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# Intermittence of blood flow in liver sinusoids, studied by high-resolution in vivo microscopy

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**MacPhee, P. J., E. E. Schmidt, and A. C. Groom.** Intermittence of blood flow in liver sinusoids, studied by high-resolution in vivo microscopy. *Am. J. Physiol.* 269 (*Gastrointest. Liver Physiol.* 32): G692–G698, 1995.—Kupffer cell migration and leukocyte-vessel wall interactions cause temporary slowing and/or stoppage of blood flow through individual liver sinusoids. Such temporal heterogeneity of flow was quantified in anesthetized mice and rats. Video recordings of red blood cell flow in 44 networks containing 8–16 sinusoids each were analyzed for 5- to 10-min periods. Flow was graded "fast," "slow," "stopped," or "reversed" based on red blood cell velocity. The mean numbers of flow changes (between grades) per minute in zone 1 vs. zone 3 were 1.39 vs. 0.78 (mouse) and 1.25 vs. 0.09 (rat). The mean percentage of time for each flow grade differed significantly between zones 1 and 3 and between species. For example, fast flow was present in zone 1 sinusoids for 51% of the time in mice and for 74% in rats; in zone 3 the corresponding numbers were 76 and 95%. Flow stasis was present in zone 1 sinusoids for 19% of the time in mice and for 7% in rats; in zone 3 the corresponding numbers were 2 and 0%. Thus considerable intermittence of perfusion exists, and the flow conditions create very different microenvironments for hepatocytes in zone 1 vs. zone 3.

hepatic microcirculation; rat and mouse; zone 1 vs. zone 3; periportal; perivenular; Kupffer cell migration; leukocyte-vessel wall interactions

SPATIAL HETEROGENEITY of hepatocyte function and sinusoidal wall morphology are both well recognized in relation to location within the liver acinus. For example, a number of enzymatic systems and metabolic processes are localized to different zones [zone 1 (periportal) or zone 3 (perivenular)] (10). Patterns of fenestration of sinusoidal walls differ between zones 1 and 3 (12, 31), as do the morphology and function of endothelial cells (1). Heterogeneity is also present in sinusoidal blood flow, and in this case both spatial and temporal components are involved. A necessary consequence of the network structure of the acinar microvasculature is that a wide range of driving pressures exist across the constituent sinusoids, leading to a correspondingly wide range of mean blood flows among sinusoids. This spatial heterogeneity of flow has been documented in many studies from measurements of sinusoidal red blood cell (RBC) velocities (3, 15, 18, 28, 29) and is now a matter of general agreement. However, the variation of RBC velocity in each individual sinusoid with time, i.e., the temporal heterogeneity of flow, has usually not been measured, and divergent opinions still exist. Many reports have described sinusoidal flow as irregular or intermittent, especially in zone 1 (4, 11, 14, 21, 27, 32), whereas recent quantitative studies indicate that simultaneous perfusion of 98–100% of all sinusoids occurs (23–25).

What evidence is there in the literature concerning temporal heterogeneity of sinusoidal blood flow, in particular with regard to intermittence? For many years, investigators using in vivo microscopy have given qualitative descriptions of temporal variations in RBC velocity and attributed these changes to bulging of sinusoidal lining cells ("sphincters") and/or plugging of sinusoids with leukocytes (4, 11, 14, 21, 27, 32). Eguchi et al. (6) have quantified the relative numbers of such flow interruptions (occurring over 30-s periods) in relation to acute ethanol ingestion in mice, and to our knowledge that study presents the only measurements of flow intermittence in the literature.

We recently presented evidence for Kupffer cell migration along sinusoids in normal mouse liver, from high-resolution in vivo microscopy (19). Such migration, in addition to leukocyte interactions with vessel walls, resulted in the temporary slowing or stoppage of blood flow through individual sinusoids. In zone 1, Kupffer cells sometimes interrupted the flow for periods as long as 10 min. This surprising observation led us to analyze over a 10-min interval the extent to which flow perturbations occurred and the percentage of time that flow was zero in each of eight sinusoids within a network from zone 1. The mean percentage of time flow was zero proved to be 47% for this particular network. This value is dramatically at variance with recent reports that in rats 98–100% of sinusoids (in zones 1 and 3) are simultaneously perfused (23–25). To determine whether this discrepancy is due to a species difference, we extended our study to sinusoidal networks in rats as well as mice. Moreover, to determine whether differences exist between zones 1 and 3, where the network morphology and numbers of Kupffer cells differ (rat, see Refs. 5, 13; mouse, see Ref. 22), we analyzed both zones in livers of rats and mice. To our knowledge, the present study provides the first documentation of the absolute numbers and durations of flow changes in liver sinusoids. Our study focuses on temporal (in contrast to spatial) heterogeneity of blood flow, emphasizing the role of migrating Kupffer cells in local perturbations of flow.

## MATERIALS AND METHODS

Ten CD-1 Swiss mice (30–40 g, 7 wk old) and three Wistar rats (90–120 g) were used in these experiments. Anesthesia was induced with 6 mg/100 g body wt pentobarbital sodium. An abdominal incision was made, and the animal was placed on its side on the platform of an epifluorescence inverted microscope (Diaphot TMD, Nikon), so that one lobe of the liver rested on a glass coverslip, forming a window over the objective


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lens (magnification: ×10 to ×100) of the microscope. The liver was kept moist with saline, and the rectal temperature of the animal was monitored and maintained at 37°C with a heat lamp. The organ was protected from dehydration and kept in position by a covering of Saran Wrap, and was transilluminated obliquely by a fiber-optic light source to enhance the image contrast. The image was monitored by a video camera; time information was added to the video signal and recorded as described previously (20). Views of zone 1 and zone 3 of the liver microvasculature were recorded for 5–10 min and later analyzed. Each field of view measured approximately 140 × 100 μm (×60 objective) and contained a network of about 8–16 sinusoids, of which 5–8 lay entirely within the plane of focus and presented clear views of blood flow for analysis. Drawings were made of zone 1 and zone 3 networks of sinusoids, sometimes within the same acinus, and each sinusoid was numbered. Zone 1 areas were defined as approximately the first one-third, and zone 3 areas as the last one-third, of the distance between the opening of the terminal portal venule into the sinusoids and the terminal hepatic venule.

Temporal heterogeneity of sinusoidal blood flow was studied by two different approaches. First, frame-by-frame analysis of RBC velocities in eight sinusoids of one network was carried out every 5 s for a total of 10 min, to provide a temporal overview of the velocity fluctuations and incidence of stasis that exist in liver. Second, by grading the RBC velocities as "fast," "slow," zero, "reversed slow," or "reversed fast," we were able to analyze flow perturbations at 1-s intervals throughout 5- to 10-min periods in large numbers of sinusoids ($n$ = 284). The transition between slow and fast grades occurred at a velocity of ~68 μm/s (range 64–71 μm/s). Slow flows yielded distinct images of individual RBCs on the video monitor, whereas fast flows yielded blurred RBC images. The value of 68 μm/s also corresponds closely to the mean velocity of flowing RBCs in liver sinusoids of mice, reported previously (69 μm/s) (20). For the present analysis the numbers of flow changes between grades, occurring per 5-min interval, and the percentage of time for each flow grade were calculated for each sinusoid. Statistical significance of the results was analyzed by both analysis of variance and Mann-Whitney U-tests using Minitab software programs. Both methods gave similar results, and $P$ values from the Mann-Whitney tests have been reported. A value of $P < 0.05$ was considered statistically significant.

## RESULTS

Using high-resolution in vivo microscopy it is possible to obtain clear images of the liver sinusoids at high magnification, up to ×5,300 on the video monitor. Views of sinusoidal networks in zones 1 and 3 of mouse liver (Fig. 1) show that the microvascular geometry is quite different in the two zones. Zone 1 contains highly branched and tortuous networks with many short interconnecting segments. In contrast, zone 3 is characterized by longer and straighter sinusoids with far fewer interconnections. Visual observations of sinusoids leave the impression that vessel diameters are slightly larger in zone 3 than in zone 1. Reports in the literature are available to confirm this in rats but not in mice. Therefore, we measured sinusoid diameters in mouse livers from video images seen on the monitor. Mean values for zone 1 were 5.9 ± 0.1 μm (SE; $n$ = 100) and for zone 3 were 7.3 ± 0.1 μm (SE; $n$ = 100). These values were significantly different ($P < 0.01$).

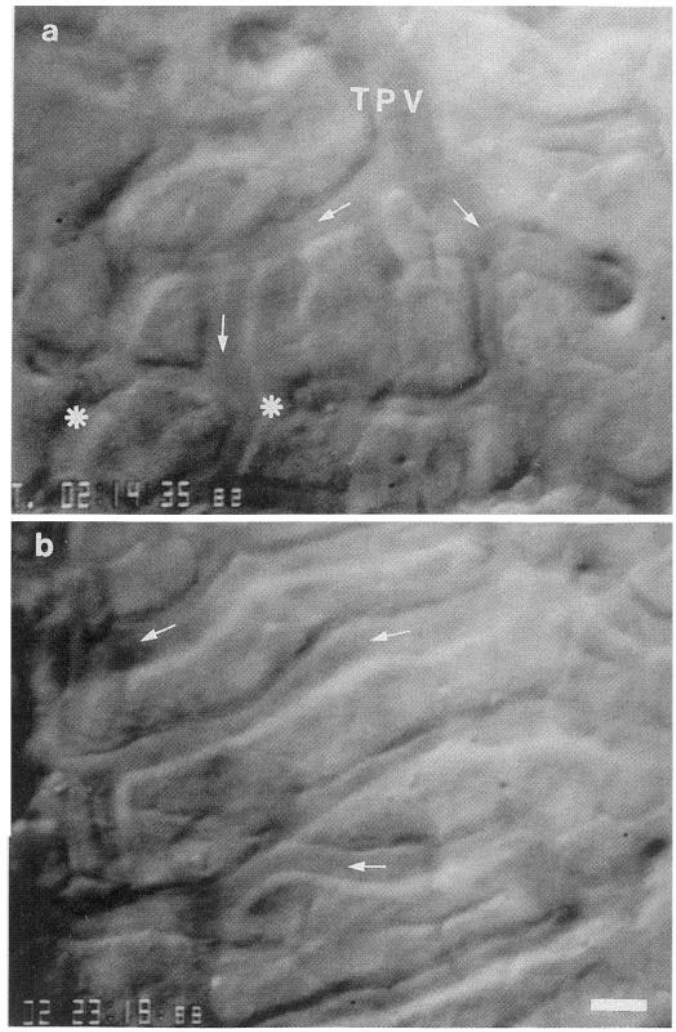


Fig. 1. In vivo microscopic views of sinusoidal networks in mouse liver, photographed from a video monitor. *A*: zone 1. Terminal portal venule (TPV) gives rise to a network of short, interconnected sinusoids. Arrows indicate direction of flow. At this particular instant, individual red blood cells (RBCs) may be distinguished in two sinusoids (*), which had slower flow. *B*: zone 3. Area adjacent to that seen in *A*, from same liver. Sinusoids are longer and straighter than in zone 1 and drain into a terminal hepatic venule that runs along the left border of the photograph and is slightly below the plane of focus. Bar = 10 μm.

Changes in RBC flow in individual sinusoids, due to temporary obstructions by leukocytes and migrating Kupffer cells, can be observed in detail and analyzed from the videotapes. A schematic diagram of part of a sinusoidal network from zone 1 is shown in Fig. 2. The sinusoids have been numbered for analysis (see Fig. 3), and locations are indicated where migrating Kupffer cells obstructed the flow and where circulating leukocytes slowed or stopped temporarily. Slowing was particularly evident in *sinusoids 1* to *3*, and many cells stopped or migrated in a narrow region of *sinusoid 4*. In most such cases blood flow in the obstructed sinusoid was blocked completely, as indicated by the stationary RBCs downstream. In a few instances, however, some plasma flow continued past the obstruction even though RBCs could not pass; this was indicated by a slow movement of

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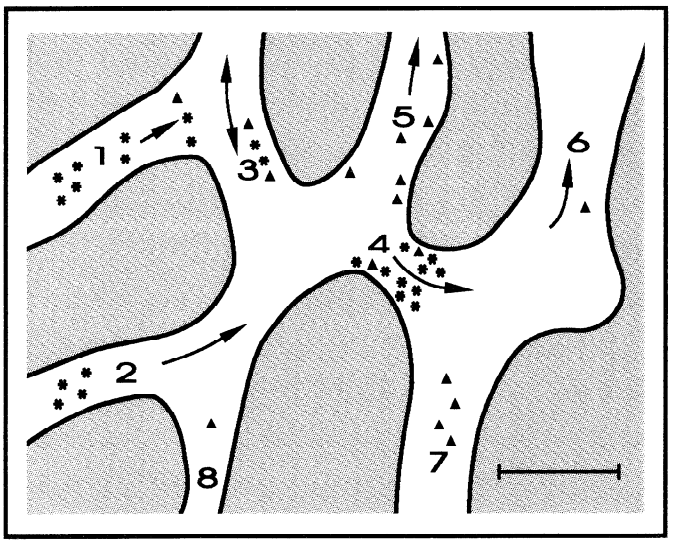


Fig. 2. Schematic diagram (drawn from video monitor) of a sinusoidal network from zone 1 in mouse liver. Sinusoids have been numbered for analysis of RBC velocity changes (see Fig. 3), and arrows indicate predominant directions of blood flow. Sites are shown where migrating Kupffer cells obstructed flow (▲) and where leukocytes carried along by the bloodstream slowed or stopped temporarily (*). In *sinusoids 7* and *8*, blood flow was stopped but Kupffer cells migrated in and out. Bar = 10 μm.

the RBCs downstream or by the occasional passage of a platelet through the narrowed region. Thus our analysis of flow perturbations does not exclude the possibility of occasional plasma flow in some vessels designated "no flow."

Absolute values of RBC velocity measured at 5-s intervals in each sinusoid of the network shown in Fig. 2 demonstrate the remarkable degree of temporal heterogeneity, including lengthy periods of stasis that occurred (Fig. 3). Only one of these sinusoids (*sinusoid 2*) showed no prolonged stasis, and this vessel had the highest RBC velocities (up to 406 μm/s). In contrast, two sinusoids (*sinusoids 7* and *8*) showed a complete absence of flow throughout the entire 10-min period of observation, and these vessels were seen to be blocked by Kupffer cells the whole time. The effects of migrating Kupffer cells and leukocyte-vessel wall interactions on the magnitude and direction of blood flow were also studied in this same network, by grading the RBC velocities fast, slow, zero, reversed slow, and reversed fast, at 1-s intervals as described in MATERIALS AND METHODS. This analysis (data not shown) showed clearly the drop in flow that occurred every time a leukocyte adhered momentarily to a vessel wall or a migrating Kupffer cell blocked the lumen. Such instants are indicated in Fig. 3 (● and ▼, respectively), but in a few cases the resulting change in velocity is not evident in this graph (because the change occurred during the 5-s interval between successive measurements). Changes of flow in one sinusoid frequently produced changes in another, including temporary arrest or even reversal of flow direction. Flow resumption after a period of obstruction by a Kupffer cell was usually due to the cell migrating further along or out of the sinusoid. The percentages of the total time for which the various flow states existed within each sinusoid of this network are shown in Table 1. There was a wide range of values but, on average, fast flow occurred for about 35% of the time, slow flow for 13%, reversed flow for 5%, and surprisingly, zero flow for 47% of the time.

Such data were collected in mouse liver from a total of 110 sinusoids in zone 1 (18 acini, 10 animals) and from 79 sinusoids in zone 3 (12 acini, 6 of the above animals). Data were also obtained in rat liver from 49 sinusoids in zone 1 (7 acini, 3 animals) and from 46 sinusoids in zone 3 (7 acini, 3 animals). Frequency distributions of the number of changes from one flow state to another (regardless of the direction of the change or its degree), occurring per sinusoid during a 5-min period, are given for mouse and rat in Fig. 4, *A* and *B*. The frequency distributions for zones 1 and 3 were not significantly different in mice, whereas in rats significant differences existed between zones for the percentage of sinusoids having 0 or 11–20 flow changes per 5 min. However, in

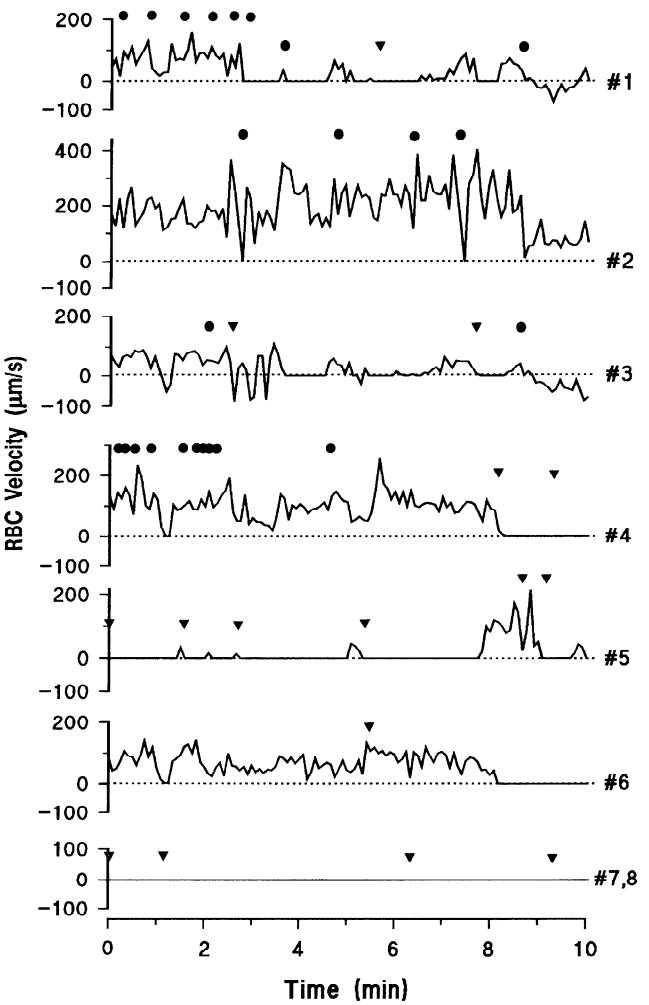


Fig. 3. Temporal overview of RBC velocity fluctuations over a 10-min period, in sinusoidal network from zone 1 of mouse liver (shown in Fig. 2). Measurements in each sinusoid were made every 5 s. Changes of flow in one sinusoid often produced changes in others. Instants are indicated at which a migrating Kupffer cell obstructed flow (▼) or a circulating leukocyte slowed or stopped temporarily (●). *Sinusoids 7* and *8* had no flow throughout the 10-min period. Kupffer cells are seen in *sinusoid 7*, and in *sinusoid 8* one Kupffer cell blocked flow throughout.

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Table 1. *Percent of time for each flow state in a sinusoidal network from zone 1 of mouse liver (shown in Figs. 2 and 3), over a 10-min period*

| Sinusoid No. | Fast | Slow | Zero | Reversed Slow | Reversed Fast |
|---|---|---|---|---|---|
| *1* | 26.5 | 29.9 | 35.0 | 8.6 | 0 |
| *2* | 82.3 | 17.6 | 0.1 | 0 | 0 |
| *3* | 25.8 | 23.8 | 21.3 | 22.6 | 6.5 |
| *4* | 75.7 | 2.2 | 22.1 | 0 | 0 |
| *5* | 7.6 | 15.3 | 77.1 | 0 | 0 |
| *6* | 65.0 | 12.9 | 22.1 | 0 | 0 |
| *7* | 0 | 0 | 100 | 0 | 0 |
| *8* | 0 | 0 | 100 | 0 | 0 |
| Mean ± SD | 35.4 ± 34.1 | 12.7 ± 11.2 | 47.2 ± 39.3 | 3.9 ± 8.1 | 0.8 ± 2.3 |

Values are given in %.

both species the mean absolute numbers of flow changes in zone 1 vs. zone 3, calculated on a per sinusoid basis, were significantly different ($P < 0.0001$). In the mouse these values were 1.39 vs. 0.78/min, whereas in the rat the values were 1.25 vs. 0.09/min.

The percentages of total time that individual sinusoids had flow in each of the five categories listed are presented in Fig. 5, *A* and *B*. In both species, significant differences existed between zone 1 and zone 3 as to the percentage of time for which flow fell into the categories

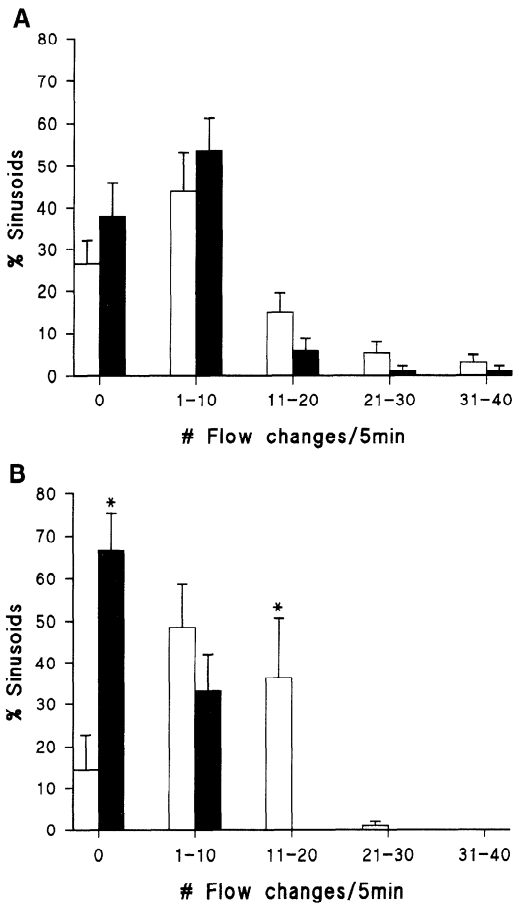


Fig. 4. Histograms showing frequency distributions of number of flow changes per 5 min (mean ± SE) in sinusoids of zone 1 (open bars) vs. zone 3 (solid bars). *A*: mouse, zones 1 ($n = 10$ animals) and 3 ($n = 6$ animals). *B*: rat, zones 1 and 3 ($n = 3$ animals). *$P < 0.05$.

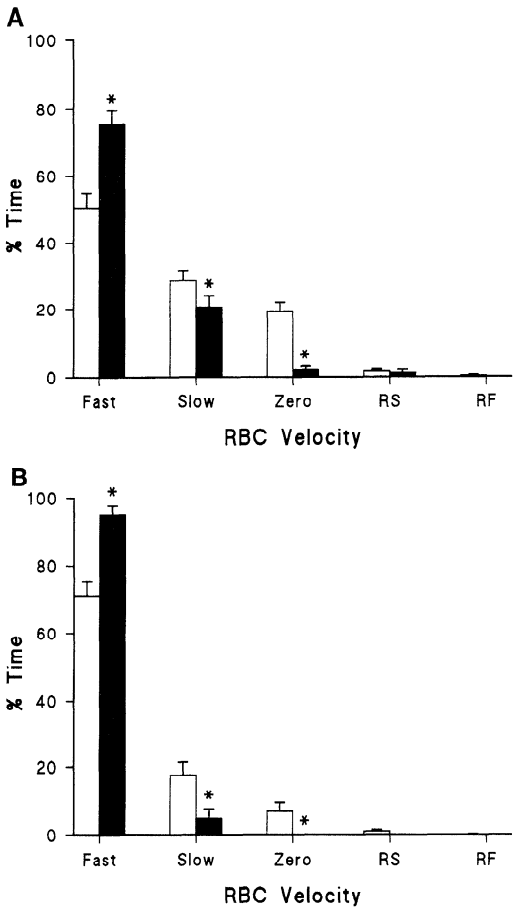


Fig. 5. Histograms showing percent of time for each flow state (mean + SE) over a 5-min period in sinusoids of zone 1 (open bars) vs. zone 3 (solid bars). RS, reversed slow; RF, reversed fast. *A*: mouse, zone 1 ($n = 110$ sinusoids) and zone 3 ($n = 79$). *B*: rat, zone 1 ($n = 49$) and zone 3 ($n = 46$). *$P < 0.05$.

fast, slow, and zero. There were no significant differences in the case of reversed flow (slow or fast). The same pattern of flow changes in zone 1 was observed in rats as in mice, although the absolute percentages of time were different. For example, fast flow occurred for 74% of the time in rats compared with 51% in mice, slow flow for 18 vs. 28%, and zero flow for 7 vs. 19%. For both fast flow and zero flow the values for rat vs. mouse were significantly different ($P < 0.003$ and $P < 0.018$, respectively), whereas for slow or reversed flow no significant differences were found. In zone 3, no examples were found of either zero or reversed flow in rat liver, whereas in mouse liver these states occurred for 3.4% of the time. Fast flow occurred for 95% of the time in rat vs. 75% in mouse, and slow flow for 5% in rat vs. 21% in mouse (both differences significant at $P < 0.0001$).

## DISCUSSION

We recently provided evidence for Kupffer cell migration along liver sinusoids, leading to significant perturbations of flow (19). Leukocytes were also responsible for flow changes, as has previously been described by others (6, 32). The perturbations included temporary stop-

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pages, changes in velocity, and alterations in direction of flow within individual sinusoids. The present study is the first to evaluate quantitatively such temporal heterogeneity and intermittence of sinusoidal blood flow in zones 1 and 3 of normal mouse and rat liver. A number of important conclusions have emerged.

In mice, all five categories of flow (fast, slow, zero, reversed slow, reversed fast) were found in both zones 1 and 3. The same categories of flow occurred in rats, except that no examples of zero or reversed flow were found in sinusoids of zone 3. Looking at the data from individual networks, it was surprising that in zone 1 of mouse the flow in an average sinusoid could be zero for as much as 47% of the time of observation (10 min). In zone 3 the comparable value was no higher than 14%. In contrast, in networks from rat much lower values were found: 13% in zone 1 vs. 0% in zone 3.

The differences between zones and between species are borne out by the overall data combining all the respective networks. *1*) Although in both species the mean absolute numbers of changes in flow per minute in an individual sinusoid of zone 1 were comparable, the corresponding values for zone 3 were very different. Because of this, the ratio of the numbers of flow changes per minute in zone 1 vs. zone 3 was approximately 2:1 in mouse but 10:1 in rat. *2*) For both species, fast flow in a sinusoid occurred, on average, for a significantly smaller fraction of the time in zone 1 than zone 3; the fast flow value for mouse was always less than that for rat. *3*) For both species the fraction of the time that flow was stopped in an average sinusoid of zone 3 was negligible (mouse) or zero (rat). In contrast, in the average sinusoid of zone 1, flow was zero for 19% of the time in mouse vs. 7% of the time in rat.

Recent studies using in vivo fluorescence microscopy (23, 24, 25) have indicated that 98–100% of all sinusoids, whether in zones 1, 2, or 3, are simultaneously perfused, although marked differences in mean RBC velocity between sinusoids exist. These data appear to imply that intermittence of sinusoidal blood flow (i.e., stoppage for any significant length of time) does not occur. This conclusion is at variance with previous reports in the literature and the findings of the present study. Numerous studies have qualitatively described sinusoidal flow as intermittent (4, 11, 14, 21, 27), the most thorough description of the leukocyte-vessel wall interactions responsible for flow intermittence being presented by Wisse and McCuskey (32). Quantitative evidence concerning the relative numbers of flow interruptions in mouse liver (acute ethanol ingestion vs. controls) has been provided by Eguchi et al. (6). In this report all the control values were listed as 100%, for both periportal (zone 1) and centrilobular (zone 3) sinusoids, and no absolute numbers of flow interruptions during each 30-s period of observation were given. The overall findings of our present study are that zero flow values occur in zone 1 sinusoids for 19% of the time in mouse and for 7% of the time in rat; for zone 3 sinusoids the corresponding values are 2% in mouse and 0% in rat. How is the marked discrepancy between these results and those indicating simultaneous perfusion of 98–100% of all sinusoids to be explained? The discrepancy is most likely due to methodological and species differences. In the studies of Menger et al. (23) and Post et al. (24, 25), sinusoidal perfusion was assessed by hepatocellular uptake of fluorescent dyes injected via the jugular vein. The concentration of the dye in the circulatory system would be expected to decrease gradually with time, and thus hepatocellular staining represents the integrated uptake of dye over a substantial time interval. This means that even in the presence of flow intermittence most, if not all, sinusoids will become fluorescently labeled, as was indeed found. Moreover, these particular studies were carried out in rat liver, in which we have shown flow intermittence to be substantially smaller than in mouse liver.

Temporal heterogeneity of RBC flow has been demonstrated in capillaries of resting skeletal muscle (7, 8). Large fluctuations in RBC velocity occur, including transient flow stoppages caused by interactions of RBCs and leukocytes with capillary bifurcations. Since the mean diameter of liver sinusoids is slightly larger than that of skeletal muscle capillaries [~6 μm for zone 1 sinusoids (6, 15, 20, 30, and present study) vs. ~5 μm for muscle capillaries (26)], one might expect fewer flow interruptions by RBCs and leukocytes in liver than in muscle. However, the opposite appears to be the case, presumably due to the lower driving pressures in the portal circulation and the presence of migrating Kupffer cells in liver sinusoids.

A number of factors may contribute to the greater degree of flow intermittence that we found in zone 1 compared with zone 3. In rat, the mean diameter of sinusoids in zone 1 is smaller than in zone 3: 5.9 ± 0.17 vs. 7.1 ± 0.29 μm (SE) (30), or 6.4 ± 0.1 vs. 8.3 ± 0.2 μm (15). In mouse, we have found a similar difference, 5.9 ± 0.1 vs. 7.3 ± 0.1 μm, although another study reports no significant difference [5.75 ± 0.14 vs. 5.91 ± 0.09 μm (6)]. The smaller the sinusoidal diameter the greater the likelihood that flow will be temporarily obstructed by leukocytes and Kupffer cells. Thus a greater degree of flow intermittence would be expected in zone 1 than in zone 3. In addition, the sinusoids in zone 1 are more highly branched than in zone 3, leading to more bifurcations on which cells impact and become arrested. The degree of branching also affects the pressure difference across arrested cells, a smaller difference existing when several alternate routes for flow are available. Consequently, arrested cells would be less easily dislodged in zone 1 than zone 3. Finally, several reports indicate that more Kupffer cells are located in zone 1 than zone 3, the ratio being approximately 5:3 [see Refs. 5, 13 (rat) and Ref. 22 (mouse)]. As we have shown, migrating Kupffer cells are a major cause of flow intermittence in liver sinusoids.

The significant differences in intermittence that we found in mouse vs. rat may be related to the species difference of flow velocity in sinusoids. In an earlier study (20) we measured RBC velocities in sinusoids by the video flying-spot method and reported mean values of 69.2 ± 4.5 vs. 180 ± 20 μm/s (SE) in mouse and rat, respectively. These differences are statistically highly

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significant. In rat liver Koo and Liang (17) reported a value of 250 ± 3 μm/s (SE), and using a video flying-spot method Koo later obtained a value of 150 ± 6 μm/s (SE) (16), which is similar to our finding. The lower mean velocity in mouse compared with rat would cause lower wall shear rates, leading to a reduced tendency for adherent leukocytes to become dislodged from sinusoidal walls. Thus the percentage of total time flow is stopped would be larger in mouse sinusoids than in rat, and the percentage of time that flow is fast would be smaller, as we have found.

Clearly, the flow perturbations in zone 1 will create a different microenvironment for hepatocytes than in zone 3. The mean time for exchange of $O_2$, nutrients, and metabolites between blood and tissue will be increased in zone 1, and augmented interaction of blood cellular elements with sinusoidal lining cells will occur. Moreover, the role of Kupffer cells in antigen presentation (9) involving interaction with lymphocytes for initiation of both T cell and B cell immune responses will be enhanced, as will be their phagocytic function. It has recently been proposed that serotonin (5-hydroxytryptamine) may play a role in the regulation of sinusoidal blood flow (3). Normotensive and hypotensive doses of serotonin caused decreased flow in a large proportion of zone 1 and zone 3 sinusoids in rats. The mechanism was thought to be constriction of sinusoids via enlargement and bulging of sinusoidal lining cells (probably Kupffer cells) into the lumen. In our experiments no pharmacological interventions were used, and active bulging of sinusoidal endothelial cells into the lumen was not observed. However, transient slowing or stoppage of flow in sinusoids occurred routinely (especially in zone 1), often due to migrating Kupffer cells. Thus in both the present study and that of Blankenship et al. (3) Kupffer cells are implicated as mediators of flow perturbations in liver sinusoids.

It is not possible to determine what percentage of flow intermittence can be attributed to Kupffer cells. In any field of view observed at high magnification only a small number of sinusoids are in sharp focus, and many flow perturbations occurring in these sinusoids are due to unseen events occurring in adjacent vessels of the network. Nevertheless, our impression based on observations of sinusoids over long periods of time is that Kupffer cells are the primary cause of prolonged flow stasis within individual sinusoids.

The observation and quantification of flow intermittence in normal liver has relevance to studies of pathological states such as ischemia-reperfusion injury. Our results show that it is incorrect to assume that under normal conditions 100% of sinusoids will be uniformly perfused. One needs a proper baseline from which to assess any experimentally induced flow changes. In addition, high-resolution in vivo microscopy offers the possibility of identifying which cells are critical in the cessation of blood flow in the sinusoids during reperfusion injury. Our results also have relevance to the modeling of metabolic processes that occur in the sinusoids, e.g., the uptake of drugs by hepatocytes. Bass et al. (2) have pointed out the problems associated with an undistributed sinusoidal perfusion model, in which it is assumed that every sinusoid receives the same afferent concentration of a given substrate and supplies the same efferent concentration to the venules. They have modified previous models to include an essential component of mixing between adjacent sinusoids but have assumed that there is no recruitment and derecruitment of sinusoids, given sufficient blood flow. However, our results indicate that future models of liver blood flow will also need to take into account the flow intermittence that occurs within individual sinusoids under normal conditions, especially in zone 1.

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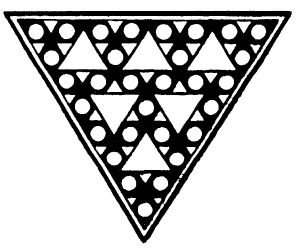

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