Caval Backflow: A Potential Problem During Blood Sampling From the Hepatic Vein

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A proper measurement of splanchnic metabolism involves sampling blood from the hepatic vein without backflow contamination of blood from the caval vein. We have investigated the potential problem of caval backflow in human volunteers with an indwelling hepatic vein catheter by sampling blood with different amounts of suction on the syringe (ie, sampling speeds). We also investigated the potential problem in pigs in which a balloon catheter was inserted in the hepatic vein. Pure hepatic vein samples were obtained with the balloon inflated and compared with samples obtained from the same catheter in the conventional manner. In overnight fasted humans, drawing blood samples from the hepatic vein with minimal suction ("slow" drawing) resulted in glucose values 9.6% higher than drawing the samples with greater suction ("fast" drawing). The calculated arterial-venous balance across the splanchnic bed was 4.8 times greater with "slow" blood drawing as compared with "fast" drawing. Values obtained from the pigs showed no concentration differences between pure hepatic vein samples and "slow" drawing from the hepatic vein. The current study indicates that it is possible to obtain a "true" hepatic vein sample, but backflow from the caval vein is a potential pitfall that can have a physiologically significant impact on calculated balance data.

THE IN VIVO quantification of organ or tissue metabolism has traditionally involved the measurement of the difference in substrate concentration between the arterial blood entering the tissue and the venous blood leaving the tissue (A-V difference). The model calculations may also be based on the measurement of additional factors, such as the arterial and venous isotopic enrichment. The central assumptions of the A-V difference technique are that the venous sample is a good representation of all venous blood draining the tissue, and that there is no contamination of the venous sample with blood from other tissues. The later assumption, while rarely questioned, is a potential complication in the collection of any venous sample from a specific site. Proper placement of the catheter is 1 potential problem.[1] For example, in the popular forearm balance technique, the venous catheter is placed retrograde into a deep forearm vein. If the catheter is unknowingly passed into a more superficial vein, the blood drawn will reflect the metabolism of skin more than the metabolism of muscle. Another potential problem, which is generally less well recognized, is that backflow into a vein from other sources may contaminate a venous sample, even if the catheter is properly placed. Whereas the potential for backflow exists with any catheter placement, sampling from a hepatic vein catheter may be particularly problematic.[2] Backflow from the right heart into the hepatic vein has been well recognized clinically for a number of years and can be easily visualized by following the flow of dye injected into a hepatic vein.Figure 1 shows an example in which iodinated contrast material was injected into the inferior caval vein. The contrast proceeds to the right heart, and then there is backflow of contrast into the hepatic vein. Whereas the clinical circumstance may influence the extent to which the type of backflow shown in Fig 1 occurs, the fact that it can occur at all raises important questions regarding the validity of a hepatic vein sample as a good reflection of the blood leaving the liver. We have therefore investigated the problem in normal volunteers with an indwelling hepatic vein catheter. We tested the effect of sampling with a varying amount of back-pressure (ie, varying the rapidity of withdrawing the sample). We have also investigated this problem in pigs using a balloon catheter to sample either a pure hepatic vein sample (obtained when the balloon is inflated) or a hepatic vein sample obtained in the conventional manner (with no balloon inflation).

MATERIALS AND METHODS

Humans

One woman and 3 men, 26 to 34years old, all moderately overweight (body mass index, 28 to 29) were included in the study. The volunteers were healthy, as indicated by comprehensive history, physical examination, and standard blood and urine tests, and all had maintained stable weights for more than 3 months before the studies. The study was approved by the Institutional Review Board for Human Investigation at the University of Texas Medical Branch and informed consents were obtained for the procedures.

After overnight fasting, the volunteers were transferred to the Vascular Radiology Laboratory where, under local anesthesia and using standard percutaneous technique, the right femoral vein was punctured and a 6-Fr Terumo Introducer Sheath, length 8 cm, (Terumo Medical Corp, Elkton, MD) was introduced into the vein for caval vein blood samples. A 5-Fr Simmons II catheter (Angiodynamics, Oueensbury, NY) with 2 distal side holes was introduced through the sheath and the catheter tip placed in the right hepatic vein. This is a catheter commonly used for hepatic vein catheterization in which the length of the catheter in the hepatic vein is 6 cm. Catheter position was confirmed with fluoroscopy and injection of iodinated contrast material (Fig 2). A 4-Fr sampling catheter was placed in the right femoral artery and in the external iliac vein. The tip of the venous catheter was about 40 cm from the confluence with the hepatic vein. The subjects rested for about an

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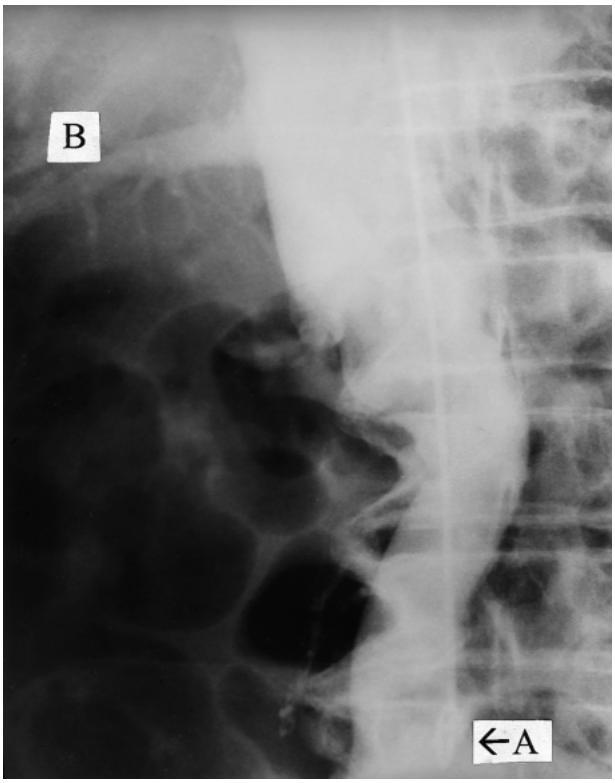

Fig 1. A straight catheter with the tip distal in the inferior caval vein (A) in a human subject. Iodinated contrast material is injected, and the contrast proceeds to the right heart, and then there is backflow of contrast into the hepatic vein (B).

hour after placement of the catheters. We then drew blood from the hepatic vein catheter at 3 different speeds; "fast", 3 mL drawn in 15 seconds; "intermediate", 3 mL drawn in 30 to 40 seconds; and "slow", 3 mL drawn in 60 to 70 seconds. After a rest of about 5 minutes, the procedure was repeated, but with the order of slow, intermediate, and fast sampling changed. After another 5 minutes of rest, the procedure was repeated for a third time with a different order of sampling. The values presented are thus the average of 3 samples. There was never more than 0.2 mg/dL difference in concentration of glucose between comparable samplings. In all cases, sampling was as continuous as possible with a free hand. Care was taken to avoid making a series of small, rapid, partial pulls of the piston of the syringe. Blood was drawn from the femoral artery and caval vein simultaneously with the hepatic vein sample. All blood samples were drawn into 3 cc syringes with an internal diameter of 0.84 cm. Plasma glucose concentration was measured immediately using an automated glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). The blood flow across the liver was calculated using Indocyanine green (ICG). The blood was drawn slowly for the ICG measurements.

Pigs

Four pigs (weight, 13 to 15 kg) were fasted overnight. Under general anesthesia, a straight balloon-catheter was placed from the right jugular vein and positioned with the tip deep into the right or middle hepatic vein. The position was confirmed with fluoroscopy and injection of iodinated contrast material. We drew blood 4 times with the balloon first deflated and then inflated. The drawing speed was "intermediate", 10 to 13 seconds/mL. Blood was drawn from the carotid artery and cava superior vein simultaneously with the hepatic vein sample.

We used perivascular flow probes around the common hepatic artery and portal vein to measure blood flow through the liver (Transonic Animal Research Flowmeter; Transonic Systems, Ithaca, NY).

The experimental protocol for isotopic tracer infusion is shown in Fig 3. The pigs received a prime of 17.6 μmol/kg followed by 140 minutes continuous infusion of (0.22 μmol/kg/min) 6,6-d_2-glucose (98% enriched; Isotec, Miamisburg, OH), and a prime of 4.02 μmol/kg, and continuous infusion of (0.2 μmol/kg/min) d_5-glycerol (98% enriched; Isotec) through a central venous catheter. Sixty minutes after starting the first 2 infusions, the pigs received a prime of 30 μmol/kg followed by 80 minutes continuous infusion of (2 μmol/kg/min) 2-^{13}C-lactate (99% enriched; Isotec). Blood was drawn simultaneously from all sites at 0, 120, 130, and 140 minutes after the start of the isotopic tracer infusions.

This experimental protocol was approved by the Animal Care and Use Committee of the University of Texas Medical Branch (ACUC 90-09-103-1).

RESULTS

Blood drawn "fast" from the human hepatic veins resulted in mean blood glucose values only 1.3% higher than when drawn from the caval vein (Table 1). Blood drawn at "intermediate"

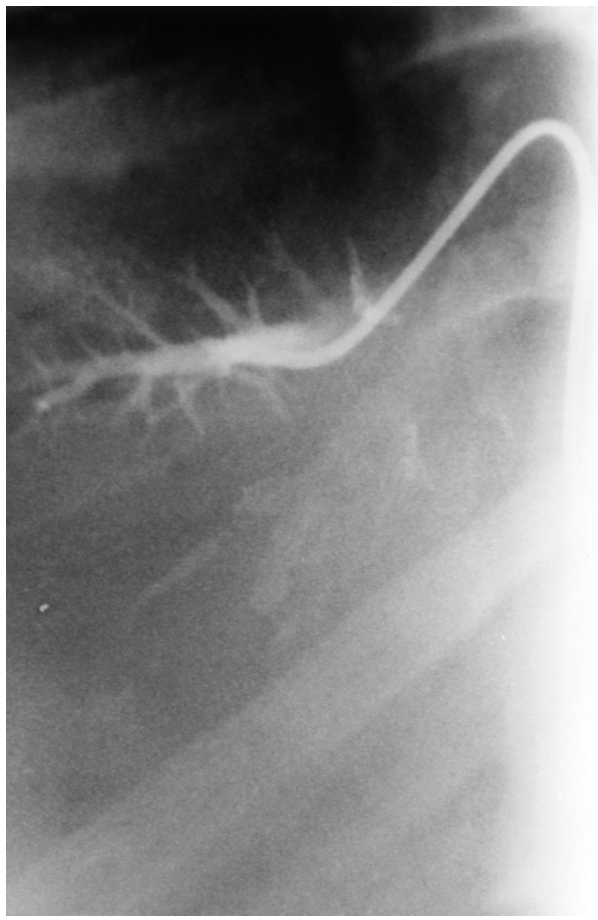

Fig 2. A catheter placed from the femoral vein with the tip properly in the hepatic vein in a human subject.

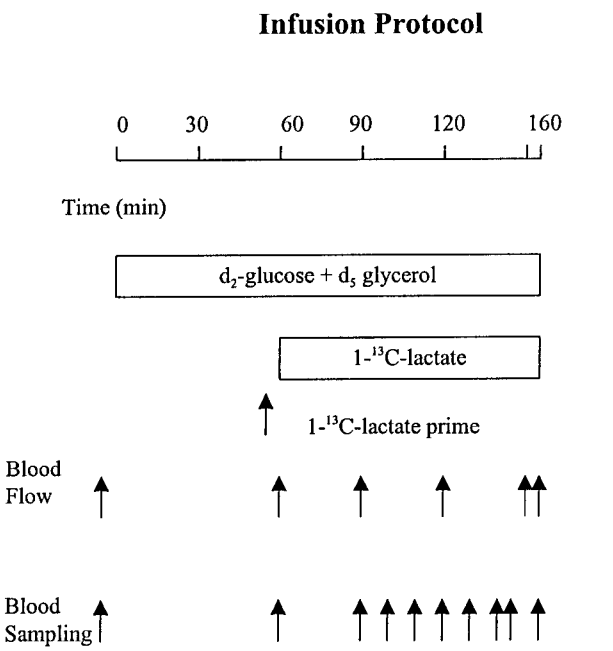

Fig 3. Schematic diagram of the experimental protocol in the pig study.

speed resulted in blood glucose values 5.5% higher than if the blood was drawn "fast". Drawing the samples with "slow" speed resulted in glucose values 9.6% higher than drawing the samples "fast".

Subject 1 was 90 kg, and blood flow across the liver was calculated to 1,223 mL/min; subjects 2, 3, and 4 were 92, 95, and 96 kg, respectively, and blood flow rates were 1,071, 1,087 and 1,142 mL/min, respectively. Blood flows were determined from samples drawn slowly.

Table 2 shows that the calculated AV-balance across the liver was 4.8 times greater with "slow" blood drawing compared with "fast" drawing.

The hepatic blood flow in the pigs varied between 340 mL/min and 430 mL/min (mean, 385 mL/min).

Table 3 shows the mean of 4 values measured in samples drawn from the hepatic vein in pigs with the balloon first deflated and then inflated. There were no significant differences in concentrations or tracer/tracee ratios across the liver between samples drawn with a deflated or an inflated balloon.

Table 1. Human Glucose Concentrations (mg/dL)

Subject	Femoral Artery	Caval Vein	Hepatic Vein Fast	Hepatic Vein Intermediate
1	85.5	88.0	89.5	91.3
2	86.2	86.8	87.9	93.7
3	86.1	86.2	87.0	94.1
4	88.4	89.2	90.3	95.1
Mean ± SEM	86.6 ± 0.6	87.6 ± 0.7	88.7 ± 0.7	93.6 ± 0.8

NOTE. Fast, intermediate, and slow refer to sampling speed.

Table 2. Arterial-Venous Glucose Balance Across the Human Liver

Subject	Fast	Intermediate	Slow
1	0.54	0.79	1.52
2	0.20	0.87	1.06
3	0.10	0.92	1.24
4	0.23	0.80	1.29
Mean ± SEM	0.27 ± 0.09	0.84 ± 0.03	1.29 ± 0.10

NOTE. Units are mg/min/kg.

DISCUSSION

The measurement of the A-V balance across tissues or organs has long been considered to be the "gold standard" for quantitation of metabolic fluxes, and when tracer-derived values have not agreed with values obtained by A-V balance, the tracer data has generally been assumed to be incorrect. However, this attitude likely stems from the conceptual simplicity of the A-V balance technique. The conceptual simplicity of the technique notwithstanding, the method requires truly representative blood samples. The current study indicates that while on the one hand it is possible to obtain a "true" hepatic vein sample, on the other hand, it is possible that backflow from the caval vein is a potential pitfall that can have a physiologically significant impact on calculated balance data.

The problem with hepatic backflow contaminating a hepatic vein sample is amplified when there is a large difference in concentration between the hepatic vein and vena caval blood. This is commonly the case for substances either produced (eg, glucose) or taken up (eg, glycerol) largely by the liver. In our human study, the glucose concentration in the hepatic vein after overnight fasting was 9.6% higher if we drew the samples slowly as compared with drawing quickly, and this resulted in almost a 5-fold difference in the calculated AV difference in the substrate concentrations. Calculation of balance also requires measurement of blood flow and with ICG contamination of the hepatic vein sample with caval blood would also affect the calculation of the rate of blood flow when the ICG technique is used. If we had drawn the ICG samples fast, contamination of hepatic vein blood with blood from the caval vein would have increased the calculated ICG concentration because the hepatic vein concentration was lower than the caval blood. This would thus diminish the apparent A-V difference of dye across the splanchnic bed, thereby causing an overestimation of the blood flow rate, which would tend to modify the error caused by the erroneous measurement of glucose.

The magnitude of the potential problem caused by contamination of a hepatic vein sample can be illustrated by considering data from a recent report from our laboratory,[3] in which regional acetate kinetics were reported. Average values were as follows: hepatic blood flow, 1.10 L/min; arterial acetate concentration, 124.9 μmol/L; hepatic vein acetate concentration, 141.7 μmol/L; and peripheral venous acetate concentration,

Table 3. Effect of Sampling Mode on Values From Pigs

	Glycerol		Glucose		Lactate	
	Concentration	Ratio	Concentration	Ratio	Concentration	Ratio
Artery						
Deflate	0.005	0.098 ± 0.006	108	0.054 ± 0.002	4.0	0.058 ± 0.002
Inflate	0.004	0.095 ± 0.003	109	0.052 ± 0.001	4.0	0.059 ± 0.003
Central vein						
Deflate	0.004	0.102 ± 0.005	109	0.055 ± 0.001	4.5	0.068 ± 0.004
Inflate	0.005	0.096 ± 0.008	110	0.054 ± 0.001	4.4	0.067 ± 0.003
Hepatic vein						
Deflate	0.002	0.011 ± 0.001	126	0.040 ± 0.001	3.2	0.046 ± 0.002
Inflate	0.002	0.013 ± 0.001	123	0.039 ± 0.001	3.3	0.057 ± 0.006

NOTE. Ratio represents tracer/tracee ratio. Glycerol concentration, μmol/mL; glucose concentration, mg/dL; and lactate concentration, mmol/L.

77.8 μmol/L. From these data, it can be calculated that the net splanchnic release of acetate was 18.5 μmol/min. If, however, the hepatic vein sample was contaminated with 10% of blood from the caval vein, this would mean that the true hepatic vein acetate concentration was actually 135.3 μmol/L (rather than 141.7 μmol/L). Using the "true" value, the newly calculated splanchnic release would be 11.4 μmol/min. Thus, a 10% contamination of sampled blood would result in a 62% overestimation of the true balance. In the case in which blood flow is determined via flow probes as we did in the pig studies reported here, contamination of hepatic vein blood would not affect the calculation of flow, and thus the ultimate value for splanchnic balance. However, in the case in which the dilution of ICG is used to calculate blood flow (as we did in the acetete experiment), then 10% contamination with caval blood would cause an overestimation of splanchnic blood flow, meaning the true balance of acetate would have been even less than 11.4 μmol/min, and thus the error in calculated splanchnic balance even greater than 68%. The same calculations can be extended to evaluate the impact of a 10% contamination on isotopic enrichment. In the particular example of acetate, the following were the enrichment values we obtained at isotopic equilibrium (tracer/tracee ratio): arterial, 0.447; hepatic vein, 0.134; and caval blood, 0.223. When the same calculations are applied as described above, we find that a 10% contamination of hepatic vein blood would cause the calculated fractional extraction to only change from 0.66 to 0.65. Thus, the magnitude of error depends on the specific values obtained and subsequent calculations. The point of this practical example is simply that what might seem to be a minor problem (ie, a 10% error) can become either magnified or diminished when final values are calculated. Given the potential for backflow, as demonstrated in Fig 1, and the influence of the speed of sampling shown in the current study, it is clear that care must be taken to ensure accurate values using the A-V balance technique.

Hepatic vein catheterization is fairly commonly executed from the femoral vein. It is safer than catheterization from the jugular or brachial vein because a catheter through the superior caval vein can easily pass into the right atrium and cause cardiac arrhythmia. Volunteers also find it more unpleasant to be punctured in the neck than in the groin. In our study, we used a catheter that is commonly used for hepatic catheterization from the femoral vein, and the length of the catheter into the hepatic vein is 6 cm. A straight catheter inserted from the jugular or brachial vein can easily be placed deeper into the hepatic vein and decrease the risk of caval backflow. However, deeper placement of the catheter tip into the liver also increases the risk of spontaneous wedging. Spontaneous wedging occurs occasionally because the liver moves with respiration and may inhibit drawing from a single distal catheter opening. To prevent this problem, it is common to make side holes in the catheter or use specially ordered catheters with 4 distal side holes.[4] In our study, we made 2 side holes 2 to 3 mm from the catheter tip. Whereas side holes decrease the likelihood of sampling being limited by wedging, side holes in a hepatic catheter increase the risk of contamination of the samples with caval blood.

In addition to problems related to caval backflow, several other problems can occur after the catheter has been placed. In our experience, dislocation of the catheter is the most common. Moving the patient from the x-ray table to the cart or to the bed, or bending at the hip, may dislocate the catheter tip to a position in which it is close to the caval junction, or actually in the caval vein. Catheter occlusion by thrombus is also a well-known technical problem. Consequently, it is necessary to confirm location of the catheter at the conclusion of an experiment.

Given the potential magnitude of the problem of contamination of hepatic vein samples, it would be useful for the investigator to have a strategy to determine before proceeding with a study that the catheters are positioned properly and that the sampling technique is appropriate. Given the large errors shown in Table 2 for glucose and the relative constancy of fasting hepatic glucose production in normal subjects,[5] it is reasonable to make a quick determination of splanchnic glucose balance, because measurements can be made quickly and accurately. Although it is never possible to be sure that the values obtained from a human study are the "true" values, because a baloon catheter is not a viable option, the results from the pig study show that the "slow" sampling technique can reflect the "true" hepatic vein values. Thus, obtaining reasonable values for splanchnic glucose balance (even if glucose is not the substrate of interest) would be a viable confirmation of the validity of the experimental technique.

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