Journal of Physiology (1989), **419**, *pp.* 703–715
With 4 text-figures
Printed in Great Britain

DYNAMIC RESPONSE OF THE CORONARY CIRCULATION TO A RAPID CHANGE IN ITS PERFUSION IN THE ANAESTHETIZED GOAT

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(*Received 6 June 1989*)

SUMMARY

1. We tested predictions of a mathematical formulation of a hypothesis of dynamic control of coronary blood flow by tissue oxygen tension.

2. The rate of change of adjustment of the coronary circulation to a step change in arterial perfusion was analysed in the cannulated main stem preparation of the anaesthetized goat. The variable studied was the ratio between driving pressure and coronary flow, each averaged per heart beat. The response of this ratio was measured following a sudden change in perfusion pressure with constant-pressure perfusion and a sudden change in flow with constant-flow perfusion.

3. The rate of change of the pressure–flow ratio was quantified by t_{50}, the time required to establish half of the completed response. For a pressure decrease t_{50} was $4{\cdot}9 \pm 0{\cdot}2$ s ($n = 35$) (mean $\pm$ S.E.M., n = number of individual measurements), $11{\cdot}3 \pm 1{\cdot}2$ s ($n = 25$) for a flow decrease, $14{\cdot}5 \pm 1{\cdot}6$ ($n = 34$) for a pressure increase and $25{\cdot}1 \pm 2{\cdot}3$ ($n = 19$) for a flow increase.

4. No effect of the level of flow or pressure on t_{50} was found for a decrease in perfusion. Furthermore, with a flow increase, the t_{50} value did not depend on the level of flow, which is in agreement with the outcome of earlier experiments where the response to a change in heart rate was measured. With a pressure increase, the mean t_{50} value of the pressure–flow ratio was lower at high perfusion pressure but the difference with low perfusion pressure was not significant ($P = 0{\cdot}11$)

5. The t_{50} value in the cases of an increase in pressure and flow are similar to those found for a change of heart rate in an earlier study.

6. Unlike step changes of metabolic rate, some of the measured responses to mechanical step changes were not predicted by the oxygen hypothesis. It is suggested that the increased rate of coronary adjustment induced by the reduction of coronary perfusion is due to arteriolar smooth muscle mechanics which apparently differ in strength depending on the direction of change of the arteriolar dimensions.

7. This suggestion is strengthened by the results of experiments in which smooth muscle responses were abolished with adenosine.

MS 7723

INTRODUCTION

Myocardial perfusion is usually well adapted to the metabolic needs of the myocardium (Eckenhoff, Hafkenschiel, Landmesser & Harmel, 1947; see among others Feigl, 1983). The pathways of the information signal responsible for this flow control are still unclear. In earlier studies we analysed (1) the steady-state relation between coronary flow on the one hand and oxygen consumption and perfusion pressure on the other (Drake-Holland, Laird, Noble, Spaan & Vergroesen, 1984; Vergroesen, Wieringa, Noble & Spaan, 1987*b*), and (2) the dynamic response of the coronary pressure–flow ratio to a sudden change in heart rate (Dankelman, Spaan, Stassen & Vergroesen, 1989). The results of these studies could be explained accurately on the assumption that tissue oxygen pressure is the controlled variable, that is, the control system is so designed as to keep this variable as independent as possible in the presence of perturbations in oxygen consumption and arterial pressure. This dynamic oxygen hypothesis also predicts the rate of change of the pressure–flow ratio in response to (a) a sudden change in perfusion pressure with constant-pressure perfusion and (b) a sudden change in flow with constant-flow perfusion.

The mathematical formulation of the hypothesis (model) predicts that (1) the rate of change will be slow with constant-flow perfusion; (2) it will be independent of the flow level; and (3) it will be faster with constant-pressure perfusion and dependent on the pressure level. Moreover, since the model is based on alterations of oxygen pressure in well-mixed compartments, the rates of change under these perfusion conditions due to alteration in either pressure or flow will be the same as with alterations in heart rate under the respective conditions. The present study was designed to test these predictions experimentally.

METHODS

Preparation

Seven goats weighing 16–24 kg were used for the present study. The goats were treated for worms using ivermectine (Ivomec, MSD, NJ, USA) 2 weeks prior to the experiment.

Three goats (first group) were anaesthetized, following sedation with 20 mg diazepam (4 ml Valium 10, Le Roche), by injection of ketamine hydrochloride (Aescoket, Aesculaap, 15 mg kg^{-1}) into the jugular vein. Subsequently, atropine sulphate (0·1 mg kg^{-1}) was administered through the same needle. Anaesthesia was maintained by continuous infusion of ketamine hydrochloride (24 mg kg^{-1} h^{-1}). Piritramide (Dipidolor, Janssen) was given intravenously as an analgesic, 3·2 mg before the left thoracotomy and 3·2 mg 4 h later.

The four other goats (second group) were anaesthetized by an intramuscular injection of a cocktail of 3 ml ketamine hydrochloride (Aescoket, 100 mg ml^{-1}), 3 ml Rompun (20 mg ml^{-1}, Bayer, FRG) and 4 ml atropine sulphate (0·5 mg ml^{-1}). Anaesthesia was maintained by intravenous injection of 50 ml fentanyl (0·05 mg ml^{-1}) and 2 ml pancuroniumbromide (Pavulon, Organon, Boxtel, the Netherlands, 2 mg ml^{-1}). Piritramide (Dipidolor, Janssen, Belgium) was given intravenously as an analgesic, 3·2 mg before the left thoracotomy and 3·2 mg 4 h later.

The goats were ventilated with a Harvard respirator using a 2:1 nitrous oxide–oxygen mixture.

A left thoracotomy was performed and the 3rd and 4th ribs removed. The pericardium was opened and a cradle formed. The left main stem of the left coronary artery was dissected and a ligature was placed around it. Another ligature was placed around the great cardiac vein, close to the junction where the left hemiazygos vein drains into the coronary sinus. If the great cardiac vein could not be cannulated, then the cannula was placed in the hemiazygos vein. The bundle of His was destroyed by local injection of formaldehyde (Steiner & Kovalik, 1986) and the right ventricle was

paced. A stainless-steel Gregg cannula was inserted into the aorta via a purse string. With continuous perfusion, the cannula was ligated into the left main coronary artery. A Herd–Barger catheter was inserted into the left anterior descending vein. Before any cannula was inserted, the goat was given heparin (3 ml, 5000 i.u. ml^{-1}, followed by a continuous infusion of 5000 i.u. h^{-1}).

Arterial perfusion/venous drainage system

The arterial perfusion system was essentially similar to the one described by Spaan, Breuls & Laird (1981). Blood from the left carotid artery was pumped into a 30 ml reservoir via a heat exchanger and filter (40 μm Pall, type SQ40S). A precision pressure regulator (Fairchild, model 10R) connected to a laboratory compressed-air system held reservoir pressure at a pre-set value. Perfusion pressure was measured at the cannula tip with a catheter (Braun FDR 1·1 × 1·7 mm) connected to a Hewlett–Packard (model 1280c) pressure transducer. An electromagnetic cannulating flow probe, interposed in the perfusion line, monitored coronary arterial flow (Statham 5 mm, model Sp2202). A clamp between flow probe and steel cannula could introduce a large resistance in the perfusion line giving the perfusion system the characteristics of a constant-flow source. In this case the pressure proximal to the resistance had to be increased to compensate for the pressure loss over the resistance. The blood reservoir was equipped with a level controller (M.S.A. automatic suction control) with feedback to the roller pump which kept the blood level in the reservoir constant.

In four goats blood from the cannulated great cardiac vein drained into a similar pressure-controlled reservoir (M.S.A.) via a 2·5 mm flow probe (Statham). The regulation of the venous pressure was adjusted to keep epicardial venous pressure, measured with the Herd–Barger catheter, as low as possible. Venous blood was pumped back into the left jugular vein via a heat exchanger and filter (40 μm Pall, type SQ40S). In the three other goats epicardial venous pressure was monitored but the great cardiac vein was not cannulated.

Measurements

Left ventricular, coronary arterial and epicardial venous pressure as well as coronary arterial and, when possible, coronary venous flow were continuously recorded on a Hewlett–Packard FM instrumentation recorder (HP 3968A) for analog back-up.

A/D conversion was carried out on-line with an Olivetti M24 PC equipped with a Teckmarboard and using the software package SALT (Fenster & Ford, 1985). Digitized data were stored on hard disc.

Haemoglobin content, pH, and arterial P_{O_2} and P_{CO_2} were measured every 30 min with an automated blood gas analyser (model ABL330, Radiometer). Arterial and coronary venous oxygen saturation were measured with a Hemoximeter (model OSM 2, Radiometer). At least twice during each protocol the perfusion line was clamped for more than 15 s to check the zero of the arterial flowmeter and to measure the peak reactive hyperaemic flow at maximal vasodilatation and the pressure at zero flow. This pressure value was considered to be the coronary wedge pressure (Spaan, Breuls & Laird, 1981).

After vasodilatation with adenosine, the arterial perfusion line was clamped again for 15 s to test whether reactive hyperaemia had disappeared. The infusion rate of adenosine was increased if necessary.

At the end of the experiment the weight of the perfused tissue was measured by injection of a mixture of gelatine and white paint (Latex) at 37 °C through the cannula into the left main coronary artery. After cooling in a freezer for approximately half an hour the coloured tissue could be dissected and weighed.

Protocol

With constant-pressure perfusion, the perfusion pressure was altered stepwise from 80 to 100 to 120 to 140 and down again. This was done for different heart rates (80–120 beats min^{-1}). With constant-flow perfusion, flow was altered stepwise in such way that the initial pressure step change had the same order of magnitude as with constant-pressure perfusion. The flow step changes were performed starting from different levels of flow and at different heart rates (80–120 beats min^{-1}). A steady state was achieved before and after every step in either pressure or flow.

Pressure and flow steps were also performed after vasodilatation, but in this case only between three levels of pressure (35–50–65 mmHg).

Data analysis

All signals were digitized on-line at a sample rate of 80 Hz for 100 s starting 15 s before the step change in perfusion. The response of the coronary bed was analysed as described by Dankelman *et al.* (1989), although no volume changes were calculated. The changes in volume, which could be determined from the digitized flow signals as described by Vergroesen, Noble & Spaan (1987*a*), were too small to be calculated accurately. In three goats it was not possible to cannulate the great cardiac vein and venous flow could not be measured. Coronary arterial pressure and flow were averaged per beat. The data with constant-flow perfusion were only analysed when perfusion pressure (averaged per beat) was above 50 mmHg to ascertain normoxic conditions of the heart. The coronary pressure–flow ratio (P/Q) was calculated as the quotient of mean driving pressure and mean arterial flow, calculated over each heart beat defined by the period between the onset of two diastoles. This onset is by definition the moment when left ventricular pressure falls below a threshold of 15 mmHg. Driving pressure is defined as the difference between coronary arterial pressure and wedge pressure. The wedge pressure is the coronary peripheral pressure after 10 s of arterial occlusion. The coronary pressure–flow ratio reflects resistance only in the steady state or under conditions where flow and/or pressure vary so slowly that capacitance effects can be neglected.

The t_{50} values were defined as the time in seconds after the step in perfusion at which the pressure–flow ratio had changed by 50% of its total final change. This value was calculated by linear regression over a period of 10 s in the range around the 50% value of the pressure–flow ratio. This range was delineated by eye on the computer screen.

To compare the time course of the responses to the different interventions, the pressure–flow ratio (P/Q) was normalized. For this P/Q was averaged over 15 s prior to the intervention yielding $(P/Q)_0$, and over 15 s when the steady state was reached after the intervention yielding $(P/Q)_1$. The normalized response of pressure–flow ratio ($(P/Q)_n$) was then given by:

$$(P/Q)_n = \frac{P/Q-(P/Q)_0}{(P/Q)_1-(P/Q)_0}.$$

The normalized response, $(P/Q)_n$, determined per beat varies from zero at the start of the intervention to unity when steady state is reached and allows the comparison of the course of the pressure–flow response, regardless of intervention.

The pressure–flow ratio and therefore the normalized response is not a continuous variable but only known once every beat. In order to make the averaging of normalized responses at different heart rates possible, the following was done. It was assumed that the pressure–flow ratio was defined at the beginning of a heart beat period. Then, this ratio was calculated for the intermediate time at 0·0125 s intervals by linear interpolation. At these intervals the average response over all heart rates could be determined.

Statistical significance was tested using Student's t test.

RESULTS

Typical results during a pressure change with constant perfusion are depicted in Fig. 1. With an increase in perfusion pressure (right-hand panel) the coronary flow increased immediately, followed by a slow decrease indicating vasocontriction. With a decrease in perfusion pressure (left-hand panel) flow first decreased, then increased indicating vasodilatation. The response of flow after a pressure decrease showed oscillation which was never the case with a pressure increase. The course of the response can be compared by the normalized response of the pressure–flow ratio. It should be noted that in dynamic conditions this pressure–flow ratio need not to be equal to resistance because of compliance effects. At both interventions the normalized responses exhibit an initial reversed phase. Further, the courses of the responses are quite different. With a pressure step up, the normalized response gradually increases to the new steady state after an initial dip. However, with the

pressure decrease, the response changes faster than with the pressure increase. Moreover, the normalized response exhibits an overshoot and approaches the new steady state with some oscillations.

Table 1 gives the averaged pressure and flow values before and after the step. One can see that the flows and the pressures are in the same ranges regardless of the perfusion system used.

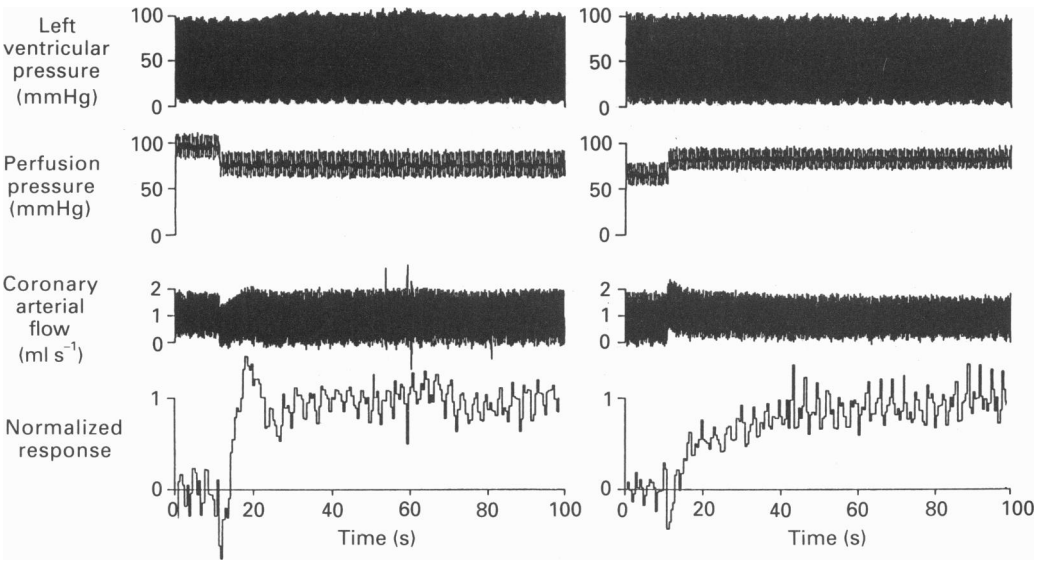

Fig. 1. Typical recordings obtained during the course of a step change in perfusion pressure. Left panel depicts the signals after a pressure decrease and right panel after a pressure increase. Lower panels: normalized response of pressure–flow ratio.

TABLE 1. Initial and final control values of coronary arterial perfusion pressure (mmHg) and flow (ml s^{-1} (100 g)$^{-1}$). Mean ± S.E.M.

	Perfusion pressure		Arterial flow	
	Initial	End	Initial	End
Pressure step up	85·2 ± 3·1	103·9 ± 3·0	1·20 ± 0·05	1·30 ± 0·06
Pressure step down	103·1 ± 3·0	83·8 ± 3·0	1·32 ± 0·05	1·18 ± 0·05
Flow step up	82·6 ± 4·7	111·0 ± 5·3	1·15 ± 0·10	1·30 ± 0·12
Flow step down	112·7 ± 4·8	81·1 ± 5·1	1·19 ± 0·10	1·04 ± 0·08

The responses of pressure–flow ratio, regardless of the level of perfusion pressure or level of flow, were grouped according to the perfusion conditions and the direction of change of pressure and flow. The averaged responses of those four groups are depicted in Fig. 2. The averages response with constant-pressure perfusion looks similar to the single responses shown in Fig. 1 apart from oscillations after the overshoot. This is due to the fact that oscillations in the different individual responses do not have the same frequency and are not in phase. With constant-flow

perfusion, the rate of response is also faster with a decrease than with an increase in flow (right panels). However, the responses at constant-pressure perfusion are faster than with constant-flow perfusion for the same direction of perfusion change. The t_{50} values are reported in Table 2. These numbers underline the differences in the rate

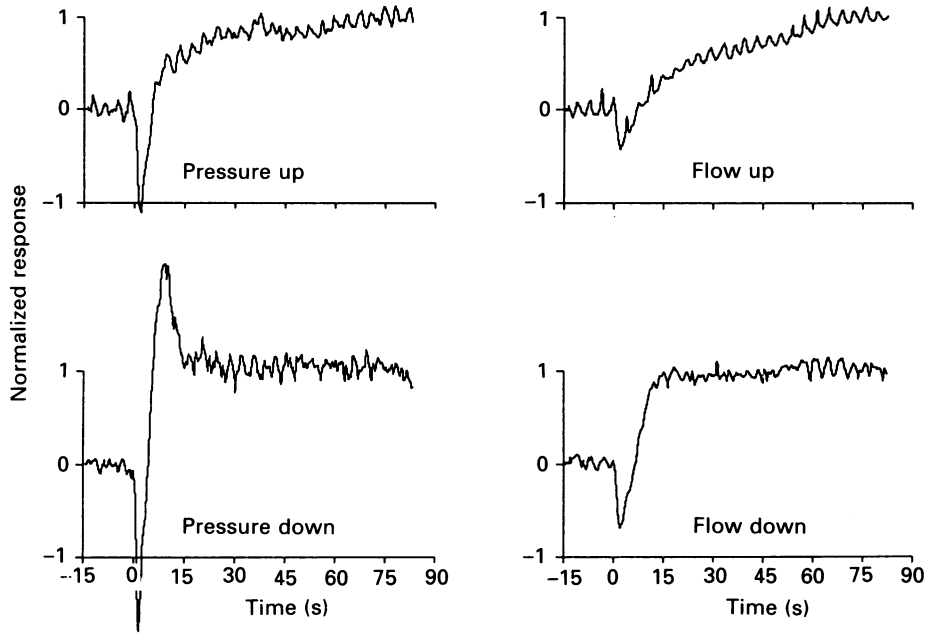

Fig. 2. Summary of the dynamic change of normalized pressure–flow ratios as a result of pressure and flow step changes. Left panels depict the results with a pressure source and right panels with a flow source. Upper panels show the averaged results of all experiments with a step up in pressure and flow, respectively, and the bottom panels show the results with a step down. Numbers and t_{50} values related to these panels are provided in Table 2 (left-hand column).

TABLE 2. t_{50} values, the time in seconds after a step in perfusion pressure or flow at which the coronary index has changed 50% of its final change (mean ± S.E.M., n in parentheses)

	t_{50}	Heart rate < 90 beats min^{-1}	Heart rate $\geqslant 90$ beats min^{-1}
Pressure step up	14·5 ± 1·6 (34)	16·2 ± 2·3 (18)	12·6 ± 2·2 (16)
Pressure step down	4·9 ± 0·2 (35)	5·2 ± 0·2 (22)	4·5 ± 0·4 (13)
Flow step up	25·1 ± 2·3 (19)	27·9 ± 3·4 (10)	22·1 ± 2·7 (9)
Flow step down	11·3 ± 1·2 (25)	14·0 ± 2·1 (12)	8·8 ± 0·5 (13)

of change of pressure–flow ratio, dependent on perfusion conditions and the direction of stimulus change. Table 3 gives the t_{50} values grouped according to levels of flow and perfusion pressure measured before the perfusion step. Note that the rate of response seems only perfusion level dependent with an increase in pressure perfusion, however, the difference is not within the statistical significance range ($P = 0{\cdot}11$).

In order to establish the purely mechanical effects of a change in pressure and flow on the normalized response, the experimental protocol was repeated after coronary vasodilatation with adenosine. The normalized responses were grouped in a manner analogous to that of the protocol with regulation intact. In order to facilitate comparison of the results obtained with regulation intact and abolished, the normalized indices with vasodilatation were multiplied by -1 (Fig. 3). In all four cases the normalized response showed an initial undershoot.

TABLE 3. t_{50} values, the time in seconds after a step in perfusion pressure (at low and high level) or flow (at low and high level) at which the coronary index has changed 50% of its final change (mean ± S.E.M., n in parentheses)

	t_{50} Low perfusion	t_{50} High perfusion
Pressure step up	12·1 ± 2·1 (18)	17·2 ± 2·3 (16)
Pressure step down	4·9 ± 0·2 (19)	5·0 ± 0·3 (16)
Flow step up	26·1 ± 2·1 (7)	24·6 ± 3·4 (12)
Flow step down	11·7 ± 2·1 (12)	10·9 ± 1·2 (13)

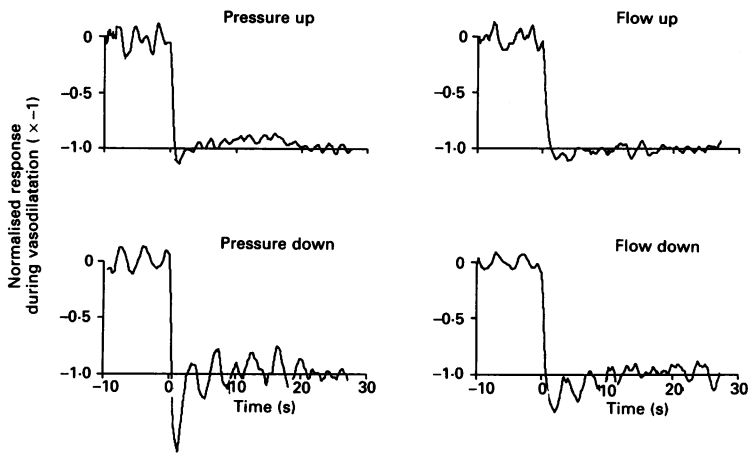

Fig. 3. Summary of experiments with vasodilatation. The panels show the averaged courses of the normalized pressure–flow ratio with a pressure source (left panels) and a flow source (right panels) obtained during vasodilatation. The normalized pressure–flow ratio was multiplied by -1 to facilitate comparison with the responses in the autoregulated bed. Upper panels are the results obtained with an increase in pressure ($n = 23$) and flow ($n = 22$), respectively. Lower panels show the results after a decrease in pressure ($n = 26$) and flow ($n = 24$).

In four goats ($n = 70$) the difference in oxygen consumption, before the change in stimulus and after a steady state was reached again, was measured using the method described by Vergroesen *et al.* (1987*b*). No difference was detected and, hence, it was likely that the responses to changes in perfusion conditions were not initiated by a change in metabolism.

No significant difference was observed for the t_{50} values of the first group of goats

and the second group, which followed a different anaesthesia procedure, except in the case of a pressure step down with constant-pressure perfusion. The t_{50} values for this case were $5{\cdot}3 \pm 0{\cdot}1$ and $4{\cdot}4 \pm 0{\cdot}4$ s for the respective two groups of goats.

DISCUSSION

The experimental results show clearly that the rate of change of the pressure–flow ratio depends on the perfusion conditions (constant-pressure *versus* constant-flow perfusion) and the intervention (increase or decrease of perfusion). Some measurements on the response to coronary inlet changes have been reported in the literature especially with constant-pressure perfusion. These earlier results are in agreement with those presented here. Driscol, Moir & Eckstein (1964) illustrated the difference between responses of coronary flow to a sudden increase and decrease of perfusion pressure. Oscillation of flow was observed only with a pressure decrease but disappeared with hypoxia. Granger, Goodman & Granger (1976) showed, however, the persistence of oscillations during mild hypoxia. Mosher, Ross, McFate & Shaw (1964) found oscillations of flow after both an increase and a decrease in perfusion pressure. A similar difference in response between an arterial pressure decrease and increase was found in the skeletal muscle by Mellander, Maspers, Björnberg & Anderson (1987). Oscillations in flow in response to a sudden pressure decrease are present in the flow tracing of Fig. 1 (left panel). However, no oscillations are apparent in the lower left-hand panel of Fig. 2 which represents the average response of thirty-five pressure steps. This is due to the variation in frequency of these oscillations in the different interventions. Dole & Nuno (1986) reported a more rapid adjustment of coronary flow to a pressure-step decrease at higher levels of oxygen consumption. This is consistent with our finding that the t_{50} value is smaller for heart rates higher than 90 beats min^{-1} than for heart rates below this value (Table 2). van Huis, Sipkema & Westerhof (1985) measured the response of arterial pressure to a step change in flow with constant-flow perfusion. They showed that pressure in the first second changed and then remained constant for about 4 s before regulation started. This plateau has not been found in our experiments.

In an earlier study (Dankelman *et al.* 1989) the rate of change of the pressure–flow ratio to a change in heart rate for different perfusion conditions could be described with a dynamic control model based on the maintenance of constant tissue oxygen pressure. The reader is referred to that paper for a detailed description of this model. Summarized, the model assumes a linear relation between tissue oxygen pressure and coronary resistance: a reduction in P_{O_2} results in a resistance decrease and an increase in P_{O_2} in a resistance increase. Tissue P_{O_2} in the model can be perturbed by changing either oxygen consumption or flow. When changing the oxygen consumption an increase will lower P_{O_2} resulting in a vasodilatation. For a change of flow, a reduction either forced during flow-controlled perfusion or by reducing perfusion pressure, will decrease tissue P_{O_2} due to a lowered oxygen supply and will result in vasodilatation as well. This model predicted that the response of the pressure–flow ratio to a heart rate step was faster with constant-pressure perfusion than with constant-flow perfusion. Furthermore, the response was only dependent on the level of perfusion in the case of constant-pressure perfusion. These model predictions were confirmed by our experimental results (Dankelman *et al.* 1989).

If the change in perfusion pressure or flow should stimulate the same control mechanism responsible for metabolic flow adjustment, one would expect that our oxygen model should predict the rate of the responses to a change in perfusion as well. However, this appeared not to be the case. In particular the direction sensitivity of the response cannot be explained with the model. The model

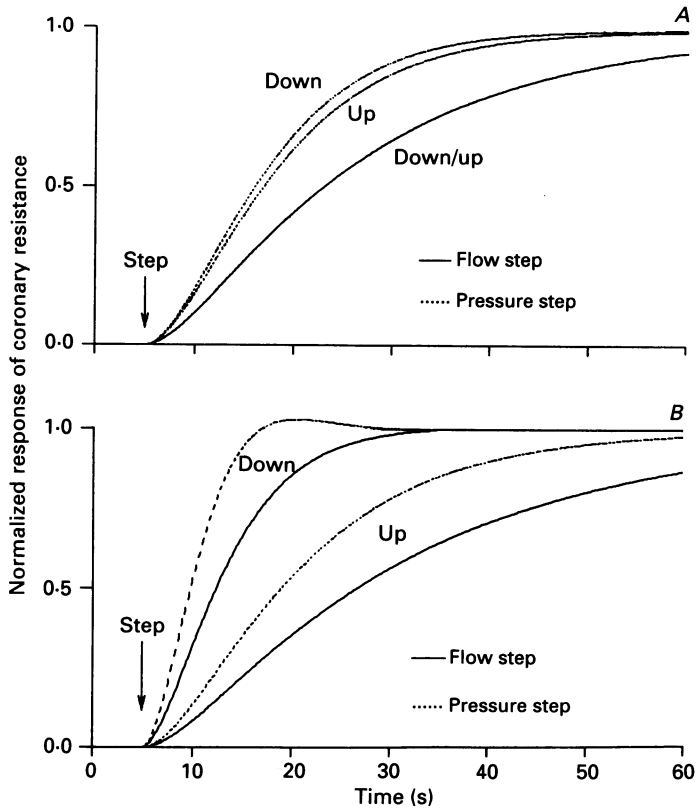

Fig. 4. Model simulation of the regulation of coronary resistance. *A*, simulations with the original model. Continuous line is the normalized response of coronary resistance to a step up and down in the level of flow. Interrupted lines are simulations of results from a pressure source. A step down in pressure perfusion showed faster response than a step up. With flow perfusion there is no difference in rate of response. *B*, modified model in which the rate of smooth muscle change has a half-time of 5 s with a decrease in tissue oxygen concentration and a half-time of 25 s with an increase. As seen in the figure the response with a pressure source (interrupted lines) showed an overshoot after a decrease in pressure. The response to a decrease in flow (continuous lines) is faster than with an increase in flow.

predictions are depicted in Fig. 4*A*. The rate of response is slightly dependent on the direction of change in the simulation with constant-pressure perfusion, but its magnitude is much smaller than that found experimentally. With constant-flow perfusion there is no direction sensitivity in the response, in contrast with the experimental finding. This discrepancy between model and experimental findings suggests that with the dynamic response to a perfusion perturbation an additional mechanism might be involved besides those active during responses to a perturbation of metabolism. As a trial, in our model we made the rate of change of resistance to

a change in tissue oxygen pressure dependent on the direction of resistance change. With this modification the model predicted responses as shown in Fig. 4*B*. The rate of change of the responses under the different perfusion conditions was now in the same order as found experimentally. Obviously, the model with a direction sensitivity for the resistance response will also predict a direction sensitivity with the coronary adjustment to a change in metabolism. However, such a strong directional sensitivity was not found, and this illustrates that a directional sensitivity must be coupled to a mechanical stimulus. In other words, a rapid reduction in arteriolar diameter would make smooth muscle cells more sensitive to a change in a metabolic parameter than a sudden increase in arteriolar diameter. It is obvious to look for such a mechanism in the mechanics of arterial smooth muscle tone, in particular the myogenic mechanism.

The myogenic mechanism was first described by Bayliss (1902) who reported that the arterial diameter responded to a sudden pressure increase first by an increase in arteriolar diameter followed by a constriction, the end diameter was smaller than before the pressure step. A myogenic response has since been demonstrated in different preparations (Sparks, 1964; Speden, 1973; Johanson & Mellander, 1975; Grände, 1979; Grände, Borgström & Mellander, 1979*a*; Borgström, Grände & Lindbom, 1981; Borgström, Grände & Mellander, 1984). These studies have been reviewed by Johnson (1980). Recently the possibility for the myogenic mechanism in the coronary circulation has been reviewed by McHale, Dube & Greenfield (1987). Because of interactions of smooth muscle tone with metabolism, intramyocardial compliance and/or poorly controlled perfusion conditions, conclusive evidence could not be found. Furthermore, the direction sensitivity of the myogenic response needed to explain our results has not been emphasized in other studies on myogenic response with the exception of Grände & Mellander (1978). Although some models on myogenic response have been presented (Johnson, 1980; Borgström, Grände & Mellander, 1982), an element able to describe the direction sensitivity is, to our knowledge, not available.

One may argue that the myogenic response coupled to sensitivity for a metabolic stimulus is indeed speculation and that it is more likely to be a purely mechanical response to stretch or relaxation of smooth muscle. In our experiments the flow step was dimensioned such that the initial pressure step related to this flow step was in the same order as the pressure step with constant-pressure perfusion. Hence, the initial mechanical stimulus for the myogenic response would be similar for both perfusion conditions while the rate of response with constant-pressure perfusion is faster than with constant-flow perfusion. This finding suggests that flow in itself is also playing a role in the phase of rapid myogenic response. It is unlikely that this flow effect is mediated by an endothelial flow-dependent factor (Landsman, 1988; Griffith, Edwards, Davies, Harrison & Evans, 1987). The studies describing the flow effect on arteriolar resistance show a dilator response resulting in a flow increase. We find a dilator response to a flow reduction. Hence the hypothesis of a directional rate sensitivity of the myogenic mechanism resulting from a metabolic stimulus is not ruled out but deserves further testing.

The myogenic mechanism is the sequence of events resulting in a vasodilatation after a decrease in diameter resulting in a pressure decrease. The decrease in arteriolar diameter with a pressure decrease, and diameter increase with pressure

increase can be inferred from the initial dip in normalized response after a sudden change in pressure induced either directly or indirectly by changing flow. This decrease can be explained by a combination of capacitance effects and change in resistance due to a change in arterial pressure. In order to establish the purely mechanical effects related to a change in perfusion pressure or flow, the protocol was repeated after pharmacological vasodilatation. As is clear from the results summarized in Fig. 3 there is a steady change of pressure–flow ratio when perfusion pressure is changed. This illustrates that the initial dip in response with regulation intact is not purely compliant in nature. It is noteworthy, however, that as was the case with the experiments with the heart rate change, there is an effect related to preceding events. The change in response exhibits an overshoot, more pronounced with constant-pressure perfusion than with constant-flow perfusion. The time that steady state is reached is somewhat longer than to be expected from capacitance effects with a time constant of 1·5 s (Vergroesen *et al.* 1987*a*). However, it might well be that mechanical effects determining resistance require some time to come to rest after a change in perfusion pressure.

The possibility that the Gregg effect (Gregg, 1963) was playing a role in our experiments was checked in four goats in which the oxygen consumption was measured in the steady state before and after the change in perfusion level. The differences in oxygen consumption could not be detected with our method. The absence or smallness of the Gregg effect in our present experiments might be due to the relatively small pressure changes involved.

A directional effect on rate of change of pressure–flow ratio induced by a change of heart rate has been reported but not interpreted by Belloni & Sparks (1977) and Dankelman *et al.* (1989). With a sudden heart rate increase the response was faster than with a heart rate decrease (Table 2 of Dankelman *et al.* 1989). This can now be interpreted as an effect of direction of change of transmural pressure at least of the vessels in the sub-endocardium. An increase in heart rate increases average tissue pressure and consequently decreases transmural vascular pressure. Transmural vascular pressure decreases also for an arterial pressure decrease, which elicited the more rapid response of pressure–flow ratio. The difference in response rate between heart rate increase and decrease is small (in the order of 12%). Alterations in tissue pressure, however, will be much stronger in the sub-endocardium than in the sub-epicardium. Hence a larger difference in response rate of the sub-epicardium.

There is an agreement between t_{50} values for a heart rate decrease with those obtained with pressure and flow increase. However a discrepancy is seen between the t_{50} values for a heart rate increase and the t_{50} values obtained with pressure and flow decrease. This strongly suggests that in the coronary circulation the myogenic effect is only of importance to increased rate of adjustment for a decrease in vascular transmural pressure. Such a mechanism may be functional since it reduces the time of possible underperfusion due to a sudden decrease of arterial pressure or increase of sub-endocardial tissue pressure.

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