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Continuous control of the lumen of feline conduit arteries by blood flow rate

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SUMMARY Dilatation of conduit arteries induced by increased blood flow was studied in feline femoral, common carotid, or renal arteries. The outer diameter of the arteries perfused under stabilised transmural pressure conditions was continuously measured with a contact capacitance type transducer. A rise in blood flow rate was shown to induce arterial dilatation, the magnitude of which depended linearly on the extent of flow increase over a wide range of flow rates (usually from 10-15 to 35-50 $ml \cdot min^{-1}$). Increase in flow above this range caused a smaller increase in diameter followed by a plateau phase. The maximal (mean(SEM)) flow induced increase in arterial diameter was 25.8(2.8)% for the femoral, 25.5(2.2)% for the common carotid, and 24.6(5.1)% for the renal artery. This dilatation almost completely compensated for the increase in flow, causing a practically unchanged pressure difference along the arteries. A pronounced dilator response to an increase in blood flow rate as small as 1 $ml \cdot min^{-1}$ could be recorded for all flow rates where the diameter-flow relation was linear. Flow induced dilatation persisted during perfusion with a solution free of vasoactive substance. Thus in the arterial wall some mechanism provides effective continuous control of the lumen and, consequently, hydraulic resistance of the arteries in response to increases in blood flow.

An increase in blood flow in conduit arteries is accompanied by their dilatation. This response was first reported by Schretzenmayr in cat femoral artery during contractions of the calf muscles.[1] Since the response had failed to be reproduced after isolation of the artery from the calf[1–3] it had been attributed to a hypothetical peripheral conducting mechanism. However, having found that the dilatation persisted after dissection of the distal part of the femoral artery, Lie and colleagues considered it to be a local response.[4] They regarded an increase in blood flow to be the cause of the dilatation. This conclusion has been confirmed by Smiesko and colleagues, who established that the increase in blood flow caused dilatation of the dog gracilis artery independently of the changes in transmural pressure,[5 6] thus rejecting the proposal of others for a possible role of Bayliss' myogenic response.[7] Since then a dilatation induced by an increase in blood flow was demonstrated in the saphenous, jejunal, thyroid,[8] coronary,[9 10] and internal carotid[11] arteries of the dog. Recently, the dilatation has been shown to be endothelium mediated.[10 12–14]

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The functional significance of flow induced dilatation is determined by its magnitude. The increase in arterial diameter induced by a large increase in flow has been shown in most studies to be about 3-10%. Such dilatation would not reduce arterial hydraulic resistance to any great extent, and the functional significance of this reaction still remains unclear. At present it is also unknown whether the dilatation occurs at a high blood flow rate only or whether the arterial lumen is being continuously adjusted to the blood flow rate.

The first aim of the present study was to determine the magnitude of the dilatation in cat conduit arteries caused by an increase in flow within the physiological range and to establish whether the dilatation occurred at high blood flow rates only or whether there was continuous control of the arterial hydraulic resistance by the blood flow rate. For this purpose the external diameter of one of three arteries — left femoral, renal, or common carotid — was continuously measured under different flow rates and stabilised perfusion pressure. Pressure stabilisation was essential since changes in arterial diameter in response to small increases in flow rate may be indistinguishable from fluctuations in diameter caused by systemic pressure changes.

Our second aim was concerned with the mechanism of arterial flow sensitivity. Since previous workers concluded that the response was a local one[4] and ignored a possible role of blood borne humoral factors we attempted to determine whether the flow induced dilatation was a truly local arterial response persisting during the perfusion of feline conduit arteries by using solutions free of vasoactive substances.

Material and methods

Experiments were performed on cats of either sex weighing 2.0-4.5 kg, anaesthetised with intravenous urethane (0.6 g·kg^{-1}, Sigma) and chloralose (40 mg·kg^{-1}, Merck). The animals were intubated to ensure a free airway. The right femoral or carotid artery was connected with an electromanometer (BMT-301, RFT) for monitoring systemic pressure.

SURGICAL PROCEDURE

The cervical part of the common carotid artery or the whole femoral artery was exposed after longitudinal incision of the skin. All the side branches of the artery were ligated. A segment in the middle of the artery, 4-5 mm in length, was freed from surrounding tissues before measurement with the diameter transducer. After heparin administration (1500 U kg^{-1} iv, Gedeon Richter) the proximal and distal ends of the artery were cannulated and connected to the perfusion system (fig 1). The incised skin was tied to a thick wire frame and the cavity formed was filled with Krebs-Henseleit solution, with the temperature maintained at 35.5-36.5°C using a heating lamp.

The left renal artery and a 2 cm segment of the aorta distal to the origin of the renal arteries were exposed after the abdomen was opened and the intestines extirpated; the right renal artery was ligated. After heparinisation the left renal artery just before its bifurcation was cannulated and connected with the right femoral vein. The aorta was ligated just upstream and 2 cm downstream of the renal arteries. A T piece cannula connected to the outlet of the perfusion pump (see below) and to an electromanometer was introduced into the aorta just distal to the renal arteries. The inlet of the pump was connected to the right common carotid artery. To minimise displacement of the renal artery due to respiratory movements the animals were immobilised with succinilcholine-chloride (0.15 mg·kg^{-1}·min^{-1}, iv, Germed) and ventilated artificially. The respiratory rate was 30 per min and the inspiratory volume was adjusted in relation to animal body weight according to the

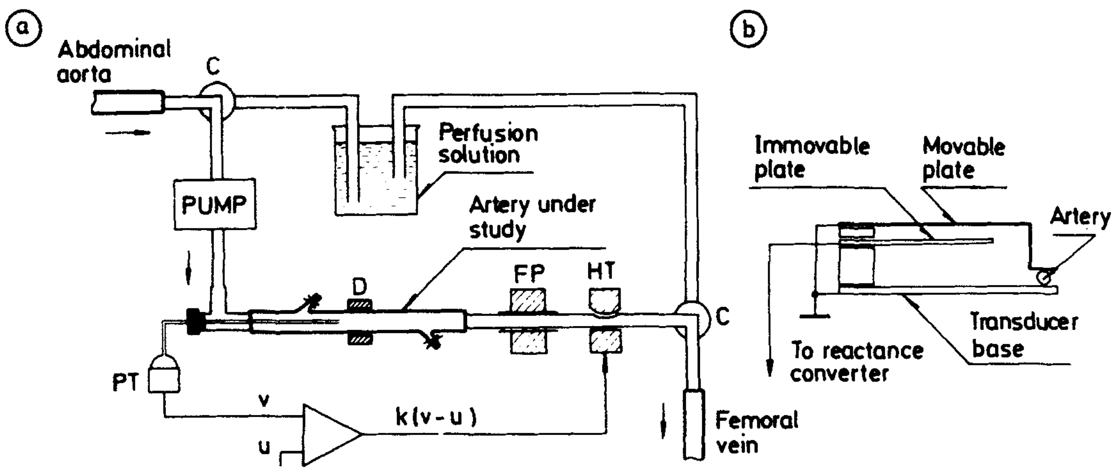

FIG 1 *(a) Schematic drawing of experimental arrangement for recording flow induced dilatation of femoral artery. PT=pressure transducer; FP=flow probe; D=displacement transducer for the arterial diameter measurements; HT=electrohydraulic throttle; C=three way stopcocks, shown in a position corresponding to blood perfusion. (b) Diagram of capacitive transducer for measuring arterial diameter. Width of each plate=3 mm, thickness of upper plate=0.05 mm. Force exerted on artery by upper plate is <50 mg, which is negligible compared with tension in arterial wall.*

nomograms of Kleinman and Radford.[15] The abdominal cavity was filled with Krebs-Henseleit solution, the temperature of which was maintained at 37(0.5)°C.

PERFUSION PRESSURE STABILISING SYSTEM

The pressure in the artery under study was stabilised with a custom made automatic servosystem (fig 1a).[16] The proximal end of the artery was connected via a T branch cannula to the perfusion pump (PN-4).[17] A movable metallic catheter (outer diameter 0.4 mm) inserted into the artery through the cannula was connected to an electromanometer (Statham P23Db) for measuring pressure near the site of the diameter measurement. The voltage V from the manometer was compared with the voltage U, which is proportional to assigned pressure in the artery. The amplified error signal (V-U) is fed to the electrohydraulic throttle controlling the lumen of a thin walled rubber tube located between the artery and the vein. The hydraulic resistance of the tube is changed so as to maintain pressure in the artery at a virtually constant level. (The system provides pressure stability within 2.5 mmHg.)

MEASUREMENTS OF ARTERIAL DIAMETER

The outer diameter of the artery was measured with a contact capacitance type transducer,[18] which was a plane capacitor with a movable upper plate (fig 1b). The artery was placed on the immovable base of the transducer and the upper plate touched the artery from above. Dilatation of the artery causes a decrease in transducer capacitance, which is transformed to an increase in voltage with the aid of a reactance converter (Disa Electronics, 51E01).

EXPERIMENTAL PROTOCOL

After preparation the blood flow rate was set at 10-15 $ml \cdot min^{-1}$ for the femoral artery, 15-20 $ml \cdot min^{-1}$ for the common carotid artery, and 20-25 $ml \cdot min^{-1}$ for the renal artery under 100 mmHg perfusion pressure, and the vessel was allowed to stabilise for 30 min. The pump output was then increased steeply to 40-60 $ml \cdot min^{-1}$ for 60-150 s and the changes in diameter determined. If the increase in arterial diameter was <5% of its ongoing value and did not increase for 1 h the experiment was abandoned as technically unsuccessful. If the increase in diameter was >5% one of three experimental protocols was used.

In the first protocol the dependence of the magnitude of flow induced response on the transmural pressure was determined on 8 femoral and 12 carotid arteries. The dilator responses of the arteries caused by an increase in flow from 10 to 40 $ml \cdot min^{-1}$ were measured at different transmural pressures from 60 to 160 mmHg at steps of 20 mmHg. At each pressure four measurements were made (two when pressure was increased from 60 to 160 mmHg and two when it was decreased).

In the second protocol the rate of blood flow in the artery was increased stepwise from its initial value to 45-60 $ml \cdot min^{-1}$ with a step of 5 or 10 $ml \cdot min^{-1}$ each lasting 60-100 s (the intervention was repeated 2-5 times). From these measurements the diameter-flow relation was determined. The pump output was then increased by 1 $ml \cdot min^{-1}$ starting from different initial flow rates and the diameter changes were recorded. At the end of each experiment 2 ml of 2% papaverine (Gedeon Richter) was applied to the artery to determine its maximal diameter; this allowed arterial smooth muscle tone to be assessed. After the experiments the 2-3 cm segment of artery was excised, blotted with filter paper, and weighed on a torsion balance. Assuming the density of the wall material to be 1.05 $g \cdot cm^{-3}$, the internal diameter was calculated using the values for the outer diameter and the volume of the unit length of the wall. This protocol was applied in 40 cats (on 14 femoral, 18 common carotid, and 8 renal arteries).

The third protocol was used to determine whether arterial dilatation could be induced by an increase in flow rate of a plasma substituting solution free of vasoactive substances. For this purpose the plastic tube from the hydraulic throttle was disconnected from the vein and the inlet tube of the pump was connected to a thermostabilised flask containing perfusion fluid. The connections and artery were washed out for 5-10 min and then a closed perfusion system was created. The temperature of perfusate on entry into the artery was maintained at 37(0.5)°C. The changes in arterial diameter associated with an increase in perfusate flow were recorded and compared with the blood perfusion values. All measurements were made at a virtually unchanged pressure in the artery of 100 mmHg. Each hour the solution in the flask was changed to a fresh one. This protocol was applied to 16 femoral and 11 common carotid arteries.

PERFUSION SOLUTIONS

The arteries were perfused with Krebs-Henseleit bicarbonate solution of the following composition (in $mmol \cdot litre^{-1}$): NaCl 115.0; KCl 5.0; $CaCl_2$ 2.1; $NaHCO_3$ 25.0; NaH_2PO_4 1.2; $MgSO_4$ 1.2; $CaNa_2EDTA$ 0.026; glucose 5.5. The solution was saturated with 95% O_2 and 5% CO_2 at 10°C. Serum bovine albumin (2 g, Sigma) was added to 100 ml of the solution to preserve the arterial myogenic regulation.[19] As albumin bonds calcium, its physiological concentration was maintained by adding calcium chloride in accordance with Baker and colleagues.[20] The viscosity of the solution was increased to resemble that of blood by adding 5% of dextran (molecular weight $6\text{-}9 \cdot 10^4$, Fluka), or of ficoll

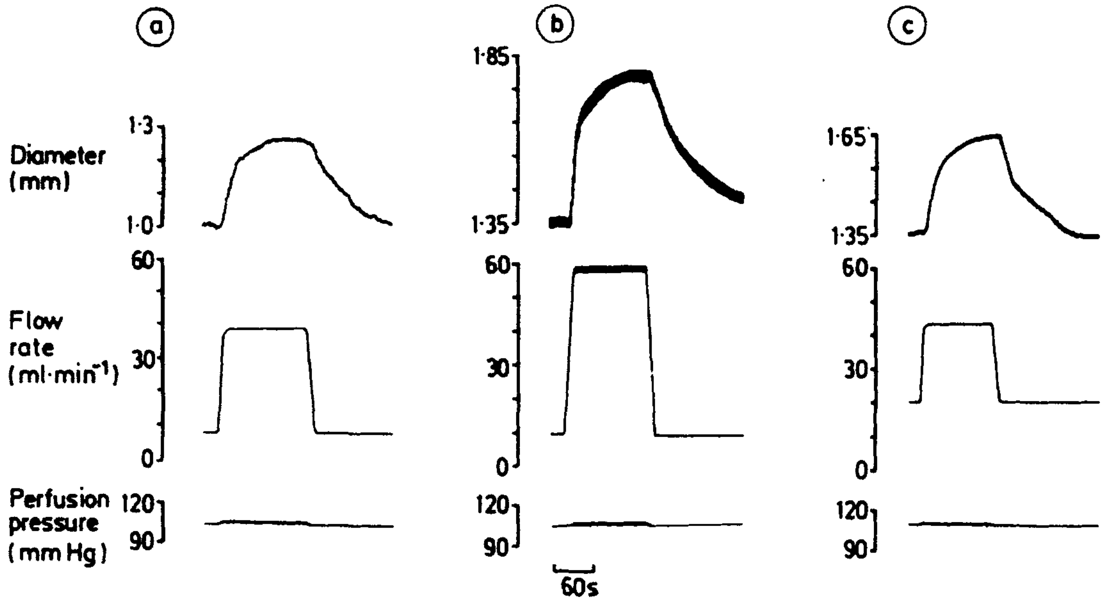

FIG 2 *Dilator responses of femoral (a), common carotid (b), and renal (c) arteries to a steep increase in bloodflow rate.*

(molecular weight $4\cdot10^5$, Serva), or 4% gelatine (Merck). The pH of the solution at 37°C was 7.4 and increased without aeration to 7.6 during 1 h. In some cats pituitrin (0.05-0.5 IU, Spofa) or L-phenylephrine (0.1 mg, Serva) were added to 100 ml of the solution to increase arterial smooth muscle tone.

RECORDINGS

The signals from a reactance converter (arterial diameter), electromagnetic flowmeter (RKE-1) (the rate of flow), and electromanometers (perfusion and systemic pressure) were recorded on two dual channel recorders (KSP-4).

STATISTICS

Results are presented as mean(SEM).

Results

The responses of cat femoral, common carotid, and renal arteries to steep increases in blood flow are shown in fig 2. Since the transmural pressure was stabilised and the arteries were disconnected from both central and peripheral vascular beds these dilator responses were evidently induced by an increase in flow rate. These results suggest that flow induced dilatation is an inherent property of feline conduit arteries.

DEPENDENCE OF FLOW INDUCED DILATATION ON TRANSMURAL PRESSURE

Hilton noted that the magnitude of the dilator response of feline femoral artery after tetanic contraction of the calf muscles usually increased when the systemic arterial pressure was raised.[3] However, such a tendency was not found in our preliminary experiments when we attempted to increase a flow induced response by increasing the systemic pressure. We then examined the dependence of the magnitude of the dilatation, caused by an increase in flow rate from 10 to 40 ml·min^{-1}, on the transmural pressure (fig 3). The dilator response was maximal at a transmural pressure of 80-100 mmHg (that is, at the range of mean systemic pressure in the cat at rest). Both an increase and a decrease of transmural pressure beyond this

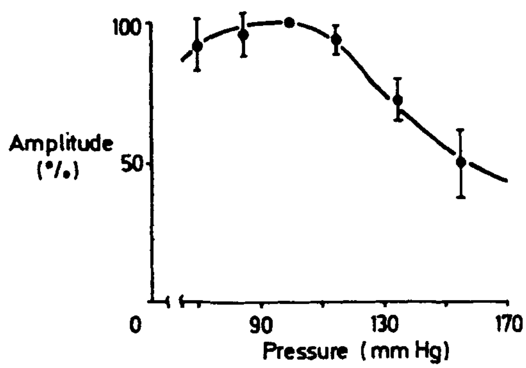

FIG 3 *Relation of amplitude of femoral artery dilator response caused by increase in bloodflow rate from 10 to 40 ml·min^{-1} to transmural pressure. (Magnitude of response at 100 mmHg = 100%.)*

TABLE *Characteristics of arterial dilatation induced by a threefold increase in blood flow rate. Values are mean(SEM)*

Artery	*Resting flow (ml·min⁻¹)*	*Resting diameter (mm)*	*Increased flow (ml·min⁻¹)*	*Increased diameter (mm)*	*Diameter increase (%)*	
					External	*Internal*
Femoral (n=11)	11.5(0.6)	1.22(0.02)	34.8(1.7)	1.47(0.03)	19.8(2.1)	29.5(3.0)
Carotid (n=16)	15.4(0.9)	1.40(0.03)	44.8(3.9)	1.73(0.03)	18.9(5.1)	28.2(1.9)
Renal (n=7)	20.8(1.7)	1.37(0.05)	58.7(5.1)	1.69(0.06)	21.6(7.0)	29.1(9.9)

range lead to a decrease in the magnitude of the dilator response. It should be stressed that the increase in transmural pressure above 160 mmHg led to a sharp decrease in the magnitude of the flow induced dilator response, which remained weak for 1-2 h even after pressure had returned to 100 mmHg. In conformity with these data all recordings of flow induced arterial responses were carried out at a pressure of 100 mmHg.

CHARACTERISTICS OF FLOW INDUCED DILATATION OF FELINE CONDUIT ARTERIES

After a latency of 7-20 s, steep increases in blood flow rate caused a dilatation of the arteries, which was completed within 60-90 s (fig 2). Restoration of the initial flow was followed by arterial constriction, which occurred significantly more slowly than the dilatation and was completed within 3-10 min. The magnitude of the response usually increased to a steady level during the first 1-1.5 h of perfusion because of a slow progressive narrowing of the arteries during this period; *ceteris paribus*, the less the initial arterial diameter the greater the dilator response. Responses with magnitudes >5% were observed in 11 femoral, 16 carotid, and seven renal arteries. The amplitude characteristics of flow induced dilator responses obtained in these experiments are summarised in the table. In six cats the dilatation was weak (<5% in amplitude), which usually resulted from low myogenic tone (papaverine induced increase in diameter in these cases was about 3-6%).

Figure 4 shows the changes in diameter of the arteries induced by successive increases in blood flow of 5 or 10 ml·min^{-1}. Each separate increment in flow rate caused an arterial dilatation, an increase in diameter being approximately equal in response to each step in the range of flow rates from its initial value up to 35-50 ml·min^{-1}. The diameter-flow relation obtained on the basis of these measurements (fig 5) is nearly linear for a wide range of flow rates. Only with rates of flow over 35-50 ml·min^{-1} is the linear dependence disturbed and the curve reaches a plateau. Such a relation was obtained in most experiments, but when the segment of the artery exposed for the diameter measurements was long (6-10 mm), an S type curve was observed. In these cases gentle elongation of the artery by slight pulling of the distal cannula transformed the curve to the shape as in fig 5.

Maximal enlargement of the outer diameter caused by an increase in flow from its initial value up to 50-60 ml·min^{-1} (plateau level) was 25.8(2.8)% for the

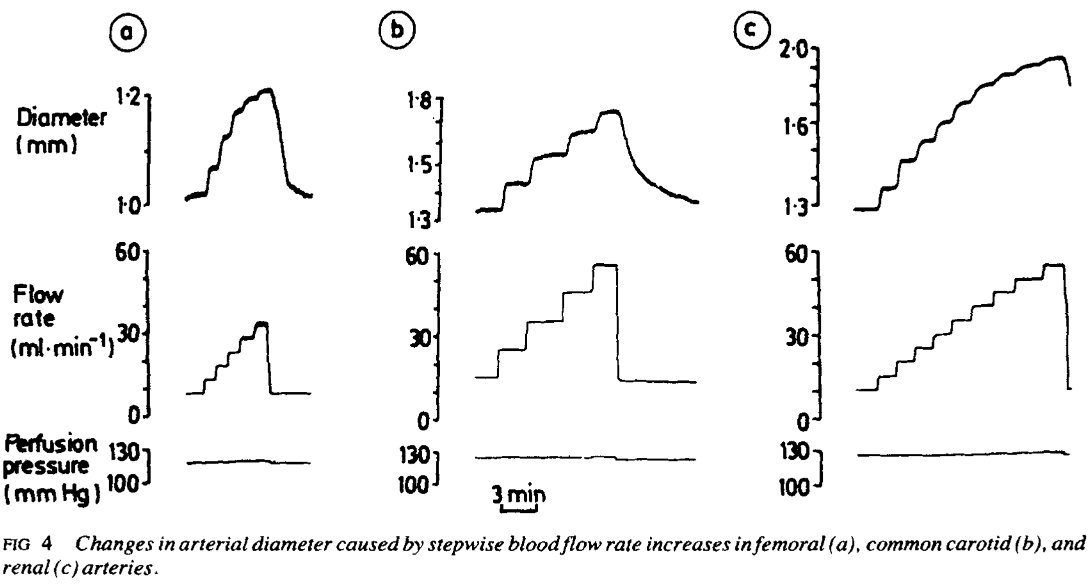

FIG 4 *Changes in arterial diameter caused by stepwise blood flow rate increases in femoral (a), common carotid (b), and renal (c) arteries.*

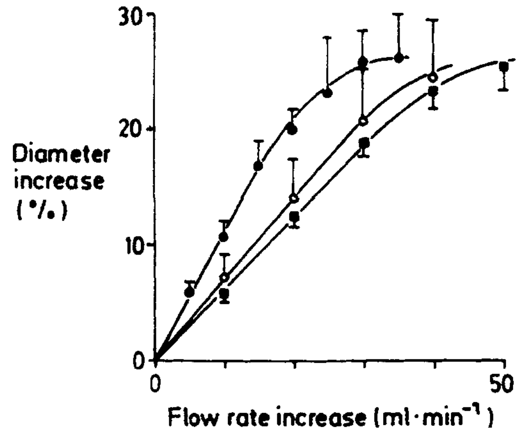

FIG 5 *Relation between increases in diameter and blood flow rate in femoral (●), common carotid (■), and renal (○) arteries. Data were obtained with transmural pressure held at 100 mmHg.*

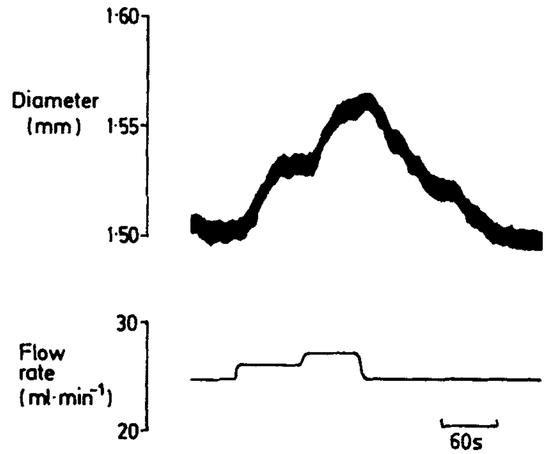

FIG 6 *Dilator response of cat renal artery caused by two 1 ml·min^{-1} steps in bloodflow rate. Transmural pressure was stabilised at 100 mmHg.*

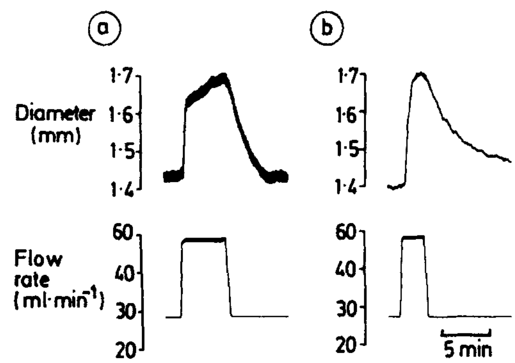

FIG 7 *Dilator responses of femoral artery after an increase in bloodflow (a) and perfusion with albumin containing solution (b) at 3 mPa·s viscosity. (b) Trace was recorded after death, which explains the absence of low frequency pulsations associated with respiration.*

femoral, 25.5(2.2)% for the common carotid, and 24.6(5.1)% for the renal artery. In some animals the arterial diameter was increased by 60-70%.

To establish whether arteries continuously adapt their lumen to the flow rate we attempted to detect the dilator response of the arteries to small increases in blood flow. Figure 6 shows the response of a renal artery induced by flow rate increases of 1 ml·min^{-1}. Even such a small increase in flow caused pronounced dilatation throughout the whole range of flow rates characteristic of the arteries. Such a response could be demonstrated only under pressure stabilised conditions since the response amplitude was of the same magnitude as and the fluctuations in diameter associated with systemic pressure changes. No dilatation induced by a smaller increase in flow rate could be demonstrated reliably in most experiments since in this case the arterial response was masked by spontaneous variations in diameter.

INDEPENDENCE OF FLOW INDUCED DILATATION FROM BLOOD BORNE HUMORAL FACTORS

The dilator responses of the common carotid artery of the same cat caused by an increase in flow of blood and of perfusion solution of 3 mPa·s viscosity are shown in fig 7. Dilatation persisted when the artery was perfused with a solution, and the responses in both cases were similar. They differed only in the rate of constriction following restoration of the initial flow; the constriction occurred much more slowly when the artery was perfused with solution.

In 16 of 27 cats at the beginning of perfusion with a solution the arteries, while dilating in response to the increase in flow rate, did not return to their initial diameter after the experiment. After several such experiments the arteries became considerably wider and the dilator response was abolished. In these cases the addition of pituitrin or L-phenylephrine to the solution restored the arterial diameter to the same value as when perfused with blood, increased the rate of arterial constriction, and increased the amplitude of the dilator response. In 11 cats the dilator response could be reproduced many times during perfusion of the arteries with solutions not containing any constrictors. Thus no constrictor agent is necessary for the dilatation caused by an increase in flow rate. The dilator responses of the femoral and common carotid arteries induced by an increase in flow rate of the solutions could be reproduced for 5-6 h even after the animal's heart had been deliberately stopped.

Discussion

The most important finding of this study is that conduit arteries continuously adapt the diameter of their lumen and, consequently, permanently adjust their hydraulic resistance to the rate of blood flow. The need for dilatation of the arteries during active hyperaemia is obvious. Indeed, the blood flow rate in intensively contracting cat gastrocnemic muscle may increase 5-6 times compared with that at rest.[21] The pressure difference between arterial vessels and 70 μm arterioles in cat skeletal muscle at rest is about 20 mmHg.[22] In the absence of arterial dilatation, a sixfold rise in blood flow should increase the pressure difference to 100-120 mmHg. The latter pressure is close to the mean central pressure and this situation is, in fact, impossible. Thus, even this simple consideration leads to the conclusion that the achievement of high blood flow during intensive muscle contraction is impossible without profound dilatation of upstream arteries.

However, the flow dependent dilatation observed previously could not produce considerable changes in vascular hydraulic resistance. Based on the observation that after tetanic contraction of feline calf muscles femoral artery diameter increased by only 3%. Hilton concluded that this dilatation could not play a significant role in active hyperaemia.[3] Lie and coworkers in turn postulated that the dilatation induced by increases in blood flow only helped to prevent arterial collapse under decreased transmural pressure.[4] These conclusions seem to be reasonable because these workers observed increases in internal diameter of 5-6% corresponding to only a 20-25% fall in hydraulic resistance. This was insufficient for an effective decrease of the pressure drop along the artery during extreme increases in flow during intensive active hyperaemia. An analogous conclusion may be deduced from other studies of flow dependent arterial dilatation since the observed increases in the diameter of canine conduit arteries during a 2-5-fold increase in blood flow rate was only about 5-10%.[10 23 24]

Our preliminary experiments also showed a dilator response of the femoral artery to a fivefold increase in flow rate of only 10%.[25] However, as our experience increased the magnitude of the dilatation increased steadily to the values reported in the present study. This was presumably due to the minimisation of arterial trauma during preparation and stabilisation of the transmural pressure at the level providing maximal amplitude of the response (fig 3). Thus the magnitude of experimentally observed flow induced arterial dilatation is directly related to technical experience.

Our recent data indicate that the flow sensitivity of conduit arteries is very effective in changing their resistance. Indeed, the mean increase in internal diameter of the femoral artery with a threefold rise in flow rate was 29.5% (table). According to Poiseuille's law such a dilatation results in about a 2.8-fold decrease in hydraulic resistance and causes a practically unchanged pressure drop along the artery. The same conclusion applies to carotid and renal arteries. This finding was noted on an arterial segment detached from its surroundings, which might be the reason why the flow rate increase was inadequately compensated by the dilator response. Probably, further minimisation of arterial trauma will increase the amplitude of flow induced dilatation to values providing complete stabilisation of the pressure drop along the arteries.

The results of our experiments show that dilatation of conduit arteries follows not only significant increases in flow but also increases in blood flow as small as 3-5% (fig 5). Such a response throughout the whole physiological range of flows suggests that there is not only a high flow induced dilatation but a continuous control of the lumen of the arteries, and, consequently, their hydraulic resistance, by blood flow rate. In other words, the flowing of blood itself causes smooth muscle relaxation and a certain degree of arterial dilatation.

It should be emphasised that the control of the lumen in accordance with flow rate is characteristic not only of arteries supplying organs that show great active hyperaemia but also of renal and internal carotid[11] arteries, which supply organs without very great variations in total flow. Thus in addition to a decrease in vascular resistance with high organ activity such a control has probably another aim. It seems reasonable that the arterial flow sensitivity, acting jointly with the sensitivity of the arterioles to transmural pressure, causes stability of the vascular bed. Indeed, a rise in flow induced, for instance, by dilatation of terminal arterioles should cause a decrease in distending pressure in the larger arterioles. The latter should dilate in accordance with Bayliss' mechanism, which results in a further increase in flow rate. A positive feedback, which makes the system potentially unstable is evident. Flow induced arterial control restoring the transmural pressure in the arterioles should prevent their further dilatation caused by the Bayliss' mechanism. Although there is no experimental evidence for this mechanism of vascular resistance stabilisation, it seems quite reasonable.

The other important finding of this study is that the control of the arterial lumen by the flow rate is local. This was postulated by Lie and coworkers,[4] when they confirmed that dilatation of the femoral artery was independent of any signal that could come from the periphery. However, a possible role for blood borne humoral factors was ignored by them. We did not consider this conclusion to be obvious but deliberately confirmed that the arterial flow sensitivity persisted during perfusion with a physiological solution containing only albumin. This indicates that the mechanism adjusting the arterial lumen to blood flow rate is independent of blood borne vasoactive agents and is localised entirely in the arterial wall. The addition of albumin was necessary to preserve the flow induced response; perfusion with saline containing no albumin abolished the response in 20-30 min.[26] Since the addition to saline of 6% dextran (molecular weight 60 000) did not prevent the loss of arterial sensitivity to flow rate this action of albumin was, apparently, not connected with any osmotic effects. On the other hand, the endothelium permeability barrier is lost after brief incubation in saline[27] and albumin is likely to prevent this process, thus providing normal operation of both endothelium and smooth muscles.

In conclusion, this study demonstrates that in vessel walls there exists a mechanism that continuously adjusts the lumen and, consequently, the hydraulic resistance of the arteries in accordance with blood flow rate. This mechanism allows considerable change in arterial hydraulic resistance, which stabilises the pressure drop along the arteries at increased blood flow rates. It, apparently, also plays an important role in physiological vascular reactions. Demonstration of a similar controlling mechanism in small intraorgan arteries would contribute to the development of a novel concept of vascular system operation.

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