# Sympathetic Discharge to Mesenteric Organs and the Liver

## Evidence for Substantial Mesenteric Organ Norepinephrine Spillover

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## Abstract

**This study used sampling of blood from the portal vein, in addition to arterial and hepatic sites, to estimate separately spillovers of norepinephrine from mesenteric organs and the liver in seven patients undergoing upper abdominal surgery. Conventional measurements in arterial and hepatic venous plasma provided a measure of net hepatomesenteric NE spillover (403 pmol/ml) that indicated a 13% contribution of these organs to total body spillover of NE into systemic plasma (3,071±518 pmol/min). The net hepatomesenteric spillover of NE into systemic plasma was much lower than the spillover of NE from mesenteric organs into portal venous plasma (1,684±418 pmol/min). This and the hepatic spillover of NE into systemic plasma (212±72 pmol/min) indicated a considerable combined spillover of NE from hepatomesenteric organs (1,896±455 pmol/min). The sum of the latter estimate with the difference between total body and net hepatomesenteric NE spillovers provided an adjusted total body spillover of NE into both systemic and portal venous plasma (4,564±902 pmol/min). Mesenteric organs made a 37% contribution, and the liver made a 5% contribution to the adjusted total body spillover of NE. Thus, a substantial proportion of total body sympathetic outflow is directed towards mesenteric organs; this is obscured by efficient hepatic extraction of NE (86±6%) when measurements are restricted to arterial and hepatic venous plasma. (*J. Clin. Invest.* 1996. 97:1640–1646.) Key words: sympathetic nervous system • splanchnic circulation • portal system • portal vein • liver**

## Introduction

Sympathetic nerves regulate several important processes in mesenteric organs (i.e., gastrointestinal tract, pancreas, and spleen) and the liver (1–5). Examination of the extent and function of sympathetic outflow to hepatomesenteric organs is, however, hindered by the relative inaccessibility of these organs to physiological investigation and the limitations of available methods to study sympathetic function in vivo.

Measurements of plasma NE, the primary transmitter released by sympathetic nerves, provide the most commonly used index of sympathetic outflow. Regional examination of sympathetic outflow requires more complex analysis that includes intravenous infusions of trace amounts of tritium-labeled NE ([$^3$H]NE) and sampling of blood flowing into and out of the organ or tissue under investigation (6). Increased dilution of the tracer with endogenous NE from inflowing to outflowing plasma reflects local release of transmitter and provides the basis of NE spillover measurements. These measurements reflect the amount of NE escaping local sites of release into the bloodstream and provide a reasonable index of sympathetic outflow (7). However, estimated NE spillovers are also dependent on removal processes that intervene between sites of release and measurement in the bloodstream (8).

Clinical studies combining the above radiotracer methodology with sampling of blood from arterial and hepatic venous sites indicated a $< 6\%$ contribution of hepatomesenteric organs to total body NE spillover (6, 7, 9, 10). This minor contribution is surprising given the extensive and dense sympathetic innervation of mesenteric organs (11) and the importance of this organ system for hemodynamic regulation (5). However, previous clinical studies of hepatomesenteric NE spillover (6, 7, 9, 10) ignored the portal nature of the hepatomesenteric circulation, where efficient removal of NE by the liver may obscure NE release into portal venous plasma from mesenteric organs.

Studies in pigs, that accounted for the efficient hepatic extraction of NE by sampling blood from the portal vein in addition to the commonly used arterial and hepatic venous sites, revealed that mesenteric organs make a major contribution to total body NE spillover (12) and turnover (13). Estimates of net hepatomesenteric NE spillover, derived from arterial and hepatic venous blood samples, were found to be much lower than the combined spillovers from mesenteric organs and the liver that were estimated using additional blood samples taken from the portal vein (12). Whether a similar situation occurs in humans has not been established, but could impact importantly on existing evidence that in humans hepatomesenteric organs receive a negligible proportion of total body sympathetic outflow (6, 7, 9, 10).

In the present study, blood was sampled from the portal vein, in addition to arterial and hepatic venous sites, to estimate spillovers of NE separately from mesenteric organs and the liver in seven patients undergoing upper abdominal surgery. Other procedures were carried out in pigs to establish whether any difference in the hepatic extraction of NE from portal venous and arterial inflows could affect estimates of NE spillover from the liver. The study addressed two central issues: (*a*) How do separate estimates of mesenteric and hepatic NE spillovers relate to estimates of net hepatomesenteric NE spillovers? (*b*) What is the extent of sympathetic outflow to mesenteric organs and the liver relative to total body sympathetic outflow?

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*Received for publication 18 September 1995 and accepted in revised form 19 January 1996.*

The Journal of Clinical Investigation
Volume 97, Number 7, April 1996, 1640–1646

## Methods

### *Clinical studies*

*Subjects.* Seven patients (two females, five males; age 47–71 yr, mean 63) gave their informed, written consent to participate in the study, which was approved by the Ethics Committee of Göteborg University. All patients were undergoing surgery for medium to well differentiated gastric adenocarcinoma. No signs of hepatic or distant metastases were found in any patient. Blood hemoglobin and serum levels of alanine aminotransferase, alkaline phosphatase, bilirubin, and electrolytes were within normal limits in all subjects except one; in this patient alanine aminotransferase was elevated for unknown reasons (2.4 mkat/liter). All patients received omeprazole daily. One patient was receiving metoprolol and spironolactone for primary hypertension. The others received no additional drugs and had no history of cardiovascular disease. All above medications were withdrawn and patients were fasted for 12 h before surgery.

*Anesthesia.* Lorazepam (1 mg) was administered 2 h preoperatively. Anesthesia was induced with sodium thiopental (3–5 mg/kg body wt) and vecuronium bromide (1.5 mg/kg) and maintained using enflurane (0.5–0.7 minimum alveolar anesthetic concentration). Fentanyl (2.5–3 mg/kg) was given at induction of anesthesia as a bolus. All patients were intubated and mechanically ventilated with 30% oxygen and 70% nitrous oxide. Atropine, catecholamines, and β-blockers were avoided during studies. Subjects were not volume loaded, and central venous pressure was within normal limits.

*Radiotracer infusion.* Tritium-labeled NE (levo-[2,5,6-$^3$H]NE, 40–60 Ci/mmol; New England Nuclear, Boston, MA) was diluted in 0.9% saline containing 1 mM ascorbic acid and infused continuously into an antecubital vein at 1.0 μCi/min (0.4 ml/min). The radiotracer infusion was started at least 30 min before blood sampling to ensure attainment of steady-state plasma [$^3$H]NE levels (14).

*Placement of catheters and flow probes.* A catheter was placed percutaneously in a radial artery for sampling blood and recording blood pressure. Another catheter (7 French) was placed, under fluoroscopic guidance, into the right hepatic vein via a femoral vein using the Seldinger technique. An upper midline laparotomy was performed. The portal vein and the hepatic artery were dissected free in the hepatoduodenal ligament, with care not to damage perivascular nerve fibers. Ultrasound transit-time flow probes (Transonic Systems Inc., Ithaca, NY) were positioned around the portal vein (16–18 mm inner probe diameter) and the hepatic artery (6–8 mm inner probe diameter). Both probes were connected to a HT207 dual channel flowmeter (Transonic Systems Inc.).

*Blood samples and flow measurements.* Portal venous blood flow (ml/min, $Q_{PV}$) and hepatic arterial blood flow (ml/min, $Q_{HA}$) were measured after a 30 min stabilization period. Blood samples (20 ml) were then collected simultaneously from arterial, hepatic venous, and portal venous (direct venipuncture) sites into ice-chilled plastic syringes. Samples were transferred immediately into ice-chilled plastic tubes containing EDTA and reduced glutathione and placed on ice until the end of the study. Anesthetic and surgical procedures were then continued as required for each patient.

### *Preclinical studies*

*Animals.* Nine Swedish landrace pigs of either sex, weighing 32±2.8 kg (mean±SD), were used in the study, which was approved by Göteborg Committee for Ethical Review of Animal Experiments. Animals were fasted overnight with free access to water.

*Anesthesia and preparation for study.* Anesthesia was induced by intramuscular injection of ketamine (30 mg/kg) and maintained with α-chloralose as described in detail elsewhere (12). Catheters were placed in the femoral artery, the hepatic artery (via the pancreaticoduodenal artery), the portal vein, and the internal jugular vein (advanced to a central venous position).

*Procedure.* Tritium labeled NE (levo-[2,5,6-$^3$H]NE, 40–60 Ci/mmol; New England Nuclear) was injected as a bolus (2.74 μCi in 5 ml 0.9% saline) into the hepatic artery, the portal vein, and the internal jugular vein. Injections were randomized and carried out at 30 min intervals to avoid interference from previous injections. Femoral arterial blood was sampled for 90 s using a constant withdrawal syringe pump (model 351; Sage Instruments, Orion Research Inc., Cambridge, MA) starting immediately upon delivery of each bolus. Samples were transferred immediately into ice-chilled plastic tubes containing EDTA and reduced glutathione and placed on ice until the end of the study. Cardiac arrest was induced by intravenous infusion of 20 ml of 1 M KCl at the end of each study.

### *Analytical methods*

*Analysis of blood samples.* Blood samples were centrifuged at 4°C, and plasma was separated and stored at −80°C until assayed. Plasma concentrations of endogenous NE were determined by liquid chromatography with electrochemical detection (15). Timed collection of the [$^3$H]NE in the eluant leaving the detection cell enabled quantification of tritium content by liquid scintillation counting. Interassay coefficients of variation were 6.5% for endogenous NE and 3.9% for [$^3$H]NE. Intraassay coefficients of variation were 1.9% for NE and 1.2% for [$^3$H]NE.

*Analysis of clinical data.* The total body clearance of NE from arterial plasma ($CL_{TB}$, ml/min) and the total body spillover of NE into systemic plasma ($S_{TB}$, pmol/min) were calculated according to the equations (6):

$$CL_{TB} = I / [^3H]\,NE_A \tag{1}$$

$$S_{TB} = CL_{TB} \cdot NE_A \tag{2}$$

where $I$ is the infusion rate of [$^3$H]NE (dpm/min), $[^3H]NE_A$ is the arterial plasma concentration of [$^3$H]NE (dpm/ml), and $NE_A$ is the arterial plasma concentration of endogenous NE (pmol/ml).

Fractional extractions of NE ($F$), i.e., fractions of NE removed from plasma during passage through hepatomesenteric organs, were estimated using the equation:

$$F = ([^3H]\,NE_I - [^3H]\,NE_o) / [^3H]\,NE_I \tag{3}$$

where $[^3H]NE_I$ and $[^3H]NE_O$ are the respective inflowing and outflowing plasma concentrations of [$^3$H]NE (dpm/ml). Inflowing plasma concentrations of [$^3$H]NE for mesenteric organs represent arterial concentrations, whereas inflowing plasma concentrations of [$^3$H]NE for the liver were estimated from both arterial and portal venous plasma concentrations according to Eq. 6.

Regional spillovers of NE ($S_R$, pmol/min), i.e., mesenteric organ spillover of NE into portal venous plasma, hepatic spillover of NE into systemic plasma, and the net hepatomesenteric spillover of NE into systemic plasma, were calculated according to the equation described by Esler et al. (6):

$$S_R = [(NE_o - NE_I) + (NE_I \cdot F)] \cdot Q \cdot (1 - Hct) \tag{4}$$

where $NE_I$ and $NE_O$ are the respective concentrations of NE in inflowing and outflowing plasma (pmol/ml), $Q$ is the regional blood flow, $Hct$ is the hematocrit, and $F$ is the fractional extraction of NE described in Eq. 3.

Regional rates of removal of NE ($R_R$, pmol/min) from inflowing plasma by hepatomesenteric organs were calculated using the equation:

$$R_R = NE_I \cdot F \cdot Q \cdot (1 - Hct) \tag{5}$$

where $NE_I$ is the plasma concentration of NE in inflowing plasma, $F$ is described by Eq. 3, $Q$ is the regional blood flow, and $Hct$ is the hematocrit. Under steady state conditions, total body rates of removal of NE can be assumed to equal total body spillovers estimated by Eq. 2.

Mesenteric organ spillover and removal of NE were estimated using measurements in inflowing arterial and outflowing portal venous plasma. Mesenteric NE spillover represents the rate of entry of locally released NE into portal venous plasma. Mesenteric NE removal

reflects the rate of removal of NE from inflowing arterial plasma. Measurements in inflowing arterial plasma and outflowing hepatic venous plasma were used to obtain net estimates of hepatomesenteric NE spillover and removal; these represent the rate of entry of locally released NE into systemic plasma and the rate of removal of NE from arterial plasma.

The liver presents a special problem due to the dual inflows from the portal vein and the hepatic artery. Inflowing plasma concentrations of [$^3$H]NE or NE to the liver ($[NE]_I$, pmol/ml or dpm/ml) were therefore calculated from both portal and hepatic arterial concentrations, weighted according to portal and hepatic arterial flows. This required use of the previously described equation (12):

$$[NE]_I = ([NE]_A \cdot Q_{HA} + [NE]_{PV} \cdot Q_{PV})/(Q_{HA} + Q_{PV}) \quad (6)$$

where $[NE]_A$ and $[NE]_{PV}$ are the respective arterial and portal venous plasma concentrations of [$^3$H]NE (dpm/ml) or NE (pmol/ml), and $Q_{HA}$ and $Q_{PV}$ are the hepatic arterial and portal venous blood flows (ml/min). Use of the above equation to estimate inflowing plasma concentrations of [$^3$H]NE or NE to the liver, and thus hepatic NE spillovers and removals by Eqs. 4 and 5, assumes equal hepatic fractional extractions of NE from arterial and portal venous plasma. This assumption was examined in separate preclinical studies in pigs.

*Analysis of preclinical data.* Hepatic fractional extractions of NE from inflowing portal venous ($F_{PV}$) or hepatic arterial ($F_{HA}$) plasma were estimated using the equations:

$$F_{PV} = ([^3H]\ NE_{CV} - [^3H]\ NE_{PV})/[^3H]\ NE_{CV} \quad (7)$$

$$F_{HA} = ([^3H]\ NE_{CV} - [^3H]\ NE_{HA})/[^3H]\ NE_{CV} \quad (8)$$

where $[^3H]NE_{PV}$, $[^3H]NE_{HA}$, and $[^3H]NE_{CV}$ are the arterial plasma concentrations of [$^3$H]NE (dpm/ml) after respective bolus injections of [$^3$H]NE into portal venous, hepatic arterial, and central venous sites.

*Statistical analysis.* Data are presented as means±SEM ($n$ = 7). Statistical analysis was by Wilcoxon's matched pairs signed rank sum test (16). Statistical significance was defined as $P < 0.05$.

## Results

### *Clinical results*

*Hemodynamic variables.* Blood pressure and heart rate in the seven patients undergoing elective gastrectomy were within normal limits for anesthetized patients (Table I). Portal venous blood flow was 2.1-fold higher than hepatic arterial blood flow; together these flows indicated a total hepatic blood flow of 1,078±57 ml/min.

*Plasma concentrations of NE and $[^3H]NE$.* There was considerable interindividual variation in arterial and portal venous plasma concentrations of NE (Fig. 1 *A* and *B*); however, all subjects showed consistently higher (163±29% higher, $P <$ 0.02) concentrations of NE in outflowing portal venous plasma than in inflowing arterial plasma. In contrast, concentrations of NE were consistently lower (77±5% lower, $P < 0.02$) in outflowing hepatic venous plasma than in inflowing plasma to the liver (inflowing plasma concentrations to the liver calculated from arterial and portal venous concentrations using Eq. 6).

Plasma concentrations of [$^3$H]NE were consistently lower ($P < 0.02$) in outflowing than in inflowing plasma for the sequential perfusion of both mesenteric organs and the liver (i.e., the artery to the portal vein for mesenteric organs and the artery and portal vein to hepatic vein for the liver) (Fig. 1 *C* and *D*). The lower concentrations of [$^3$H]NE in outflowing than inflowing plasma indicated that mesenteric organs extracted 42±5% of the NE from the arterial inflow, whereas the liver extracted 86±6% of the NE from the combined portal venous and arterial inflows. Together, the liver and mesenteric organs extracted 90±4% of the NE from their arterial plasma inflows.

*Table I. Hemodynamic Variables*

| | | |
|---|---|---|
| Systolic BP | (mmHg) | 95±4 |
| Diastolic BP | (mmHg) | 53±3 |
| Heart rate | (bpm) | 59±3 |
| Portal venous blood flow | (ml/min) | 730±21 |
| Hepatic arterial blood flow | (ml/min) | 348±42 |

Values are mean±SEM ($n$ = 7 patients). BP, blood pressure.

*NE spillover and removal.* Spillover of NE from mesenteric organs into portal venous plasma was 7.9-fold higher ($P < 0.02$) than spillover of NE from the liver into systemic plasma (Fig. 2 *A*). In contrast, the rate of removal of NE by the liver from inflowing arterial and portal venous plasma was 6.6-fold higher ($P < 0.02$) than removal of NE from inflowing arterial plasma by mesenteric organs.

The sum of the mesenteric organ spillover of NE into portal venous plasma and hepatic spillover of NE into systemic plasma was fivefold higher ($P < 0.02$) than the net hepatomesenteric spillover of NE into systemic plasma (Fig. 2 *B*). The latter represented only 15±4% of the total body spillover of NE into systemic plasma. This, however, largely ignores the substantial spillover of NE into portal venous plasma. The difference between total body and net hepatomesenteric spillovers of NE into systemic plasma provides an estimate of total body NE spillover that excludes the contribution of hepatomesenteric organs (clear area of column 4 in Fig. 2 *B*). The sum of this variable and separately measured mesenteric organ and hepatic NE spillovers provided an adjusted estimate of total

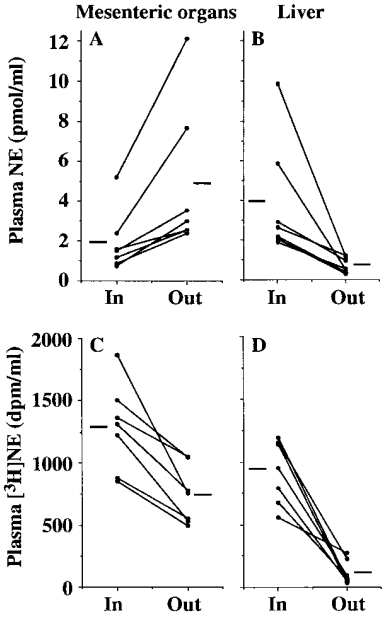


*Figure 1.* Concentrations of NE and [$^3$H]NE in inflowing (*In*) and outflowing (*Out*) plasma of mesenteric organs and the liver for individual subjects. (*A*) Concentrations of NE in outflowing portal venous plasma compared to inflowing arterial plasma. (*B*) Concentrations of NE in outflowing hepatic venous plasma compared to inflowing arterial and portal venous plasma (calculated as weighted means of arterial and portal venous concentrations using Eq. 6). (*C*) Concentrations of [$^3$H]NE in outflowing portal venous plasma compared to inflowing arterial plasma. (*D*) Concentrations of [$^3$H]NE in outflowing hepatic venous plasma compared to inflowing arterial and portal venous plasma (calculated using Eq. 6). Mean values are shown by the horizontal bars.

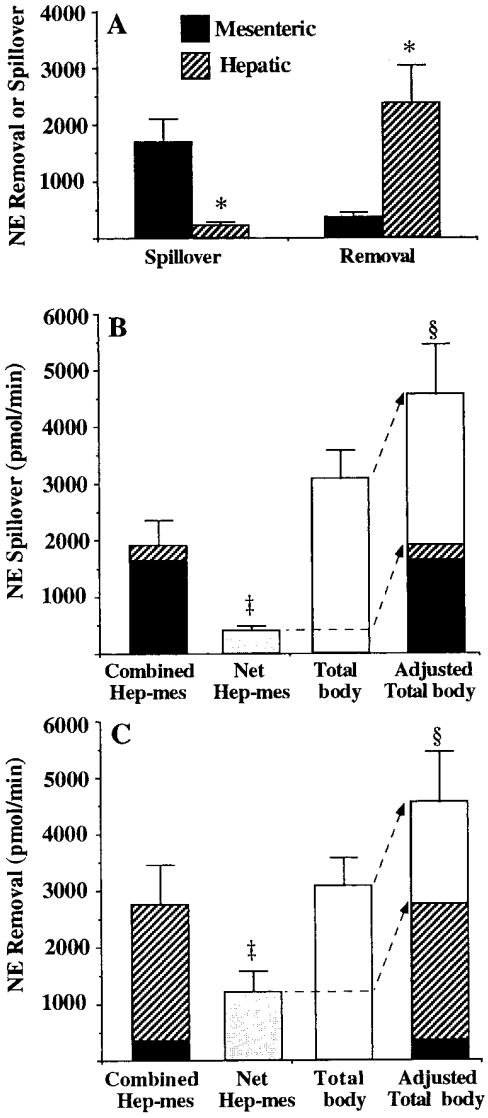


*Figure 2.* Relationships of separately estimated mesenteric organ and hepatic spillovers or removals of NE to conventional measurements of total body and net hepatomesenteric spillovers or removals of NE. (*A*) Spillover of NE from mesenteric organs into portal venous plasma or from the liver into systemic plasma and removal of NE by mesenteric organs from inflowing arterial plasma or by the liver from inflowing arterial and portal venous plasma. (*B*) The combined spillover of NE from hepatomesenteric organs (*Combined Hep-mes*) was estimated from the sum of hepatic and mesenteric NE spillovers, whereas the net spillover of NE from hepatomesenteric organs into systemic plasma (*Net Hep-mes*) was estimated from arterial and hepatic venous measurements alone. The sum of the combined hepatomesenteric NE spillover with the difference between the total body NE spillover (*Total body*) and the net hepatomesenteric NE spillover provided an adjusted total body spillover of NE into portal venous and systemic plasma (*Adjusted Total body*). (*C*) The combined hepatomesenteric removal of NE (*Combined Hep-mes*) was derived from the sum of separate hepatic and mesenteric NE removals, whereas the net hepatomesenteric removal of NE (*Net Hep-mes*) was estimated from arterial and hepatic venous measurements alone. The sum of the combined hepatomesenteric NE removal with the difference between the total body NE removal (*Total body*) and the net hepatomesenteric NE removal provided an adjusted total body removal of NE from both portal venous and systemic plasma. *Denotes a different ($P < 0.02$) mesenteric organ versus hepatic NE spillover or removal. ‡Denotes a lower ($P < 0.02$) net hepatomesenteric NE spillover or removal than the combined hepatomesenteric NE spillover or removal. §Denotes a higher ($P < 0.02$) adjusted total body NE spillover or removal than the unadjusted total body NE spillover or removal.

body NE spillover that included spillover into both portal venous and systemic circulations.

The sum of the rate of removal of NE from arterial plasma by mesenteric organs and from portal venous and arterial plasma by the liver was twofold higher ($P < 0.02$) than the net hepatomesenteric removal of NE from arterial plasma (Fig. 2 *C*). The latter represented a 36±5% contribution to the total body removal of NE from arterial plasma. This, however, largely ignores the substantial hepatic removal of NE from portal venous plasma. The difference between total body and net hepatomesenteric removals of NE from arterial plasma provides an estimate of total body NE removal that excludes removal by hepatomesenteric organs (clear area of column 4 in Fig. 2 *C*). The sum of this variable and separately measured rates of NE removal by mesenteric organs and the liver provided an adjusted estimate of total body NE removal that included removal of NE from both portal venous and arterial plasma.

*Preclinical results*

Arterial plasma concentrations of [$^3$H]NE were lower after injection of an identical bolus dose of [$^3$H]NE into the hepatic artery than into the portal vein of swine (815±41 versus 1,136±76 dpm/ml, $P < 0.03$). Comparison of these values with the arterial concentration of [$^3$H]NE obtained after injection of [$^3$H]NE into the central venous site (2,141±180 dpm/ml) indicated that the hepatic extraction of NE from arterial plasma was 30% higher ($P < 0.03$) than from portal venous plasma (Fig. 3).

## Discussion

This study shows that a major proportion of sympathetic outflow in humans is directed to mesenteric organs. The liver is responsible for removing a large proportion of the NE released into plasma, a substantial amount of which is derived from mesenteric organs. Thus, most of the NE released into the portal venous circulation from mesenteric organs does not reach the systemic circulation (Fig. 4).

Previous clinical studies underestimated sympathetic outflow to mesenteric organs by confining sampling to arterial and hepatic venous sites (6, 7, 9, 10). Esler and colleagues reported that hepatomesenteric organs made a minor contribution to total body NE spillover (6, 7, 10). Henriksen and colleagues failed to detect any contribution of hepatomesenteric organs to total body NE spillover (9). These previous measurements of hepatomesenteric NE spillover may correctly estimate the net contribution of hepatomesenteric organs to spillover of NE into the systemic circulation, but they do not account for spillover of NE into the portal venous circulation. Evaluation of NE spillover for the latter circulation requires additional sampling of blood from the portal vein. In agreement with our other studies in anesthetized pigs (12, 13), the present results show large arterial-portal venous increases in plasma concentrations of NE that reflect substantial mesenteric organ NE

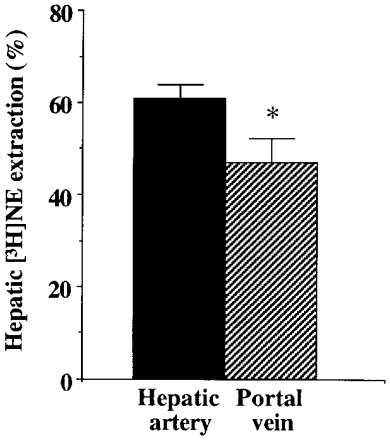


*Figure 3.* Extraction of [$^3$H]NE by the liver from inflowing arterial compared to inflowing portal venous plasma in swine. Data are shown as the mean±SEM ($n$ = 9). *Denotes a lower ($P < 0.03$) extraction from portal venous than arterial plasma.

spillover (Fig. 4). Earlier failures to document the large NE spillover from mesenteric organs can be ascribed to the efficient hepatic extraction of NE, which conceals the extent of NE release into the portal venous circulation.

The NE spillover from mesenteric organs that is not accounted for by sampling blood from arterial and hepatic venous sites equals the difference between the net hepatomesenteric spillover of NE into central venous plasma (430 pmol/min) and the sum of separately estimated mesenteric and hepatic NE spillovers (210 + 1,680 pmol/min). This difference (1,460 pmol/min) added to standard estimates of total body NE spillover (3,070 pmol/min) produces an adjusted total body NE spillover (4,530 pmol/min) that accounts for spillover of NE into portal venous as well as systemic plasma.

Spillover of NE from the liver accounted for 5% and from mesenteric organs 37% of the adjusted total spillover, a result slightly lower than in pigs where mesenteric organs provided a 49% contribution (12). In both humans and pigs, there is

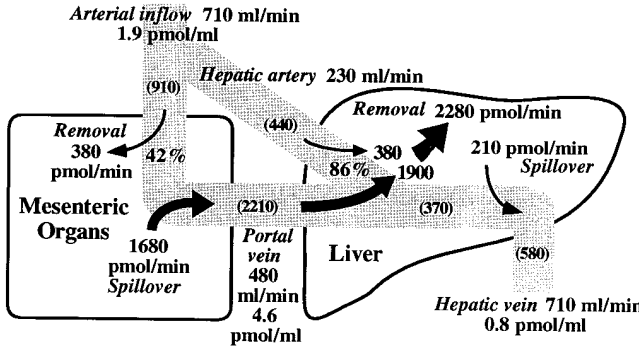


*Figure 4.* Schematic summary of hepatomesenteric circulatory system showing rates of spillover and removal of NE by mesenteric organs (pmol/min), plasma flows (ml/min), and plasma concentrations of endogenous NE (pmol/ml) in arterial, portal venous, and hepatic venous plasma. Values in parentheses represent total rates of passage of NE (pmol/min) into and out of organs. Rates of removal of NE by the liver are shown for removal from arterial and portal venous inflows assuming equal fractional extractions (86%) from both sources. Rates of net hepatomesenteric NE spillover (403±77 pmol/min) or NE removal (1,226±339 pmol/min), estimated from arterial and hepatic venous plasma concentrations alone, are much lower than the combined separate estimates of mesenteric and hepatic NE spillover (1,680 + 210 pmol/min) or removal (380 + 2,280 pmol/min) shown in the diagram.

clearly a substantial sympathetic outflow to mesenteric organs. This is in agreement with anatomical evidence for a dense and extensive sympathetic innervation of mesenteric organs (11).

The substantial proportion of sympathetic outflow directed towards mesenteric organs is also consistent with the important role of sympathetic nerves in the control of various gastrointestinal functions including intestinal water and electrolyte absorption (1), gastric acid and bicarbonate secretion (2, 17), and blood flow (5). The hepatomesenteric circulation receives close to 25% of resting cardiac output and holds ~ 30% of the total blood volume in venous capacitance vessels (18). The substantial mesenteric spillover of NE may reflect the potential importance of mesenteric sympathetic nerves in maintaining cardiovascular homeostasis by actions on hepatomesenteric vascular resistance and venous capacitance.

The importance of hepatomesenteric organs for removal of circulating NE has been reported in previous clinical studies that showed large decreases in plasma catecholamine concentrations from arterial to hepatic venous sampling sites (6, 14, 19). In the present study, the additional samples obtained from portal venous sites establish that removal of circulating NE by hepatomesenteric organs largely reflects removal by the liver. The results also show that the full extent of NE removal by the liver is not apparent when sampling of blood is confined to arterial and hepatic venous sites. Thus, the net hepatomesenteric removal of NE from the systemic circulation was < 50% that of separately estimated mesenteric and hepatic removals. This difference was due to the additional hepatic removal of NE released by mesenteric organs into the portal circulation. Comparison of rates of NE removal by the liver and mesenteric organs with the adjusted total body removal of NE from systemic and portal venous circulations shows that 52% of circulating NE is removed by the liver and 8% by mesenteric organs. Thus, whereas mesenteric organs make a larger contribution than the liver to spillover of NE into plasma, the liver is much more important than mesenteric organs for removal of circulating NE.

The liver limits effectively the amount of NE released by mesenteric organs that reaches the systemic circulation (Fig. 4). Thus, reduced hepatic NE clearance capacity may increase net hepatomesenteric NE spillover, independent of any change in neuronal NE release. Larger net hepatomesenteric NE spillovers in patients with hepatic cirrhosis than in control subjects (7, 9, 10) may therefore reflect impaired hepatic handling of catecholamines rather than increased NE release. These considerations indicate that adequate investigation of sympathetic outflow to hepatomesenteric organs requires separate estimation of mesenteric and hepatic NE spillovers.

Clearly, NE spillover from an organ does not equal local NE release from sympathetic nerves, but reflects the amount of NE released that escapes neuronal and extraneuronal removal to enter the venous drainage (8). As discussed in detail by Halbügge et al. (20), this limitation of NE spillover measurements is especially important for organs, such as the lungs, that exist in a series arrangement of circulations. The hepatomesenteric circulation (Fig. 4) represents another series arrangement of circulations where spillover of NE at an upstream site can be affected by removal at a separate downstream site. A further issue is presented by the dual portal venous and arterial circulatory inflows to the liver.

Estimation of hepatic NE spillover or removal ideally requires separate estimation of NE extraction from hepatic arte-

rial and portal venous inflows. This, however, was not possible using the intravenous infusions of [$^3$H]NE required for the present clinical study. Thus, the present estimates of hepatic spillover and removal of NE assumed equal extractions of NE from arterial and portal venous inflows. The additional studies of hepatic extractions of [$^3$H]NE injected into the portal vein and hepatic artery of anesthetized pigs were carried out to test this assumption. The higher hepatic extraction of [$^3$H]NE from arterial than portal venous inflows is consistent with previous findings in isolated rat liver where NE was removed more efficiently when perfused into the hepatic artery than into the portal vein (21).

The potential impact of the above difference in hepatic NE fractional extractions on estimated rates of hepatic NE spillover and removal warrants analysis. If all the NE entering the liver via the hepatic artery were extracted, the hepatic fractional extraction of portal venous NE would be 76% for the observed overall hepatic extraction of 86%. Using these extraction fractions to estimate rates of hepatic removal or spillover of NE indicates that the present results could represent a 5% overestimate of NE removal and up to a twofold overestimate of hepatic NE spillover. Thus, the assumption of equal hepatic extractions of arterial and portal venous NE has minimal influence on calculated rates of hepatic NE removal; however, accurate estimation of hepatic NE spillover requires separate measurements of hepatic fractional extractions of [$^3$H]NE from inflowing portal venous and arterial plasma. This can be achieved by injections of tracer-labeled NE into portal venous and hepatic arterial inflows to the liver.

A clinical study with the present experimental design is only feasible in anesthetized patients in whom dissection of the hepatoduodenal ligament is warranted for therapeutic benefit. While the study provides unique possibilities to separate events occurring in mesenteric organs and the liver, both the anesthetic procedures and the selection of patients warrant discussion. Anesthesia was maintained using enflurane, which like other halogenated volatile anesthetics may depress mesenteric sympathetic activity (22). In addition, thiopental reduces sympathetic nerve activity (23). In contrast, nitrous oxide may cause sympathoexcitation (24). The other anesthetics used in the study (fentanyl, lorazepam, and midazolam) are not known to interfere with sympathetic transmission at the doses used (25). All patients underwent surgery for malignant carcinoma. Cachexia observed in cancer may increase sympathetic tone (26). Total body and net hepatomesenteric spillovers of NE observed in the present study were, however, comparable to those previously reported in awake, healthy humans (6, 7). It remains possible that hepatic and mesenteric organ NE spillovers may have been influenced by regional changes in sympathetic outflow resulting from surgical anesthesia.

In summary, the present study demonstrates in anesthetized humans that mesenteric organs receive a previously unrecognized major proportion of total sympathetic outflow. Efficient hepatic extraction of NE minimizes overflow of NE from mesenteric organs into the systemic circulation and obscures the substantial spillover of NE from mesenteric organs when sampling is confined to arterial and hepatic venous sites.

## Acknowledgments

This study was made possible by the generous and excellent professional support of the staff at the Department of Surgery, Team 19, and the Department of Anesthesiology and Intensive Care, Sahlgrens University Hospital. The authors are grateful to Irwin J. Kopin for help in the design of studies and analysis of results and to Lena Henriksson and Annika Henningsson for their clinical assistance. Excellent technical assistance was provided by Ms. AnneLie Ambring. Thanks are extended to Lennart Appelgren, for valuable criticism of the manuscript.

Financial support was provided by the Göteborg Medical Society, the Swedish Society of Medicine, the Swedish Society of Medical Sciences, and the Swedish Medical Research Council (projects 760, 2855, 8663, 9047, 11133).

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