Liver and spleen as venous reservoirs

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The liver lacks a muscular capsule or trabeculae and contains no sequestered erythrocytes (8). However, it also has been regarded as a substantial reservoir since 1915 on the basis of pharmacologic studies with thermosmuths (9, 10).

More recently, indirect evidence has accumulated that reservoirs are not present in man (11) and, furthermore, are not necessary to support increased cardiac output (12–14). Gibson et al. (15) have even questioned the existence of reservoirs in the dog.

The present study was undertaken to determine if the dog’s liver and spleen vary in volume and, if so, under what conditions. In particular we wished to establish if the acute adjustments of the cardiovascular system are predictably associated with a change in volume of the liver and spleen, which would suggest a reservoir function for these organs.

METHODS

Thirty-seven dogs of random breed and sex were studied. Transducers were sutured on the capsule of the liver and spleen under aseptic conditions with pentobarbital anesthesia. The animals were then allowed to recover completely. The effects of drugs and hemorrhage were initially studied in the unanesthetized animal; however, no qualitative or quantitative difference was observed with light pentobarbital anesthesia, and after the first 20 animals, light anesthesia was used, which permitted recording of intraarterial pressure.

In one-third of the animals, terminal calibration was performed by injecting the animal’s own blood into the splenic artery or hepatic veins after clamping the splenic vein or portal vein and hepatic artery, respectively, for the spleen and liver.

Four types of transducers were used to obtain records of dimensions of the liver and spleen (Fig. 1). The sonodistometer (16) used was modified from the original design of Rushmer et al. (17) to permit studies at diameters of 5 mm or less. Barium titanate crystals 1 mm in thickness and 5 mm in diameter were sutured to opposite surfaces of the spleen and across the cephalad-caudad axis of the left lobe of the liver. The actual transit time for a \( \gamma \)-Mc pulse may be determined at any instant on an oscilloscope and recorded with a direct-writing Sanborn 350 oscillograph. This method

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allows a quantitative assessment of diameter changes as a percentage or, after terminal infusions of known amounts of blood, the changes may be expressed in terms of volume. The chief disadvantage of the sonodistometer method is the requirement of exact alignment of the crystals. The liver is soft and plastic and it is difficult to find opposing surfaces. Under the conditions cited the beam of ultrasound is relatively narrow, and proper alignment of the crystals in the supine position did not necessarily persist when the animal was standing.

Total impedance (18) across the organ was measured with the 2,400-cycle source of a Sanborn carrier amplifier (Fig. 1B). The barium titanate crystals are silver-coated and served as the electrodes. Excellent sensitivity and stability were possible, but in our opinion the variations of hematocrit in the spleen and, to a lesser extent, in the liver cast doubt on the specificity of the changes recorded.

Mercury-in-rubber variable-resistance gauges (19, 20) were anchored by Teflon disks on opposite surfaces of the organ after drawing the fine rubber tubing through the body of the liver or spleen (Fig. 1C). The resistance changes produced by lengthening and shortening of the mercury column are linear over a considerable range. This technique has excellent sensitivity and stability, but the durability of the gauges in chronic preparations was disappointing and calibration was frequently impossible.

Figure 1D illustrates the use of mutual inductance in monitoring the diameter of the liver and spleen (21). The transducer contains 400 turns of 1-mil wire on a flat nylon spool, the center of which contains a barium titanate crystal for the sonar system described above. One coil is connected to the 2,400-cycle oscillator of a Sanborn carrier amplifier; the other coil is connected to the detector of the same amplifier. This combined transducer was extremely helpful for the liver, whose geometry and plasticity made good sonar recordings difficult during exercise. Excellent low-noise recordings could be obtained by mutual inductance and the sonar provided quantitative data simultaneously.

RESULTS

The results are presented in sequence to answer the following questions: first, whether the liver and spleen do change in size due to physical and pharmacological factors; second, whether these changes occur predictably in the intact animal during acute adjustments of the cardiovascular system.

Physical factors. Quiet respiration produced relatively large variations in the liver volume; inspiration consistently caused an increase in volume, frequently as much as 100 ml. The spleen was more variable; in approximately half the animals the spleen got larger, and in the other half, smaller (Fig. 2). Whining (a canine equivalent of the Valsalva maneuver) and stretching both produced transient enlargement of the liver and spleen.

The liver consistently demonstrated pulsations with the heartbeat, of much less amplitude than those due to respiration. The heartbeats are not seen in most of the illustrations because of the lower amplification. The spleen, even with very high amplification, does not regularly show cardiac pulsations.

In Fig. 2, in the period before exercise began, slow cyclical variations in the spleen diameter are obvious. These waves are less common in the liver and, when present, are out of phase with those of the spleen, usually lagging by approximately 45°. Traube-Hering waves were observed during quiet standing, sleep, mild shock, and in almost every situation except severe shock or large doses of sympathomimetic amines.

Both organs are reasonably soft and deformable by external force. Greater changes in liver diameter were produced by the animal lying on his belly than by any

![Figure 2. Recording at slow and fast paper speeds of spleen (mutual inductance and sonar), liver (mutual inductance), and respiration (pneumograph). Note correspondence between the two methods of recording spleen diameter and presence of Traube-Hering waves in splenic records before exercise.](http://ajplegacy.physiology.org/Downloadedfromhttp://ajplegacy.physiology.org/)
FIG. 3. Effects of various pharmacologic agents given intravenously.

experimental procedure. Changes in spleen diameter due to posture, however, were considerably less than those due to active contraction.

Pharmacological responses (Fig. 3). Epinephrine in quantities as small as 8–10 μg consistently produced a large decrease in spleen diameter. The average decrease in volume was 85 ml; the average duration of contraction was 10 min. Assuming a normal blood volume of 8–9% of total weight, the spleen with fairly vigorous contraction expelled an average of 5–6% of the total blood volume. In some animals considerably larger amounts can be expelled; a 20-kg animal expelled 200 ml, approximately 12% of its blood volume. The liver response to epinephrine was unpredictable and relatively small. In 30 injections in 19 dogs, there was an increase in liver diameter in 10%, a decrease in 30%, and no change in 60%. The quantities of epinephrine were in the physiological range—less than 5 μg/kg min; 20 μg was the median dose. Normal saline, in comparable volume of 5–10 ml, produced no change in the liver or spleen.

Norepinephrine produced splenic contractions identical in quantity and duration to contractions produced by identical doses of epinephrine when given under the same conditions. (In Fig. 3 injection of norepinephrine did not occur in immediate sequence after epinephrine.) The response of the liver to norepinephrine was similar to the response to epinephrine.

Isoproterenol was of considerable interest because of its ability to mimic exercise in some of its effects on the cardiovascular system (22), particularly an increase in cardiac output and lowered resistance. With very small amounts (1–5 μg, slowly), it was possible to produce tachycardia, lowered diastolic pressure, and tachypnea without significant change in splenic diameter. Larger doses, in the range used for epinephrine (20 μg), consistently produced contractions of the spleen of equal magnitude to those produced by epinephrine. The effect on the liver was similar to the effect
FIG. 4. Effects of exercise on liver and spleen, and effect of training on splenic response. Lowest record of spleen in terminal portion indicates effect of deliberate frightening of the animal.

of epinephrine: an increase in 10%, decrease in 10%, and no change in 80% of the trials.

Angiotensin in relatively large quantities (25 µg) produced a large reduction in spleen size. A small dose with pressor response equal to 20 µg of norepinephrine produced a much smaller contraction of the spleen than was produced by norepinephrine. Angiotensin was available for trial in only three animals; the liver became slightly smaller in one, and no change was observed in the two other animals.

Acetylcholine, in quantities large enough to lower the blood pressure substantially, invariably led to splenic contraction of the same degree produced by epinephrine, although the duration was less than half that for epinephrine. Acetylcholine caused frequent but unpredictable changes in liver size. The liver became larger in 25%, smaller in 45%, and no change was observed in 30%.

Histamine in doses of 5-10 µg, reported by Mautner and Pick (9) to cause massive hepatic enlargement, failed to produce changes in either liver or spleen. Doses of 20-50 µg failed to change liver size, but if the blood pressure dropped significantly the spleen contracted.

Pentobarbital has been reported to cause dilatation of the spleen (23), but enlargement was seen only when the spleen had been contracted within the preceding 5 or 10 min by some other mechanism. With small doses given slowly no appreciable change was seen, but when enough pentobarbital was given to cause a fall in blood pressure the spleen always contracted (Fig. 3C). The liver was found to increase slightly in about half the injections of pentobarbital and was usually most pronounced when the spleen definitely contracted (see Fig. 6).

Neurohumoral responses. The response of the spleen to fright was immediate and consistent but the response of the liver was negligible. The decrease in spleen volume with fright varied from 10 to 100 ml (avg. 80 ml) and lasted 4 min. The fright response of the spleen was so strong and easy to provoke in most animals that it became a considerable obstacle in evaluating the response of the organ to exercise (Fig. 4, lower record).

The spleen diameter was recorded satisfactorily during
FIG. 5. Effects of hemorrhage on spleen and liver diameters. There is a progressive decrease in spleen diameter and a transient decrease in liver size, succeeded by a return to basal levels, although blood pressure continues to fall.

Hemorrhage (in 18 animals) invariably produced a reduction in diameter of the spleen (Fig. 5). In most animals the rate of reduction paralleled the rate of hemorrhage, but in three animals there was no significant change in spleen diameter until a considerable drop in blood pressure occurred. The maximal volume change in the spleen with hemorrhage varied from 35 to 300 ml (avg. 110 ml); in percentage of total blood volume the range was 3–19% (avg. 8%). In half the animals the liver did not change in diameter with hemorrhage; the remainder showed a gradual decrease in liver size, paralleling the decrease in total blood volume. Figure 5 demonstrates events during a hemorrhage of 30% of the total blood volume. There was a transient decrease in liver diameter, succeeded by a return to the control level, although the blood pressure continued to fall and the spleen continued to become smaller. In only one animal did the liver decrease by a significant amount—150 ml or 9% of total blood volume.

Hypoxia was produced by injections of pentobarbital,

treadmill exercise 62 times in 13 animals. In no instance did the spleen become larger with initiation of exercise. In approximately half the runs the spleen became smaller when the treadmill started, and in half there was no change (Fig. 4). When the spleen contracted at the onset of exercise, the diameter tended to return to near resting levels during continued exercise (Fig. 2). In general, as the animals became accustomed to the treadmill there was less tendency to splenic contraction. In the more adaptable dogs it was easy to achieve mill speeds of 4 mph at a 5% grade for 10 min without splenic contraction. Training was facilitated by a treadmill with variable-speed control, allowing gradual starts.

Liver diameter during exercise was recorded satisfactorily 64 times in 18 animals. In four instances the liver became smaller; in the remaining 60 runs the liver actually became larger in one-half, and no change occurred in the other half.

There were no consistent or significant changes in either liver or spleen with eating except for an occasional dog that became intensely excited by food, when strong splenic contractions occurred. These animals usually wolfed their food and appeared very apprehensive about losing it.
FIG. 6. Effect of hypoxia on liver and spleen. Note terminal increase in diameter of the liver associated with a profound splenic contraction.

which caused apnea. Hypoxia produced the most vigorous splenic contractions observed, usually exceeding the contractions occurring with profound hemorrhage. The liver usually became larger terminally by a volume nearly the same as the decrease in splenic volume (Fig. 6).

DISCUSSION

The spleen, on the basis of its anatomy, the physiologic studies by Roy (5), and the proof of sequestration of red cells by Barcroft and Barcroft (6), cannot seriously be questioned as a reservoir in the dog. The present study confirms the spleen as a precisely regulated reservoir responding to fright, stress, blood loss, and any stimulus that lowers systemic blood pressure. However, exercise of moderate degree and duration could be initiated and maintained without splenic contraction, contrary to the expectations of Krogh (1) and Rein (2).

The liver's reputation as a reservoir rests on more dubious data. The sphincter-like structures in the hepatic vein have been cited as the anatomic basis for volume control. Although they vary in nature and location, Popper and Schaffner (24) state that they are present in all species. However, proof of their function as a reservoir is dependent on physiologic studies.

The "physiologic" studies of the liver have been largely pharmacologic studies, usually with indirect methods and under unnatural conditions. Grab, Jansen, and Rein (10) reported that the liver could release up to 20% of the animal's total blood volume under the influence of epinephrine. They did not measure any dimension of the liver, but based their figure on flows calculated from thermostrombhrs on the hepatic artery, portal vein, and hepatic vein. The precision of their method was not sufficient to warrant such balance studies.

Many studies involving more direct measurements of liver volume have utilized extirpated organs, perfused at a constant pressure or flow (25). Other studies made in situ have involved splenectomy, although the spleen contributes from 38% (26) to 60% (28) of total hepatic blood flow. In the extirpated liver, epinephrine produced a consistent decrease in volume (27). In a more physiologic preparation, MacLean, Brackney, and Visscher (28) found that epinephrine produced an increase in liver weight in four of seven dogs.

In the present study liver volume was changed by several maneuvers. The changes were small when expressed as a per cent of the control size: the largest was a decrease of 2%. When related to total blood volume, the changes were occasionally significant: up to 9% of total blood volume. Of more relevance to the question of reservoir function is the consistency of response to exercise and hemorrhage. The liver released blood during exercise in only 4 of 64 runs and actually became larger in half the exercise periods. During hemorrhage the liver became smaller in only half the animals, and there were no instances of a dramatic change as was seen in the spleen with active contraction. Considering the capacity of the hepatic vascular bed, failure of the liver to consistently become smaller with hemorrhage suggests that this organ may be one site of relative pooling of blood in shock.

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