



# The impact of local anesthetics on perioperative microcirculation and coagulation

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## Abbreviations:

ICU: intensive care unit  
LA: local anesthetic/local anesthesia  
EA: epidural anesthesia  
TEA: thoracic epidural anesthesia

## Abstract

*Local anesthetics are widely used to produce surgical anesthesia and postoperative analgesia. Antiarrhythmic effect of local anesthetics is well recognized and used during reanimation, in the ICU or in general anesthesia. Other effects of this drug group and their influence on perioperative stress response are poorly understood. This article focuses on changes in tissue microcirculation produced by perioperative application of local anesthetics. Vasodilatation, changes in the blood flow velocity and tissue perfusion may be particularly important. The effects on perioperative coagulation, especially (particularly) in high-risk vascular patients, are reviewed.*

## INTRODUCTION

Analgesic effects and complications of various anesthetic techniques related to their perioperative application (were commonly examined) (have frequently been investigated). Some recent studies suggest that local anesthetics may have additional beneficial effects on postoperative outcome by attenuating perioperative stress response and hypercoagulability. Vasodilatation, a well-known effect of local anesthetics may lead to better tissue oxygenation, especially in hypotensive patients. This article discusses the results of some recent preclinical studies, focusing the effects of local anesthetics on microcirculation, tissue perfusion, and possible implications on postoperative outcome.

## VASODILATATION

Vasodilatation is the first clinically apparent effect of local anesthetics. Vasodilatation after lidocaine infiltration is believed to be mainly due to the inhibition of action potentials via sodium channel blocking in sympathetic nerves. Another important mechanism contributing to the vasoactivity of local anesthetics is nitric oxide release. After co-injection of the nitric-oxide-synthase inhibitor a 60% reduction in vasodilatation after 20 minutes will be observed (1).

Vasodilatation after injection of local anesthetic will result in a rapid, significant and dose-dependent increase in microvascular blood flow measured by laser Doppler imaging increases (2). Comparable effects are produced by injection of lidocaine, bupivacaine and levobupivacaine. A significant increase in the blood flow was observed in a study by Newton *et al.* even after intradermal injection of only 0.1 mol of 0.125, 0.25, 0.5, and 0.75% of bupivacaine and levobupivacaine (2).

Vasodilatation can be observed both in the tissue after infiltration of local anesthetic and in the area innervated after nerve or plexus block. Lind and coworkers measured blood flow in the forearm after brachial plexus blockade. Vasodilatation resulting from nerve blockade produced a more than 3-fold increase in blood flow, and was not followed by an increase in metabolic glucose uptake. On the contrary, a tendency towards a reduction was seen. The authors attributed this effect to the sympathetic activity blockade (3). Skeletal muscle paralysis may also contribute to lower metabolic glucose uptake.

Clinical benefits of vasodilatation were observed in microvascular surgery. Two principal methods of local anesthetic application are currently investigated: a topical intravascular injection into graft arteries and nerve block or regional anesthesia, which enhances blood inflow to the graft. *In vitro* and *in vivo* studies confirmed that lidocaine 20%, and lidocaine 2 or 20% combined with papaverine significantly increase blood flow in the rabbit carotid artery after microvascular anastomosis (4). An increased index of tissue perfusion after nerve blocks may enhance graft temperature and survival, especially in microvascular procedures, alleviate stress response, and reduce neutrophil migration and reperfusion injury (5, 6). As stress response was blunted, complementary opioid consumption in reconstructive microvascular surgery will decrease (5).

The vasoactive effect of local anesthetics was found to be biphasic and dose related. Newton confirmed that vasodilatation diminishes 40 minutes after injection of both bupivacaine and levobupivacaine (2). Vasodilatation and tissue perfusion thereafter decrease below baseline. Vasoconstriction was observed after intradermal injection of lower, subclinical concentrations (0.008–0.0625%) of both anesthetics (7). Significant constriction of the central nervous system vasculature with a decrease in heart rate was also observed after a large intravenous dose (4 mg/kg) of ropivacaine (8). The clinical relevance of these effects was not investigated.

The addition of epinephrine  $2.5 \mu\text{g mL}^{-1}$  will significantly reduce vasodilatory response to clinical doses of lidocaine and bupivacaine, producing net vasoconstriction at the infiltration site. The analgesic effect of local anesthetics will be prolonged at the site of injection (7). After epidural injection of 2% lidocaine with epinephrine, more rapid recovery of motor and sensory block can be achieved with the use of 30 mL normal saline epidural washout (9).

## HYPOTENSION

Vasodilatation in regional anesthetic techniques usually produces hypotension, varying in duration and intensity, depending on the type of drug, anesthetic/analgesic technique and on patient comorbid disorders. A decrease in mean arterial blood pressure may be the effect of reduced regional sympathetic nervous activity and vasodilatation mediated via nonadrenergic mechanisms (1, 3, 10).

Hypotension that may provoke hypoperfusion was frequently an excuse for evading central neuraxial blocks. Preclinical and clinical studies do not support this presumption. Vagts and coworkers found no differences in the mesenteric blood flow during hypotension in epidural anesthesia (EA) in an animal study (11). A randomized study conducted by Spackman confirmed that EA resulted in improvements in gastric mucosal perfusion in critically ill patients with peritonitis (12). The outcome of these patients traditionally not subjected to epidural catheterization was not reported in this study.

Hypotension observed after central neuraxial blockades does not per se lead to changes in blood volumes and hemoglobin concentration. It could not be prevented by volume infusion (11). Van den Oever *et al.* observed no benefit from this maneuver. Volume loading using hydroxyethyl starch will produce hypervolemic hemodilution with no change in capillary density, venular diameter, or flow velocity in the microcirculation of anesthetized patients. It will only slightly increase the arterial blood pressure (13).

A significant decrease in hemoglobin concentrations can be observed after hydroxyethyl starch infusion. Therefore ephedrine injections should be preferred to acute hypervolemic hemodilution in patients with cardiopulmonary diseases in which perioperative fluid overload is undesirable (14).

## TISSUE PERFUSION AND OXYGENATION

Perioperative tissue hypoperfusion is a major contributing factor leading to organ dysfunction. Central neuraxial blockades were proven as safe in preserving tissue perfusion and oxygenation. Intestinal oxygen uptake, mucosal tissue  $\text{pO}_2$ , and tissue  $\text{pCO}_2$  were unchanged during EA in an animal study (11). A decrease in the sympathetic activity results in lower muscle activity and decreased glucose uptake (3). A supplemental neural block blunts vasoconstriction caused by surgical stress and generalized adrenergic vasoconstriction during major abdominal surgery. A resultant was significantly higher intraoperative tissue oxygen tension in the combined general/thoracic epidural anesthesia group versus general anesthesia (GA) group not only in the anesthetized region, but also outside the area of the epidural block. Consequently, combined general/EA prevents a decrease of tissue oxygen tension and helps to provide sufficient tissue oxygenation (15).

Beneficial effects of locoregional anesthetic techniques on tissue oxygenation are perhaps the effects of stable visceral perfusion. Delis *et al.* observed significantly higher blood flow in the popliteal veins of patients under combined EA/GA versus GA both during surgery and recovery (16). Under physiological conditions, thoracic epidural anesthesia (TEA) effectively preserved gastric mucosal microvascular hemoglobin oxygenation and intramucosal pH despite significantly decreasing mean arterial pressure both in the animal (17) study and during major abdominal surgery in the clinical setting (18).

Similar effects of TEA in the presence of decreased perfusion pressure were registered in the gut circulation. It increased mucosal blood flow in the villus microcirculation *in vivo* (10). Better intestinal perfusion in regional anesthesia was registered in patients undergoing radical prostatectomy. TEA or spinal anesthesia resulted in significantly shorter times to first flatus and first bowel movement as compared to general anesthesia (19, 20).

However, during compromised circulatory conditions (PEEP 10 cm) TEA aggravated microvascular oxygenation and systemic oxygen-transport induced by cardiocirculatory depression (17).

## THE EFFECTS OF SYSTEMIC APPLICATION OF LOCAL ANESTHETICS

Antiarrhythmic effect of systemically injected local anesthetics is well known and widely used. A bolus of 100 mg of lidocaine administered by a pump two minutes before release of aortic cross clamping can safely decrease the incidence of reperfusion ventricular fibrillation. It is associated with better hemodynamics after weaning from cardiopulmonary bypass (21). Bupivacaine (10 mg kg<sup>-1</sup>) can decrease sympathetic activity and metabolic consumption in treated animals attenuating myocardial tissue acidosis during ventricular fibrillation (22).

Only a few studies have dealt with the effects of systemically administered LA with regard to the clinical outcome, since discrimination between the direct systemic effects of LA and the effects of neuraxial blockade (in epidural anesthesia and analgesia) cannot be easily done (15, 23). There are hints that the pharmacological effects of the local anesthetic itself may contribute to the protective effect against perioperative stress response (21, 22). Increased blood flow was suggested by Coleman as one of the crucial moments in the attenuation of tissue acidosis in the myocardial tissue of dogs during ventricular fibrillation. Owing to the vasodilatation LAs may preserve capillary bed perfusion (24). Whether some susceptible groups of patients could benefit from these effects was not widely investigated.

## COAGULATION

Changes in the coagulation profile during regional anesthesia were assessed by means of recognition of underlying mechanisms and possible influence on patient outcome. These are important especially in central neuraxial blockades, where local or systemic coagulation disorders may be particularly deleterious. Although there are presumptions on the reduced incidence of thromboembolic events after regional anesthesia techniques, these were not confirmed by large randomized clinical studies.

The clinical observations on perioperative coagulation were controversial. Some recent studies proved that intraoperative blood loss was significantly lower in an epidural vs. general anesthesia group (19), although the mechanisms are incompletely understood.

Smyth *et al.* did not confirm any clinically significant differences in the coagulation markers (fibrinogen, factor V, plasminogen, antithrombin, and FDP) between spinal and GA groups undergoing transurethral resection of the prostate (25). The same results were observed in GA and EA patients undergoing total hip arthroplasty. The values of the platelets, fibrinogen, prothrombin time, thrombin time, activated partial thromboplastin time, antithrombin, and protein C were not different at any given time point (26). A perioperative measurement of plasminogen activator inhibitor-1, beta thromboglobulin (a marker for platelet degranulation), and circulating cortisol did not confirm significant changes from control values and between two groups of patients after arterial reconstructive surgery (27).

A study of Hollman and coworkers confirmed hypercoagulability in the GA group undergoing major orthopedic surgery. In this group significant reduction of platelet-mediated hemostasis time (39%), clotting time (21%) and minor increase in the collagen-induced thrombus formation (10.3%) was observed. EA, by contrast, prevented immediate postoperative hypercoagulability. Platelet-mediated hemostasis time showed a tendency towards prolongation by 33.2% whereas no other postoperative hemostasis parameter was altered significantly (28).

Although hypotension per se may reduce bleeding, it was not confirmed as the principal factor contributing to minor blood loss during EA. This hypothesis was tested in two groups of patients undergoing hip arthroplasty by maintaining mean arterial pressure between 50 and 60 mm Hg. Intraoperative blood loss, percentage of patients receiving blood substitution, and total packed red blood cells transfused were less in patients receiving EA than in those receiving total intravenous anesthesia with propofol and remifentanyl (29). Other authors did not find any difference in the blood loss between these two groups of patients (24).

The significant increase in red cell velocity and improved capillary blood flow in terminal arterioles may be crucial in the anticoagulant effect of epidural anesthesia in various models of stress and trauma (10, 24).

Contrary to the venous stasis in elective abdominal surgery under GA and upon its recovery, EA administered as part of GA is associated with a significant enhancement of both mean velocity and volume flow. This beneficial hemodynamic effect of EA at the vulnerable stage of recovery may be critically essential in the light of enhanced blood viscosity, fibrinolytic shut-down, endothelial/platelet activation and immobility (16).

## OUTCOME

There are several clinical trials and metaanalyses focusing on the outcome after LA and GA techniques. Postoperative morbidity was especially investigated after thoracic and major abdominal surgery.

Thoracic epidural anesthesia may reduce opioid medication in patients undergoing coronary artery bypass

grafting, allowing earlier extubation and significantly less lower respiratory tract infections versus general opioid analgesia (30). In this group of patients the incidence of new supraventricular arrhythmias, acute renal failure and postoperative confusion was observed in significantly fewer patients in the TEA group (30).

Rodgers *et al.* indicate that regional anesthesia provides important improvements in major postoperative complications in major abdominal surgery (31). On the contrary, in a primary analysis of a large randomized trial in 915 high-risk patients undergoing major abdominal surgery, Peyton *et al.* found no difference in outcome between patients receiving perioperative EA and those receiving IV opioids, apart from the incidence of respiratory failure (32). A study by Park confirmed that the influence of anesthetic and postoperative analgesic techniques on perioperative outcome varies with the type of operation performed. The EA provided better postoperative pain relief after major abdominal surgery ( $n=1,021$ ). In this study the overall outcome was improved and the intubation time and intensive care stay shortened only in patients undergoing abdominal aortic operations (33).

Patients who had received EA had a faster recovery of the circulating erythrocyte mass than those who had received GA or CA. This is probably an effect of erythropoiesis inhibition by nitrous oxide, which may alter vitamin B (12) functions (34).

There are some less known effects of local anesthetics that merit further investigation. Since local anesthetics do reduce reperfusion injury and inhibit PMN adhesion and subsequent migration to the allograft, the effects of these drugs on graft survival should be a matter of clinical trial (6). The effects on cancer cells may become important, too. Lidocaine reduced the invasion ability of human cancer cells by partly inhibiting the shedding of heparin-binding epidermal growth factor such as from the cell surface and modulating intracellular  $Ca^{2+}$  concentration (35). Whether this potentially beneficial action of local anesthetic infiltration could influence tumor growth and patient outcome demands further investigation.

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