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Noninvasive functional liver blood flow measurement: comparison between bolus dose and steady-state clearance of sorbitol in a small-rodent model

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van der Hoven B, van Pelt H, Swart EL, Bonthuis F, Tilanus HW, Bakker J, Gommers D. Noninvasive functional liver blood flow measurement: comparison between bolus dose and steady-state clearance of sorbitol in a small-rodent model. *Am J Physiol Gastrointest Liver Physiol* 298: G177–G181, 2010. First published November 25, 2009; doi:10.1152/ajpgi.90688.2008.—Plasma clearance of D-sorbitol, a nontoxic polyol, occurs predominantly in the liver and has been used to measure functional liver blood flow after bolus and steady- state intravenous administration. However, it is not known which of these two administration methods is superior. Therefore, plasma D-sorbitol clearance was studied in an animal model both after a bolus dose and under steady-state (SS) conditions and compared directly with liver blood flow, under normal conditions, and after the induction of endotoxin (LPS) sepsis. Adult male Wistar rats (526 ± 38 g body wt; $n = 27$) were anesthetized and mechanically ventilated. Hemodynamics, hepatic arterial flow, and portal venous flow were measured. Two groups were studied, namely healthy animals that served as controls and a sepsis group that received 5 mg/kg LPS intravenously (*Escherichia coli* O127:B8). Each animal received either a SS infusion (0.1 mg/100 g body wt per min) or a bolus (3 mg/100 g body wt) of a 5% D-sorbitol solution intravenously in a randomized order. After the initial measurements and a 60-min pause time in between ($T_{1/2,\text{sorbitol}} = 9$ min), a crossover was done. The hepatic clearance of D-sorbitol in the control group showed a good correlation between bolus and SS (Spearman's $r = 0.7681$, $P = 0.0004$), and both techniques correlated well with total liver blood flow (TLBF) ($r = 0.7239$, $P = 0.0023$ and $r = 0.7226$, $P = 0.0023$, respectively). Also in the sepsis group there was a good correlation between bolus and SS sorbitol clearance ($r = 0.6655$, $P = 0.0182$). In the sepsis group, only the SS clearance correlated with TLBF ($r = 0.6434$, $P = 0.024$). In conclusion, in normal and under septic conditions, hepatic clearance of D-sorbitol either by bolus or a SS infusion is comparable. In healthy animals, this also correlated well with TLBF but not in septic conditions. However, this is expected because of the changes in the liver microcirculation, shunting, and decreased hepatocyte function in sepsis.

microcirculation; rats; sepsis

MONITORING BLOOD FLOW to the liver is difficult without invasive techniques because of the dual blood supply of the liver, i.e., the admixture of portal venous and hepatic arterial blood. Apart from determining plasma liver enzymes and products such as albumin or clotting proteins, the plasma clearance of several substances has been used to monitor liver function (2, 6, 9, 19).

The ideal substance is nontoxic and inert (i.e., it should not induce an intrinsic physiological or metabolic effect), is administered intravenously, and should be exclusively cleared by the liver in a flow-dependent manner (i.e., with a high extraction ratio). For instance, galactose and ethanol have been used, but these substances reach saturation of the metabolic system early, after which the extraction is no longer flow dependent. Lidocaine, propranolol, indocyanine green (ICG), and sulfobromphthalein, as well as radioactive-labeled albumin, have been used and have the advantage of reaching steady-state metabolism early but are influenced by plasma protein levels and composition (14).

Molino et al. (15, 16) used the clearance of D-sorbitol, a nontoxic sugar with a very high flow-dependent extraction ratio in the liver, both with steady-state infusion and after a bolus dose injection. Sorbitol is metabolized through the fructose pathway in the liver in humans and animals (4). In healthy volunteers and in cirrhotic patients, hepatic vein catheterization showed a higher extraction ratio of D-sorbitol than ICG (0.90 ± 0.05 vs. 0.51 ± 0.14, and 0.51 ± 0.23 vs. 0.22 ± 0.11, respectively) (13). Almost no extrahepatic, extrarenal clearance was found for D-sorbitol, and the elimination capacity of D-sorbitol was found to be twice that of galactose (16). On the basis of these findings, D-sorbitol is superior to ICG or galactose for clearance studies to estimate functional liver plasma or blood flow (10, 23).

Most studies have used sorbitol elimination (either bolus or steady state), but none has compared both methods in the same subject. Therefore, the present study aimed to validate a noninvasive technique to measure functional liver blood flow (FLBF) (Q_{funct}) in a small-rodent model, under normal circumstances, and after the induction of a septic state by endotoxin infusion, using steady-state pharmacokinetics of D-sorbitol and comparing this with bolus dose. Both methods are also compared with direct measurements of total liver blood flow (Q_{total}) using small Doppler bidirectional ultrasound probes on the hepatic artery and portal vein.

MATERIALS AND METHODS

Preparation and animal surgery. The experimental protocol was approved by the Animal Experiments Committee under the national Experiments on Animals Act and adhered to the rules laid down in this national law that serves the implementation of *Guidelines on the Protection of Experimental Animals* by the Council of Europe (1986), Directive 86/609/EC. All animals had free access to food and water until the start of the experiment.

Adult male Wistar rats ($n = 15$; 526 ± 38 g body wt) were anesthetized with isoflurane 2% (Rhodia Organique Fine; Avonmouth, Bristol, UK) in a 1:1 oxygen/nitrous oxide mixture before

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Table 1. *Data on hemodynamics and flow parameters*

Parameter	Control Group			LPS (Sepsis) Group		
	Bolus Phase, mean (SD)	Steady State, mean (SD)	Bolus vs. Steady State	Bolus Phase, mean (SD)	Steady State, mean (SD)	Bolus vs. Steady State
HR	327 (26)	328 (27)	NS	373 (35)	371 (27)	NS
MAP	91 (19)	92 (12)	NS	57 (10)	59 (11)	NS
RA	6 (3)	6 (2)	NS	6 (2)	6 (1)	NS
CO	108 (20)	101 (17)	$P = 0.0105$	144 (33)	149 (42)	NS
Portal Vein	19.4 (5.1)	18.9 (5.1)	NS	13.8 (3.0)	13.9 (2.7)	NS
% of Baseline	96 (7)	94 (18)	NS	94 (17)	96 (6)	NS
Hepatic Artery	4.6 (3.0)	4.7 (3.1)	NS	2.3 (1.2)	2.3 (1.1)	NS
% of Baseline	107 (25)	137 (130)	NS	82 (17)	89 (23)	NS

Heart rate (HR) in beats per minute, mean arterial pressure (MAP) in mmHg, right atrial pressure (RA) in mmHg, cardiac output (CO), and portal vein and hepatic artery flow in ml/min were assessed. NS, nonsignificant.

instrumentation commenced. Body temperature was maintained by immobilizing the animals on an electrically warmed mattress and controlled by measuring rectal temperature with a special probe (UNO Temperature Control Unit; UNO Roestvaststaal, Zevenaar, The Netherlands). Using aseptic surgical techniques, a tracheostomy was inserted, after which the animals were mechanically ventilated in pressure-controlled mode (Sophia Infant Ventilator Mk 3S; Hoek Loos, Schiedam, The Netherlands) to maintain full anesthesia and normal gas exchange.

Thereafter, the right carotid artery was cannulated using small-bore polyethylene tubing (PE 50 Intramedic, Clay Adams Brand, ID 0.58 mm, OD 0.965 mm; Becton Dickinson, Sparks, MD) connected to a pressure-monitoring system, consisting of a pressure transducer (ART Safedraw; Becton Dickinson, Sandy, UT) connected to a hemodynamic monitor (HP 78354A; Hewlett-Packard Medical, Amsterdam, The Netherlands); data were stored on a multi-channel graphic printer (Graphtec Linearcorder F WR3701; Graphtec, Tokyo, Japan). Through the same incision, tubing was inserted in the right jugular vein and connected to the pressure-monitoring system.

Thereafter, through a cut down of the left femoral artery, a modified Swan-Ganz catheter (Becton Dickinson) was inserted and the thermistor advanced into the abdominal part of the aorta. The catheter was connected to a cardiac output computer (Baxter Edwards Vigilance; Edwards Lifesciences, Irvine, CA). Cardiac output was measured using Fick's method by injection of a 0.2-ml saline bolus into the jugular vein, adapting the catheter constant according to a method described by Lambalgen et al. (18a, 21).

To administer D-sorbitol, a line was inserted into the right femoral vein (using the tubing mentioned above) and connected to an infusion pump (Perfusor R Compact S; B. Braun, Melsungen, Germany).

Through a midline incision, the abdominal cavity was opened. Doppler flow probes (types 0.5VB and 2.0S; Transonic Systems Europe, Maastricht, The Netherlands) were attached to the hepatic artery and the portal vein, respectively. The flow probes were connected to a flow monitor (T-206, Transonic Systems Europe). The abdomen was left open and covered with gauzes soaked in warm saline and aluminum foil to reduce heat and moisture loss.

For the sepsis group, male Wistar rats (390 ± 26 g body wt; $n = 12$) were instrumented as described above. After instrumentation, 5 mg/kg LPS (*Escherichia coli* O127:B8, L-3880; Sigma, St. Louis, MO) was administered intravenously, and, after a stabilizing period of 60 min, baseline measurements were performed.

Measurements. After manipulation and reaching a hemodynamically steady state of the animals in the control group and after 60 min of sepsis in the sepsis group, D-sorbitol was administered after taking baseline measurements. The animals, both in the control group as well as in the sepsis group, were randomly assigned to start with a steady-state infusion (0.1 mg/100 g body wt per min; 50 mg/ml solution: e.g., 0.42 ml/h with body wt = 350 g) or a bolus dose (3 mg/100 g body wt, 50 mg/ml solution: e.g., 0.21 ml with body wt = 350 g; at 150 ml/h infusion rate = 5 s) intravenously injected (15).

After the initial measurement, a pause time of 60 min was allowed before a crossover was done [to avoid interference with the next phase, a time period of at least 3.5–4.0 times $T_{1/2,\text{sorbitol}}$ (9 min) was needed]. Blood samples for serum sorbitol levels were taken at $T = 0$, 1, 5, 9, and 15 min during bolus dose, and at $T = 0$, 30, 60, and 120 min during the steady-state phase. After discontinuation of the steady-state infusion, a further sample was drawn after $1.44 \times T_{1/2,\text{sorbitol}} = 13$ min to allow for a calculation of the plasma sorbitol clearance at the end of the steady-state experiment. At the end of the experiment, the urine was collected by bladder puncture.

All blood samples were taken from the carotid artery and collected in small-size sample tubes (Z serum/gel, MiniCollect, Greiner Bio-One, Kremsmünster, Austria) and centrifuged at 3,500 *g* for 10 min. All serum and urine samples were immediately frozen at −80°C.

D-Sorbitol in rat serum and urine was determined with a colorimetric D-sorbitol/xylitol test (Boehringer Mannheim, catalog no. 670 057;

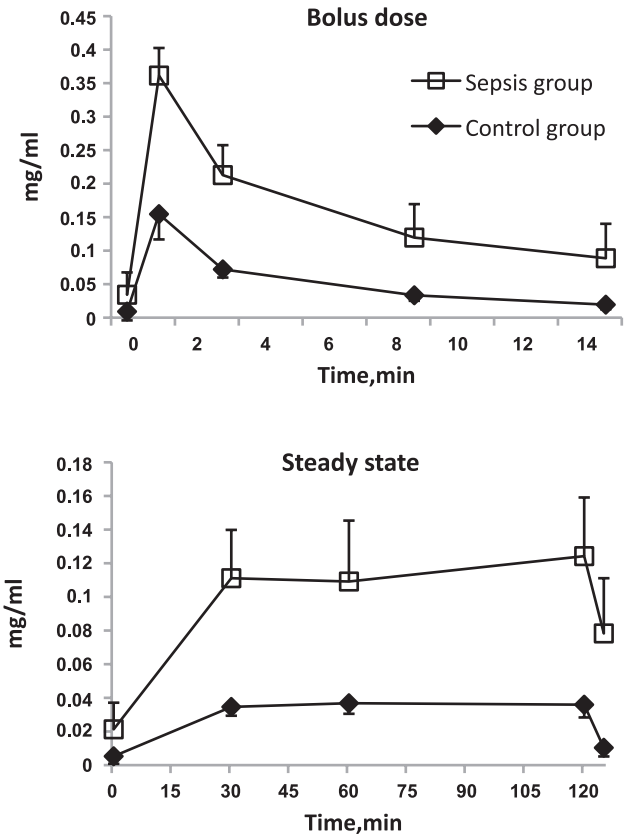

Fig. 1. Data on plasma sorbitol levels. Values are means ± SD. *Top*: bolus dose. *Bottom*: steady state.

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Roche Diagnostics, Mannheim, Germany), as described by Bergmeyer et al. (3). Sorbitol is oxidized in the presence of NAD by sorbitol dehydrogenase, giving fructose and NADH. By the action of the enzyme diaphorase, in a subsequent reaction, NADH reduces iodonitrotetrazolium to formazan, which is measured at 492 nm. The sample volume is 100 μl, and the range of detection is 1–10 μg. Higher contents have to be diluted.

Data on hemodynamics, body temperature, and flow were gathered continuously throughout the experiment. To compensate for the samples drawn, an equivalent amount of colloid (Voluven 130/0.4; Fresenius Kabi, Homburg, Germany) was administered.

Statistical analysis. Pharmacokinetic data were calculated using WinNonlin (Pharsight, Mountain View, CA). D'Agostino-Pearson's omnibus normality test, Kolmogorov-Smirnov test for normality, Kruskal-Wallis, Dunn's multiple-comparison test, Wilcoxon's matched-pairs, signed-ranks test, and Bland-Altman analysis were applied where appropriate using InStat 3 for Macintosh and Prism 5 for Macintosh (GraphPad Software, San Diego, CA).

RESULTS

Data are presented in Table 1 and Figs. 1–3. All hemodynamic parameters in the control group were comparable, except for cardiac output, which was significantly higher during the bolus phase compared with steady state (Table 1). In the sepsis group, there were no significant hemodynamic differences between steady-state and bolus phase (Table 1).

In both groups, blood flow in the portal vein and the hepatic artery were comparable between bolus and steady-state phase, both in absolute numbers and in percentage of baseline variations (Table 1). The plasma sorbitol levels for bolus and steady state for both groups are shown in Fig. 1.

Total plasma clearance in the control group of D-sorbitol was 15.35 ± 3.16 ml/min for the bolus dose and 14.64 ± 2.21 ml/min in steady state. In the sepsis group, the total plasma clearance was 6.77 ± 3.16 ml/min for the bolus dose and 5.11 ± 2.42 ml/min for the steady state. Renal clearance of D-sorbitol in the control group was 10.6 ± 4.4% of the total dose administered and 1.48 ± 1.39% in the sepsis group ($P < 0.001$). The extrarenal (hepatic) sorbitol clearance or FLBF in the control group was 13.7 ± 2.9 ml/min and 13.1 ± 2.0 ml/min for bolus and steady state, respectively (Wilcoxon, $P = 0.1688$, not significant), and showed a good correlation (95% confidence interval 12.1–15.3 and 12.0–14.2, respectively; Spearman's, $r = 0.7681$, $P = 0.0004$; Goodness of Fit $r^2 = 0.7327$, $P < 0.0001$) (Fig. 2). Bland-Altman analysis showed a trend toward higher steady-state values for lower liver blood flow and higher values for bolus injections at higher flow rates (Fig. 2). In the sepsis group, extrarenal (hepatic) sorbitol clearance was 6.65 ± 3.05 ml/min with bolus dose and 5.03 ± 2.33 ml/min in steady state (Wilcoxon's, $P = 0.0342$), both significantly lower than in the controls ($P < 0.001$), but correlated well (95% confidence interval 4.724–8.576 and 3.558–6.509, respectively, $r = 0.6655$, $P = 0.0182$, $r^2 = 0.5311$, $P = 0.0072$) (Fig. 2). Bland-Altman showed an increase in bias compared with controls (Fig. 2).

In the control group, the flow after bolus injection (Q_{bolus}) and in steady state (Q_{ss}) correlated well with the total liver blood flow (Q_{total}) ($r = 0.7239$, 95% confidence interval 0.3214–0.9049, $P = 0.0023$ and $r = 0.7226$, 95% confidence interval 0.3189–0.9044, $P = 0.0023$, respectively) (Fig. 3). In

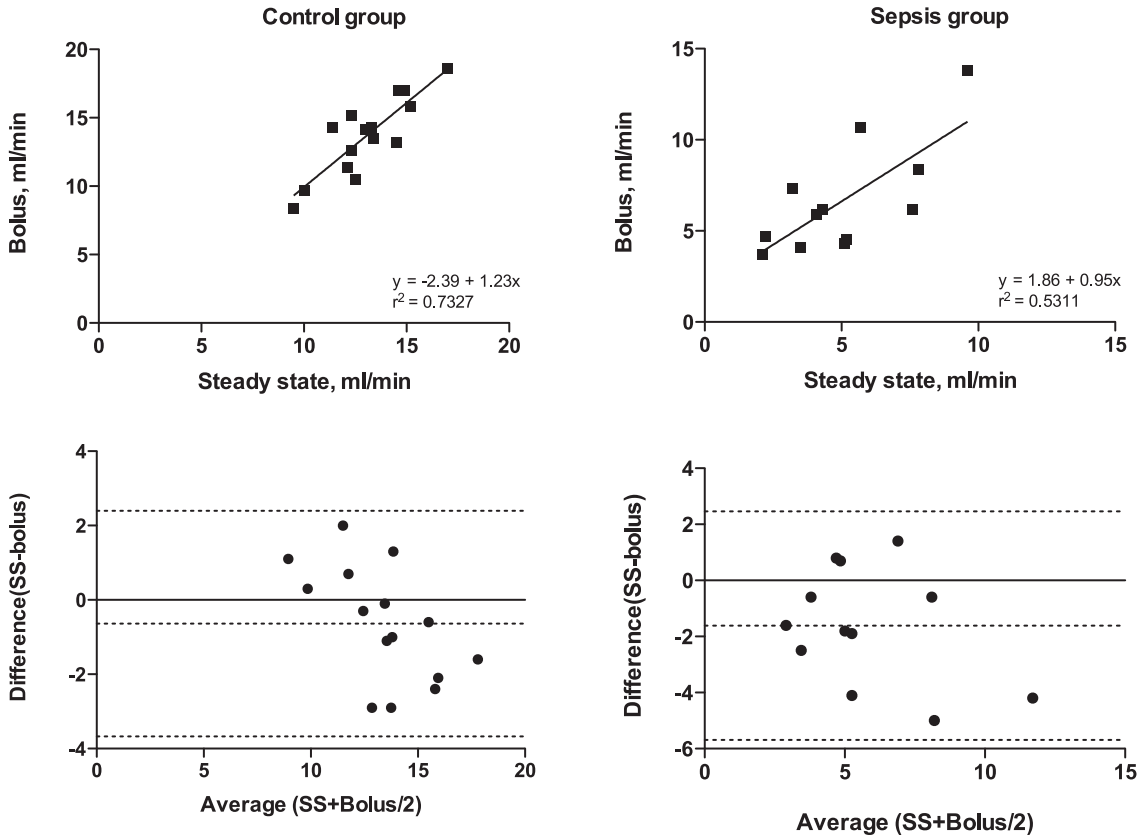

Fig. 2. Bolus vs. steady-state (SS) sorbitol.

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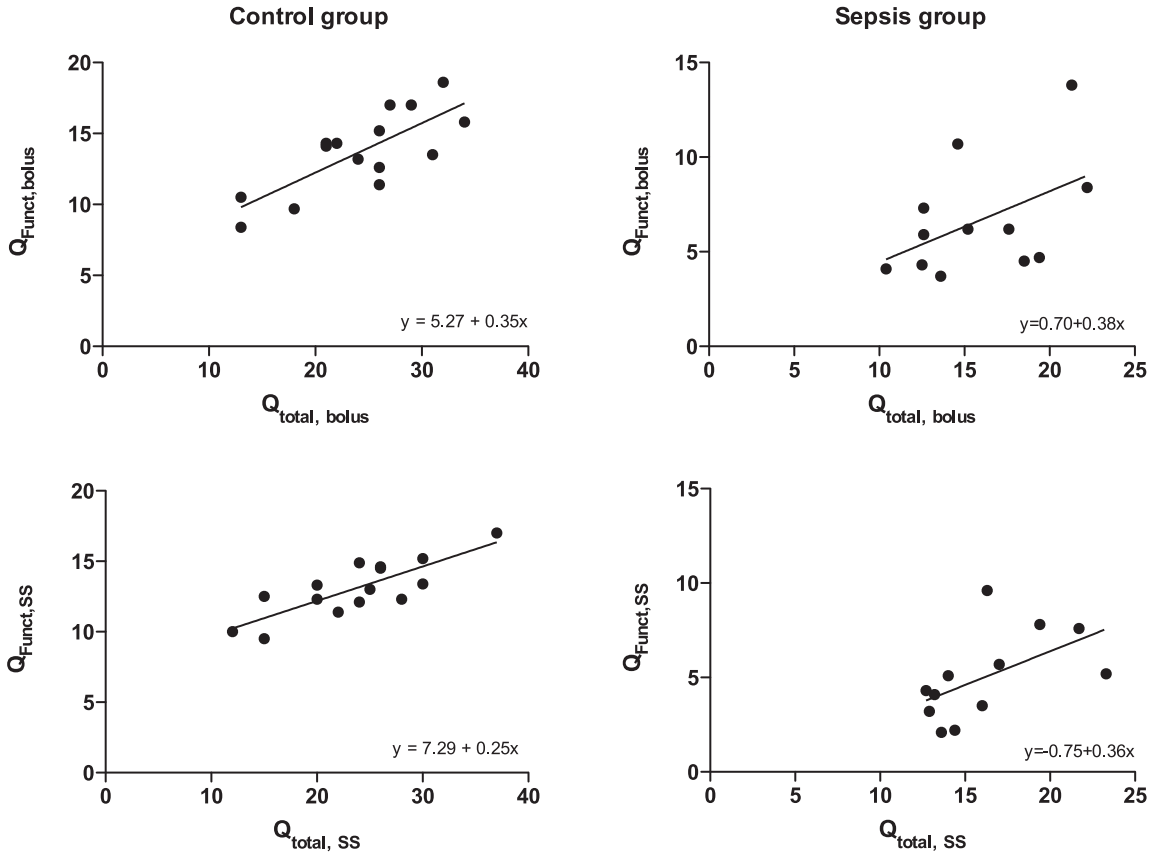

Fig. 3. Data on bolus and steady-state flow vs. total liver blood flow. Q_{funct}, functional liver blood flow; Q_{total}, total liver blood flow.

the sepsis group, only Q_{ss} correlated with Q_{total}, whereas Q_{bolus} did not (Fig. 3).

Because of the differences in the results in controls and septic animals of D-sorbitol clearance, we investigated a further two rats, before and after induction of endotoxin sepsis with sidestream dark-field imaging (SDF), a microvideo technique (8). Preliminary data show an increase in shunting of the microcirculation with a mean red cell velocity increase from 76.0 to 142.2 μm/s and a decrease in total vascular density from 29.0 to 25.9 mm/mm^2.

DISCUSSION

Our experiment showed a significant correlation of D-sorbitol plasma clearance between bolus dose and steady-state administration in normal control animals as well as in septic animals. In healthy conditions, the D-sorbitol plasma clearance also correlated well with total liver blood flow but not in sepsis. The latter could be explained by the changes in shunting of the hepatic microcirculation and decreased hepatocyte function as seen in septic conditions.

Renal clearance under normal circumstances was comparable with earlier findings (15, 23). In sepsis there was a significant reduction of renal clearance. To our knowledge, no previous data exist on renal sorbitol clearance in sepsis.

The overall hemodynamic data were stable throughout the experiment in both groups, except for cardiac output in the control group, which was significantly higher in the bolus phase. Because D-sorbitol is a substance without any known influence on cardiac performance, we have no valid explanation for this finding. However, the portal and arterial flow to the liver did not change during the experiment and did not change in the control group despite the higher cardiac output during bolus phase.

D-Sorbitol was administered using the same infusion pump for all animals to avoid any bias on the basis of possible inaccuracy of the pump itself. In contrast to others, we established a good correlation between total liver blood flow and FLBF in control animals. These may not necessarily be the same as portal and hepatic arterial blood flow because liver cell function, sinusoidal blood flow, and possible shunts in the liver circulation can vary substantially even under normal circumstances, depending, for instance, on feeding status and exertion (10, 14, 20). In our experiment, all animals had free access to food and water until the start of the experiment.

The differences of the hepatic sorbitol clearance in septic conditions compared with controls may be explained by increased shunting of the microcirculation, concomitant with differences in hepatocyte, stellate cells, and sinusoidal endothelial cell metabolism in sepsis (7, 12, 18). This may also explain that the hepatic sorbitol clearance after bolus dose did not correlate with the total inflow of blood to the liver in septic animals in contrast to steady state. During steady state, the plasma concentration of D-sorbitol is lower compared with bolus dose (Fig. 1). In a pilot experiment, we studied the subcapsular microcirculation of the liver with the SDF camera and showed that shunting is increased, consistent with the literature (8, 17).

Using D-sorbitol plasma clearance by the liver as a test substance for the estimation of liver blood flow without liver

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vein catheterization is controversial (10). In normal individuals, the extraction ratio is very high (0.90 or higher), but this can be reduced to values as low as 0.33 during liver failure (16, 23). This reduced extraction may be caused by intrahepatic shunting or by reduced hepatocyte removal of sorbitol. Even using more invasive liver vein sampling will not enable one to distinguish between this change in flow or metabolism because this will be a mixture of blood from possible shunts as well as from normal areas. Furthermore, in humans, there is a wide anatomical variation in liver vein architecture, which makes it difficult to assume that sampling in one branch is representative for the whole liver.

However, our aim was to establish the status of two techniques (applied in the same individual) of a relatively simple noninvasive measure of FLBF (1, 5, 14, 23), both under normal conditions as well as in pathological conditions such as sepsis. Our findings accentuate earlier work and in addition show a significant correlation between the two techniques. The steady-state technique will provide a reflection of FLBF over a period of several hours (14, 16), and the bolus dose method, therefore, has been used less frequently. In critically ill patients, however, the bolus dose would be more advantageous because of risk of hemodynamic instability over time. In the only study of D-sorbitol clearance in intensive care unit patients, a combination of a starting dose with short-term steady-state infusion and a single plasma sample at 60 min was used to determine liver function, but this can only give a superficial impression of the FLBF (11).

In conclusion, hepatic clearance of D-sorbitol either by bolus or a steady-state infusion is comparable under both healthy and septic conditions. In healthy conditions, this also correlated well with total liver blood flow but not in septic animals. However, this could be explained by the increase in shunting of the hepatic microcirculation in sepsis. Therefore, we believe that the bolus technique can be used in our target population of critically ill patients, and clinical studies should be performed.

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DISCLOSURES

No conflicts of interest are declared by the author(s).

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