Gastrointestinal microcirculation: still a mystery?

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Under normal conditions, the gastrointestinal tract receives about 20–25% of the total cardiac output. Usually, 60–80% of total blood flow passes to the submucosal and mucosal layers, providing nutrients and oxygen to the highly metabolically active epithelial, immune, and vascular endothelial cells. The mucosal layer of the gastrointestinal tract serves as an important barrier against chemical and bacterial threats from the luminal side while simultaneously providing a huge variety of bidirectional transport processes. Regulation of gastrointestinal blood flow at the level of the microcirculation is extremely complex and still poorly understood. Under resting conditions, experimental evidence suggests that mucosal perfusion is mainly regulated by the vasodilators nitric oxide and prostaglandin I₂, by the sympathetic nervous system and probably by the potent vasoconstrictor endothelin. In addition, arterial baro- and chemoreceptors, cardiopulmonary receptors, and afferents from skeletal muscle affect gastrointestinal blood flow and blood volume. Any physical stress and pathophysiological conditions associated with hypovolaemia, such as haemorrhage and septic shock, result in strong activation of the sympathetic nervous system and release of norepinephrine. This induces arteriolar and, to a lesser extent, venular vasoconstriction within the gastrointestinal microvasculature which redistributes venous blood volume away from peripheral tissues towards the intrathoracic compartment. Under these conditions, the vasoregulatory role of epinephrine in the gastrointestinal tract is believed to be negligible. The vasoconstrictor response evoked by major stress is strongly augmented by the simultaneous release of the hypothalamic–pituitary hormone arginine-vasopressin and activation of the renin–angiotensin system, finally resulting in the formation of angiotensin II. Despite this seemingly uniform physiological response of the gastrointestinal microvasculature to stress, experimental studies suggest major differences in the sensitivity of microvessels to catecholamine agonists, depending not only on the vessel type but also on the gastrointestinal segment investigated. For example, in a study, using intravital microscopy, of the relative sensitivity of rat mesenteric microvessels to the constrictor action of increasing dosages of topically applied epinephrine or norepinephrine, precapillary sphincters were 500- to 1000-fold more sensitive to the vasoconstrictor action of epinephrine and norepinephrine when compared with arteries or veins. In addition, when applied topically, epinephrine was a much more potent vasoconstrictor in all vessel types investigated compared with norepinephrine. Experiments in dogs demonstrated that bolus injections of norepinephrine into various arteries of the splanchnic region resulted in different degrees of vasoconstriction. The sensitivity of resistance vessels to the vasoconstrictor action of norepinephrine was much less pronounced in distal parts of the gastrointestinal tract such as the colon. This situation becomes even more complex, considering that these studies were performed in different animal species under various pathophysiological conditions, investigating tissue oxygen supply at different sites within the gastrointestinal tract while variable application modes of vasoactive drugs were used.

Focusing on norepinephrine first, animal experiments uniformly demonstrate that topical and intra-arterial injections always result in microvessel vasoconstriction. However, when norepinephrine is given i.v., the response is much less clear and depends not only on the species and gut segment investigated but also on the conditions present. For example, our group investigated effects of increasing dosages of norepinephrine (0.1–10 μg kg⁻¹ min⁻¹) on...
jejunal oxygen supply and mucosal tissue oxygen tension in an autoperfused innervated jejunal segment in pigs under total i.v. anaesthesia using midazolam and fentanyl. Infusion of norepinephrine resulted in significant increases in cardiac output, systemic oxygen delivery, and oxygen consumption. However, despite this significant increase in systemic oxygen delivery, norepinephrine failed to augment jejunal microvascular blood flow, tissue haemoglobin oxygen saturation, or mucosal tissue oxygen tension, as measured by laser Doppler velocimetry, tissue reflectance spectroscopy, and Clark-type multiwire surface electrodes, respectively. Until now, most studies in humans have involved patients who are receiving norepinephrine, after fluid resuscitation, in order to achieve a predefined systemic perfusion pressure. These studies have shown either no adverse effects or improvement, in the indices of gastrointestinal oxygen supply. In particular, patients with septic shock who had received fluid resuscitation but were still hypotensive seem to benefit from normalization of mean arterial pressure by infusion of norepinephrine.

Similarly, epinephrine, when given topically or intravenously, decreases gastrointestinal blood flow. Under different experimental conditions in various animals, the results of i.v. infusion of epinephrine varied depending on the model used and the gastrointestinal segment investigated. The majority of studies performed in critically ill patients suggest that epinephrine decreases gastrointestinal blood flow, in particular to the mucosal compartment and thus possibly jeopardizing adequate mucosal tissue oxygen supply.

In this issue of the British Journal of Anaesthesia, Schwartz and colleagues have introduced an inspiring insight into the complex regulation of the gastrointestinal microcirculation. They report the effects of increasing dosages of epinephrine and norepinephrine during two different types of anaesthesia (propofol or sevoflurane) on systemic oxygen transport parameters and gastric tissue oxygen supply in dogs. The latter was assessed by measuring tissue haemoglobin oxygen saturation (\(\mu\text{HbO}_2\)) using tissue reflectance spectroscopy. These elegant experiments were performed as a double-randomized cross-over study in chronically instrumented, haemodynamically stable dogs subjected to anaesthesia without the stress and the adverse consequences of acute surgery. Surprisingly, not only the type of catecholamine administered, but also the anaesthesia given to the animals was a major determinant of the gastric microvascular response to catecholamine administration. Norepinephrine significantly increased \(\mu\text{HbO}_2\) by approximately 10% during sevoflurane anaesthesia but had virtually no effect at identical dosages during propofol anaesthesia. Both catecholamines significantly increased systemic oxygen delivery (epinephrine by 140% and norepinephrine by 60%) regardless of the type of anaesthesia. However, epinephrine induced only minor changes in gastric \(\mu\text{HbO}_2\), despite an increase in systemic oxygen delivery; twice as high when compared with norepinephrine. Only the infusion of incremental dosages of epinephrine induced increasing metabolic lactic acidosis in the animals. In their conclusion, the authors correctly summarized that catecholamine effects on the gastrointestinal tract seem to depend on type of anaesthesia provided and that regional effects on \(\mu\text{HbO}_2\) cannot be anticipated from changes in systemic oxygen transport parameters.

How do these results fit into our current knowledge of the effects of anaesthetics and catecholamines on gastrointestinal oxygen supply? As mentioned previously, catecholamine effects can differ depending on the animal species, the pathophysiological condition, and the gastrointestinal segment under investigation. During total i.v. anaesthesia with midazolam and fentanyl, epinephrine significantly increased jejunal microvascular blood flow, mucosal tissue oxygen tension, and jejunal \(\mu\text{HbO}_2\) in an acutely instrumented, haemodynamically stable pig model using a nearly identical experimental protocol with a stepwise increase in epinephrine from 0.01 to 2 \(\mu\text{g} \text{kg}^{-1} \text{min}^{-1}\). Similar to the dogs, pigs developed progressive lactic acidosis during incremental i.v. epinephrine infusion without any change in arterial-mesenteric venous lactate concentration gradient, suggesting that the intestine was not the source of increased lactate production.

The effects of the type of anaesthesia on gastrointestinal oxygen supply parameters have been studied previously. For example, under normal conditions, pentobarbital, chloralose-urethane, halothane, isoflurane, and enflurane given at the dose required to attain surgical anaesthesia have all been shown to decrease intestinal blood flow. In contrast, ketamine and morphine increased blood flow, but the opioids meperidine and fentanyl had no effect on gastrointestinal blood flow. Recent studies also suggest that the effect of a particular anaesthetic on gastrointestinal oxygen supply may differ depending on the conditions present. For example, ketamine anaesthesia in an intestinal ischaemia/reperfusion injury model in rats significantly reduced intestinal injury and abolished intestinal transit delay when compared with pentobarbital sodium anaesthesia. In another pig model using combined general and thoracic epidural anaesthesia with and without additional volume loading, there was no effect on intestinal oxygen uptake, mucosal tissue oxygen, and tissue carbon dioxide partial pressure. However, when an epidural block was performed during progressive hypoxia in rabbits or haemorrhage in rats, the impairment in gastrointestinal perfusion was attenuated.

Another major problem when interpreting the effects of different drugs within the gastrointestinal tract relates to the variety of methods used to assess tissue oxygen supply. Each method has constraints which have to be kept in mind when interpreting experimental results. In this regard, tissue reflectance spectrophotometry represents a non-invasive method for assessing haemoglobin oxygen saturation (\(\mu\text{HbO}_2\)) and changes in tissue haemoglobin concentration. Previous experiments in pigs have demonstrated that the light signal is able to penetrate the whole gastrointestinal wall. Therefore, the backscattered light from tissue used to calculate \(\mu\text{HbO}_2\) is not only limited to the mucosal/submucosal layer but also represents tissue of the muscularis and serosal layers of the gut wall. Although changes in \(\mu\text{HbO}_2\) under various experimental
conditions are directly correlated to similar alterations in microvascular blood flow, this assumption cannot hold true under all circumstances. For example, any change in tissue oxygen metabolism induced by a certain drug will alter $\mu$HbO$_2$ without necessarily changing microvascular blood flow. In addition, appearance of new functional arteriovenous shunts induced either by the pathophysiology of acute disease or administration of vasoactive drugs, or even a combination of both, may in principle reverse the relationship between total blood flow and $\mu$HbO$_2$ measurements. In a recent experiment, our group investigated microvascular blood flow in the tongue in patients under constant cardiopulmonary bypass where systemic perfusion pressure was raised by 20 mm Hg with i.v. phenylephrine.$^{28}$ Increasing systemic perfusion pressure without changing flow led to dramatic decreases in capillary perfusion observed with the orthogonal polarizing spectral imaging technique.$^{27}$ At the same time, microvascular blood flow measured using laser Doppler velocimetry and $\mu$HbO$_2$ significantly increased, suggesting the presence of acutely induced microvascular blood flow shunting somewhere at the microcirculatory level.

Despite the complexity involved in explaining the effects of drugs on the gastrointestinal microcirculation and the associated limitations in the accurate interpretation of experimental results related to methodological reasons, this study by Schwarte and colleagues$^{20}$ has to be highlighted for introducing a new facet into the discussion of drug effects on the gastrointestinal microcirculation. To the best of my knowledge, the authors have demonstrated for the first time that an important interaction may exist between certain vasoactive drugs and simultaneously given anaesthetics. However, at present, it might be too early to extend these experimental results into the clinical situation. Uncertainties exist relating to species heterogeneity, differences in drug effects related to the conditions present, and the possibility of major disparities regarding drug effects within different segments of the gastrointestinal tract.

However, it is to be hoped that in the near future, we will see studies investigating the gastrointestinal oxygen supply in patients undergoing surgery using different anaesthetic agents and receiving vasoactive drugs in order to achieve predefined clinical haemodynamic goals.

**Conflict of interest**

None declared.

**References**

Mice, men, and medicine

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There are many hundreds of peer-reviewed medical and scientific journals in circulation, many of which publish research involving the use of animals. Clearly, publication of research is crucial for researchers, funders, and universities and as such, journals are in an ideal position to influence scientific conduct and disseminate good practice via their editorial policies. Reduction, refinement, and replacement (the 3Rs) in terms of animal research was a phrase coined by Russell and Burch in 1959 and some 50 yr later, it remains the cornerstone of animal welfare principles for researchers. Most people probably do not realize that the Declaration of Helsinki, which we all associate with standards of ethical conduct of research in humans, also contains a statement safeguarding the welfare of animals used in research.

Most journals publishing research involving animals fail to provide editorial policies on the use and the reporting of animal-based research. The editorial policies of a random sample of 288 English language peer-reviewed journals that publish original research involving the use of animals were recently evaluated. The aim was to identify how many of the journals had editorial policies regarding the use of animals and if these policies are designed to promote the principle of the 3Rs within the scientific community. The authors found that 47% of journals publishing original research involving animals had no editorial policy relating to the use of animals. Of those journals that did have policies, most stated only that the research be undertaken in accordance with standard regulatory requirements.

This rather half-hearted approach is not surprising, since the International Committee of Medical Journal Editors (ICMJE) mentions animal experimentation in only a single sentence within its 1200-word document on uniform requirements for manuscripts submitted to biomedical journals: ‘When reporting experiments on animals, authors should indicate whether the institutional and national guidelines for the care and use of laboratory animals were followed’. It is clear, however, that national guidelines vary considerably between countries and in some countries guidelines differ even between institutions. Brazil, for example, has only recently developed recommendations for animal studies at a national level.

A revised European directive designed to harmonize animal research legislation across Europe has been agreed by the European Council, and it is likely that the UK government will implement the directive, with new regulations coming into force at the beginning of 2013. For researchers in the UK, there will be little change, as the UK has tough regulations and one of the best records of animal welfare in the world. An international collaboration of organizations including Understanding Animal Research (UK), Americans for Medical Progress (USA), National Association for Biomedical Research (USA), and the European Coalition for Biomedical Research (EU) contribute to the website www.animalresearch.info to provide publically accessible...