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# **Human taurine metabolism: fluxes and fractional extraction rates of gut, liver and kidneys**

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## ABSTRACT

Taurine is involved in numerous biological processes. However, taurine plasma level decreases in response to pathological conditions, suggesting an increased need. Knowledge on human taurine metabolism is scarce and only described by arterial-venous differences across a single organ. Here, we present taurine organ fluxes using arterial-venous concentration differences combined with blood flow measurements across the three major organ systems involved in human taurine metabolism in patients undergoing hepatic surgery. In these patients, we collected blood from an arterial line, portal vein, hepatic vein and renal vein, and determined blood flow of the hepatic artery, portal vein, and renal vein using Doppler ultrasound. Plasma taurine was determined by high-performance liquid chromatography, and net organ fluxes and fractional extraction rates were calculated. Seventeen patients were studied. No differences were found between taurine concentrations in arterial, portal venous, hepatic venous, and renal venous plasma. The only significant finding was a release of taurine by the portally drained viscera ( $p=0.04$ ). Our data show a net release of taurine by the gut. This probably is explained by the enterohepatic cycle of taurine. Future studies on human taurine metabolism are required to determine whether taurine is an essential aminosulfonic acid during pathological conditions and whether it should therefore be supplemented.

## INTRODUCTION

Taurine plasma levels decrease in response to surgical injury, trauma, sepsis, and cancer, which suggests an increased metabolic need<sup>1,2</sup>. Indeed, supplementing taurine in models of metabolic or ischemic stress improves postoperative insulin resistance and reduces oxidative stress and ischemia-reperfusion injury<sup>3-6</sup>.

The main organs involved in taurine metabolism are the gut, liver, and kidneys. The gut regulates taurine uptake from the diet by a specific taurine transporter<sup>7</sup>. The liver is involved in endogenous taurine production and in formation of bile acids containing taurine<sup>8</sup>. The kidneys are the main sites of excretion of taurine<sup>9</sup>.

Current knowledge on taurine metabolism mainly stems from animal experimental work, with very few human data. Further knowledge on human taurine metabolism is needed because taurine supplementation is considered in stress states. Therefore, an exploratory study was performed in humans undergoing hepatic surgery to determine taurine organ fluxes and fractional extraction (FE) rates across the gut, liver, and kidneys.

## PATIENTS AND METHODS

This exploratory study was set up as part of a study that investigated the metabolism of dimethylarginines in human liver and kidneys<sup>10</sup>. The institutional review board and local medical ethics review committee approved the study. Informed consent was obtained.

### Patients

Patients underwent partial liver resection for colorectal metastases at the VU University Medical Center, Amsterdam, the Netherlands. Inclusion and exclusion criteria were similar to those described by Siroen et al<sup>10</sup>. Patients were scheduled for surgery at the beginning of the day after an overnight fast. Measurements were done in a steady state of anesthesia and after gaining access to the abdominal cavity.

### Doppler ultrasound measurements

An experienced radiologist measured blood flow during surgery by color Doppler ultrasound (Aloka Prosound SSD 5000, Aloka, Tokyo, Japan) as previously described by Siroen et al<sup>10</sup>.

### Blood sampling and analysis

After flow measurements, one blood sample each was collected from an arterial line, the portal vein, the hepatic vein, and the right renal vein. Blood samples for taurine

measurement were collected, processed, and measured as previously described<sup>11</sup>. Kidney and liver function was analyzed by routine laboratory procedures.

### Calculations

Net organ fluxes. Net taurine fluxes across the portally drained viscera (PDV) (representing the gut), liver, and kidneys were calculated using the following equation: net organ flux (nmol/L) = ([A] - [V]) \* F, where [A] is the arterial plasma taurine concentration, [V] is the venous plasma taurine concentration, and F is the plasma flow through the organ. A negative value indicated release, and a positive value indicated uptake.

The net PDV flux was calculated using the portal vein plasma flow [F(PV)] and the arterial - portal venous ([PV]) taurine concentration difference: net PDV flux = ([A] - [PV]) \* F(PV).

The net kidneys flux was calculated using the renal plasma flow [F(RV)] and the arterial - right renal venous ([RV]) taurine concentration difference of the right kidney. Flow through both kidneys was calculated by multiplying the measured renal flow by two: net kidneys flux = ([A] - [RV]) \* (F(RV) \* 2).

The net liver flux was calculated using the splanchnic flux and the flux across the PDV: net liver flux = splanchnic flux - PDV flux; net splanchnic flux = ([A] - [HV]) \* F(HA + PV), where [HV] is the plasma taurine concentration in the hepatic vein and F(HA + PV) is the mean plasma flow in hepatic artery plus the mean plasma flow in the portal vein.

Net FE. Net FE of taurine by the PDV and kidneys was calculated using the following equation: net FE = ([A] - [V]) / [A]. The FE of taurine by the liver was calculated as previously described by Siroen et al<sup>10</sup>. A positive value indicated a net uptake. If the value is negative, the FE was considered to be absent.

### Statistical analysis

Results were presented as median and interquartile range (IQR). The Wilcoxon signed rank test was used to determine if the organ fluxes and FE rates differed significantly from zero. Statistical analysis was performed with SPSS 18.0 for Windows (SPSS, Chicago, IL). A P value < 0.05 was considered significant.

## RESULTS

### Patients

Patient characteristics (n = 17) are presented in Table 1.

**Table 1.** Demographic data

Characteristics	Values
Number of patients	17
Sex: male / female	12 / 5
Age (years; median (range))	65 (37-79)
Weight (kg)	78 (70-87)
Height (cm)	173 (164-178)
BMI	25 (24-27)
Biochemical markers of hepatic function	
- Bilirubin ( $\mu\text{mol/L}$ )	8 (6-9)
- AST (U/L)	21 (18-30)
- ALT (U/L)	17 (16-30)
- LD (U/L)	334 (316-495)
- $\gamma$ -GT (U/L)	29 (21-51)
- AP (U/L)	91 (81-122)
- PT (INR)	1 (0.98-1.1)
- Albumin (g/L)	39 (35-41)
Biochemical markers of inflammation	
- CRP (mg/L)	4.0 (2.5-10.5)
- ESR (mm/hr)	11 (6-23)
- WBC ( $10^9/\text{L}$ )	6.8 (5.9-7.5)
Biochemical markers of renal function	
- Creatinine ( $\mu\text{mol/L}$ )	88 (78-94)
- Creatinine clearance* (mL/min)	90 (71-106)
- Urea (mmol/L)	5.2 (4.3-5.8)

Data are presented as median and IQR unless otherwise stated; \*Creatinine clearance is calculated using the Cockcroft Gault formula and then corrected by multiplying with the body surface area. Abbreviations: BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LD: lactate dehydrogenase;  $\gamma$ -GT:  $\gamma$ -glutamyl transpeptidase; AP: alkaline phosphatase; PT: prothrombin time given as INR (International Normalised Ratio); CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell count.

### Organ plasma flows and taurine plasma concentrations

Mean arterial blood pressure remained stable during the Doppler ultrasound measurements. Table 2 presents gut, liver, and kidney plasma flows and taurine concentrations in the different vessels. The plasma concentrations of taurine were similar and in the reference range (38-197  $\mu\text{mol/L}$ )<sup>11</sup>.

**Table 2.** Gut, liver and kidney plasma flows and taurine plasma concentrations

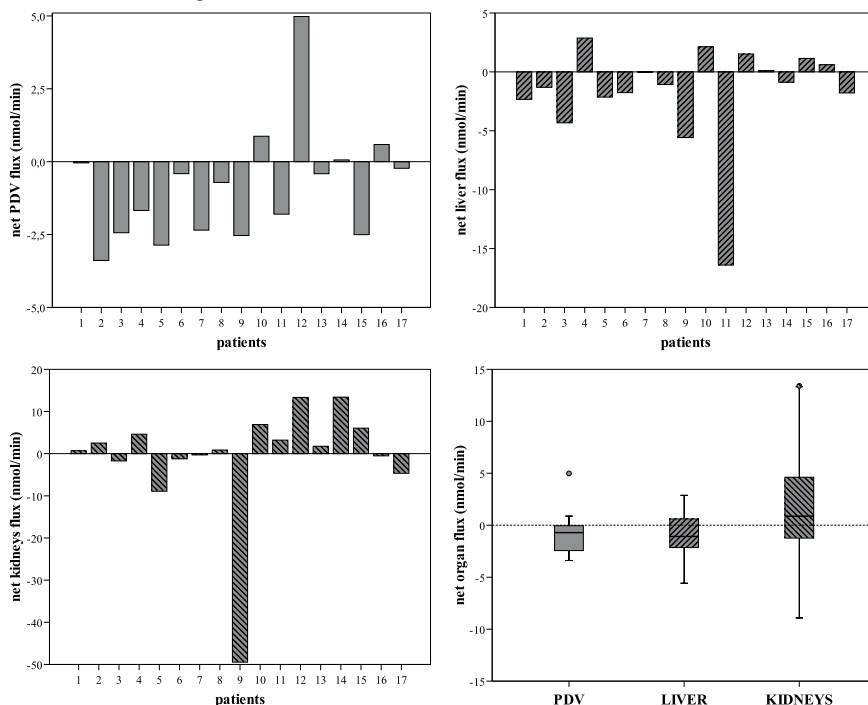
	Flow (mL/min)	Taurine ( $\mu\text{mol/L}$ )
<b>Gut</b>		
Portal vein	316 (178-421)	72 (65-80)
<b>Liver</b>		
Hepatic artery	67 (41-188)	-
Total (portal vein + hepatic artery)	372 (285-583)	-
Hepatic vein	-	72 (70-84)
<b>Kidney</b>		
Right renal vein	284 (132-414)	69 (63-75)
<b>Artery</b>	-	72 (62-76)

Data are presented as median and IQR.

### Net PDV flux, net liver flux, net kidneys flux, and FE's

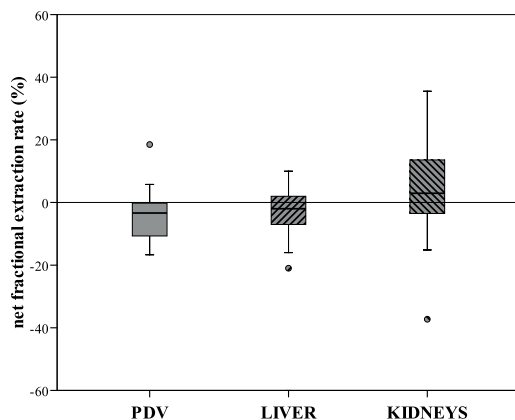
The individual and group net PDV fluxes of taurine, representing the net gut flux, are shown in Figure 1A and D. The main finding was a mean release of taurine by the gut ( $P = 0.04$ ). The mean net liver flux was not significantly different from zero ( $P = 0.12$ ) (Figure 1B, D). The mean net kidney flux was not significantly different from zero ( $P = 0.33$ ) (Figure 1C, D).

**Figure 1.** Net taurine organ fluxes



**A.** Net taurine flux over the PDV per patient; **B.** Net taurine flux over the liver per patient; **C.** Net taurine flux over the kidneys per patient; **D.** Box plots of the net taurine organ fluxes over the PDV, liver and kidneys.

Figure 2 shows the FE of taurine. Gut FE of taurine was significantly different from zero ( $P = 0.04$ ). No FE of taurine by the liver or kidneys was observed.



**Figure 2.** Net fractional extraction rates

The PDV FE rate differs significantly from zero ( $p = 0.04$ ). The liver and kidney FE rates differ not significantly from zero ( $p = 0.23$  vs.  $p = 0.41$ ).

## DISCUSSION

This study is the first to show taurine net organ fluxes and FE rates across the PDV, liver, and kidneys in humans. An important finding of the present study was release of taurine by the gut. Felig et al <sup>12</sup> also found a gut release of taurine using arterial-portal venous concentration differences in patients undergoing elective cholecystectomy. In rats, Garcia and Stipanuk <sup>13</sup> also showed gut release of taurine using arterial-venous concentration differences. They suggested that gut release of taurine depends on intraluminal turnover as part of the enterohepatic cycle because the gut lacks the appropriate enzymes for taurine production <sup>13</sup>. Houdijk et al <sup>14</sup> showed gut uptake of taurine when depleting the gut lumen from biliary taurine by interrupting the enterohepatic cycle using bile duct ligation. O'Flaherty et al <sup>15</sup> noticed a significant depletion of taurine in duodenal mucosa of critically ill patients, suggesting a gut storage function for taurine. This makes sense considering the very high intramucosal concentration of taurine in normal human duodenum (90 times higher than plasma level).

The quality of blood flow measurement is crucial in the determination of organ substrate net fluxes. A small arteriovenous concentration difference may result in a substantial substrate flux in the presence of high blood flows. We used a Doppler ultrasound method with the probe in direct contact with the vessel of interest. Other known methods for measurement of blood flow across intra-abdominal organs are more indirect and not suitable for comparing results, such as the Doppler ultrasound method used with the probe on the skin, contrast-enhanced ultrasound, or p-aminohippuric acid



clearance<sup>16-18</sup>. Using the direct Doppler ultrasound technique, Van de Poll et al<sup>19</sup> and Vermeulen et al<sup>20</sup> found similar mean portal and renal plasma flow rates in patients undergoing partial hepatectomy (portal, 320 mL/min; mean 2 kidneys, 606 mL/min) and in patients undergoing major abdominal surgery (portal, 375 mL/min; median renal, 225 mL/min), respectively.

### **Strengths and weaknesses**

Taurine concentrations were measured in plasma and not in whole blood, in which concentrations are 3.6 times higher. However, differences in cellular blood volume did not influence our results because hematocrit values of the blood samples did not differ<sup>12,13</sup>.

Plasma samples taken at a single time point only reflect a momentary status of the taurine metabolism, which is dynamic in character. Therefore, the results should be interpreted with caution. Another unavoidable limitation of the study is that blood samples were taken during surgery and not in unstressed healthy subjects. However, human blood samples from both afferent and efferent vessels of the gut, liver, and kidneys can only be collected during surgery.

Using net organ fluxes only allows conclusions on release from or uptake by an organ, but gives no information on consumption or production of the substrate. Our results therefore can only be interpreted bearing this in mind. Studies using isotopes of precursor molecules of the substrate itself are needed to investigate metabolic turnover at the organ level.

## **CONCLUSION**

This study showed that the gut releases taurine during surgery, which in the fasted state probably results from uptake of deconjugated taurine containing bile acids.

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