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Diastolic-systolic Differences in Coronary Blood Flow: Effect of Stenosis and Tachycardia in the Anaesthetized Dog

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Summary

Blood flow in the left coronary artery is lower in the systole than in the diastole. This difference is attenuated in the presence of severe stenosis, which affects the flow more during the diastole than during the systole. Some explanations have been suggested: epicardial vasodilatation distal to the stenosis, a decrease in myocardial contractility and impairment of the intramyocardial pump effect. The present investigation in anaesthetized dogs showed that, in the presence of severe stenosis, the attenuation of the diastolic-systolic coronary flow differences occurs together with distal vasodilatation in the epicardial layers of the myocardium. This attenuation may be even greater if further vasodilatation is induced by increasing the heart rate. No evidence of reduced myocardial contractility was observed. In addition, it was found that the onset of the systolic rise of the coronary blood pressure below the stenosis occurs before that of the aortic blood pressure. This finding may serves as evidence for the role played by the intramyocardial pump mechanism in causing the systolic reduction of coronary flow. Since this mechanism is believed to propel some blood back into the aorta during the systole, the impairment of this retrograde flow caused by the stenosis could also account for the reduction of the diastolic-systolic flow differences.

Key words

Coronary flow – Coronary stenosis – Intramyocardial pump

Introduction

Arterial blood flow shows rhythmic fluctuations depending on cardiac activity, i.e. an increase during the systole and a decrease during the diastole. This general pattern is reversed in large coronary arteries, where the flow in the systole is lower than in the diastole, because myocardial contraction compresses the intramyocardial vessels (Gregg and Green 1940, Wiggers 1954, Gregg *et al.* 1965, Klocke 1976). The waterfall model of Permutt and Riley (1963) has been used to describe the systolic reduction of coronary flow (Downey and Kirk 1975). Another model of the coronary circulation, "the intramyocardial pump model" suggested by Spaan and his group provides a quantitative relationship between the myocardial systolic compression and diastolic relaxation and the diastolic-systolic coronary flow differences (Spaan *et al.* 1981, Bruinsma *et al.* 1985, Spaan *et al.* 1986, Spaan and Dankelman 1989). The extent of the systolic reduction of coronary flow has recently been attributed to the myocardial contractility (Krams *et al.* 1989b). It is known that the severe stenosis of a large coronary epicardial artery not only causes a reduction in the mean flow, but also modifies the pattern of the phasic flow (Furuse *et al.* 1975, Mates *et al.* 1978). There is a decrease in diastolic coronary flow which is not accompanied by a similar decrease in systolic coronary flow, the latter being less reduced, unchanged or slightly increased, so that the differences of diastolic-systolic flow are attenuated.

The hypotheses proposed to explain the above changes have considered that myocardial contractility is reduced, that vasodilatation occurs in the epicardial layers of the myocardium distal to the stenosis (Mates *et al.* 1978) and that the effect of the intramyocardial

pump is impaired (Spaan *et al.* 1981). In the present study we tried to verify the hypothesis that vasodilatation is a major factor in the attenuation of the diastolic-systolic coronary flow differences in the presence of severe stenosis. We examined the diastolic-systolic coronary flow differences before and after the production of severe flow limiting stenosis; then, with the stenosis in place, the heart rate was increased to raise oxygen consumption resulting in vasodilatation. Records of the left ventricular pressure were used to assess possible changes in myocardial contractility.

Preliminary results of this study have been presented to the British Physiological Society (Gattullo *et al.* 1993).

Methods

The experiments were performed on six mongrel dogs weighing 18–27 kg. General anaesthesia was induced by i.v. injection of sodium pentobarbitone in a dose of 30 mg/kg. After the trachea had been intubated with a Magill tube, artificial positive pressure ventilation was started using a Harvard respiratory pump (Model 607, Harvard Apparatus Co., Dover MA, U.S.A.).

The neck was opened along the ventral midline and the right external jugular vein, the common carotid arteries and the vagal nerves were dissected free. A catheter was inserted into the vein to administer the solutions needed for the maintenance of anaesthesia and of the acid-base balance. Two catheters connected to Statham P23Db electromanometers (Statham Laboratories, Hato Rey, Puerto Rico) were inserted into the common carotid arteries: the tip of one was pushed into the aortic root to transmit aortic blood pressure (ABP) near the coronary ostia; the tip of the other was pushed into the left ventricle to transmit left ventricular pressure (LVP).

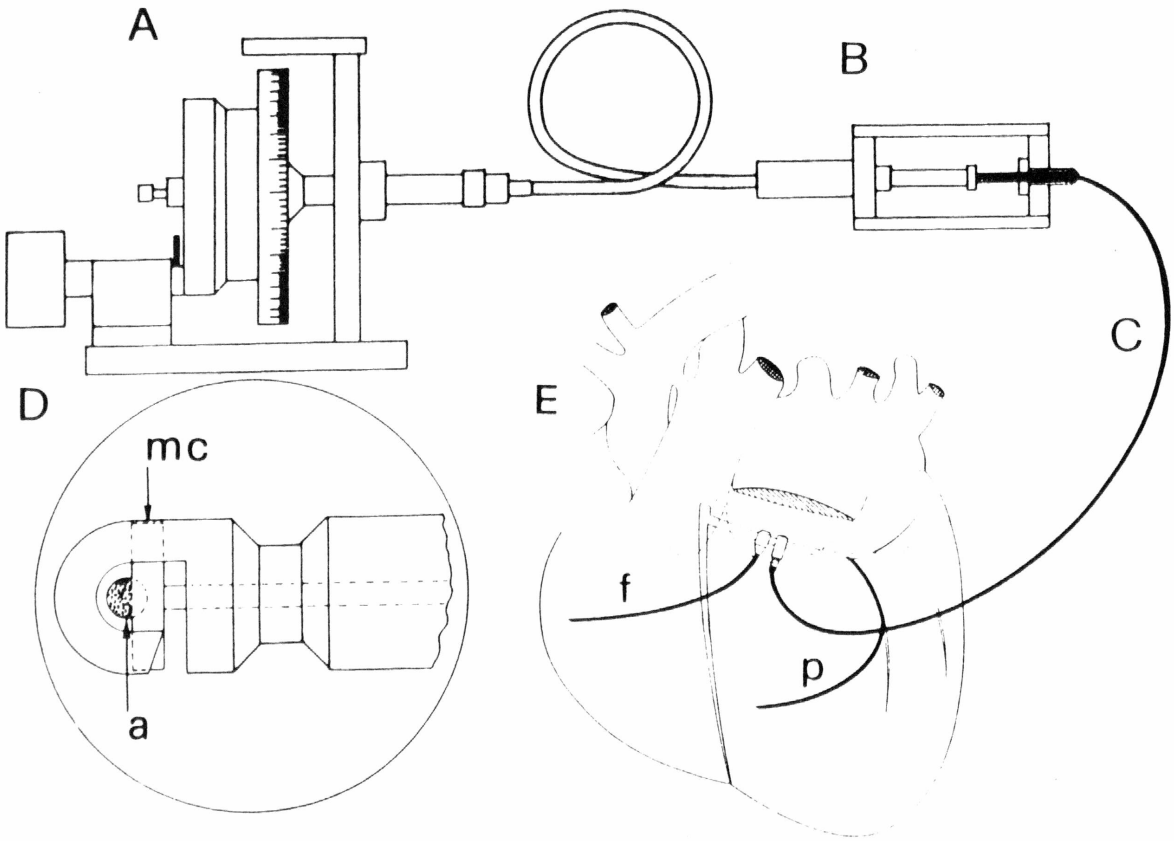

Fig. 1
Schematic drawing of the constrictor device.
A= Micromanipulator. B= Joining support between the piston of the micromanipulator and the camera shutter release. C= Camera shutter release. D= Magnification of the perspex housing with the metal cylinder compressing the artery. The artery (a) is partially constricted by the metal cylinder (mc). E= Positions on the heart of the constrictor, the flow probe (f), and the coronary pressure catheter (p).

After a left thoracotomy in the fourth intercostal space, the pericardium was opened parallel to the left phrenic nerve and the heart suspended in a pericardial cradle. To record coronary blood flow (CBF), a flow probe connected to a 400 c.p.s. electromagnetic flowmeter BL 310 (Biotronics Laboratories Inc., Silver Spring, MD, U.S.A.) was placed around the initial part of the left circumflex coronary artery. Distal to the flow probe, a constrictor device was placed around the artery (Dalla Valle and Di Lavore 1988). The device surrounded the artery with curved housing of rigid Perspex and a metal cylinder (Fig. 1) attached to a micromanipulator by a camera shutter release, about 20 cm long. The micromanipulator produced small movements in the metal cylinder which, when driven towards the housing, constricted the artery to the required extent. Due to the characteristics of the constrictor an eccentric rather than a concentric stenosis could be obtained. The extent of the constriction was read on the scale of the micromanipulator. It was expressed in terms of percentage constriction, 100 % being the fully occluded artery and 0 % as the fully open vessel (Dalla Valle and Di Lavore 1988). The constrictor was also used to occlude the artery for obtaining the level of the zero flow line.

Another flow probe connected to a 1000 c.p.s. 310 BL electromagnetic flowmeter was placed around the ascending aorta, just beyond the aortic valve, to record aortic flow (AF) assisting in the continuous monitoring of the condition of the animal.

Coronary blood pressure (CBP) distal to the constriction was transduced by a third Statham P23Db electromanometer, connected to a catheter inserted into the marginal artery, a branch of the left circumflex coronary artery.

After the vagi had been sutured, the right vagus distal to the occlusion was placed inside electrodes connected to a San'ei ES-103 stimulator (San'ei Instruments Ltd.). Stimuli of 4–7 V and 2 ms in duration at 6–8 c.p.s. were delivered to slow the heart rate and to enable pacing of the heart rate at 100 b.p.m. The heart was paced using a double concentric ring platinum electrode sewn to the left auricular appendage and connected to a Grass 11 stimulator (Grass Medical Instruments, Quincy, MA, U.S.A.), which delivered stimuli of 3–6 V and 4 ms in duration.

Needle electrodes were inserted into muscles of the proximal part of the limbs to record ECG from one of the limb leads.

To prevent changes in pressure in the proximal part of the aorta, a plastic snare was placed around the descending thoracic aorta 6–8 cm above the diaphragm. During pacing the snare was used to maintain aortic upstream pressure constant at about 100 mm Hg.

Anaesthesia was maintained by continuous i.v. infusion (12.5 μg/kg/min) of sodium pentothal, and an hourly injection (1.0 μg/kg) of fentanyl (opiate-related analgesic, Fentanest, Carlo Erba, Milano, Italy). Samples of arterial blood were taken from the right femoral artery and analyzed for P_{O_2}, P_{CO_2}, pH, bicarbonate concentration and base excess using an IL 1302 gas analyzer (Instrument Laboratory System). Acid-base and respiratory status were maintained within normal limits of the dog (Altman and Dittmer 1964) by regulating the respiratory pump and infusing, a bicarbonate solution, when required. Body temperature was monitored by an Ellab DU rectal thermistor probe (Ellab Co., Copenhagen, Denmark) and kept within normal limits using an electric pad and/or an infrared ray lamp.

ECG, ABP, LVP, CBP, CBF, AF and the time trace were recorded using a DR-8 cathode ray recorder (Electronics for Medicine, White Plains, NY, U.S.A.).

At the end of the experiments the animals were killed by i.v. injection of an excess of sodium pentobarbitone.

Experimental protocol

Following surgery, the experiments were started after a steady-state had been obtained with respect to the anaesthesia and the acid-base status. In each animal the heart was paced at the rate of 100 b.p.m. during the control period. Then the left circumflex coronary artery was constricted by about 85 % of the range determined on the scale of the micromanipulator. Owing to the characteristics of the arterial wall and the shape of the constrictor, it is possible only to indicate the degree of constriction in terms of a percentage change in the constrictor and not in terms of the actual reduction of the arterial lumen. However, in order to quantitate the influence of the stenosis, the extent of changes in coronary resistance has been assessed by calculating these changes in terms of the total coronary resistance (see below). With the artery constricted, the pacing was continued initially at 100 b.p.m. and then increased to 160 b.p.m.

At each step, records were obtained after a steady state had been achieved with respect to the heart rate (HR), ABP, LVP, CBP, CBF and AF.

Analysis of data

The mean values of pressures and flows were obtained by planimetry of the relevant areas.

Mean ABP, mean CBP and CBF were calculated throughout the entire cardiac cycle. Mean diastolic ABP, mean diastolic CBP, mean diastolic LVP and diastolic CBF were calculated during the slow filling phase (diastasis), when myocardial contraction and tension do not affect the flow and there is little or no change in coronary vascular capacitance during the period of measurement. As shown in Fig. 2, the slow

filling phase of the cardiac cycle may be revealed by analysing the LVP curve during the diastolic period. During this period, pressures and coronary flow are steady enough to allow the measurement of the resistance to flow (Losano and Guiot 1987, Dambrosio *et al.* 1990).

Systolic CBF was calculated during the interval between the end of the isovolumic systole and the protodiastole, i.e. the period of ventricular ejection, when the extravascular compression on the intramyocardial coronary vessels is at the maximum level. This period is included between the two sharp falls in coronary blood flow identified in Fig. 2 by the two dotted vertical lines.

Total coronary resistance (TCR) was calculated as the ratio of the difference between the mean diastolic ABP and the mean diastolic LVP to diastolic CBF. Distal coronary resistance (DCR), i.e. the resistance distal to the occlusion, was calculated as the ratio of the difference between the mean diastolic CBP and the mean diastolic LVP to diastolic CBF. Large artery resistance (LAR) was calculated as the ratio of the difference between mean diastolic ABP and the mean diastolic CBP to diastolic CBF. In the absence of stenosis LAR is the resistance of the large coronary artery proximal to the resistance vessels; in the presence of constriction, it can be considered to be the actual resistance produced by the stenosis.

Student's t-test for paired data was used to evaluate the statistical significance of the changes in measured variables. Data are given as mean ± S.D.

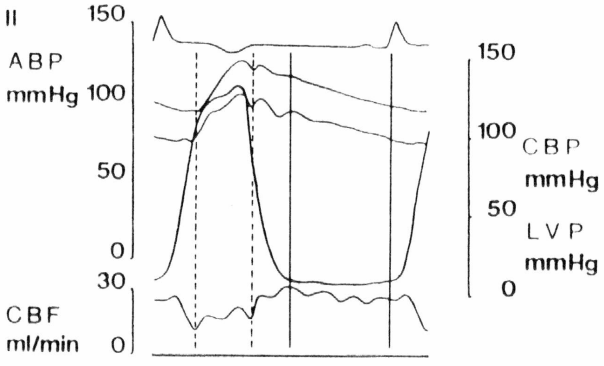

Fig. 2
Experimental records showing the periods of measurement of some haemodynamic parameters. The two vertical dotted lines include the ventricular ejection (on ABP curve) corresponding to the period of measurement of systolic CBF. The two vertical continuous lines include the slow filling phase (on LVP curve) corresponding to the period of measurement of mean diastolic ABP, mean diastolic LVP and diastolic CBF. From top to bottom: II, electrocardiogram; ABP, aortic blood pressure; CBP, coronary blood pressure; LVP, left ventricular pressure; CBF, coronary blood flow.

Table 1
Effect of coronary stenosis and increased heart rate on coronary resistance (means ± S.D.; n = 6)

	Controls HR 100 b.p.m.	85 % Constriction HR 100 b.p.m.	85 % Constriction HR 160 b.p.m.
TCR (mm Hg/ml/min	3.66 ± 1.26	4.15 ± 1.16#	3.32 ± 1.02*
DCR (mm Hg/ml/min)	3.57 ± 1.19	3.16 ± 0.85#	1.59 ± 0.54###***
LAR (mm Hg/ml/min)	0.09 ± 0.10	0.98 ± 0.40##	1.73 ± 0.99##*

*TCR, total coronary resistance; DCR, distal coronary resistance; LAR, large artery resistance. Significantly different from: the controls #p < 0.05, ##p < 0.01, ###p < 0.001; the constriction at the heart rate of 100 b.p.m. *p < 0.05, ***p < 0.001.*

Results

The haemodynamic parameters observed in the control period at the heart rate of 100 b.p.m. and after constriction of the left circumflex coronary artery at heart rates of 100 and 160 b.p.m. are shown in Fig. 3 and in Table 1.

When the left circumflex coronary artery was constricted at a heart rate of 100 b.p.m., the pressure distal to the occlusion decreased significantly. The difference between ABP and CBP (about 2 mm Hg in the control) ranged from 6 to 30 mm Hg (average = 18 ± 9 mm Hg) and that between their mean diastolic values ranged from 12 mm Hg to 34 mmHg (average = 22 ± 8 mm Hg) (Fig. 3).

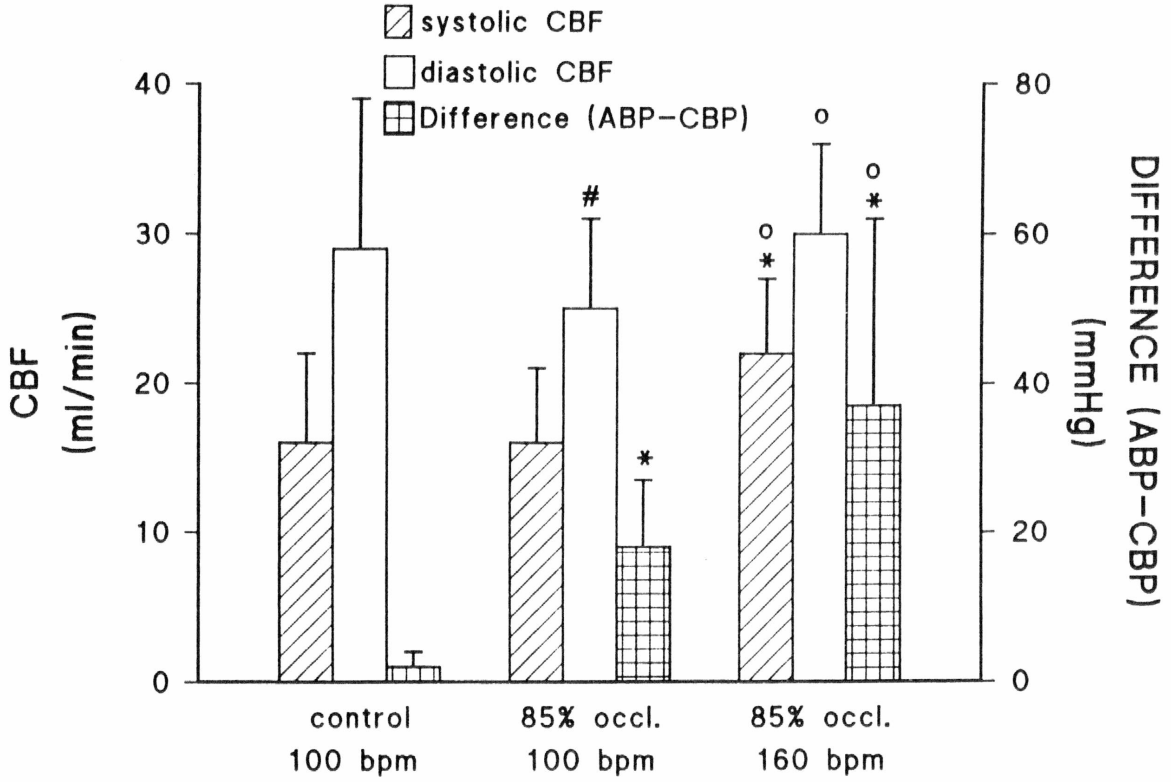

Fig. 3
Systolic and diastolic coronary blood flow and the difference between aortic blood pressure and distal coronary pressure in the control condition and after the constriction at the heart rate of 100 and 160 b.p.m. (means ± S.D., n = 6). CBF, ABP and CBP as in Fig. 2. Statistical significance in comparison with the controls # $p<0.05$, * $p<0.01$ and in comparison with the constriction at the heart rate of 100 b.p.m. ^{o} $p<0.05$.

It was observed that the onset of the systolic rise of CBP during the control period occurs simultaneously with, or only slightly before, the onset of the systolic rise of ABP. After constriction, the time difference between the two onsets was greater, the onset of the systolic rise of CBP occurring well before that of the systolic rise of ABP and shortly after the onset of the systolic rise of ventricular pressure (Fig. 4).

After constriction, CBF and diastolic CBF decreased significantly ($p<0.05$ for both) by about 13 % and 14 % from 24 ± 7 to 21 ± 5 ml/min and from 29 ± 10 to 25 ± 6 ml/min, respectively. Unlike diastolic CBF, systolic CBF did not exhibit any significant reduction; it either decreased less than the diastolic flow, or remained unchanged or increased (Fig. 3). Moreover, its phasic pattern underwent some changes consisting in a reduction or disappearance of the two sharp falls of flow in time with the isovolumic systole and protodiastole. As a consequence of these changes in systolic flow and of the reduction of diastolic flow, the typical oscillations of phasic coronary flow were damped (Fig. 4).

The constriction also caused a significant ($p<0.05$) increase of TCR by 13 %, and a significant ($p<0.05$) decrease of DCR by 11 % Following the constriction of the artery, LAR increased 10 times from 0.09 ± 0.10 to 0.98 ± 0.40 mm Hg/ml/min ($P<0.01$) so that LAR was 24 % of TCR (Table 1).

In the presence of constriction, when HR was increased from 100 to 160 b.p.m., while diastolic ABP was kept constant, a further decrease was observed in the pressure distal to the occlusion. The difference between ABP and CBP ranged from 13 to 79 mm Hg (average = 37 ± 25 mm Hg) and that between their mean diastolic values ranged from 19 to 86 mm Hg (average = 49 ± 25 mm Hg). With respect to the pacing at 100 b.p.m. after the constriction, both differences in pressure were significantly increased during the pacing at 160 b.p.m. ($p<0.05$ for both) (Figs 3 and 4).

Also at 160 b.p.m., the onset of the systolic rise of CBP began before the onset of the systolic rise of

ABP and shortly after that of LVP (Fig. 4). Furthermore, coronary pulse pressure, which had already increased after the constriction, increased further when the heart was paced at 160 b.p.m. (Fig. 4).

The increase in heart rate produced a significant increase in CBF from 21±5 to 26±5 ml/min ($P<0.01$), in diastolic CBF from 25±6 to 30±6 ml/min ($P<0.05$) and in systolic CBF from 16±5 to 22±5 ml/min ($P<0.05$). Although there was no significant difference between the increase in flow during the systole and the increase during the diastole, in some experiments the systolic increase in CBF was much more marked than the diastolic increase, thus contributing to a further decrease in the diastolic-systolic flow differences as shown in Fig. 4.

The increase in HR also resulted in a significant decrease of 20 % ($p<0.05$) in TCR and of 50 % ($p<0.001$) in DCR. LAR, which at the heart rate of 100 b.p.m. was 24 % of TCR, was 52 % at 160 b.p.m. Such an increase depended not only on the reduction in DCR, but also on the change in the absolute value of LAR from 0.98±0.4 to 1.73±0.99 mm Hg/ml/min ($p<0.05$) (Table 1).

Finally, there were no changes in the rate of the systolic increase in LVP (dLVP/dt) and in the peak systolic LVP after coronary constriction indicating no deterioration in ventricular contractility. The curve of aortic flow did not also show any sign of reduced contractility.

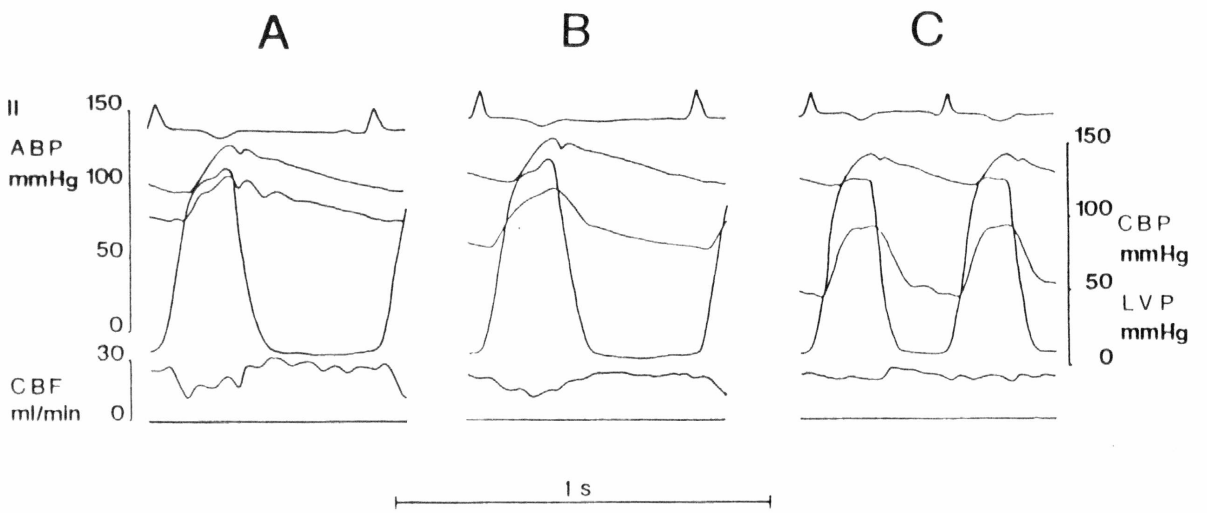

Fig. 4
Haemodynamic effects of coronary stenosis and vasodilatation on phasic coronary flow and coronary blood pressure. A= control; B= 85 % constriction at heart rate of 100 b.p.m.; C= 85 % constriction at heart rate of 160 b.p.m. With the constriction in place (B and C) in LVP curve there is no evidence of deterioration of myocardial contractility. From top to bottom: II, ABP, CBP, LVP and CBF as in Fig. 2.

Discussion

The stenosis produced in these experiments cannot be expressed in terms of reduction of the cross sectional area of the coronary artery, but as a reduction of the coronary flow. With respect to the control, CBF decreased by 13–14 %. A greater reduction could not be obtained because CBF suddenly fell to almost zero when we tried to produce a constrictions above 85 % of the range determined on the scale of the micromanipulator.

In the present investigations, the severe eccentric stenosis of the left circumflex coronary artery not only reduced of the mean diastolic CBF, but also attenuated the diastolic-systolic differences in the coronary flow, as previously described by Furuse *et al.* (1975), Mates *et al.* (1978) and Spaan *et al.* (1981). These changes occurred because the reduction of the diastolic CBF was not accompanied by any significant reduction in the systolic CBF. In the presence of constriction, the systolic flow either decreased less than the diastolic flow, or remained unchanged or increased. Moreover, the reduction or disappearance of the two falls in flow which characterize the end of the isovolumic systole and the protodiastole contributed to the reduction of the diastolic-systolic coronary flow differences. Then, in spite of the constriction, both diastolic and systolic CBF increased significantly when the heart rate was increased from 100 to 160 b.p.m. Increasing the heart rate was chosen as a simple physiological means of causing coronary vasodilatation without the use of any drug.

Together with the reduction of mean flow and the changes in the pattern of phasic coronary flow, the

constriction caused an increase in LAR and TCR and a reduction in the resistance and pressure distal to the occlusion. It is important to remember that in our experiments CBF was measured about 1 cm proximal and CBP about 2 cm distal to the position of the stenosis (see Fig. 1). In the presence of severe stenosis, the reduction of the resistance distal to the occlusion partially counteracted the increase in LAR and limited the increase in total coronary resistance. As a consequence, a constriction which reduced the arterial lumen by about 80 % of its internal diameter, reduced diastolic coronary blood flow by about 15 % only, with a reduction of 11 % in the distal resistance. These results are consistent with the predictions made by Mates *et al.* (1978) using a simple mathematical model. If the distal coronary bed had been previously vasodilated and no autoregulation was possible, an 80 % constriction of the arterial lumen would be expected to cause a marked reduction of the coronary flow. If, however, the distal bed is autoregulated, as was the case in our experiments, the flow would show little change until an 80–85 % constriction is exceeded. Thus the autoregulation represents a distal vasodilatory reserve which limits the effect of the stenosis, as is suggested in our investigation.

These results suggest that a subepicardial vasodilatation may have played a role in limiting the reduction of flow in the systole. A coronary vasodilatory reserve is believed to be available mainly in the resistance vessels of the epicardial layers in the myocardium (Gould *et al.* 1975, Gallagher *et al.* 1980, Gewirtz *et al.* 1983, Pantely *et al.* 1985, Aversano and Becker 1985). Since the resistance in these layers is only slightly affected by myocardial contraction (Klocke 1976), systolic coronary flow, which is strongly affected by the contraction in the absence of stenosis, is now less influenced because the vasodilatation mainly concerns vessels which escape the compressive effect of the ventricular systole. In the presence of the constriction, diastolic CBF is more affected than systolic CBF, since the stenotic increase in LAR limits the relatively high diastolic flow more than the relatively low systolic flow.

When the HR was increased to 160 b.p.m. in the presence of a constant ABP and constriction, further reduction of the distal resistance in the epicardial layers increased the difference between ABP and CBP and allowed coronary flow to increase to the same extent in both systole and diastole, sometimes with a further attenuation of the amplitude of the oscillations. These observations seem to confirm the importance of vasodilatation in reducing the systolic-diastolic flow differences.

The occurrence of an increase in flow, when a vasodilatory stimulus is acting on the coronary bed, in the presence of severe stenosis of a large epicardial artery, is a matter of controversy (e.g. Schwartz *et al.* 1981, Bristow *et al.* 1987). In particular the failure of an increase in heart rate to produce an increase in flow through the stenosis of a large coronary artery (Schwartz *et al.* 1981) can be attributed to the severity of stenosis as well as to other factors such as the aortic pressure, the extent of distal vasodilatation and the difference in pressure across the stenosis. In our experiments, the constriction was not severe enough to prevent the increase in flow resulting from the rise in HR.

The increase in LAR which follows the elevation of HR could be attributed to the distal vasodilatation which reduces the pressure beyond the stenosis, thus producing turbulence and energy dissipation. Berguer and Hwang (1974), Mates *et al.* (1978) and Walinsky *et al.* (1979) stress the role of the pressure difference in increasing a stenotic resistance.

In the present experiments, no evidence of deterioration of myocardial contractility was detected by observing the aortic flow and the rate of the systolic increase in LVP (dLVP/dt). Thus, although the amplitude of the systolic reduction of the flow in the absence of stenosis was demonstrated to be proportional to the myocardial contractility (Krams *et al.* 1989a,b), there was no support in our experiments for the hypothesis that reduced myocardial contractility is responsible for reducing the diastolic-systolic coronary flow differences after constriction. On the contrary, distal vasodilatation appeared as a result of the stenosis and was enhanced by tachycardia.

From these experiments, evidence is also provided in favour of the importance of the intramyocardial pump model for explaining some of the events observed in the coronary circulation (Spaan *et al.* 1981, Bruinsma *et al.* 1985, Spaan *et al.* 1986, Spaan and Dankelman 1989). According to this model, myocardial contraction increases the tissue pressure in deep myocardial layers, so that some coronary blood is pushed back towards the aorta. If the aortic pressure is low, the coronary-aortic flow exceeds the forward flow and a systolic backflow is seen. If the forward flow is not exceeded, only a reduction of the flow occurs in the systole. In both cases a systolic increase in the coronary pressure is produced by the intramyocardial pump. In our experiments, in the presence of the constriction the onset of the systolic rise of CBP occurs well before that of ABP and shortly after that of LVP, i.e. immediately after the beginning of the isovolumic contraction. This timing of the onset of the systolic rise of CBP serves as evidence for the role played by the rhythmic changes in ventricular tissue pressure in producing oscillations of the coronary pressure and movement of some blood from the endocardial layers towards the large epicardial vessels and the aorta. In addition to the epicardial vasodilatation, it may be suggested that the dependence of the systolic reduction of the flow on the intramyocardial pump mechanism also contributes to the attenuation of the diastolic-systolic coronary flow differences after the stenosis. If the intramyocardial

pump pushes some blood back towards the aorta during a systole, thus contributing to the systolic decrease in flow, the backward movement may be impaired by the stenosis, whilst the forward movement is less affected by the stenosis because of distal vasodilatation.

The possibility that a stenosis reduces the amplitude of the phasic oscillations of the coronary flow by impairing the retrograde effect of the intramyocardial pump is also suggested by the results of Spaan *et al.* (1981). However, in their experiments, care was taken to prevent the stenosis from reducing the mean coronary pressure and flow by altering the perfusion pressure. It may thus be assumed that no distal metabolic vasodilatation occurred. On the contrary, in our experiments the reduction of DCR and the proportional increase of both diastolic and systolic CBF after the increase in heart rate speaks in favour of the importance of distal epicardial vasodilatation in modifying the pattern of the phasic coronary flow in the presence of a flow limiting stenosis.

Conclusions

From the experimental results and theoretical considerations it appears that a severe flow limiting stenosis of a large coronary artery reduces the diastolic-systolic coronary flow differences by inducing distal epicardial vasodilatation and by preventing the backward effect on the flow the intramyocardial pump. No evidence was found that a reduction of myocardial contractility plays a role in the production of the observed changes.

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