Anesthesia and the Microcirculation

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Abstract

There is increasing evidence that the microcirculation and its regulation are severely compromised during many pathological conditions, such as hemorrhage, sepsis, or trauma. The effects of anesthetic agents on macrohemodynamics were investigated intensively in the last several decades. Research regarding modern anesthetics and anesthesia techniques has increased knowledge regarding the nonanesthetic effects of anesthetic agents, including those on organ perfusion and the microcirculation. Alterations in microvascular reactivity, nitric oxide pathways, and cytokine release are presumably the main mechanisms of anesthetic-induced tissue perfusion changes. This review summarizes current methods of microcirculatory status assessment and current knowledge regarding the microcirculatory effects of intravenous and potent volatile anesthetics and anesthesia-related techniques under both normal and pathophysiological conditions.

Keywords

anesthetic agents, microcirculation, organ perfusion, fluid therapy

Introduction

The microcirculation is severely compromised during many pathological conditions that are often faced by anesthesiologists, and there is a growing body of evidence that anesthetic agents may intrinsically alter the microcirculation at different regions of the body. Changes in the microcirculation resulting from exposure to anesthetic agents may also be affected by variable vascular reactivity in patients with vascular disease. The number of such patients who undergo major and complicated surgical procedures is increasing continually in developed countries. Knowledge regarding the microcirculatory effects of anesthetic agents could alter the anesthetic plan in certain procedures and in certain patients. This review summarizes current techniques of microcirculatory status assessment and also current knowledge regarding the microcirculatory effects of anesthetic agents and anesthesia-related techniques.

Current Methods for Microcirculatory Status Assessment

Analysis of microvascular blood flow alterations provides a unique perspective to study processes at the microscopic level in clinical medicine. Despite the critical role of the microcirculation in the pathogenesis of numerous chronic and acute diseases, such as diabetes, hypertension, sepsis, or multiple organ failure,1,2 current methods for direct microcirculation assessment at the bedside are very limited. Recently, new optical technologies have been successfully introduced into clinical and experimental research. Orthogonal polarization spectral (OPS) imaging and sidestream dark-field (SDF) imaging are noninvasive optical methods allowing visualization of the microcirculatory network through erythrocyte movement detection.3-5 Probes for OPS and SDF imaging have been implemented in a handheld device suitable for experimental and clinical use. SDF imaging is an improved method to visualize microcirculatory beds, providing better resolution and clarity when compared with the OPS technique.6 Both OPS and SDF technologies are suitable for use on mucosal surfaces, especially within the oral cavity and on the surface of internal organs. The principles, basic methodologies of OPS and SDF imaging, and current limitations have been reviewed in detail previously.7,8
Techniques using laser Doppler flowmetry (LDF) for microvascular imaging are based on frequency shifts when low-energy laser light encounters erythrocytes, whereby blood flow in a specific tissue microvolume (0.3-0.5 mm³) is measured continuously. LDF probes are designed for skin, mucosal, and internal organ surfaces; needle and endoscopic probes are also common in experimental and clinical research. Basic technical aspects, current clinical and experimental uses, and limitations have been reviewed numerous times.9-13

The intraoperative period during hospital care and also in experimental settings is a unique opportunity for continuous tissue perfusion and microcirculatory status monitoring when using the methods mentioned above, especially during major abdominal and cardiothoracic surgery. For example, the hepatosplanchnic, renal, or pulmonary microcirculations can be monitored intraoperatively. Otherwise, for clinical purposes, these techniques are limited to easily accessible surfaces, such as the sublingual and buccal mucosal surfaces.

**Microcirculatory and Tissue Perfusion Changes During Anesthesia**

**Microcirculatory Effects of Intravenous and Potent Volatile Anesthetics Under Normal and Pathophysiological Conditions**

The mechanisms underlying the hemodynamic effects of intravenous anesthetics have been intensively studied at the microcirculatory level in recent decades. The nonanesthetic effects of propofol, thiopental, and ketamine, specifically focusing on macrohemodynamics, have been investigated in clinical and experimental settings.14-16 It has been demonstrated that propofol and thiopental act centrally to inhibit sympathetic nervous system activity in contrast to ketamine’s sympathomimetic actions. Heart contractility is decreased by propofol, which attenuates β-adrenergic signal transduction in cardiac myocytes via inhibition of cAMP production.17-19 In vitro studies have shown local vasodilatory effects of thiopental, propofol, and ketamine that are mediated by inhibition of L-type voltage-gated Ca²⁺ channels.20-23 Assessment of the roles of prostaglandins and nitric oxide (NO) in the arteriolar responses of rat diaphragm to intravenous anesthetics (ie, etomidate, propofol, and thiopental) have elucidated a predominant effect of prostaglandins with etomidate when compared with propofol and thiopental.24 In recent years, concomitant with advances in anesthetic techniques, there have been efforts to elucidate the nonanesthetic effects of anesthesia drugs, focusing on the adequacy of organ perfusion. In addition to compromised macrohemodynamics, alterations of immune responses and NO pathways by intravenous anesthetics are the most important factors affecting organ perfusion and the microcirculation.25-27

Beyond cardiopulmonary stability during the perioperative period, adequate hepatosplanchnic perfusion is crucial in preserving intestinal mucosal barrier function, so as to prevent toxin translocation. Intestinal mucosal barrier failure plays a key role in multiple organ dysfunction syndrome development during hepatosplanchnic low-flow states.28,29 There are only a limited number of animal studies assessing direct hepatosplanchnic microcirculation under various techniques of intravenous anesthesia. It has been demonstrated that the diameters of rat mesenteric arterioles and venules were larger during propofol/fentanyl anesthesia, when compared with ketamine and thiopental; capillary diameter and macromolecular leakage were not significantly different between the groups.30 There are some studies demonstrating an anti-inflammatory effect of propofol, which can be explained by its ability to preserve hepatosplanchnic blood flow and thus maintain intestinal mucosal barrier integrity.31 The molecular mechanisms of the propofol-induced anti-inflammatory and vascular effects described above have not been satisfactorily explained. Recently, an in vitro and ex vivo study in surgical patients anesthetized with propofol showed increased constitutive NO production and decreased inducible NO production.32 Another anti-inflammatory mechanism of propofol consists of altered cytokine balance in favor of the anti-inflammatory interleukins (IL-10, IL-1 ra).33 Immune responses to various intravenous anesthetics have been reviewed at length.34 An experimental study in dogs demonstrated a dose-dependent effect of propofol on regional organ blood flow in the kidney, small intestine, and large intestine.35 Higher doses of propofol (24 mg/kg/h) led to a significant reduction in renal, myocardial, and large-intestinal blood flow; small-intestinal blood flow was unaffected. Fluid loading allowed myocardial and renal perfusion to be maintained. No significant changes in splanchnic and myocardial perfusion were observed at a propofol infusion rate of 12 mg/kg/h. Recently, the effects of propofol administration on the sublingual microcirculatory network was investigated in patients of ASA physical status I. Decreases in total microvascular density by 9% and of continuously perfused capillaries by 16% were observed.36 The clinical importance of these findings and further consequences are unclear.

Potent volatile anesthetics in current clinical practice are the halogenated ethers desflurane, sevoflurane, and isoflurane; they are most commonly administered in concentrations of less than 1 minimal alveolar concentration (MAC), and the cardiovascular effects are dose dependent—decreasing mean arterial blood pressure as a result of a decrease in systemic vascular resistance. Within the usual ranges of anesthetic concentrations administered to healthy humans, the cardiac index is not altered significantly, and
Heart rate acceleration is dose related. Halothane was shown to decrease blood pressure by reduction of cardiac output, whereas heart rate was unaffected.

Preservation of global hemodynamic parameters during various pathological states, however, may not ensure adequate tissue perfusion at the microcirculatory level. There is the issue of whether the potent volatile anesthetics compromise the microcirculation while systemic parameters are within normal ranges. Hepatic, intestinal, and renal perfusion at the microcirculatory level has been the frequent subject of both clinical and experimental studies assessing the effects of potent volatile anesthetics. In patients undergoing major abdominal surgery, steady-state jejunal and hepatic blood flow were assessed by LDF at 1 MAC desflurane and isoflurane. Desflurane anesthesia was associated with significantly greater gut blood flow when compared with isoflurane; hepatic arterial blood flow did not differ between the 2 anesthetics. Previous studies in dogs using flow probes and microspheres have shown that neither desflurane nor isoflurane was associated with changes in hepatic and duodenal regional blood flow. At deeper levels of anesthesia (2 MAC), desflurane, but not isoflurane, decreased total hepatic blood flow. Another study in dogs also found that both isoflurane and sevoflurane caused mild decrease in portal blood flow but no changes in arterial hepatic blood flow. Although potent volatile anesthetics may affect portal blood flow, current evidence suggests that there is well-maintained hepatic and intestinal perfusion in relation to oxygen demand.

Renal perfusion has been studied extensively during potent volatile anesthetic administration. Previous studies in dogs and pigs have demonstrated that desflurane, isoflurane, and sevoflurane do not alter renal blood flow. In cats, administration of desflurane and isoflurane within usual ranges of anesthetic concentrations did not alter the autoregulation of renal blood flow at perfusion pressures >90 mm Hg.

In dogs, desflurane and isoflurane did not alter the pattern of myocardial blood flow distribution. In pigs, sevoflurane decreased myocardial perfusion by an amount consistent with the associated decrease in myocardial work. Other studies in dogs have shown that isoflurane and sevoflurane increased coronary blood flow and decreased coronary vascular resistance, including resistance through the collateral circulation. The possibility that potent volatile anesthetics induce coronary steal phenomena and transient ischemia has been studied over 2 decades. Currently, there is no reliable evidence of coronary steal phenomena or myocardial ischemia caused by desflurane, isoflurane, or sevoflurane. Moreover, potent volatile anesthetics, including isoflurane, sevoflurane, and desflurane, appear to be as effective as ischemic preconditioning in the protection of the myocardium from ischemic injury.

Sevoflurane and isoflurane were demonstrated to decrease proinflammatory cytokine (IL-1β) and tumor necrosis factor [TNF]-α production in humans. Sevoflurane, isoflurane, and halothane reduced neutrophil uptake in the coronary circulation. Also, reduction of hydroxyl radical release associated with isoflurane and halothane has been described in the ischemic myocardium.

In summary, potent volatile anesthetics currently used in clinical practice have similar effects on regional tissue perfusion. Within the usual ranges of inhaled anesthetic concentrations, vital organ perfusion remains sufficient and adequate in relation to oxygen demand in healthy patients.

Pathophysiological conditions. The effects of intravenous and potent volatile anesthetics on regional tissue perfusion and microcirculation in the studies cited above are mostly described under stable anesthetic conditions. It is reasonable to hypothesize that these effects may be different under pathophysiological conditions, such as hemorrhage, multiple trauma, or sepsis. There is increasing evidence that anesthetic agents may differentially alter the response of the microcirculation to hemorrhage. During hemorrhage or hemorrhagic shock, altered pharmacokinetics and pharmacodynamics of anesthetics must be considered. After hemorrhage, the highest degree of constriction of mesenteric arterioles, capillaries, and venules was observed under propofol/fentanyl anesthesia, compared with thiopental and ketamine anesthesia. Mesenteric vasodilation, however, was greatest under propofol/fentanyl anesthesia without hemorrhage. This phenomenon may be explained by propofol-dependent inhibition of the vasoactive response to endogenous NO during hemorrhage. A recent study in pigs compared the effects of intravenous drugs (ketamine, midazolam, and buprenorphine) and isoflurane anesthesia on organ perfusion (tissue oxygen saturation) and cytokine release during uncontrolled hemorrhage. End-organ perfusion with intravenous anesthesia appeared to be equivalent or inferior to isoflurane anesthesia; no differences in inflammatory cytokine release were detected between the groups. Preserved vascular reactivity is a key adaptive mechanism in hemorrhagic shock. A recent study in mice demonstrated the beneficial effect of coadministered nitrous oxide on vascular contractility under isoflurane anesthesia during hemorrhagic shock. The current literature indicates that vascular reactivity and its regulation during anesthesia in hemorrhagic shock may be influenced both by different anesthetics and different mechanisms.

The role of inhaled and intravenous anesthetics and hypnotics in sepsis is mostly discussed in the context of their possible anti-inflammatory effects. Such immune alterations may be of great importance in the daily practice of intensive care, including possible impact on clinical outcome. A recent study in rats that focused on the role of inducible NO synthase (iNOS) suggested that the interaction
of propofol and iNOS-derived NO impaired the autonomic regulation of cardiovascular function during endotoxemia; this effect was dose dependent. The immune effects of commonly used sedatives in intensive care practice (benzodiazepines, propofol, opioids, and α-2 adrenergic receptor agonists) were reviewed in detail recently. Sevoflurane, isoflurane, and enflurane decreased proinflammatory cytokine (IL-1β, TNF-α) production by human leukocytes in vitro. Further research should further refine the possible clinical consequences of sedatives and anesthetics on immune responses in patients suffering from sepsis.

**Microcirculatory Effects of Epidural Anesthesia**

Epidural anesthesia is a commonly used regional anesthetic technique not only for surgical patients but also for obstetric and trauma patients and for treatment of chronic pain. The physiological effects of epidural anesthesia are well described, especially the effects of epidural blockade on cardiopulmonary and splanchnic at both the macrocirculatory and microcirculatory levels. During thoracic epidural anesthesia (TEA), decreased heart rate, and systolic and diastolic blood pressures are observed both in healthy volunteers and in surgical patients. TEA has been shown in canine models to improve cardiac regional blood flow so as to favor the endocardium.

One important question currently being addressed in both experimental and clinical studies is the complex effects of epidural anesthesia on gastrointestinal perfusion. Interruption of sympathetic activity and mesenteric venodilation by TEA are dose dependent and related to the extent of the block. Epidural blockade limited only to the lumbar segments shows mesenteric venoconstriction caused by the increase in splanchnic sympathetic activity. Major surgical procedures, pain, or shock states may increase sympathetic nervous system activity with the potential for gastrointestinal hypoperfusion. Thus, the main hypothesis investigated in recent years is the effect of a blunted sympathetic nervous system on the response to stressful stimuli during TEA.

In animal studies, TEA increased gastrointestinal blood flow and improved perfusion at the microcirculatory level. A previous TEA study in dogs demonstrated improved gastric microcirculation during esophagectomy, as revealed by OPS imaging. Intestinal and gastric mobilities were improved after the procedure. TEA in rats increased the ileal mucosal blood flow and decreased intermittent flow in the villous microcirculation. Results from clinical studies are less consistent, mainly because of the technical aspects of splanchnic blood flow assessment in clinical practice. With the exception of the intraoperative period, only indirect techniques are feasible, such as gastrointestinal tonometry or measuring proinflammatory mediators and circulatory vasoactive substance release. Intraoperative laser Doppler flow analysis during bowel surgery revealed a colonic blood flow increase of 41% in patients receiving TEA. In contrast, another study using the same assessment technique showed a 65% decrease in mean colonic serosal blood flow.

In animal models of epidural anesthesia, there is increasing evidence of the positive effects of TEA on splanchnic blood flow and the microcirculation. Recent clinical studies focusing on splanchnic perfusion under TEA have yielded conflicting results, probably because of different assessment methods for splanchnic perfusion and because of different anesthetic and study protocols. There is also evidence that the microcirculatory effects of neuroaxial blockade may be partly mediated via systemic effects of absorbed local anesthetics.

**Microcirculatory Effects of Cardiopulmonary Bypass (CPB)**

CPB is a very specific part of perioperative care in cardiac surgery. The pathophysiology of CPB was described in detail recently. CPB may specifically activate systemic inflammatory responses, likely from contact of blood with artificial surfaces, ischemia-reperfusion injury after aortic cross-clamping, or indirectly from endotoxemia when the intestinal mucosal barrier is damaged. Inadequate immune system activation is mediated via complement, cytokines, coagulation, and endothelium and may lead to the systemic inflammatory response syndrome with variable clinical presentations, including the risk of life-threatening multiple organ dysfunction syndrome. Adequate splanchnic blood flow plays a crucial role in mucosal barrier preservation and avoidance of gut translocation of endotoxins. Previous clinical studies have yielded conflicting results when assessing splanchnic blood flow. Splanchnic blood flow did not decrease during hypothermic CPB when measured using 2 indicator dilution techniques. In contrast, another clinical study showed a 19% reduction in splanchnic blood flow during hypothermic CPB. Splanchnic oxygen transport and normal lactate levels were preserved during normothermic CPB in humans. These conflicting results from clinical studies may be related to different techniques used for splanchnic blood flow assessment under clinical conditions.

OPS imaging is another technique that has been used recently for sublingual microcirculation assessment during CPB in humans. Preliminary results indicate a decrease in functional capillary density by 10% just after the start of CPB and its restoration after discontinuation of CPB. The clinical relevance of these findings remains unclear, and further clinical studies using additional techniques for organ perfusion assessment are needed to reconcile laboratory and clinical investigation findings.

The choice of anesthetics may influence the proinflammatory state during and after CPB. Recent clinical trials...
have suggested that volatile anesthetics in general and sevoflurane in particular are good cardioprotective and anti-inflammatory agents when used during open-heart surgery.\textsuperscript{83}

**Perioperative Fluid Management, Early Goal-Directed Therapy, and the Microcirculation**

In patients undergoing major surgery, perioperative normothermia,\textsuperscript{84} treatment with supplemental oxygen,\textsuperscript{85,86} volume optimization, and goal-directed hemodynamic therapy (GDHT) may decrease the incidence of various perioperative complications and length of hospital stay.\textsuperscript{87-89} Nevertheless, optimal perioperative fluid management remains a matter of debate.\textsuperscript{90,91}

Several methods are clinically available for perioperative monitoring of intravascular volume, cardiac output, and fluid responsiveness, including esophageal Doppler, arterial pressure wave analysis, indicator dilution, thoracic bioimpedance, partial nonrebreathing systems, and mixed venous oxyhemoglobin oxygen saturation.\textsuperscript{92} However, despite recent studies of fluid-volume optimization, there is still insufficient information on the influence of GDHT on blood flow distribution among and within different organs.\textsuperscript{93} In addition, no clinical data have yet been reported regarding the effects of perioperative fluid management and GDHT on the microcirculation in specific organs or injured tissues.\textsuperscript{94}

Perioperative LDF, near infrared spectroscopy, transcutaneous oxygen measurements, microdialysis catheters, and tissue pH monitors have all been used for the assessment of tissue perfusion in major surgery but not as tools to guide perioperative fluid management.\textsuperscript{87} LDF has the potential to monitor perioperative microvascular perfusion continuously in different organs: skin, gastrointestinal tract, brain, liver, and kidney. The main disadvantage of currently available LDF technology is the use of fiberoptic sampling of very small tissue volumes (<1 mm\textsuperscript{3}), with the resultant inability to assess the heterogeneity of flow as well as the microvascular architecture. Laser Doppler perfusion imagers could overcome this problem by their capability to obtain images from larger tissue areas, but their routine applicability in operating rooms is limited by long image acquisition times and complicated hardware settings. Using high-speed cameras would resolve the problem with long-term image processing.\textsuperscript{95} Video imaging of the sublingual microcirculation is an attractive and easily performed procedure for visualizing the microcirculation. OPS or SDF allow noninvasive observation of the human microcirculation in accessible tissue surfaces with thin epithelial layers (eg, sublingual). OPS has been used mainly in critical care\textsuperscript{96,97} and experimental research settings.\textsuperscript{98,99}

Despite its broad experimental use in different locations and clinical situations, OPS and SDF have not yet been used as tools to guide perioperative fluid management.

Splanchnic hypoperfusion and hypoxia may be a determinant of postoperative complications as the intestine is considered to be central in the origin of postoperative sequelae.\textsuperscript{94,100} Hence, specific targeting of the splanchnic circulation with monitoring techniques such as tonometry have been attempted to recognize and prevent perioperative tissue hypoperfusion.\textsuperscript{101-104} However, although experimental and clinical studies suggested the usefulness of gut tonometry in visceral tissue perfusion assessment during the perioperative period, several methodological drawbacks limit this approach.\textsuperscript{105} On the other hand, these data indicate that the microcirculation might be a key diagnostic and therapeutic target in the perioperative setting.

Indeed, it has been shown that surgical trauma produces marked microcirculatory alterations, mainly as a result of early systemic inflammatory responses, tissue hypoperfusion, and direct tissue injury.\textsuperscript{106} In addition, the association between reduced microvascular blood flow and impaired anastomotic healing supports the causative role of microcirculatory dysfunction in postoperative complications.\textsuperscript{107,108}

It is important to note that recent clinical studies suggest that these surgical trauma–induced microcirculatory alterations might contain important prognostic information. In a group of patients undergoing major abdominal surgery, Jhanji et al\textsuperscript{109} demonstrated that impaired sublingual microvascular flow was associated with more frequent postoperative complications and increased length of hospital stay. Sublingual microvascular perfusion reduction, albeit slight and transient, was even described during uncomplicated hypothermic cardiac surgery.\textsuperscript{82}

Although therapeutic strategies aimed at alleviating microvascular dysfunction during major surgery have not been evaluated thus far, there are some recent experimental data supporting the extension of the concept of GDHT to surgical patients. Hiltebrand et al\textsuperscript{110} demonstrated that goal-directed therapy targeted to achieve a mixed venous oxygen saturation greater than 60% with colloid fluid improved intestinal microcirculatory blood flow and tissue oxygen tension, whereas goal-directed crystalloid and restricted crystalloid administration had no such effects in the setting of porcine abdominal surgery. Furthermore, using an identical approach, the same group of authors showed that in contrast to goal-directed crystalloid therapy, only goal-directed colloid therapy considerably increased oxygen tension and perfusion in healthy and perianastomotic colon tissue.\textsuperscript{111} Taken together, these experimental results highlight the potential role of microcirculation-targeted fluid resuscitation and add new understanding of the possible mechanisms responsible
for the beneficial effects associated with goal-directed therapy in major abdominal surgery.

In conclusion, recent studies suggest that microvascular alterations may have a pivotal role in postoperative complications. Furthermore, it appears that microvascular-oriented therapy could have the potential to beneficially affect the outcome of high-risk surgical patients. This reasoning is corroborated by the observation that GDHT in septic patients that was associated with improved microcirculatory flow during protocol-directed resuscitation was associated with reduced multiorgan dysfunction.112 Nevertheless, further studies are needed not only to provide definitive evidence for a causal relationship but also to demonstrate that individualized, microcirculation-oriented GDHT approaches are capable of improving the outcome of high-risk surgical patients.

Summary

Surgery and anesthesia are known to compromise blood flow in various body regions, and microvascular alterations may play an important role in the development of organ dysfunction in the postoperative period. Recent advances in technology have allowed the assessment of the microcirculation during various clinical conditions, including anesthesia. There is growing interest in assessing the effects of various anesthetic agents, techniques, and organ-supporting strategies on the microcirculation. Current evidence suggests that there are different effects with different anesthetic agents and that some of these effects cannot be explained by systemic hemodynamic differences. Agent-specific effects on the microcirculation may thus play an important role.

The effects of intravenous and potent volatile anesthetics on regional tissue perfusion and the microcirculation as mentioned above are mostly described under stable anesthetic conditions. Therefore, further research is necessary to ascertain the effects of anesthetics on the microcirculation under pathophysiological conditions, such as hemorrhage, multiple trauma, or sepsis. In the future, we may choose anesthetic agents and related management techniques according to their microcirculatory effects.

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