Anesthesiology 2009; 111:561–5

Baroreflex Sensitivity Is Impaired in Patients with Obstructive Jaundice

Jian-gang Song, M.D., Yun-fei Cao, M.D.,† Yu-ming Sun, M.D.,‡ Yan-hu Ge, M.D.,§ Xue-wu Xu, M.D.,† Li-qun Yang, M.D.,† Zhi-qiang Liu, M.D.,‖ Shao-li Song, M.D., Ph.D.,# Wei-feng Yu, M.D.***

Background: **Obstructive jaundice is associated with enhanced susceptibility to hypotensive shock, renal failure, and toxic effects of endotoxin, which results in high perioperative morbidity and mortality. Since the normal arterial baroreflex function is necessary for hemodynamic homeostasis and improving survival in sepsis, this study aimed to determine whether baroreflex sensitivity was impaired in jaundiced patients.**

Methods: **Thirty-five patients with obstructive jaundice scheduled for surgery were included, and 30 nonjaundiced patients served as controls. A modified Oxford pharmacologic technique was used for evaluating baroreflex sensitivity immediately before the surgery. Potential factors that may affect baroreflex sensitivity in jaundice, such as liver biochemistry, plasma concentrations of methionine-enkephalin, atrial natriuretic peptide and nitrate, were also measured.**

Results: **Patients with obstructive jaundice had decreased sensitivity in both the sympathetic and vagal components of the baroreflex, as compared with the controls ($P < 0.01$). There was a significant inverse correlation between plasma atrial natriuretic peptide concentration and decreased sympathetic baroreflex sensitivity in the jaundiced group ($r = -0.44$, $P = 0.008$).**

Conclusions: **Baroreflex sensitivity is impaired in patients with obstructive jaundice, which may contribute to their enhanced susceptibility to the well-known perioperative complications. The underlying mechanisms for such a change may be associated with an increased level of plasma atrial natriuretic peptide.**

PATIENTS with obstructive jaundice are prone to hypotensive shock, acute renal failure, sepsis, and multiple organ failure under a wide range of conditions, such as anesthesia, surgery, hemorrhage, and infection.[1,2] Morbidity and mortality in jaundiced patients receiving surgical treatment are higher than in nonjaundiced patients.[3,4] Reasons for this increased susceptibility are not well characterized at present. Potential mechanisms include extracellular water depletion,[5,6] defective vascular reactivity,[7,8] subclinical myocardial dysfunction,[9,10] systemic endotoxemia that frequently accompanies obstructive jaundice,[11,12] and exaggerated release of proinflammatory cytokines in response to endotoxin challenge.[13,14]

Arterial baroreflex is an important short-term neural control mechanism that maintains cardiovascular stability. The reflex consists of two parts: A sympathetic and a vagal (parasympathetic) limb.[15] A reduction in sympathetic baroreflex sensitivity (BRS) results in greater hemodynamic liability when the patient is challenged with hypotension, hemorrhage, or general anesthesia.[16,17] An intact vagal baroreflex recently has been found to be necessary for improving survival in sepsis.[18,19] Based on these findings, we hypothesized that arterial baroreflex function may be compromised in patients with obstructive jaundice, which may help to explain the enhanced susceptibility to those well-known perioperative complications. The current study was designed to test this hypothesis.

Besides cholestasis and liver damage, overproduction of nitric oxide,[20,21] accumulation of endogenous opioid peptides (methionine-enkephalin),[22] and elevated plasma level of atrial natriuretic peptides (ANP),[10,23,24] are frequently observed in patients with obstructive jaundice or in animal models of biliary obstruction. These factors are implicated in the regulation of arterial baroreflex function and/or autonomic nervous system activity.[25–28] Accordingly, we included these measures in the hope to find some underlying mechanisms for impaired baroreflex in jaundiced patients.

Materials and Methods

Patients

The study was approved by the Institutional Ethics Committee (Eastern Hepatobiliary Surgery Hospital, Shanghai, China). Informed consent was obtained from all participating patients. Thirty-five consecutive men with obstructive jaundice (serum total bilirubin $>20\ \mu M$) caused by a tumor in the bile duct or in the head of the pancreas were included in the study. Thirty men with asymptomatic gallbladder polypus without jaundice were recruited as controls. All participating patients were scheduled for elective surgery for the underlying diseases. Exclusion criteria were as follows: Age >70 yr or <50 yr; body mass index >30 kg/m^2 or <18 kg/m^2; history of diabetes, cardiovascular, respiratory, or renal diseases; hepatic encephalopathy, psychiatric illnesses, or neuropathy; complication of acute cholangitis, gastrointestinal bleeding, or ascites; electrolyte or acid-base disturbance, sepsis, or cachexia defined as weight loss ≥2% in the past 2 months or ≥5% in the past 6 months; and use of medi-

* Assistant Professor, Department of Anesthesiology, # Attending Physician, Department of Nuclear Medicine, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China. † Associate Professor, ‡ Assistant Professor, § Resident, ** Professor and Director, Department of Anesthesiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China. ‖ Associate Professor, Department of Anesthesiology, Shanghai First Maternity and Infant Health Hospital, Tongji University, Shanghai, China.

Received from the Department of Anesthesiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China. Submitted for publication December 31, 2008. Accepted for publication April 29, 2009. Supported by departmental sources and Shanghai Leading Academic Discipline Project (No. S30203; Shanghai, China). Drs. Jian-gang Song and Yun-fei Cao contributed equally to this work.

Address correspondence to Dr. Yu: Department of Anesthesiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China. songjg1993@126.com.

cations that could interfere with cardiovascular function (*e.g.*, β-blockers, calcium channel blockers, digoxin).

Baroreflex Sensitivity Measurement

Baroreflex sensitivity was measured using a modified Oxford pharmacological method[29] before anesthesia on the day of surgery. On arriving at the operating room after an 8–10 h fast, an electrocardiography monitor (lead II), a central intravenous catheter, and an arterial (radial) blood pressure catheter were placed. Electrocardiogram and blood pressure were continuously monitored. Acetate Ringer's solution was administered intravenously at a rate of 2 $ml \cdot kg^{-1} \cdot h^{-1}$ throughout the entire procedure. The patients did not receive any premedication that could otherwise interfere with the subsequent baroreflex testing, and were allowed to rest in a supine position for at least 20 min before the experiment. Testing was carried out using an intravenous bolus injection of 100–200 μg phenylephrine, followed by 100–250 μg sodium nitroprusside to increase/decrease systolic blood pressure by 15–30 mmHg, respectively. The pressor and the depressor tests were separated by a period of stabilization, usually 5 min, for the heart rate and systolic blood pressure to return to 95–105% of the pretest level. The slope of the linear portion of the relationship curve between the pulse interval and the preceding systolic blood pressure was analyzed using a least-square regression as an index for baroreflex sensitivity. Seven to 12 pairs of systolic blood pressure and pulse intervals were used for each test. Squared correlation coefficient was greater than 0.8 for all samples. Patients proceeded to anesthesia and surgery after the BRS experiment was completed. The observers were unaware of the study design or the study purpose.

Blood Sampling and Hormonal Assays

Before the BRS test, a sample of venous blood was collected. Arterial gas analysis was performed using samples of arterial blood collected during the BRS test. A liver function test was carried out using conventional methods and included total bilirubin, bile acids, alanine transaminase, and albumin. As for hormonal assays, a blood sample was collected into chilled tubes containing 2 mg/ml EDTA and 400 KIU/ml aprotinin (Trasylol; Sigma Chemical, St. Louis, MO). Samples were centrifuged at 3,000 g for 15 min at 4°C, and stored at −20°C until use. A radioimmunoassay kit was used to determine ANP (h-ANP, Cob. I-AR55 Co; Tokyo, Japan; reference value: 20–60 pg/ml).[10] Because of the extremely short half-life of nitric oxide, its production was estimated by measuring the plasma nitrate concentration using a gas chromatography-mass spectrometry method.[30] Plasma met-enkephalin was determined using a radioimmunoassay kit (Peninsula Laboratories, Inc., San Carlos, CA). At 50% binding, the inter- and intraassay variation coefficient was 9.5% ± 0.5% and 6.8% ± 0.7%, respectively. The affinity of the antibody for methionine-enkephalin is 4×10^{-12} pM.

Table 1. Demographic Data

	Control	Obstructive Jaundice
n	30	35
Age (yr)	58.7 ± 5.3	57.6 ± 6.1
Weight (kg)	65.2 ± 8.0	63.8 ± 6.0
Temperature (°C)	36.3 ± 0.6	36.1 ± 0.4
HR (beats/min)	79.0 ± 9.9	74.5 ± 13.5
SBP (mmHg)	128.3 ± 12.4	127.3 ± 10.7
DBP (mmHg)	78.0 ± 7.0	73.7 ± 6.4

Values are mean ± SD.

DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

Statistical Analysis

Data are presented as mean ± SD, and analyzed using an unpaired Student's *t* test. $P < 0.05$ was considered to be statistically significant. A multivariate analysis was performed to identify factors associated with changes of BRS in the group of jaundiced patients. Candidate factors included significantly altered liver biochemistry and/or hormones, as compared with controls. Variables with $P > 0.1$ were excluded from the regression analysis using a stepwise method (SPSS 11 for Windows [SPSS Inc., Chicago, IL]).

The BRS measurements of eight jaundiced patients and eight nonjaundiced patients were taken in the preliminary trial. The vagal BRS of jaundiced patients and control patients were 5.14 ± 2.63 and 7.21 ± 2.98 ms/mmHg, respectively; and the sympathetic BRS were 3.07 ± 1.78 and 4.64 ± 2.16 ms/mmHg, respectively. Based on the difference between two groups, the formula for normal theory, and assuming a two-sided type I error rate of 0.05 and a power of 0.80, 30 patients in each group were required to reveal a statistically significant difference.

Results

The two groups did not differ in age, weight, body temperature, baseline blood pressure, and heart rate (table 1). Blood pH, arterial oxygen and carbon dioxide, sodium, potassium, ionized calcium, and glucose were all within the normal range in all patients. No arrhythmia was observed during the testing.

Representative responses to phenylephrine and nitroprusside are shown in figure 1. In control patients, BRS was 8.98 ± 2.86 and 5.81 ± 2.53 ms/mmHg for the vagal and sympathetic limbs, respectively. Both measures were significantly reduced in patients with jaundice (5.28 ± 2.68 and 3.19 ± 1.52 ms/mmHg, $P < 0.001$; fig. 2).

As expected, serum concentrations of total bilirubin, bile acids, and alanine transaminase were significantly higher in patients with jaundice. Plasma concentrations

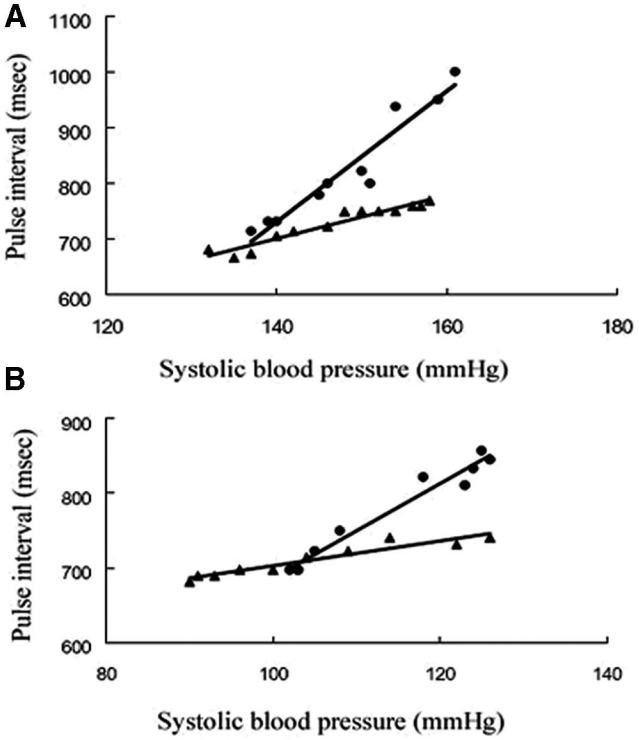

Fig. 1. (*A*) Sensitivity of the vagal component of arterial baroreflex in representative subjects. Patients received a bolus phenylephrine injection. Pulse interval was plotted against systolic blood pressure (SBP). The slope of the curve reflects the sensitivity of the vagal response. Closed circles: Control subject; pulse interval = 11.7 SBP −909, R^2 = 0.92, P < 0.001; SBP range = 137–161 mmHg. Triangles: Subject with obstructive jaundice. Pulse interval = 3.87 SBP + 159, R^2 = 0.92, P < 0.001; SBP range = 132–158 mmHg. (*B*) Sensitivity of the sympathetic component of arterial baroreflex in representative subjects. Patients received a bolus nitroprusside injection. Pulse interval was plotted against SBP. The slope of the curve reflects the sensitivity of the sympathetic response. Closed circles: Control subject; pulse interval = 6.31 SBP + 56, R^2 = 0.96, P < 0.001; SBP range = 124 mmHg–103 mmHg. Triangles: Subject with obstructive jaundice; pulse interval = 1.65 SBP + 538, R^2 = 0.91, P < 0.001; SBP range = 126 mmHg–90 mmHg.

of methionine-enkephalin and ANP were higher in patients with jaundice as compared with controls. The concentrations of plasma nitrate and albumin did not differ between the two groups (table 2). Consequently, plasma total bilirubin, bile acids, alanine transaminase, methionine-enkephalin, and ANP were chosen as possible candidate risk factors associated with impaired BRS of jaundice patients for a multivariate regression analysis. As a result, a significant inverse correlation between the plasma ANP concentration and sympathetic BRS in patients with obstructive jaundice was found, and the equation of the regression line was sympathetic BRS (ms/mmHg) = 5.0951–0.0156 ANP (pg/ml), with R^2 of 0.1938 (fig. 3). No parameter was associated with vagal BRS.

Table 2. Liver Biochemistry and Hormone Levels

	Control	Obstructive Jaundice
Total bilirubin (μM/l)	10.7 ± 6.6	209.7 ± 113.2*
Bile acids (μM/l)	4.3 ± 2.7	53.7 ± 40.1*
Albumin (g/l)	40.7 ± 4.4	38.4 ± 6.0
Alanine aminotransferase (U/l)	39.2 ± 8.6	243.3 ± 126.0*
ANP (pg/ml)	51.4 ± 22.7	121.9 ± 42.9*
Met-enkephalin (pg/ml)	28.1 ± 6.3	44.0 ± 11.7*
Plasma nitrate (μM/l)	22.7 ± 10.3	27.6 ± 7.0

Values are mean ± SD.

* P < 0.05 *versus* the control.

ANP = atrial natriuretic peptide.

Discussion

It is well established that the autonomic function of regulating the cardiovascular system is impaired in primary biliary cirrhosis, a chronic cholestatic liver disease with a probable autoimmune etiology.[31] Results from the current study for the first time extended these findings to patients with obstructive jaundice. Specifically, we found significantly decreased sensitivity in both sympathetic and vagal baroreflex as compared with aged match controls.

A potential confounding factor in the current study is the presence of tumor in the jaundiced group but not the control group. Since cachexia caused by neoplasm has been reported to be associated with autonomic dysfunction,[32] stringent criteria were adopted in the current

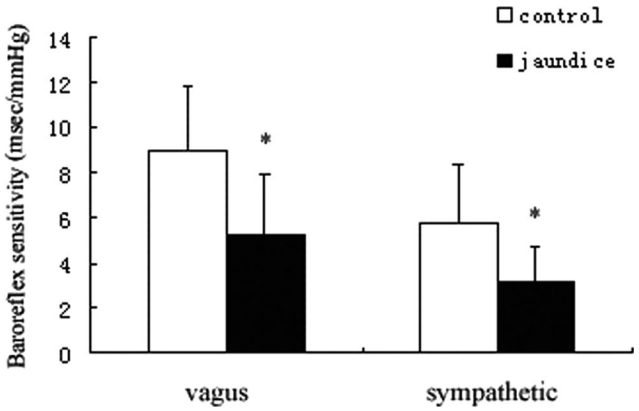

Fig. 2. Sympathetic and vagal baroreflex sensitivity in patients with obstructive jaundice *versus* the controls. Values are mean ± SD. *P < 0.05 *versus* the control group.

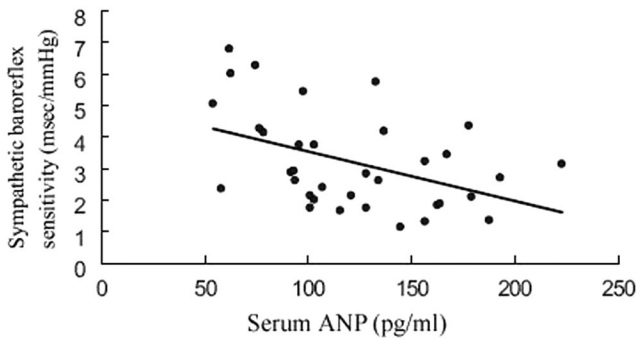

Fig. 3. Correlation between the serum atrial natriuretic peptide (ANP) and sympathetic baroreflex sensitivity in patients with obstructive jaundice (P = 0.008).

study to minimize this factor. Also, the normal plasma albumin of the jaundiced group indicated a relatively good condition. Consequently, it is reasonable to attribute impaired BRS in jaundiced patients to extrahepatic biliary obstruction, and not the systemic effects of the tumors.

The current study did not confirm the cause-effect relationship between reduced BRS in patients with obstructive jaundice and their susceptibility to hypotensive shock, acute renal failure, sepsis, or multiple organ failure. However, it is only reasonable to assume that impaired sympathetic BRS would lead to insufficient compensatory responses to hypotension, blood loss, or other hemodynamic disturbances in the perioperative period, which may predispose jaundiced patients to organ hypoperfusion or ischemic events. Decreased vagal BRS may also be a critical contributing factor to the greater susceptibility of these patients to sepsis. Endotoxemia is a frequent condition that accompanies obstructive jaundice as a result of increased endotoxin absorption from the intestinal lumen and decreased clearance by the hepatic reticuloendothelial system.[11,12] Furthermore, in obstructive jaundice, endotoxins produce more severe organ damage, mainly through exaggerated release of proinflammatory cytokines.[13,14] Using a rodent model, Tracey *et al.* recently discovered that an efferent vagus nerve attenuates the development of endotoxin-induced shock by inhibiting the release of proinflammatory cytokines such as tumor necrosis factor.[33] Su *et al.* observed a significant correlation between vagal BRS and survival time in rat models of experimental sepsis induced by lipopolysaccharide[18] or cecal ligation and puncture.[19] Based on these findings, we hypothesize that decreased vagal BRS in jaundiced patients may, at least in part, result in an endotoxin hypersensitivity state of cholestatic host that eventually leads to multiple organ damage. This hypothesis is consistent with the previous findings that the presence of vagal neuropathy is an independent predictor for reduced survival in patients with chronic liver diseases.[34]

Consistent with previous human and animal studies,[10,24] we found increased plasma ANP concentration in patients with obstructive jaundice. In addition, a multivariate analysis revealed an inverse relation between plasma ANP and sympathetic BRS in jaundiced patients. In addition to diuresis and vasodilation, ANP also influences sympathetic nervous outflow.[28] Several human studies demonstrated that infusion of exogenous ANP lowers the activity of sympathetic but not parasympathetic nerves.[35,36] Animal studies have also shown that reflex tachycardia and sympathoexcitation did not occur during hypotension caused by ANP, whereas similar levels of hypotension produced with nitroglycerin provoked an appropriate reflex tachycardic response.[37,38] Thus, negative correlation between sympathetic BRS and plasma ANP suggested that increased ANP may produce a relative sympatho-inhibitory action, which, at least in part, results in impaired sympathetic BRS in jaundiced patients. Regarding the cause of increased ANP, a previous study by Martínez-Ródenas *et al.*[24] in rabbits with a biliovenous shunt suggests that the passage of bile components to the circulation may be responsible. The presence of bile products in the blood may diminish cardiac contractility, which in turn may result in increased ANP synthesis through stretching of the atria. Indeed, a correlation between subclinical myocardial dysfunction and increased ANP was found in patients with obstructive jaundice.[10]

In addition, we also found an increased level of circulating methionine-enkephalin in patients with obstructive jaundice, which is consistent with previous reports in cholestatic rodents and patients.[22,39] Since endogenous opioids have been implicated in the central inhibition of sympathetic tone and baroreceptor reflexes,[26,27] elevated methionine-enkephalin may have also contributed to observed BRS dysfunction in patients with obstructive jaundice in the current study. However, we were unable to detect a direct correlation between BRS and plasma methionine-enkephalin. In addition, we did not find changes in plasma nitrate levels in patients with obstructive jaundice. This result is consistent with the findings by Padillo *et al.* in jaundiced patients,[40] but not studies using rodent models of acute cholestasis.[20,21]

Somewhat surprisingly, we did not find a significant correlation between impaired BRS and blood biochemical measures indicative of liver damage and/or the degree of jaundice, such as serum alanine transaminase, bilirubin, or bile acids, in patients with obstructive jaundice. In fact, in chronic cholestatic liver diseases, association between autonomic dysfunction and disease severity has not been confirmed. For example, Newton *et al.*[41] suggested that abnormalities of heart rate variability and BRS in primary biliary cirrhosis are not specific to advanced disease but associated with fatigue severity. Keresztes *et al.*[42] showed that risk factors for autonomic dysfunction include duration and severity of primary biliary cirrhosis but not markers of cholestasis. The lack of relationship between BRS and liver function in patients with obstructive jaundice suggests that reduced BRS may be the result of pathologic processes (such as increased ANP in circulation) to which obstructive jaundice acts as a permissive factor or cofactor in some way, rather than a direct consequence of jaundice itself. In other words, the changes secondary to liver damage and/or cholestasis may contribute more to autonomic dysfunction than liver damage and/or cholestasis *per se*. It should be pointed out that the strategy of including only the significant or known variables in the multivariate analysis carries the risk of excluding some potential confounding relations, but also minimizes unexplainable or spurious associations. Consequently, risk factors underpinning the impairment of BRS warrant further study.

In conclusion, the present study demonstrated that both the sympathetic and vagal components of arterial baroreflex are depressed in patients with obstructive jaundice. Reduced BRS may, at least in part, contribute to enhanced susceptibility to hypotensive shock, renal failure, and sepsis in patients with obstructive jaundice during the perioperative period. The underlying mechanisms for such a change may be associated with increased level of plasma ANP.

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