Viewpoint

Interpatient heterogeneity in hepatic microvascular blood flow during vascular inflow occlusion (Pringle manoeuvre)

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Hepatic inflow occlusion (Pringle manoeuvre), is a widely used technique, consisting in temporary intermittent or continuous clamping of the hepatic pedicle. This technique was described in 1908 by Pringle to minimize blood loss during emergency surgery for liver trauma. Therefore, in hepatobiliary surgery, the Pringle manoeuvre assumes a primary role especially in complex liver resections where an intraoperative blood loss could be significant. Afterwards, selective vascular occlusions, notably the glissonean approach described by Takasaki (1), were proposed as an alternative to the Pringle manoeuvre to decrease oxidative stress and postoperative complications in major and minor liver resections. However, this technique also presents some drawbacks as it can increase post-hepatectomy liver failure (PHLF) secondary to prolonged ischemia, especially on fibrotic or cirrhotic livers.

After the inflow clamping, the re-establishment of blood circulation worsens the ischemic damage in a process called ischemia reperfusion injury (IRI) (2). Briefly, the initial hypoxia together with the lack of biomechanical stimulus is followed by an accumulation of reactive oxygen species (ROS) and damage associated molecular patterns (DAMPS) as well as with the increasing in share stress after the restoration of the oxygen supply, leading the infiltration of neutrophils. In liver transplantation, IRI is a dreadful vascular complication responsible for up to 10% of early transplant failures (3). Additionally, IRI mechanism alters the normal function of hepatic regeneration especially in patients undergoing extensive resections for which the risk of PHLF may be increased. Moreover, reperfusion damage was experimentally shown to be particularly detrimental in aged liver where the role of statins was successful in reducing IRI damage (4).

The article proposed by Shen *et al*. (5), shows a heterogeneous response in hepatic microvascular flow to Pringle manoeuvre in two homogeneous patient groups called partial responders and full responders. The authors highlight that residual flow in the hepatic microcirculation was still observed despite the total vascular inflow occlusion. Furthermore, backflow from the hepatic venous system and the presence of portal-systemic and arterial collaterals are proposed as possible explanation of the heterogeneous response to the manoeuvre. In particular it has to be noticed that the left and right triangular ligaments have constantly a minimal arterial supply, that may increase in certain conditions such as cirrhosis. These aspects, which remained unclear to date, could be the subject of future studies especially if focused on the role of the endothelial phenotype impairment in PHLF. While this could explain the heterogeneity of response to the Pringle manoeuvre, at the same time it may explain how the outcome of the regenerative process varies depending on different surgical techniques and the different associated procedures such as portal vein embolization (PVE), liver vein deprivation (LVD) and Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS). Additionally, ALPPS

presents the theoretical advantage of the suppression of the collateral circulation, if the remnant liver is fully mobilized and the partition is complete.

In advanced liver disease numerous intra- and extra-hepatic changes in the circulation contribute in the heterogeneity of response to IRI. These vascular remodelling, especially in cirrhosis and fibrosis, arise from an altered molecular interaction that disrupts the normal balance in mechanical force between cells and extracellular matrix. Among the many actors that are involved (such as hepatocytes, Kupffer cells, hepatic stellate cells, macrophages, platelets and neutrophils), liver endothelial cells (LSECs) are important targets due to their protective role controlling vascular homeostasis (2). Consequently, an intraoperative and non-invasive monitoring of hepatic microcirculation during the Pringle manoeuvre (ischemic time) is a promising technique. Moreover, different phenotypes of LSECs and the respective subpopulations among patients may contribute to the heterogeneity of the response to the ischemic insult discussed in the article (5). In addition, the lactate analysis was found to increase in both groups of patients during the whole surgical procedure. As coherently stated by the authors, the analysis of intrahepatic (capillary) lactate would furnish a better correlation between the local oxidative stress and the lobular microvascular dysfunction. This analysis would help in validating incident dark field imaging (IDFI) providing a quantitative relation between optical and biological properties. Temporary sinusoidal collapse was correctly found at the end of VIO with IDFI and with the microvascular flow index as well. Thus, a proper mathematical correlation between the capillary lactate and the quantitative assessment via IDFI would be highly suggested in order to find similarities in different liver diseases. Finally, the authors conclude that the cytocam IDFI may be a suitable tool for the assessment of hepatic microcirculation during vascular inflow occlusion (VIO). Overall, we found that this could be an interesting technique that would deserve additional studies and validations. Nevertheless, excluding the ultrasound which represent a clinical standard, other non-invasive and innovative techniques showed positive results in the intraoperative assessment of hepatic microcirculation such as hyperspectral imaging (HSI) and confocal endomicroscopy performed over the Glisson's capsule (6,7). IDFI presents a limitation due to the relatively small field of view when compared with the hyperspectral imaging which is able to furnish an immediate oxygenation map of the liver surface that was shown to be representative of the overall ischemic lobe. In conclusion, a more detailed and comparative analysis in a preclinical setting would be therefore highly suggested. The authors coherently concluded that this proof of the concept would need further studies.

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Footnote

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