Circulating Biomarkers As Indices of Hepatocellular Integrity During Hypotensive Anesthesia A Comparative Study between Sevoflurane and Propofol Anesthesia

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LIST OF ABBREVIATION

Abbreviation	The Full Term
Acetyl CoA	Acetyl-coenzyme A
ALT	Alanine aminotransferase
ASK1	Apoptosis signal-regulating kinase 1
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
β-AR	Beta adrenergic receptor
CBF	Cerebral blood flow
cGMP	Cyclic guanylate monophosphate
CO	Carbon monoxide
EEG	Electroencephalogram
ELISA	Enzyme linked immunosorbent assay
F	Fluoride
5`-NT	5'-nucleotidase
GABA	Gamma amino butyric acid
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transferase
GST	Glutathione S-transferase
HA	Hyaluronic acid
HCV	Hepatitis C virus
HFIP	Hexafluoroisopropanol
ICP	Intracranial pressure
ICU	Intensive care unit
INR	International Normalized Ratio
IV	Inravenous
JNK1	Jun N-terminal kinase 1

LAP	Leucine aminopeptidase
LECs	Liver endothelial cells
MAC	Minimal alveolar concentration
MAP kinase	Mitogen-activated protein kinase
MAP	Mean arterial blood pressure
NO	Nitric oxide
PEEP	Positive end expiratory pressure
PGE_1	Prostaglandin E_1
PIFE	Pentafluoro-isopropenyl fluoromethyl ether
PT	Prothrombin time
RNA	Ribonucleic acid
SNP	Sodium nitroprusside
T3	Tri-iodothyronine
T4	Thyroxine
TFA	Trifluoroacetic acid
TIVA	Total intravenous anesthesia
UDP	Uridine diphosphate
VIMA	Volatile induction and maintenance of anesthesia

ABSTRACT

Hypotensive anesthesia offers a dry surgical field and may reduce blood loss and hence the need for transfusion. The influence of hypotensive anesthesia on splanchnic perfusion is ground for research. With the acknowledgment that almost all anesthetic techniques reduce liver blood flow, it would seem wise that during procedures performed under hypotensive anesthesia, where further reduction of liver blood flow may be detrimental, that the techniques and the agents used should be those that have the least effect on liver blood flow, and on hepatocellular integrity.

The aim of this work is to assess hepatocellular integrity during hypotensive anesthesia, using more specific and sensitive markers [□ and □] GST and hyaluronate, comparing sevoflurane and propofol, both with relatively less predictable hepatic insult, in an attempt to find out the best anesthetic agent and technique and recommend it during such procedures.

We conclude that sevoflurane anaesthesia is associated with a transient increase in plasma GST concentrations reflecting a minor degree of impaired hepatocellular integrity especially during hypotensive anaesthesia.

KEY WORDS:

- Transaminases
- Alpha glutathione S- transferase
- Hyaluronic acid
- Pie glutathione S- transferase
- Propofol
- Sevoflurane
- Hypotensive anesthesia
- Nitroglycerin
- Esmolol
- Labetalol

INTRODUCTION AND AIM OF THE WORK

Hypotensive anesthesia offers a dry surgical field and may reduce blood loss and hence the need for transfusion. It is used in a variety of surgical procedures (orthopaedic, facio-maxillary, vascular, spinal, middle ear surgery, radical prostatectomy, as well as organ transplant surgeries [(1)].

With the acknowledgment that almost all anesthetic techniques reduce liver blood flow [(2)], it would seem wise that during procedures performed under hypotensive anesthesia, where further reduction of liver blood flow may be detrimental, that the techniques and the agents used should be those that have the least effect on liver blood flow, and on hepatocellular integrity.

Hepatic injury is documented to occur during long as well as short procedures, using halothane. Isoflurane, on the other hand, tends to preserve autoregulation and hepatic arterial blood flow, whereas halothane decreases blood flow and autoregulation and both agents have been shown to reduce portal venous blood flow [(2)].

Sevoflurane has many desirable clinical attributes, including a low blood-gas solubility coefficient, which provides rapid induction and emergence, and a non pungent smell. In direct comparison with isoflurane in surgical patients, or enflurane anesthesia in volunteers, sevoflurane produced no differences in plasma aspartate aminotransferase or alanine aminotransferase levels [(3)].

Renewed interest in the use of intravenous techniques to provide balanced anesthesia has been prompted partly by this very concern on the potential of volatile anesthetics to cause tissue and organ toxicity [(4)].

The most widely used method of assessing drug-induced hepatocellular damage in man is the measurement of transaminase activity in plasma. However, these measurements lack sensitivity and may have poor organ specificity [(5)].

The measurement in plasma of the hepatic isoenzymes of glutathione S-transferase (GST) using enzyme linked immunosorbent assay (ELISA), is a sensitive and specific method, proposed as an alternative for the detection of acute and early drug-induced hepatocellular damage [5].

The major hepatic form is (α) GST. It is relatively a small enzyme (MW 50,000) present in high concentration in the hepatocyte cytosol. Thus it is rapidly detectable in the circulation following hepatocellular damage. In addition, it has a short plasma half-life (<90 min), which provides a more accurate reflection of the activity of hepatocellular damage. π GST is a more specific marker of biliary epithelial cell integrity [6].

Hyaluronic acid (HA), on the other hand, is an endogenous polysaccharide whose clearance is predominantly by the liver sinusoidal cells and is sinusoidal flow dependent. Its fractional turnover is rapid, and occurs mainly through receptor-mediated uptake and degradation by hepatic sinusoidal endothelial cells. In human beings, the normal half-life of circulating HA is 2.5-5.5 min. When liver function is normal, hyaluronan clearance is directly proportional to hepatic blood flow [7].

Hyaluronic acid was thus successfully utilized in assessing reliably sinusoidal endothelial cell function and perfusion. Experimental data indicate that hyaluronate elimination may be a more sensitive marker of liver endothelial cell function after a short period of ischaemia after orthotopic liver transplant. Serial studies demonstrate that the endothelial cell is a more susceptible target for the immune response than the hepatocyte. Thus, serum hyaluronate concentration may be a better indicator in the early assessment of graft function [7].

AIM OF THE WORK

This study was designed to assess and compare impact of sevoflurane and propofol anesthesia on hepatocellular integrity during hypotensive anesthesia, using more specific and sensitive markers α-GST, π-GST and hyaluronate, in an attempt to find out the best anesthetic agent and technique and recommend it during such procedures.

HEPATIC PHYSIOLOGY AND CIRCULATION

Because of the large functional reserves of the liver, clinically significant hepatic dysfunction following anesthesia and surgery is uncommon. Such dysfunction is limited chiefly to patients with preexisting hepatic impairment and to those with rare idiosyncratic reactions to halogenated volatile anesthetics [8].

Blood from hepatic arterioles and portal venules mingles in the sinusoidal channels, which lie between the cellular plates and serve as capillaries. Two types of cells line the hepatic sinusoids: endothelial cells and macrophages (also called Kupffer cells) [9].

The space of Disse lies between the sinusoidal capillaries and the hepatocytes. Venous drainage from the central veins of hepatic lobules coalesces to form the hepatic veins (right, middle, and left), which empty into the inferior vena cava (Fig. I). The caudate lobe is usually drained by its own set of veins [10].

The liver is supplied by sympathetic nerve fibers, parasympathetic fibers (right and left vagus), and fibers from the right phrenic nerve. Some autonomic fibers synapse first in the celiac plexus while others reach the liver directly via splanchnic nerves and vagal branches before forming the hepatic plexus. The majority of sensory afferent fibers travel with sympathetic fiber[11].

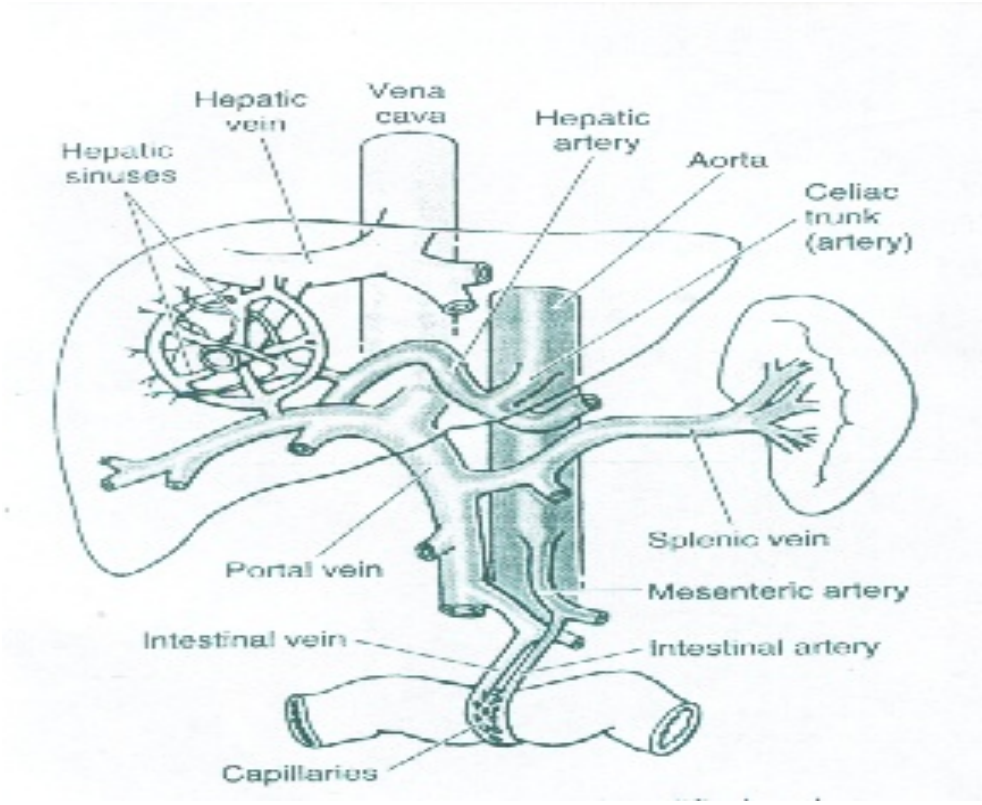

Fig. I: Hepatic blood flow.

HEPATIC BLOOD FLOW

Vascular Functions of the Liver

Control of hepatic blood flow

Normal hepatic blood flow is about 1500 $ml.min^{-1}$ in adults, of which 25% is derived from the hepatic artery and 70-75% from the portal vein. The hepatic artery supplies 45-50% of the liver's oxygen requirements while the portal vein supplies the remaining 50-55%. The pressure within the former is arterial, whereas that in the latter is normally less than 10 mmHg. Portal vein oxygen saturation is normally 85%. The

total blood flow from this dual supply represents 25-30% of total cardiac output [12].

Hepatic arterial flow appears dependent on metabolic demand postprandially (autoregulation), while flow through the portal vein is dependent on blood flow to the gastrointestinal tract and the spleen. Although autoregulation of hepatic arterial flow may not be appreciable during fasting a reciprocal though somewhat limited mechanism exists, such that a decrease in either hepatic arterial or portal venous flow results in a compensatory increase in the other [12].

The hepatic artery has α_1-adrenergic vasoconstricting receptors as well as $ß_2$ adrenergic and dopaminergic (D_1) vasodilator receptors. The portal vein has only α_1-adrenergic and dopaminergic (D_1) receptors. Sympathetic activation results in vasoconstriction of the hepatic artery and mesenteric vessels, decreasing hepatic blood flow [13].

Reservoir function

Portal vein pressure is normally only about 7-10 mmHg, but the low resistance of hepatic sinusoids allows relatively large blood flows through the portal vein. Small changes in hepatic venous tone (and pressure) thus can result in large changes in hepatic blood volume, allowing the liver to act as blood reservoir. Normal hepatic blood volume is about 450 ml (almost 10% of total blood volume). A decrease in hepatic venous pressure, as occurs during hemorrhage, shifts blood from hepatic veins and sinusoids into the central venous circulation and augments circulating blood volume as much as 300 ml. In patients with

congestive heart failure, the increase in central venous pressure is transmitted to hepatic veins and causes blood to accumulate within the liver. As much as 1 L of blood can effectively be removed from the circulation in this way at the expense of causing hepatic congestion [14].

Blood-cleansing function

The Kupffer cells lining the sinusoids are part of the monocyte-macrophage system. Their functions include phagocytosis, processing of antigens, as well as the release of various proteins, enzymes, cytokines and other chemical mediators. Their phagocytic activity is responsible for removing colonic bacteria and endotoxin entering the bloodstream from the portal circulation. Cellular debris, viruses, proteins and particulate matter in the blood are also phagocytosed [15].

Regulation of Liver Blood Flow

Intrinsic regulation

Intrinsic regulation occurs by mechanisms that regulate blood flow independently of the influence of nerves and blood-borne vasoactive compounds. Three major mechanisms are responsible for intrinsic regulation of hepatic blood flow: autoregulation, metabolic control and the hepatic arterial buffer response [16].

Autoregulation

Autoregulation is due to the tendency for local blood flow to remain constant inspite of changes in arterial pressure. It is hypothesized