and nine dogs pre-treated with propranolol hydrochloride (2 mg/kg, I.V.). As confirmed by the position of the catheter at autopsy, adenosine was infused into the anterior descending branch of the left coronary artery in one dog of each series and into the circumflex branch in all other dogs.

Drugs. The adenosine used was from E. Merck A.G. and propranolol from Imperial Chemical Industries, Ltd.

RESULTS

All values reported in the Tables are means ± S.E. Changes that occurred during the intracoronary infusion of adenosine were analysed statistically by the *t* test for paired values. A *P* value less than 0·05 was considered to indicate significance.

During the 50 min infusion period, the heart rate, aortic mean and diastolic pressures, left ventricular end-diastolic pressure, time from onset of left ventricular contraction to peak dP/dt, peak dP/dt and left ventricular tension–time index did not deviate significantly from the control values. Stability of these parameters was observed both in the normal dogs (Table 1) and the propranolol-treated animals (Table 2).

TABLE 1. Heart rate, aortic pressure and left ventricular pressure in ten normal dogs submitted to a continuous infusion of adenosine (150×10^{-9} M/min) into the left coronary artery. Values are means ± S.E. *P* refers to mean change from control

Parameter	Control	Adenosine infusion		
		10 min	30 min	50 min
Heart rate (beats/min)	109 ± 9	110 ± 9 ($P > 0·7$)	111 ± 10 ($P > 0·8$)	109 ± 10 ($P > 0·9$)
Aortic pressure				
Mean (mm Hg)	136 ± 5	135 ± 4 ($P > 0·7$)	136 ± 4 ($P > 0·9$)	136 ± 4 ($P > 0·8$)
Diastolic (mm Hg)	118 ± 4	118 ± 4 ($P > 0·9$)	119 ± 4 ($P > 0·5$)	118 ± 4 ($P > 0·9$)
Left ventricular pressure				
End-diastolic (mm Hg)	3·5 ± 0·5	3·8 ± 0·8 ($P > 0·4$)	4·0 ± 0·7 ($P > 0·2$)	4·0 ± 0·6 ($P > 0·2$)
Time to peak dP/dt (msec)	65 ± 2	64 ± 2 ($P > 0·3$)	64 ± 2 ($P > 0·3$)	66 ± 2 ($P > 0·5$)
Peak dP/dt (mm Hg/sec)	1828 ± 74	1872 ± 74 ($P > 0·2$)	1854 ± 67 ($P > 0·6$)	1784 ± 89 ($P > 0·5$)
Tension-time index (mm Hg.sec/min)	2760 ± 198	2779 ± 201 ($P > 0·7$)	2758 ± 202 ($P > 0·9$)	2693 ± 208 ($P > 0·3$)

In both series of dogs, the myocardial blood flow averaged three times the control value at the 10th min of the infusion. Thereafter, the myocardial blood flow response did not change significantly in the normal dogs but was found to be reduced at the 50th min of the infusion in the propranolol-treated animals (Table 3).

TABLE 2. Heart rate, aortic pressure and left ventricular pressure in nine dogs pre-treated with propranolol (2 mg/kg, I.V.) and submitted to a continuous infusion of adenosine (150×10^{-9} M/min) into the left coronary artery. Values are means ± S.E. *P* refers to mean change from control

		Adenosine infusion		
Parameter	Control	10 min	30 min	50 min
Heart rate (beats/min)	92 ± 3	90 ± 3 ($P > 0{\cdot}2$)	91 ± 3 ($P > 0{\cdot}7$)	92 ± 2 ($P > 0{\cdot}9$)
Aortic pressure				
Mean (mm Hg)	126 ± 5	126 ± 6 ($P > 0{\cdot}5$)	127 ± 6 ($P > 0{\cdot}5$)	126 ± 5 ($P > 0{\cdot}6$)
Diastolic (mm Hg)	108 ± 5	107 ± 6 ($P > 0{\cdot}3$)	104 ± 3* ($P > 0{\cdot}7$)	109 ± 5 ($P > 0{\cdot}4$)
Left ventricular pressure				
End-diastolic (mm Hg)	7·3 ± 1·4	7·0 ± 1·4 ($P > 0{\cdot}1$)	7·1 ± 1·6 ($P > 0{\cdot}8$)	6·9 ± 1·6 ($P > 0{\cdot}4$)
Time to peak dP/dt (msec)	69 ± 4	69 ± 4 ($P > 0{\cdot}9$)	71 ± 4 ($P > 0{\cdot}2$)	69 ± 4 ($P > 0{\cdot}9$)
Peak dP/dt (mm Hg/sec)	1572 ± 183	1599 ± 192 ($P > 0{\cdot}1$)	1575 ± 183 ($P > 0{\cdot}8$)	1546 ± 191 ($P > 0{\cdot}4$)
Tension-time index (mm Hg.sec/min)	2537 ± 225	2460 ± 221 ($P > 0{\cdot}1$)	2501 ± 234 ($P > 0{\cdot}5$)	2481 ± 241 ($P > 0{\cdot}4$)

* Eight dogs only.

TABLE 3. Myocardial blood flow response to the continuous infusion of adenosine (150×10^{-9} M/min) into the left coronary artery. Values are means ± S.E. *P* refers to mean change between observations

	Myocardial blood flow (ml./100 g.min)			
		Adenosine infusion		
Dogs	Control	10 min	30 min	50 min
Normal (no. 10)	97 ± 6	286 ± 12	295 ± 20	271 ± 16
	$P < 0{\cdot}001$	$P > 0{\cdot}6$		
		$P > 0{\cdot}3$		
Propranolol-treated (no. 9)	72 ± 3	209 ± 24	195 ± 16	149 ± 13
	$P < 0{\cdot}001$	$P > 0{\cdot}5$		
		$P < 0{\cdot}05$		

DISCUSSION

The rate of adenosine infusion was selected on the basis of a study by Rubio *et al.* (1969) who found that less than 5% of the adenosine infused at a rate of 100 to 200×10^{-9} M/min into the circumflex branch of the left coronary artery could be recovered in the coronary sinus blood. The absence of arterial hypotension in our experiments indicates that the infused adenosine did not leave the heart in amounts sufficient to lower the systemic resistance. It may thus be considered that the action of exogenous adenosine was confined to the heart.

Adenosine is known to slow the heart rate (Drury & Szent-Györgyi, 1929) as a result of a direct action on the sino-atrial pace-maker (James, 1965). This negative chronotropic effect persists after propranolol administration (Buckley, 1970*a*). In all dogs but two, adenosine was infused into the circumflex branch of the left coronary artery. Bradycardia did not occur, as was also observed by Hirche (1966). This is consistent with the fact that the sinus node in most canine hearts receives its main blood supply from the right atrial artery (Hashimoto, Tanaka, Hirata & Chiba, 1967). The lowered resistance in the atrial branches of the circumflex coronary artery probably diverted blood from right to left through the anastomotic network between the dorsal right and the ventral left atrial artery around the superior vena cava (Hashimoto *et al.* 1967), thereby preventing adenosine from reaching the sinus node.

Since heart rate, left ventricular end-diastolic pressure (pre-load) and aortic diastolic pressure (after-load) were not modified by the infusion, the stability of both the time from onset of left ventricular contraction to peak dP/dt and the value of left ventricular peak dP/dt indicates that adenosine did not affect the velocity of contraction of the left ventricular muscle mass (Gleason & Braunwald, 1962; Mason, 1969; Morgenstern, Arnold, Höljes & Lochner, 1970). The tension developed by the left ventricle, as measured by the tension–time index (Sarnoff *et al.* 1958), was also unaffected. Since only one of the two main branches of the left coronary artery was infused, it is unlikely that the entire left ventricular musculature was exposed to an increased concentration of adenosine. However, it would be difficult to conceive that a definite positive or negative inotropic effect in the area supplied by a main branch of the left coronary artery would not modify the functional state of the whole left ventricle over a 50 min period.

It is thus concluded that a regional increase in adenosine concentration in the left ventricular wall has no effect on the contractile properties of the left ventricle. Our results confirm and extend the earlier studies on isolated rabbit hearts (Wedd, 1931; Drury, 1932). As mentioned in the Introduc-

tion, Buckley (1970*a*, *b*) observed that adenosine increased the left ventricular contractile force in Langendorff preparations of rabbit hearts and reduced this force in propranolol-treated or noradrenaline-depleted preparations. He concluded that adenosine exerts a positive inotropic effect secondary to the release of myocardial noradrenaline. Our experiments do not confirm this conclusion in the intact animal with a regional increase in adenosine concentration in the left ventricular wall. From the present study, it is inferred that adenosine diffusing from an ischaemic area of the left ventricle has no direct effect on the functional state of the surrounding well oxygenated myocardium when the adrenergic mechanisms are normal or depressed.

The myocardial blood flow response to adenosine was stable in the normal dogs but declined with time in the propranolol-treated animals. The reason for the discrepancy remains conjectural. Indeed, β- adrenergic receptor blockade does not influence the coronary dilator action of adenosine (Hirche, 1966; Buckley, 1970*a*; Paoloni & Wilcken, 1971; Pauly & Bittar, 1971). Furthermore, as discussed above, left ventricular contractility and developed tension were unaffected by the infusion and remained remarkably stable throughout the 50 min observation period in both series of dogs. Nevertheless, autoregulation remains a possibility since it has been shown that overperfusion of the myocardium at constant aortic pressure and cardiac work leads to an increase in resistance reducing the coronary flow toward control value (Berne, 1964). The exact mechanism of autoregulation in response to overperfusion at constant cardiac work is still unknown but the magnitude of the myocardial oxygen requirements cannot be excluded as a determining factor. Although the effect was much delayed in our experiments, it may be hypothesized that the autoregulatory mechanism was enhanced at the lower myocardial oxygen requirements of the propranolol-treated dogs while, in the normal dogs, it was insufficient to overcome the potent coronary dilator action of adenosine.

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