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REVIEW ARTICLE

Gastrointestinal Tonometry in the Perioperative Period of Liver Transplantation: An Integrative Review

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ABSTRACT

Introduction: Gastric tonometry is a useful tool for examining regional splanchnic perfusion as it provides an indirect assessment of the state of the liver graft. This is because splanchnic hypoperfusion is a critical parameter in the context of liver transplantation, being associated with the development of problems such as acute liver failure and multiple organ failure. **Objective:** To analyze the effects of gastrointestinal tonometry in the perioperative period of patients undergoing liver transplantation. **Methodology**: This is an Integrative Review using the PubMed and VHL databases. The following descriptors were used: "Tonometry", "Splanchnic circulation" and "Liver transplantation" with the Boolean operator "AND", and articles of relevance to the topic were selected. Initially, 24 articles were selected, all published in the last 20 years, in Portuguese and/or English. After analysis, 6 articles matched the proposed objective. **Results:** It was observed that the difference between PraCO2 at the end of surgery and in the anepathic phase was greater in patients without liver graft dysfunction. A positive correlation was found between ΔpraCO2 and peak ALT after liver transplantation. In another study, it was found that the relationship between poor graft function was the presence of elevated liver enzymes, worsening synthetic liver function, coagulopathy and encephalopathy. It has also been shown that intramucosal gastric pH can predict early graft function. In a group with liver dysfunction, patients had an intramucosal gastric pH of less than 7.3 in the perioperative period, which remained low until the 24th hour postoperatively, while the group without dysfunction had an intramucosal gastric pH of more than 7.3, except in the anepathic phase when it was below this value. **Conclusion:** The usefulness of gastrointestinal tonometry to monitor splanchnic circulation and liver graft function during liver transplantation has been described and although support for this statement was found in some studies, this review had limitations due to the small number of articles available, which prevents it from covering a wide range of scientific evidence.

Descriptors: Tonometry; Splanchnic circulation; Liver transplantation.

Tonometria Gastrointestinal no Perioperatório do Transplante Hepático: Uma Revisão Integrativa

RESUMO

Introdução: A tonometria gástrica é uma ferramenta útil para examinar a perfusão esplâncnica regional por permitir o fornecimento de uma avaliação indireta do estado do enxerto hepático. Isso ocorre devido à hipoperfusão esplâncnica ser um parâmetro crítico no contexto do transplante de fígado, estando associada ao desenvolvimento de problemas como insuficiência hepática aguda e falência de múltiplos órgãos. **Objetivo:** Analisar os efeitos da tonometria gastrointestinal no perioperatório dos pacientes submetidos ao transplante hepático. **Metodologia:** Trata-se de uma Revisão Integrativa realizada nas bases de dados PubMed e BVS. Foram utilizados os descritores: "*Tonometry*", "*Splanchnic circulation*" e "*Liver transplantation*", incluindo o operador booleano "*AND*", e selecionados artigos de relevância para o tema. Foram selecionados inicialmente 24 artigos, todos publicados nos últimos 20 anos, em português e/ou inglês. Após análise, seis artigos corresponderam ao objetivo proposto. **Resultado:** Observou-se que a diferença entre a PraCO2 no final da cirurgia

e na fase anepática foi maior em pacientes sem disfunção do enxerto hepático. Foi identificada uma correlação positiva entre ΔpraCO2 e o pico de ALT após o transplante de fígado. Em outro estudo, verificou-se que a presença de enzimas hepáticas elevadas e a piora da função hepática sintética, coagulopatia e encefalopatia estava relacionada à má função do enxerto. Também foi comprovado que o pH gástrico intramucoso pode predizer a funcionalidade precoce do enxerto. Em um grupo com disfunção hepática, os pacientes apresentaram pH gástrico intramucoso abaixo de 7,3 no período perioperatório, mantendo-se baixo até a 24ª hora pós-operatória, enquanto o grupo sem disfunção apresentou pH gástrico intramucoso acima de 7,3, exceto na fase anepática, quando ficou abaixo desse valor. **Conclusão:** Descreve-se a utilidade da tonometria gastrointestinal para monitorar a circulação esplâncnica e a função do enxerto hepático durante o transplante hepático. Embora alguns estudos ofereçam suporte a essa afirmação, esta revisão apresenta limitações devido à quantidade restrita de artigos disponíveis, o que a impede de abranger uma ampla gama de evidências científicas.

Descritores: Tonometria; Circulação esplâncnica; Transplante de fígado.

INTRODUCTION

Splanchnic hypoperfusion is a critical parameter in the context of liver transplantation (LTx) as it is associated with the development of problems such as severe graft dysfunction and multiple organ failure (MOF). Therefore, gastric tonometry is a useful device for examining regional splanchnic perfusion as it makes it possible to provide an indirect assessment of the status of the liver graft[1]. Intramural gastric pH (pHi) is the most used parameter among tonometrics, while the regional-arterial CO2 gradient (PraCO2) has been shown to be more sensitive and reliable in detecting splanchnic hypoperfusion[1].

After LTx, early and rapid estimation of graft function is important to establish the diagnosis of failure or initial non-functioning of the graft, allowing reevaluation of the operative technique or contributing to the indication of retransplantation. This can be done through continuous measurement of intramucosal pH with an air tonometer that automatically measures the regional CO2 pressure (PrCO2) of the stomach and intestinal mucosa[2]. This instrument works as a simple and non-invasive monitoring of the splanchnic region, making it possible to evaluate the supply of O2 and the energy balance of cells by measuring tissue CO2 and changes in levels[2]. The results obtained from this technique reflect the metabolism of the intestinal mucosa, which in turn is quite sensitive to hypoxia and perfusion.

It is postulated that inadequate tissue oxygenation occurs during transplantation in the intestinal mucosa as it is highly susceptible to reduced blood flow[3]. This fact may be more relevant during the anhepatic phase when portal vein clamping is necessary for the recipient's hepatectomy. Poor intestinal perfusion can induce mucosal barrier dysfunction and the translocation of bacteria and endotoxins to the systemic and lymphatic circulations[3]. In orthotopic liver transplantation (OLT), the occurrence of endotoxemia was recorded during the procedure, with the highest concentrations measured at the end of the anhepatic phase, before graft reperfusion[3]. Furthermore, it was found that the level of endotoxemia correlates with patients' postoperative results[3].

In the anhepatic phase of OLT, the portal vein, suprahepatic inferior vena cava and infrahepatic inferior vena cava are clamped, resulting in gastrointestinal and lower limb venous congestion[4]. Therefore, to avoid the deleterious effects of portal clamping on intestinal perfusion and to limit the progression of tissue hypoxia, veno-venous bypass (VVB) was suggested, which drains portal blood to the superior vena cava[3]. However, mucosal oxygenation was not evaluated during LTx, and because of this, it is not known whether mucosal ischemia is related to the procedure, to endotoxemia or whether the use of VVB preservation, in fact, mucosal oxygenation[3] . From this, it is suggested that pHi is a sensitive marker of decreased intestinal blood flow and sufficient oxygen deficit in the mucosa.

The viability of grafts in OLT is determined through liver metabolic tests, which take many hours to evaluate. For this reason, these tests only become conclusive in most patients in the postoperative period. However, other indicators can be used, such as ischemia of the gastrointestinal mucosa, which is one of the first manifestations of impairment in seriously ill patients[5]. This can be measured through the acidosis of the gastrointestinal tissue using the tonomitor, a nasogastric catheter that combines a tonometer for the indirect determination of pHi with a gastric reservoir[5]. This tool is considered an early indicator of reduced O2 supply, metabolic imbalance and tissue oxygenation.

Therefore, in LTx, gastrointestinal tonometry with the calculation of pHi has been used as an indicator of splanchnic hypoperfusion, and the presence of intramucosal acidosis has been correlated with an increased incidence of sepsis, renal and liver graft dysfunction. Therefore, this study aims to analyze the available literature on the use of gastrointestinal tonometry in the perioperative period of LTx, highlighting the benefits resulting from the use of such a technique.

METHODOLOGY

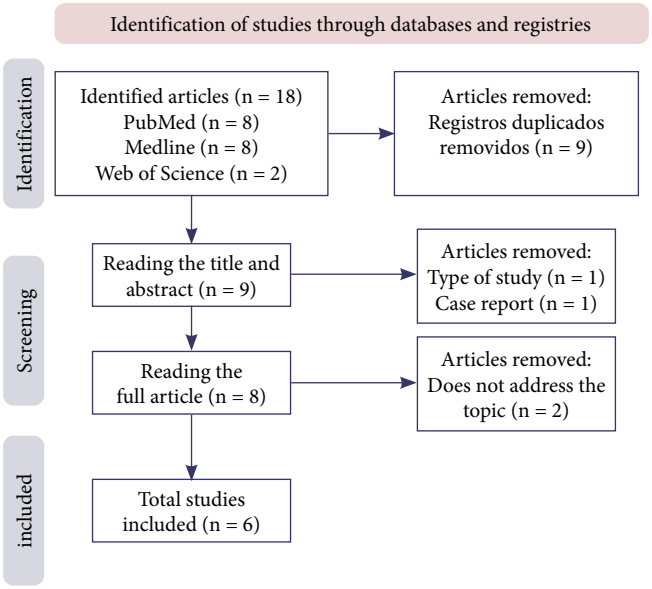
This is an integrative literature review constructed from the following steps: 1) Identification of the topic and elaboration of the research question; 2) Establishment of criteria for inclusion and exclusion of studies; 3) Definition of the information to be extracted from the selected studies; 4) Critical analysis of the included studies based on the levels of evidence; 5) Discussion of results; and 6) Presentation of the integrative review[6].

In view of this, the review was formulated according to the PICO strategy, which represents an acronym for Patient (Person/Problem), Intervention (Intervention), Comparison (Comparison) and Outcomes (Results), being the guiding question. Therefore, the following research question was developed: what are the benefits of using gastrointestinal tonometry in the perioperative period of patients undergoing LTx?

The bibliographic search was carried out systematically in the following databases: PubMed, Web Of Science and Virtual Health Library (VHL). In the last one, only scientific articles from Medline were found. The descriptors used were validated by the Health Sciences Descriptors (DeCS), namely: "Tonometry", "Splanchnic circulation," and "Liver transplantation". The descriptors were exchanged using the Boolean operator "AND", with no time lapse restriction. The choice of descriptors in English is due to the databases' functioning since most indexed articles are available in English. This prevents the search with descriptors in Portuguese from restricting the results to articles that provide versions in Portuguese and English.

In the three databases, the descriptors were used, and the searches were expanded to all fields, resulting in 8, 8 and 2 articles, respectively. In the end, 18 articles were totaled.

For the systematic selection of articles, the Rayyan – Intelligent Systematic Review tool was used, following the PRISMA Statement 2020 search strategy, under the Equator Network's CARE Guidelines for Systematic Reviews, as shown in Fig. 1[7].



Source: Prepared by the authors.

Figure 1. Screening of articles using the PRISMA Statement 2020 flowchart for systematic reviews.

In screening the articles, screening criteria (inclusion and exclusion) were applied, excluding duplicate articles, those that did not fit into the types of publication accepted in an integrative review and those that did not address the focus of the research on the use of gastrointestinal tonometry in the perioperative period of LTx. Therefore, the priority of the search was directed exclusively to scientific articles that described the general view on the use of gastrointestinal tonometry in LTx, the management of gastrointestinal tonometry in the early prediction of liver graft viability and possible criticisms of the use of gastrointestinal tonometry for the splanchnic perfusion monitoring.

The articles that fit the theme were analyzed and classified according to the levels of evidence, which depend on the methodological approach adopted and represent the quality of scientific evidence[6]. This study categorized all articles at level 2, indicating retrospective and prospective studies. The results are described in Table 1.

Table 1. Summary of studies included in the integrative review.

Author	Periodical/Year	Objective	Types of studies	Result	Level of evidence
Perilli V. et al.	Annals of Hepatology, 2014	To determine whether changes in tonometric parameters, related to splanchnic perfusion, can predict poor graft function in patients undergoing liver transplantation.	Retrospective study	Fifteen patients experienced poor graft function, with one patient classified as grade 4 and 14 patients experiencing grade 3, according to the Toronto classification. Fifty-two patients had good graft recovery. No differences were observed between the two groups regarding preoperative characteristics. Only one patient was excluded due to a very high PraCO2 at the beginning of surgery, suggesting lack of fasting. No significant differences were found for MAP, HR, SvO2, CO and lactate in patients with and without poor graft function. The difference in PraCO2 between T2 and T1 was significant; therefore, the test demonstrated that it was an effect of poor graft function for the difference in PraCO2. An intragroup paired test of PraCO2 at T1 versus T2 showed a significant difference in patients without poor graft function and no differences in patients with poor graft function.	II
Mándli T. et al.	Clinical Transplantation,2003	Apply tonometry as a rapid estimate of early liver graft function.	Retrospective study	In Group 1, with adequate graft function in the postoperative period, the pHi value was above 7.3, except in the anhepatic phase, when it falls below this value. The lowest pHi value in this group was 7.0, and the PrCO2 value was 70 mmHg. In Group 2, with early deterioration of graft function, the pHi values measured were mostly below 7.3 in the perioperative period, remaining low until the 24th postoperative hour. The lowest pHi value was 6.6, and PrCO2 was 97 mmHg. The differences were highly significant between Group 1 and Group 2 from the beginning of the operation until the 36th postoperative hour, both in pHi and PrCO2.	II
Welte M. et al.	British Journal of Anaesthesia, 1996	To evaluate the pH of the gastric and sigmoid mucosa during the perioperative phase of orthotopic liver transplantation.	Prospective study	pHi indicates mucosal ischemia during liver transplantation and is not necessarily associated with endotoxemia. Furthermore, intraoperative pHi monitoring does not appear to be a valuable predictor of postoperative graft failure and organ dysfunction.	II
Frenette L. et al.	Transplantation, 1994	To test the hypothesis that low pHi is an early indicator of non-primary graft function, and that normal or alkaline pHi is an early indicator of good primary graft function during the neohepatic stage of orthotopic liver transplantation.	Observational study	Twenty-four patients in Group 1, with pHi equal to or greater than 7.30, had normal pHi 30 minutes after reperfusion and throughout the surgery. Eleven patients in Group 2, pHi lower than 7.30, presented abnormal pHi 30 minutes after reperfusion. The pHi in ten patients returned to normal within 3 hours after reperfusion.	II
Ronholm E. et al.	Acta Anaesthesiollogica Scandinavica, 1999	To investigate gastrointestinal perfusion in patients undergoing liver transplantation using gastric tonometry, with the determination of tonometric PCO2 and the tonometric-arterial PCO2 gradient.	Prospective study	Arterial PCO2 varied between 4.7 kPa and 5.6 kPa, with the highest values found from 2 min to 10 min after reperfusion. Tonometric PCO2 increased from 4.6 kPa preoperatively to 5.6 kPa during the dissection phase and 5.5 kPa during the anhepatic phase. This significant increase in tonometric PCO2 persisted throughout the remainder of the measurement period. The tonometric-arterial PCO2 gradient increased from – 0.3 kPa preoperatively to 0.6 kPa during the dissection phase and 0.7 kPa during the anhepatic phase, returning, however, 30 min after reperfusion, to values not significantly different from the gradient. preoperative arterial tonometry of PCO2. A negative tonometric-arterial PCO2 gradient was found in 12 patients preoperatively, one patient during the dissection phase, five patients during the anhepatic phase, eight patients 30 min after reperfusion, seven patients 120 min after reperfusion, and eight patients on the 1st postoperative day. Changes in pHa over time were characterized by a decrease to 7.29 at 2 minutes post-reperfusion. Furthermore, pHa did not show a significant deviation in relation to the preoperative value until the first postoperative day, when it increased slightly to 7.43.	II

Continue...

Table 1. Continuation.

Author	Periodical/Year	Objective	Types of studies	Result	Level of evidence
George T. et al.	The American Surgeon, 2001	To investigate whether changes in pHi occurred during major abdominal surgeries, as well as to evaluate their correlation with a series of important perioperative variables. Explore any potential relationship between pHi and the postoperative outcome of patients.	Prospective study	Intraoperative and early postoperative pHi is a reliable predictor of patient outcome after major abdominal operations. Splanchnic ischemia may play an important role in determining early complications and survival.	II

Source: Prepared by the authors. Subtitle: PraCO2 Regional arterial carbon dioxide pressure; MAP Mean arterial pressure; HR Heart rate; SvO2 Central venous oxygen saturation; CO Carbon monoxide; T1 End of the anhepatic phase; T2 End of surgery; pHi intramural gastric pH; PrCO2 Regional carbon dioxide pressure; PCO2 Carbon dioxide pressure; pHa pH arterial

RESULTS

From the studies found it was possible to analyze the impact of using gastrointestinal tonometry on OLT. In one study, gastric tonometry was used together with the measurement of PraCO2, arterial blood gas analysis, hemodynamic monitoring through mean arterial pressure (MAP), heart rate (HR) and carbon monoxide (CO) and metabolic monitoring through central venous oxygen saturation (SvCO2) and lactate during surgery in all patients undergoing LTx. Two moments were analyzed: the end of the anhepatic phase (T1) and the end of surgery (T2). The difference between PraCO2 at the end of surgery and in the anhepatic phase (ΔpraCO2) was used as the dependent variable to evaluate the effect of graft recovery. It was reported that 22% of patients had poor graft function, while 76% had good graft recovery. There was no difference between the two groups regarding preoperative characteristics. There were also no significant differences for MAP, HR, venous oxygen saturation (SvO2), CO and lactate in patients with and without poor graft function. The ΔpraCO2 between T2 and T1 was significant; the test demonstrated an effect of poor graft function for ΔpraCO2. An intragroup paired test of PraCO2 at T1 versus T2 showed a significant difference in patients without poor graft function and no differences in patients with poor graft function. Furthermore, a positive correlation was also found between ΔpraCO2 and the ALT peak after TxF[1].

In another study, 45 patients undergoing LTx were examined. Patients were retrospectively distributed into two groups according to early graft function. In Group 1, with 28 patients, adequate postoperative graft function was found, while in Group 2, with 17 individuals, an early deterioration in graft function was demonstrated. Criteria for poor graft function included the presence of elevated liver enzymes, worsening synthetic liver function, coagulopathy, and encephalopathy. There were no significant differences between the two groups in preoperative characteristics, and the underlying diseases were similar. Red blood cell replacement therapy and fresh frozen plasma during the operation was significantly longer in Group 2. The surgical procedure time was significantly longer in Group 1 compared to Group 2. In the postoperative phase, the mechanical ventilation time, days spent in the ICU and mortality were worse in Group 2 compared to Group 1[2].

In Group 1, the pHi value remained above 7.3, except in the anhepatic phase, when it remained below this value. The worst pHi value in this group was 7.0, and the regional mucosal CO2 pressure (PrCO2) was 70 mmHg. In Group 2, measured pHi values were mainly below 7.3 during the perioperative period and remained low until the 24th postoperative hour. The lowest pHi value was 6.6, and the PrCO2 value was 97 mmHg. The differences were highly significant between Group 1 and Group 2 from the beginning of the operation until the 36th postoperative hour, both in pHi and PrCO2. PrCO2 was close to 40 mmHg in Group 1, but exceeded 50 mmHg in Group 2 during the anhepatic phase[2].

Still in the previous study, cardiac output (CO) and mean arterial pressure (MAP) values were lower in Group 2 compared to Group 1. Oxygen supply (DO2) showed parallel changes in the period examined, with significantly higher values in Group 1 at the beginning of the operation. Changes in oxygen consumption (VO2) values were similar in both groups, with significantly higher values in Group 1 after the reperfusion phase. Base excess (BE) showed a greater difference in Group 2, but after the end of the operation, the difference became equal. This discrepancy was significant from the anhepatic phase until the 1st postoperative hour. Important differences were found in serum bilirubin values from the 4th postoperative day onwards[2].

In another research, six patients undergoing liver resection and 18 OLT performed in 16 adult patients were analyzed. Hemodynamic and oxygenation variables remained unchanged throughout the surgery. Although pHi decreased slightly in all patients after laparotomy, no significant effects of time on arterial pH and gastric pH were observed. In the two patients in whom

portal blood flow was temporarily interrupted by clamping of the hepatoduodenal ligament, the pH decreased instantly. The lowest pHi value was 6.95, found in the patient with the longest clamping time, 63 minutes. After the release of portal clamping, pH returned to the baseline range and did not differ from the pH in patients without portal clamping at the end of the procedure. In two patients, retransplantation was performed 4 and 51 days after the first transplant due to primary graft nonfunction and chronic rejection, respectively. Central hemodynamic variables and the DO2 index remained essentially unchanged throughout the perioperative period. MAP decreased slightly during the anhepatic and neohepatic phases, being lower at the end compared to the beginning of surgery. The VO2 index was low during TOH and increased after ICU admission. Mixed venous lactate concentration increased continuously during transplantation, peaked after graft reperfusion, and decreased to baseline values 30 hours after ICU admission. SVO2 remained constant at a high level of 87% during OLT and began to decrease after the operation, reaching the lowest value 30 hours after ICU admission. Arterial pH decreased significantly from 7.39 at the start of OLT to 7.32 during VVB. After graft reperfusion, arterial pH remained below baseline values and recovered to normal values after admission to the ICU[3].

pHi decreased significantly from baseline values of 7.28 to 7.19 during VVB and remained below during the anhepatic phase. After graft reperfusion, pH increased within 30 minutes and did not differ from baseline values at the end of OLT. After the operation, pHi increased further, reaching the highest values 18 and 30 hours after ICU admission. The intraoperative course of pH in the sigmoid colon region (pHs) showed the same pattern as pHi, with the lowest values being measured during VVB, and pHs, at the end of surgery, did not differ from the baseline value. Postoperative liver function, assessed by plasma factor V activity and prothrombin time, and the degree of hepatocellular damage, assessed by serum ALT, do not correlate with pH after graft reperfusion or at the end of surgery[3].

In another study, carried out with 35 patients undergoing OLT, the average pHi in the pre-anepathic period (P1) and in the anhepatic phase (P2) was as follows: P1 at 60 minutes, 7.34; P1 at 120 minutes, 7.32; P2 at 30 minutes, 7.30; and P2 at 90 minutes, 7.30. To measure pHi 30 minutes after reperfusion during the neohepatic period (P3), patients were divided into two different groups. A pHi of less than 7.30 was defined as abnormal. Patients with pHi equal to or greater than 7.30 were allocated to Group 1, comprising 24 patients. Patients with pHi below 7.30 were assigned to Group 2, comprising 11 patients. The pHi in Group 1 during P3, 30 minutes after reperfusion, was higher when compared to Group 2. The pHi at 90 minutes was, on average, 7.38; in 120 minutes, it was 7.38; and in 180 minutes, it was 7.38. 24 patients in Group 1 had normal pHi 30 minutes after reperfusion and throughout the surgery.The 11 patients in Group 2 presented altered pHi 30 minutes after reperfusion. The pHi in ten patients returned to normal within 3 hours after reperfusion, but the pHi in 1 patient remained below 7.30 and did not normalize. This patient subsequently underwent retransplantation the following day[5].

In a study involving nine patients undergoing OLT, arterial carbon dioxide pressure (PCO_2) ranged from 4.7 kPa to 5.6 kPa, with the highest values observed 2 min and 10 min after reperfusion. Tonometric carbon monoxide pressure (PCO) was characterized by an increase of 4.6 kPa preoperatively, reaching 5.6 kPa during the dissection phase and 5.5 kPa during the anhepatic phase. This significant increase in tonometric PCO persisted throughout the remainder of the measurement period. The PCO tonometric-arterial gradient increased from – 0.3 kPa preoperatively to 0.6 kPa during the dissection phase and 0.7 kPa during the anhepatic phase. However, 30 minutes after reperfusion, it returned to values not significantly different from the preoperative tonometric-arterial PCO_2 gradient. Changes over time in arterial pH were characterized by a decrease to 7.29 within 2 minutes after reperfusion – otherwise, arterial pH did not deviate significantly from the preoperative value until the first postoperative day, when arterial pH increased slightly to 7.43. There was a decrease in pHi to 7.25 during the dissection phase and 7.27 during the anhepatic phase, with a return to the preoperative pHi level within 120 minutes after reperfusion[4].

In a scenario of elective and emergency abdominal surgeries, the mean values of intra- and postoperative pHi (pHiIO and pHiPO), PrCO2 ($PrCO_2IO$ and $PrCO_2PO$), pHg (pHgIO and pHgPO) and PCO2g (PCO2gIO and PCO2gPO) were calculated.). The pHiIO ranged between 7.03 and 7.58, while the pHiPO ranged from 6.89 to 7.56. There was a significant decrease in gastric pHi in the first hour of the intraoperative period compared to the pHi after induction of anesthesia. A strong and significant correlation was observed between pHiIO and pHiPO values, both in patients who developed complications and in those with an uncomplicated course. Patients undergoing emergency abdominal procedures had lower pHiIO and pHiPO values compared to the elective group. The group of patients who required ICU admission had significantly lower pHiIO and pHiPO measurements. Likewise, $PrCO_2IO$ and $PrCO_2PO$ were significantly higher among ICU patients. In general, lower pHiIO and pHiPO, as well as elevated $PrCO_2IO$ and $PrCO_2PO$ values were correlated with the need for preoperative mechanical ventilation, length of ICU stay, and occurrence of postoperative complications and mortality. At the cutoff point of 7.32 for gastric pHiIO and 45 mmHg for $PrCO_2IO$, both tonometric parameters showed similar sensitivity and specificity for predicting postoperative complications and death[8].

DISCUSSION

Overview on the use of gastrointestinal tonometry in TxF

Gastric tonometry is a very sensitive and specific measure of tissue oxygenation in critically ill patients, being a significant indicator of morbidity and mortality in the ICU. pHi-guided therapy can serve as a sentinel marker of tissue hypoperfusion in shock states, contributing to improved outcomes in patients with OMF and severe sepsis[1].

Primary graft nonfunction is generally determined by the criteria of elevated enzymes, little or no bile production, unchanged encephalopathy, and coagulopathy. However, liver enzymes take more than 4 hours to decrease after OLT, indicating that intraoperative liver enzyme measurements are not useful for early determination of primary graft nonfunction. Bile production from the new graft is an early positive sign, but this sign can be misleading if bile production is less than 100 ml every 24 hours or if the bile is watery, scanty, or greenish. It is impossible to determine encephalopathy or deterioration of mental status in the operating room under general anesthesia and correction of coagulopathy based on normalization of prothrombin time and activated partial thromboplastin time may confound coagulation parameters[5].

An exception may be the clearance of indocyanine green (ICG), which is a rapid marker of liver function – however, its value depends not only on liver excretion but also on perfusion of the splanchnic area. During the anhepatic phase, cross-clamping of the cava and portal veins induces a reverse decrease in splanchnic blood flow and causes venous congestion. In patients undergoing LTx, gastric tonometry can be used as an indicator of splanchnic hypoperfusion. It was identified that, in the neohepatic stage, a pHi permanently lower than 7.30 is a good indicator of primary graft non-function[2].

Management of gastrointestinal tonometry in early prediction of liver graft viability

Under stress conditions, the splanchnic circulation is the most sensitive to endogenous vasoconstrictors. The innermost layers of the intestine may represent the most sensitive area of the splanchnic circulation for detecting ischemia. To detect the presence of cellular ischemia, a metabolic marker of the adequacy of cellular oxygenation must be measured, such as the ADP/ATP ratio, cellular lactates, cytochrome redox state or tissue pH. The tonomitor, which consists of a silicone balloon freely permeable to CO, is inserted into a segment of intestine long enough so that the CO in the fluid equilibrates with the PCO in the superficial layer of the mucosa with which it is in contact. The PCO_2 of the fluid in the tonomitor provides an indirect measure of the PCO in the superficial layers of the mucosa. Determination of pHi by the tonomitor depends on the assumption that the bicarbonate concentration in the mucosa is equivalent to that in arterial blood. pHi is calculated by substituting the measurement of PCO in luminal fluid and bicarbonate in arterial blood into the Henderson-Hasselbalch equation. This results in a good correlation between the pHi obtained by the tonomitor and the pH obtained by the pH probe of the submucosal space of the intestine. A normal pHi suggests adequate oxygenation, while a functional graft may be reflected by a normal or alkalotic pHi and a non-functioning graft will be reflected by an acidotic pHi. In one study, it was possible to confirm a functional graft as early as 30 minutes after reperfusion. Only one patient required retransplantation, being the only one with an abnormal pHi at the end of surgery[5].

In one study, it was found that a group composed of patients undergoing OLT had pHi values mainly above 7.3, and liver graft function was improving. All patients survived the immediate postoperative period. In another group, pHi values were mostly below 7.3 and led to deterioration in graft function. In the immediate postoperative period, four patients died, one of them on the second postoperative day due to a surgical complication. In the late postoperative period, three patients died from OMF. CO values showed significant differences in a similar way to pHi values. Oxygenation parameters showed small differences only in the revascularization phase[2]. Perfusion parameters, with regard to splanchnic circulation, can behave in a completely different way than what the measured global hemodynamic parameters show. From this, it can be stated that pHi and PrCO2 resulted in good prognostic separation and could provide useful information in the early detection of graft function[9].

From the studies, it can be seen that patients with poor graft function had a higher ΔpraCO2 than patients without poor graft function. This means that patients with poor graft function did not experience a significant improvement in PraCO2 at the end of surgery. Poor reperfusion of the graft, with consequent limitation of blood flow through the liver, may be the reason for this poor improvement in the absence of significant macrohemodynamic changes. The relationship observed between ΔpraCO2 and peak ALT seems to confirm this hypothesis[1]

ΔpraCO2 between the anhepatic phase and the end of surgery was used to evaluate the effect of the graft, since variations in PraCO2 can better reflect splanchnic perfusion. The difference between PraCO2 at the end of surgery (T2) and before graft reperfusion (T1) may reflect changes in splanchnic perfusion related to the presence of a new liver. PraCO2 values at the end of the anhepatic phase, as well as at the end of surgery, showed moderate hypoperfusion, even though no signs of hypoxia were detected1. Clinically, a PraCO2 below 25 should be considered as a goal to avoid hypoperfusion and hypoxia[10]

A decrease in mucosal pH is considered to reflect inadequate oxygen supply to the intestine to meet metabolic demands. Consequently, a relationship was found between acute changes in splanchnic perfusion and mucosal pH. From liver resections, it

can be proven that the acute interruption of intestinal blood flow was closely reflected by a decrease in tonometrically measured pHi. In one study, two of six patients in whom portal blood flow was intentionally interrupted by clamping the hepatoduodenal ligament showed a decrease in pHi within 30 minutes after portal occlusion. After releasing the portal clamp, pHi returned to baseline values at the end of surgery. In patients without portal clamping, pHi remained essentially unchanged[3].

Based on the results obtained during liver resection, the reversible reduction in gastric and sigmoid pH during the anhepatic phase of OLT suggests the development of a transient intramural hypoxia of the gastrointestinal mucosa. Furthermore, pH decreased, although portal blood flow was maintained by VVB, allowing total flow rates of up to 50% of CO. As intraoperative pH, changes were similar in both locations, stomach and sigmoid colon. The decrease in pHi cannot be attributed to changes in the perfusion of the gastric mucosa induced by surgical manipulations or falsely low pH values caused by reflux of alkaline duodenal fluid. In mucosal microvascular perfusion during LTx, the reduction in pH observed during the anhepatic phase suggests that preservation of portal blood flow through VVB did not achieve adequate distribution of intestinal blood flow. In one study, a decrease in pH was observed within 30 minutes after the onset of the anhepatic phase, suggesting that the brief period of complete portal clamping, necessary to allow insertion of the VVB cannula into the portal vein, may be long enough to induce impairment due to prolonged microvascular perfusion of the mucosa[3].

The DO2 index remained unchanged during OLT, but VO2 decreased in the anhepatic phase resulting from intraoperative hypothermia and lack of metabolic liver function. During the procedure, SVO2 remained elevated, which is typical in cirrhotic patients, and tended to increase even further during the anhepatic phase. As a consequence, continuous intraoperative monitoring of SVO2 appears to be an inadequate method for detecting tissue hypoxia in hydrodynamic cirrhotic patients. The decrease in pH demonstrates that the intestinal mucosa is a site of tissue hypoxia. In this study, no correlation was found between intraoperative pHi or pHs, measured after reperfusion, and postoperative graft viability. However, it is worth mentioning that the literature reports an association between intraoperative pHi, values < 7.32, and graft dysfunction, acute renal failure, sepsis and the need for ventilatory support after OLT. Furthermore, the high systemic concentration of endotoxin was a prognostic factor for primary graft non-function, postoperative pulmonary complications and mortality[3].

The main findings of a study with nine patients undergoing LTx included an increase in tonometric PCO and the tonometric-arterial PCO gradient during the dissection and anhepatic phases. These changes were accompanied by a decrease in pHi. During periods of gastrointestinal hypoperfusion with aerobic metabolism, O2 extraction increases, and local tissue PCO_2 may increase as a result of normal oxidative phosphorylation and impaired CO2 removal. In the intestinal mucosa, the maximum tissue PCO2 that can be attributed to aerobic metabolism is 16-19 kPa. The presence of greater PCO_2 tissue tension indicates gastrointestinal hypoperfusion with anaerobic metabolism and CO_2 release secondary to bicarbonate buffering. Thus, the increase in tonometric PCO_2 found in the present study suggests an increase in local tissue PCO2 secondary to the reduction in gastrointestinal perfusion in the aerobic metabolism range. Changes in tonometric PCO are not compatible with the reduction in gastrointestinal perfusion in the anaerobic metabolism range[4]. From this study, it was observed that the arterial PCO tonometric gradient is probably better than the tonometric PCO_2 as an indicator of gastrointestinal hypoperfusion. The small increase in PCO arterial tonometric gradient may indicate reduced gastrointestinal perfusion in the range of aerobic metabolism but does not support the presence of gastrointestinal hypoperfusion with anaerobic metabolism.

Under aerobic conditions, venous PCO and the gradient between tissue PCO2 and venous PCO increase with decreasing flow. With the onset of anaerobic metabolism, the exchange between tissue and venous blood is reduced, and PCO in tissue increased considerably, while PCO_2 in venous blood increased to a lesser extent. Therefore, during LTx, the decrease in gastrointestinal blood flow must be accompanied by an increase in PCO2 in the portal vein[9]. However, in one study, portal vein PCO_2 was not elevated nor was there any significant difference between portal vein PCO_2, arterial PCO, or tonometric PCO. Normal portal vein PCO2 suggests that gastrointestinal hypoperfusion is not present during the OLT procedure[4]

A state of relative perioperative hypovolemia, in association with the vasodilatory effects of general anesthesia, can lead to hypoperfusion of the intestinal mucosa, identified by a drop in pHi. In one study, the accurate prediction of postoperative complications, mainly sepsis and OMF, as well as mortality due to abnormally low pHi, was closely associated with the need and duration of postoperative mechanical ventilation, in addition to prolonged ICU stay and general hospitalization[8]

Criticisms of the use of gastrointestinal tonometry for monitoring splanchnic perfusion

The use of pHi for monitoring gastrointestinal perfusion has been criticized due to several flaws in the tonometric technique used to determine pHi. In principle, the arterial bicarbonate concentration is not equivalent to the intracellular and interstitial bicarbonate concentration. During hypoperfusion severe enough to induce anaerobic metabolism, tissue bicarbonate is used to buffer hydrogen ions, resulting in a tissue bicarbonate concentration lower than the arterial bicarbonate concentration[4]. This, in turn, underestimates the magnitude of intramucosal acidosis.

Another issue is that changes in arterial bicarbonate, as in cases of metabolic acidosis not related to gastrointestinal hypoperfusion, would affect the pHi calculation. During LTx, the accumulation of lactate associated with systemic metabolic acidosis and the decrease in arterial bicarbonate concentration result in low pHi, which does not necessarily imply gastrointestinal hypoperfusion. Likewise, a normal pHi after intravenous administration of bicarbonate does not necessarily indicate normal gastrointestinal perfusion, since this administration will increase the arterial bicarbonate concentration and may correct the calculated pHi, despite the presence of gastrointestinal hypoperfusion[9]. Thus, pHi reflects the local tissue situation in relation to systemic acid-base disorders, but the calculation of pHi cannot be considered to correctly monitor gastrointestinal perfusion.

FINAL CONSIDERATIONS

Gastrointestinal tonometry may be useful for monitoring splanchnic circulation and liver graft function during OLT. Both pHi measurements in the perioperative period and those taken 10 to 30 minutes after liver reperfusion can contribute to the diagnosis and therapeutic fate of the patient, since the liver represents the main target of oxygen deprivation of the splanchnic circulation, and changes in pHi predict the future viability of this organ.

The predictive power of tonometry was also important between the anhepatic phases and the end of surgery, with high sensitivity. Furthermore, the occurrence of deficient mucosal oxygenation, even with the maintenance of portal flow, suggests the need to investigate other mechanisms related to perfusion during OLT. Finally, measurements of tonometric PCO and the tonometric-arterial gradient of PCO_2 indicate that LTx is associated with gastrointestinal perfusion in the aerobic range of metabolism, but not in the anaerobic one.

CONFLICT OF INTEREST

Nothing to declare

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Silva HRS, Lima MI, Fonseca Neto OCL; **Conception and design:** Brito TCS, Xavier SPS, Silva LF, Teixeira BP, Silva CE, Falcão JA, Santana AGC, Batista PHMS, Lima MI, Fonseca Neto OCL; **Data analysis and interpretation:** Brito TCS, Xavier SPS, Silva LF, Teixeira BP, Silva CE, Falcão JA, Santana AGC, Batista PHMS; **Article writing:** Brito TCS, Xavier SPS, Silva LF, Teixeira BP, Silva CE, Falcão JA, Santana AGC, Batista PHMS; **Critical revision:** Lima MI, Fonseca Neto OCL; **Final approval:** Fonseca Neto OCL.

DATA AVAILABILITY STATEMENT

Todos os conjuntos de dados foram gerados ou analisados no estudo em curso.

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