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MICROVASCULAR FILLING PATTERN IN RAT LIVER SINUSOIDS DURING VAGAL STIMULATION

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SUMMARY

1. The terminal microcirculation in the transilluminated ventral margin of the rat liver was observed and recorded by a video-microscope system. The volumetric flow rate in a liver sinusoid was calculated from the observed diameter of the sinusoid and the intra-sinusoid erythrocyte flow velocity.

2. The topographic distribution of liver sinusoids within an arbitrary boundary of a microscopic field of terminal liver microcirculation was observed and the total inflow and outflow in the field were determined.

3. Both vagus nerves at the lower end of the oesophagus were stimulated at supramaximal voltage. Vagal stimulation dilated the calibre of liver sinusoids and paradoxically diminished the erythrocyte flow velocity in each individual liver sinusoid, but the total volumetric flows in a microscopic field remained unchanged.

4. Vagal stimulation also increased the number of liver sinusoids in a microscopic field by opening previously closed liver sinusoids. This recruitment contributed two-thirds of the total increase of the sinusoidal capacity while the other one third was the result of distension of existing liver sinusoids.

INTRODUCTION

The significance of autonomic innervation on the liver circulation is controversial and previous reports indicate that parasympathetic cholinergic fibres have little effect on the liver vascular bed (Bradley, 1963; Greenway & Stark, 1971). Many earlier investigators found that stimulation of intact or cut distal ends of vagus nerves produced no obvious change in the intrahepatic vascular resistance (Seneviratne, 1949; Ginsburg & Grayson, 1954; Deal & Green, 1956; Andrews, Hecker & Maegraith, 1958; Green, Hall, Sexton & Deal, 1959; Greenway, Lawson & Mellander, 1967). In the perfused liver circulation, infusion of the cholinergic neurotransmitter acetylcholine also produced little change though a vasodilator effect was obvious if the perfused liver circulation is rendered constricted (Andrews, Hecker, Maegraith & Ritchie, 1955; Andrews, Hecker & Maegraith, 1956). It is possible that some unknown intrahepatic mechanisms acting upon the liver microcirculation are implicated during acetylcholine administration or vagal stimulation. Indeed, recent studies from our

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laboratory suggest that there exists a cholinergic vascular neuroeffector system in the terminal liver microcirculation which has the capacity for vagal cholinergic vasodilatation (Koo, 1978; Koo & Liang, 1979*a*, *b*).

In the rat liver microcirculation, direct *in vivo* observations on the transilluminated liver have shown that the liver sinusoids are arranged as a network of series and parallel elements interposed between the portal and the hepatic venules (Koo, Liang & Cheng, 1975). Changes in the haemodynamics of the liver microcirculation are related to the number of liver sinusoids being perfused and to the calibre of the perfused sinusoids (Koo & Liang, 1977). Recruitment of previously closed liver sinusoids and distension of existing liver sinusoids can both increase the liver sinusoidal capacity but may not necessarily change the liver blood flow to the same extent. The failure of previous investigators to obtain a significant change in the liver circulation by vagal stimulation or acetylcholine administration could be a failure to differentiate the intrahepatic microvascular distribution of blood flow. Therefore, the experiments described in this paper are aimed at evaluating the relative roles of recruitment and distension of liver sinusoids in the terminal liver microcirculation during stimulation of intact vagus nerves.

METHODS

The techniques of intravital microscopy of the liver microcirculation had been described previously (Koo *et al.* 1975; Koo & Liang, 1977). Briefly, thirty male Sprague-Dawley rats weighing 250 g were anaesthetized with sodium pentobarbitone 40 mg.kg^{-1} intraperitoneally. Systemic arterial and hepatic portal venous pressures were monitored continuously by Statham transducers (P23AA and P23BB respectively) via catheters in the right common carotid artery and a tributary of the superior mesenteric vein respectively. A hollow metal T-piece was interposed between the carotid artery and the catheter for intermittent sampling of arterial blood for pH and P_{CO_2} determinations. The rat breathed spontaneously via a tracheal cannula and its body temperature was maintained at 37 °C by a heating pad. The ventral margin of the liver was exposed by an upper midline incision in the abdomen. The movement of the liver was minimized by interposing a metal shield between the liver and the diaphragm, preventing the transmitted cardiac and respiratory excursions. The exposed liver margin was transilluminated by a fibre-optic light-guide and was observed directly with an Olympus Vanox microscope, using a 40 × /0·75 objective lens. The light path coming out from the microscope was directed to a close-circuit video system (RCA camera 4532A) which provided a video display of the liver microcirculatory bed at an overall linear magnification of 1840 ×. The resolution of the optical system was 0·3 μm. The video information was stored on a videotape recorder (National NV-5120A) and time reference was recorded on the videotape and simultaneously displayed on a video monitor screen (Conrac SNA 23) by a digital video timer which enabled the videotape to be referred to the correct time sequence in subsequent analysis.

The diameter of a liver sinusoid was analysed from the videotape by direct measurement on the video monitor screen after prior calibration, using a pair of slide calipers. On the video screen, diameter measurement was accurate to $\pm$ 0·5 mm, or an equivalent of $\pm$ 0·3 μm under a magnification of 1840 ×. The erythrocyte flow velocity in a liver sinusoid was measured from the recorded videotape by the two-window video densitometric technique of Intaglietta, Silverman & Tompkins (1975), which is a variation of the two-slit photometric method of Wayland & Johnson (1967). Recent *in vivo* studies on the single file motion of the erythrocytes in capillaries of 6–10 μm diameter, to which the liver sinusoids belong, have shown that the photometrically measured 'centre-line' erythrocyte flow velocity (V_{CL}) is related to the mean velocity of erythrocytes plus plasma (V_{mean}) by a factor of 1·3, i.e., $V_{CL}/V_{mean} = 1{\cdot}3$ (Lipowsky & Zweifach, 1978). The volumetric flow rate in a liver sinusoid was thus calculated from the

observed erythrocyte flow velocity and the observed diameter of the liver sinusoid by the following expression:

$$\text{volumetric flow rate} = \text{erythrocyte velocity} \times \frac{1}{1{\cdot}3} \times \frac{\pi}{4} \times \text{diameter}^2,$$

assuming that all liver sinusoids were uniform and cylindrical.

Dynamic microvascular flow in a microscopic field was calculated following the morphometric methods described by Wiedman (1963) and Zweifach & Lipowsky (1977). Briefly, a group of

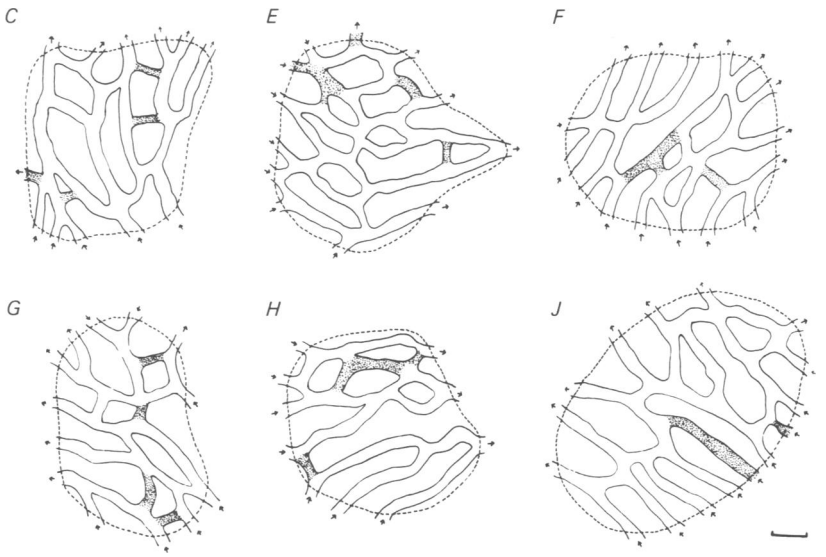

Fig. 1. Line drawing of six typical microscopic fields (field codes nos. *C*, *E*, *F*, *G*, *H*, *J*) of liver sinusoids. The dashed line circumscribing each field encloses the planar area served by each. Arrows point direction of blood flow. Shaded area indicates the recruited sinusoids. Bar = 20 μm.

liver sinusoids was chosen from the video screen and an arbitrary boundary was drawn to enclose most of the visible sinusoids (Fig. 1). The liver sinusoids which cut this arbitrary boundary were either inflow or outflow sinusoids. The volumetric flow rate in each of these inflow and outflow sinusoids was calculated and the summation of volumetric flow rates of inflow and outflow systems were separately determined. Further, the total number of sinusoids in each field, their respective diameters and lengths as well as the planar area of the liver tissue within the field were measured. Total volume ($\pi/4 \times \text{diameter}^2 \times \text{length}$) and total exchange surface area ($\pi \times \text{diameter} \times \text{length}$) of the liver sinusoids were also calculated.

The vagus nerves at the lower end of the oesophagus were cleared of surrounding tissue and maintained intact. Platinum bipolar electrodes were used for electrical stimulation. Square-wave stimuli of 8–10 V, 1 msec duration at a frequency of 8 Hz were delivered to the electrodes for 5 sec from a Grass stimulator (model S-88) after passing through an isolation unit (model SIU 5A). Preliminary studies showed that the stimulation voltage was supramaximal and that in the first 5 sec of vagal stimulation, changes in the erythrocyte velocity in the liver sinusoids were uniform whereas after 5 sec the changes of erythrocyte velocity were not predictable, presumably because changes in systemic and portal pressures began to occur after 5 sec of vagal stimulation and affected the erythrocyte flow velocity.

TABLE 1. Observed data and some significant derived values of morphometric and flow parameters of liver sinusoids in ten representative microscopic fields

			Liver sinusoid				Microscopic field	
Field code no.	Planar area (10^3 μm^2)	Number of sinusoids	Mean diameter (μm)	Mean length (μm)	Mean erythrocyte flow velocity (mm.sec^{-1})	Mean volumetric flow rate (μl. sec^{-1})	Inflow (10^{-6} μl. sec^{-1})	Outflow (10^{-6} μl. sec^{-1})
A	26	43	6·2	24	0·26	6·0	56	55
B	12	13	6·4	24	0·26	6·4	38	37
C	20	30	6·2	27	0·25	5·8	34	35
D	8	10	6·3	22	0·24	5·6	26	28
E	21	34	6·4	22	0·25	6·1	35	33
F	18	26	6·4	18	0·26	6·3	61	59
G	17	28	6·3	26	0·24	5·9	45	47
H	18	21	6·3	25	0·26	6·1	37	35
I	28	23	6·3	23	0·25	6·1	46	46
J	28	33	6·4	19	0·24	6·0	49	47
Mean	20	27	6·3	23	0·25	6·0	43	42
S.E.	2·2	3·3	0·02	0·9	0·003	0·08	3·6	3·4

RESULTS

Typical configurations of sinusoids in the terminal portion of the liver microcirculation described previously (Koo *et al.* 1975) are shown in Pl. 1 and Fig. 1. An arbitrary dashed line enclosing twenty to thirty liver sinusoids in one microscopic field approximated the planar area of liver tissues served by these liver sinusoids. The volumetric flows of all liver sinusoids entering and leaving this circumscribed area were calculated and the summation of volumetric flows of all inflow liver sinusoids were found to be approximately equivalent to that of all outflow liver sinusoids. The morphometric data obtained in ten representative microscopic fields among thirty liver preparations are listed in Table 1. In all fields, the mean value of the summation of volumetric flows of inflow liver sinusoids did not deviate significantly from that of outflow liver

TABLE 2. Mean and S.E. of some derived morphometric and flow data in the liver sinusoids in ten representative microscopic fields

Derived parameter	Mean	S.E.
Number of sinusoids per unit area (10^{-3} μm^{-2})	1·4	0·08
Total exchange surface area (10^3 μm^2)	15	1·7
Exchange area per tissue area ($\mu m^2.\mu m^{-2}$)	0·75	0·022
Total volume of liver sinusoid (10^{-6} $\mu l.$)	24	2·9
Volume per sinusoid (10^{-6} $\mu l.$)	0·91	0·044
Exchange area per sinusoid (10^3 μm^2)	0·57	0·027

sinusoids; the difference ranged from 0·8 % to 5·3 %. The number of liver sinusoids in each microscopic field varied from ten to forty-three, however, when the planar area of the liver tissue was considered, the average number of liver sinusoids per unit area was fairly uniform, i.e., approximately 1·4 liver sinusoids per 10^{-3} μm^2 liver tissue (Table 2). Histological sections showed that the thickness of liver tissue was $62 \pm 2{\cdot}3$ μm (mean $\pm$ S.E., $n = 12$). The mean values of the flow parameters in the ten representative microscopic fields are presented in Table 1. The frequency distribution of morphometric and flow parameters of these liver sinusoids are shown in Fig. 2.

During stimulation of intact vagus nerves at the level of the lower end of the oesophagus, two related phenomena were observed in the terminal liver microcirculation. First, all existing liver sinusoids were dilated but paradoxically showed a decreased intra-sinusoid erythrocyte flow velocity (Table 3 and Fig. 2). As the percentage decrease in erythrocyte flow velocity exceeded the percentage increase of the diameter, the calculated volumetric flows also decreased compared with the pre-stimulation value of flow. Secondly, in all of the microscopic fields examined, vagal stimulation induced an opening of previously closed liver sinusoids such that flow could be observed in these recruited sinusoids. Thus, vagal stimulation induced a distension of flowing liver sinusoids and a recruitment of previously closed sinusoids, thereby increasing the capacity of the terminal liver microvascular bed. Table 3 also shows the relative increase of sinusoidal capacity by distension and by recruitment. Except in fields *C* and *D* in which the distension was relatively more important, in all other fields, the recruitment of liver sinusoids is 2–3 times greater than that of distension.

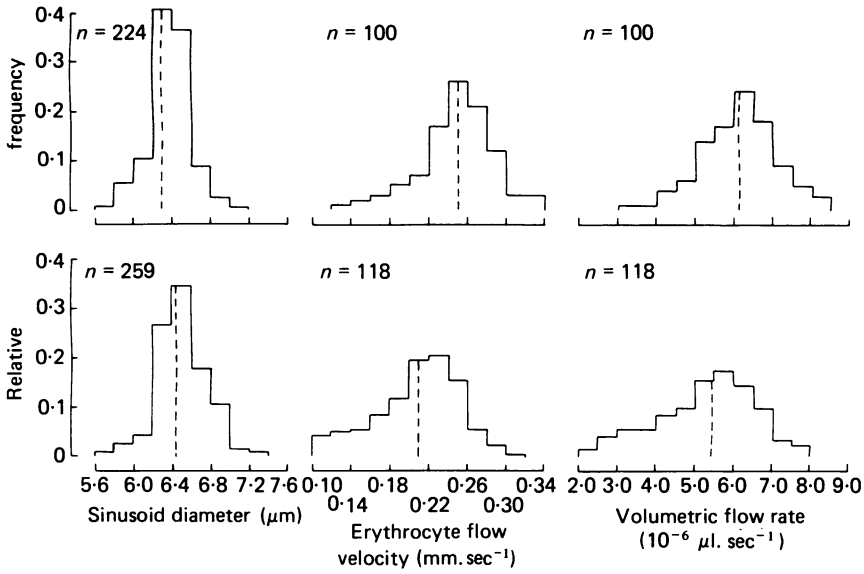

Fig. 2. Frequency distribution of the sinusoid diameter, erythrocyte flow velocity and volumetric flow rate in the rat liver sinusoids before (upper) and during (lower) vagal stimulation. Dashed lines indicate the mean value. *n* represents number of liver sinusoids.

TABLE 3. Morphometric and flow changes in the liver sinusoids during vagal stimulation. All values are expressed as percentage change of control value, (+) denotes increase and (−) denotes decrease

Field code no.	Number of sinusoids	Diameter	Erythrocyte velocity	Total volume	Distension	Recruitment
A	+14	+3	−13	+18	+6	+12
B	+23	+2	−23	+17	+4	+13
C	+13	+2	−14	+9	+5	+4
D	+10	+2	−16	+11	+5	+6
E	+18	+2	−20	+13	+3	+10
F	+19	+4	−19	+19	+8	+11
G	+14	+4	−13	+19	+7	+12
H	+19	+3	−18	+30	+11	+19
I	+17	+2	−21	+15	+5	+10
J	+6	+2	−10	+10	+3	+7
Mean	+16	+3	−17	+16	+6	+10
S.E.	1·7	0·3	1·4	2·0	0·8	1·4

With respect to the total volumetric flows into and out of the entire microscopic field, vagal stimulation did not provoke a change as remarkable as changes observed in each individual liver sinusoid. Half of the microscopic fields showed a decrease (range −0·8 % to −3·8 %) of volumetric flows during vagal stimulation while the other half showed an increase (range +0·9 % to +3·1 %), but the mean change of the total inflow and total outflow in the ten microscopic fields was an insignificant increase of 0·3 %. Therefore, as far as the total flows in a particular field was concerned, vagal stimulation had a minimal effect, though inside this area both re-

cruitment and distension of liver sinusoids had occurred. In all observations, no significant changes were detected within the first 5 sec of vagal stimulation on systemic arterial pressure ($131 \pm 3{\cdot}2$ mmHg, mean $\pm$ S.E., $n = 12$) and portal venous pressure ($9{\cdot}2 \pm 0{\cdot}11$ mmHg). Values of venous haematocrit ($46 \pm 0{\cdot}9\%$), arterial pH ($7{\cdot}4 \pm 0{\cdot}003$) and P_{CO_2} ($34 \pm 0{\cdot}3$ mmHg) did not show significant change before and after stimulation of the vagus nerves.

DISCUSSION

The present investigation illustrates one aspect of the study of the microcirculation, viz., the quantitative measurement of the topographic arrangement of a terminal microcirculatory unit. In the liver, either the hexagonal or the acinus unit is applicable to the present study (see Rappaport, 1973) but neither of these units is used because dimensionally they are too large for microscopic analysis. In the present video-microscope system with a linear magnification of $1840\times$ giving adequate optical resolution for measuring the diameter of the liver sinusoids, the visible area in one microscopic field only comprises twenty to thirty liver sinusoids which in turn only occupy a small fraction of either the hexagonal or the acinus unit. Therefore, in the present study, an arbitrary boundary is used to enclose as many as possible of the liver sinusoids. Further, the exact volume of liver tissue is not considered because shrinkage of liver tissue may occur during the histological preparation. Since the primary interest is in comparing morphometric and flow patterns of each microscopic field before and during vagal stimulation, the use of a planar area to represent a volume of liver tissue seems justified.

The present *in vivo* study demonstrates that excitation of intact vagus nerves produces dilatation of the liver sinusoids. The finding that vagal stimulation does not elicit any significant change in the total volumetric flow also conforms with results from many earlier investigators who claimed that vagus nerves had little effect on the liver vascular bed (see Introduction). However, the result demonstrates that vagal stimulation induces opening of previously closed liver sinusoids in addition to dilatating the existing ones. In this manner, a redistribution of blood flow occurs such that total flow in an area remains unchanged. Stimulation of vagus nerves thus produces changes in the liver microcirculation, and the failure to demonstrate such effects by previous investigators is because the pattern of filling of the liver sinusoids during vagal stimulation has not been elucidated. A similar situation is also reported in the rabbit salivary gland. Fraser & Smaje (1977) found that parasympathetic stimulation increased the total glandular flow but had little or the opposite effect on the acinar microcirculation during the first 5 sec of stimulation. The present study also shows that vagal stimulation turns a proportion of non-flowing liver sinusoids into flowing sinusoids. This recruitment accounts for two thirds of the increase of total sinusoidal capacity while the other one third is contributed by the increase of the diameter of existing liver sinusoids. In this way, vagal stimulation induces an increase of the blood volume in the liver and by recruitment of liver sinusoids, it may also create more discrete channels for metabolic exchange.

The volume changes of individual liver sinusoids as a consequence of vagal stimulation implies that some component parts of a liver sinusoid are responsible for the

change of its calibre. Since the liver sinusoids are devoid of vascular smooth muscle, the endothelial lining cells seem to be the appropriate candidates. We have recently demonstrated the presence of cholinergic fibres in the endothelial lining of liver sinusoids (Liang, Koo & Liu, 1978) and characterized the cholinergic receptors in the liver sinusoids (Koo & Liang, 1979*b*). It is possible that on vagal stimulation, acetylcholine is liberated from the cholinergic fibres and acts on the receptor sites in the liver sinusoids, thereby changing the calibre of the sinusoids.

On the other hand, the increase of the number of liver sinusoids perfusing the liver tissue seems to suggest that a separate mechanism exists in order to open previously closed liver sinusoids by vagal stimulation. Our previous observations (Koo & Liang, 1977; Koo, Tse & Yu, 1979) showed that in experimental haemorrhagic and cardiogenic shock, in which a low perfusion pressure is established, the terminal liver microcirculation responds to the change of systemic perfusion pressure by closing a substantial number of its flowing sinusoids. The closure of liver sinusoids has been postulated to be a result of the activation of noradrenaline-mediated alpha-adrenergic receptors which constrict the liver sinusoids (Koo, Liang & Cheng, 1977). Pre- and post-sinusoidal sphincters have long been suspected as the controlling sites (Bloch, 1955; Knisely, Harding & Debacker, 1957; McCuskey, 1966, 1971; Rappaport, 1973; Lautt, 1978) and it is possible that in the normal liver microcirculation, some of the pre-sinusoidal sphincters have been constricted by a tonic adrenergic stimulation such that the downstream liver sinusoids controlled by this sphincter are closed. Vagal stimulation activates the dilator cholinergic receptors and thereby counteracts the constrictive adrenergic mechanism and dilates the sphincters which in turn allow blood to pass through the downstream liver sinusoids. Certainly, the blood flow through the sphincter also depends on the perfusion pressures in its up- and downstream microvessels, but such micropressure data are unavailable at present. If the recruitment of sinusoids is a result of relaxation of previously closed pre-sinusoid sphincters, then the distension of the sinusoids by vagal stimulation could be due to further dilatation of sphincters that were previously open. The different observations reported in the present study as distension and recruitment of liver sinusoids could thus be different manifestations of the same vagal vasodilatation mechanism.

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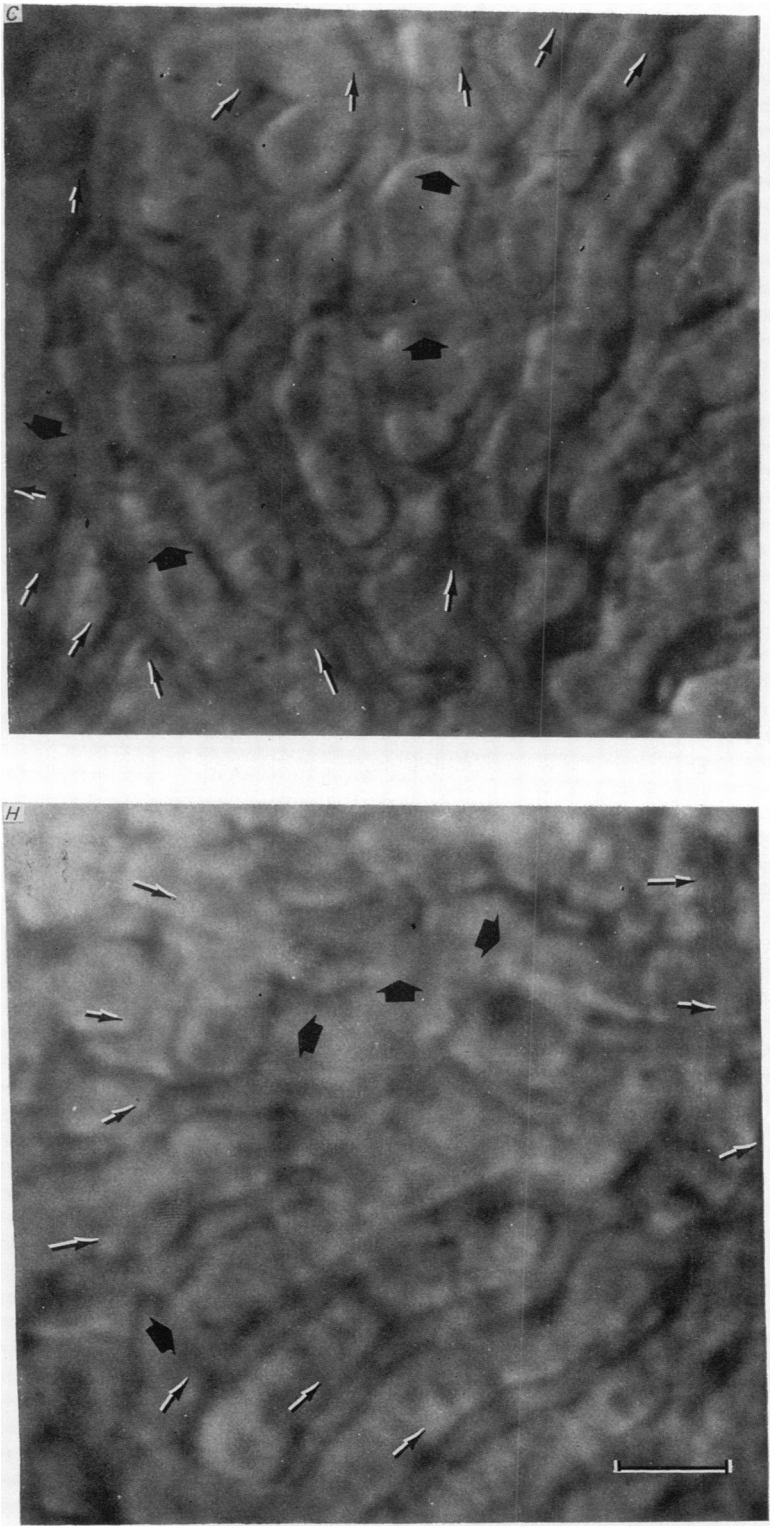

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EXPLANATION OF PLATE

Photograph taken from videotapes showing two representative microscopic fields (field code nos. *C* and *H*) of sinusoids in the terminal portion of the liver microcirculation. Small arrows point direction of blood flow and large arrows indicate recruited sinusoids. Bar = 20 μm.