Novel hybrid IGP before Esophagectomy

Subjects: Oncology
Contributor: Manuel Barberio , Eric Felli , Raoul Pop , Margherita Pizzicannella , Bernard Geny , Veronique Lindner , Andrea Baiocchini , Boris Jansen-Winkeln , Yusef Moulla , Vincent Agnus , Jacques Marescaux , Ines Gockel , Michele Diana

Esophagectomy has a high rate of anastomotic complications thought to be caused by poor perfusion of the gastric graft, which is used to restore the continuity of the gastrointestinal tract. Ischemic gastric preconditioning (IGP), performed by partially destroying preoperatively the gastric vessels either by means of interventional radiology or surgically, might improve the gastric conduit perfusion. Both approaches have downsides. The timing, extent and mechanism of IGP remain unclear. A novel hybrid IGP method combining the advantages of the endovascular and surgical approach was introduced in this study. IGP improves unequivocally the mucosal and serosal blood-flow at the gastric conduit fundus by triggering new vessels formation. The proposed timing and extent of IGP were efficacious and might be easily applied to humans. This novel minimally invasive IGP technique might reduce the anastomotic leak rate of patients undergoing esophagectomy, thus improving their overall oncological outcome.

esophageal cancer | esophageal resection | Ivor-Lewis procedure | optical imaging | anastomotic leak | hyperspectral imaging | fluorescence imaging | confocal laser endomicroscopy | ischemic preconditioning

1. Introduction

Esophageal cancer is ranked seventh worldwide among all cancers, in terms of incidence (572,000 new cases) and ranked sixth for mortality rates (509,000 deaths) [1]. The treatment is multidisciplinary and surgery plays a central role in the therapeutic strategy [2]. Esophageal resection is a major surgical high-risk procedure with considerable complication rates [3], which may negatively impact the overall oncological outcome as well as the quality of life of patients [4][5]. In particular, the incidence of anastomotic leak (AL) is relevantly higher, when compared to other gastrointestinal anastomoses [6]. The etiology of AL is multifactorial. Some risk factors to develop AL are not modifiable and include preexisting relevant comorbidities [7] (e.g., hypertension, renal failure, congestive heart failure, smoking), and probably most importantly the presence of substantial atherosclerosis [8]. Appropriate blood supply at the gastric conduit fundus (GCF) is one of the key factors to promote anastomotic healing and to reduce the risk of AL [9]. The formation of the gastric conduit implies the tubulation of the stomach, the sudden disruption of a large part of its vascular supply, with the conduit fed by the gastroepiploic arcade only (and smaller branches of the right gastric artery, if preserved). This results in relative ischemia, especially at the

apical section of the gastric graft, the former fundus, which will constitute the proximal portion of the esophagogastric anastomosis.

Ischemic gastric preconditioning (IGP) has been previously proposed to improve the relative ischemia of the GCF by enhancing local microcirculation [10][11][12]. IGP consists in the partial devascularization of the stomach, using either an endovascular or a laparoscopic approach, several days or weeks before gastric pull-up and esophagogastric anastomosis completion. Although IGP has shown promising results in experimental settings and is a recognized safe procedure, it has failed to show a significant AL rate decrease to justify its implementation in the clinical routine [10][11][12][13][14]. This probably results from the large heterogeneity in terms of adopted IGP protocols and importantly from a too short delay between IGP and esophagectomy.

As clinical intraoperative appraisal of the gastrointestinal tract blood flow is not accurate [15], several technologies have been explored to evaluate gastrointestinal perfusion during esophagectomy [16][17][18]. Fluorescence angiography (FA), a technique requiring a near-infrared (NIR) camera and the injection of a fluorophore, has become increasingly available and has shown promising results. However, FA is currently lacking a standardized quantification method. Florescence-based enhanced reality (FLER), allows for precise quantitative fluorescence angiography in the digestive tract, and it has previously shown its accuracy during experimental gastrointestinal procedures [19][20]. Hyperspectral imaging (HSI) is another intraoperative optical imaging modality, which allows for contrast-free tissue oxygen quantification. HSI has proven accurate in assessing intestinal perfusion intraoperatively [21][22]. However, both FLER and HSI allow blood flow estimation exclusively at the serosal side. Confocal laser endomicroscopy (CLE) is a high-resolution microscopic imaging modality, which has been successfully used to quantify mucosal microcirculation within the digestive tract [23][24][25][26].

2. Discussion

AL has a multifactorial etiology. However, anastomotic site perfusion is a controllable risk factor of leakage [16][17][18]. It has been previously demonstrated in a number of experimental studies [27][28][29][30] that IGP improves GCF perfusion, provided that a minimum delay of 2 to 3 weeks is observed between IGP and gastric conduit formation. Similarly, the results of the present study unequivocally demonstrate that IGP, applied 3 weeks prior to gastric tubulation, improves mucosal and serosal perfusion at the GCF, assessed by means of quantitative optical imaging technologies. These findings are supported by LCL levels, which are a robust surrogate of perfusion in the porcine digestive tract [31]. Additionally, the presence of incremented vessels and inflammatory cells (eosinophils) in both IGP groups represents an indirect sign of neovascularization [32][33]. The choice to count eosinophiles has multiple reasons. In fact, these cells have been characterized as proangiogenic actors in the last two decades [33]. In particular, they take part of the innate cells group that contribute to the production of important mediators of the angiogenic/lymphangiogenic factors [34]. Additionally, eosinophils are easily visible under light microscope even at low resolution and low magnification, given their unique bilobate shape with a cytoplasm characterized by a large number of granules confering a specific reddish coloration to these cells in the hematoxylin and eosin staining. Thus, compared with other immune cells, eosinophils are the main visible actors playing a major role in angiogenesis. The histological findings of increased vessel density were confirmed by the immunohistochemical

staining (overexpression of the reliable mature vessel indicators, such as CD31 and caldesmone within the specimens of both IGP groups [35]). Those findings, together with the increased eosinophils' count, demonstrate new vessel formation over a 21 days period, triggered by the hybrid ischemic preconditioning.

Despite promising results in experimental studies, when translated to humans, IGP has failed to exhibit a clear advantage in terms of AL reduction following esophageal resection. Yet, the clinical trials using IGP are highly heterogeneous in terms of technique (angiographic embolization [36][37][38] or laparoscopic vessels ligation [39][40][41][42]) and number of vessels involved, and they are mostly of retrospective nature. Importantly, the delay between preconditioning and esophagectomy is largely variable in those studies. This heterogeneity could account for the apparent clinical inefficacy of ischemic preconditioning. However, the severity of the anastomotic complications in patients who receive IGP seems to be milder as compared to patients who undergo esophagectomy without preconditioning.

Authors using an endovascular approach reported better results in terms of increased GCF perfusion [36] or even AL reduction [38] as compared to the ones using laparoscopy. In fact, the largest patient series using laparoscopic IGP describe shorter time intervals than 2 weeks [43]. This results from the potential adhesion formation that laparoscopic vessel ligation or complete gastrolysis might induce [44]. In this respect, performing esophagectomy 4 to 5 days after laparoscopic IGP represents a convenient strategy in order to reduce the risk of finding firm adhesions intraoperatively, hence potentially increasing the esophagectomy operative time and difficulty degree. On the other hand, when performing endovascular IGP, it was possible to mostly maintain a two-week delay with esophagectomy. Additionally, it has been observed in a clinical series that a short delay between IGP and surgery (< 15 days) might have deleterious effects on GCF blood supply, whereas a 2-week interval seemed to be protective against AL [42].

Interestingly, another group [16] found an increment in terms of mucosal oxygen saturation, measured using an endoluminal spectroscopic probe, in patients undergoing esophagectomy 4 to 5 days after laparoscopic IGP. Conversely, the same group [41] found no neoangiogenesis, assessed through VEGF (vascular-endothelial-growth-factor) increase, in the gastric fundus of patients who underwent laparoscopic IGP 4 to 5 days prior to esophagectomy. These findings suggest that there is a transitory compensating mechanism against the relative ischemia generated with IGP, involving a provisional redistribution of microcirculation, possibly via shunts opening, in its initial phases (4–5 days). This compensation eventually consolidates through the progressive formation of new capillaries, which are detectable after 2 to 3 weeks, as confirmed by our study.

The radiological IGP approach is less invasive than laparoscopy and is suitable to be performed several weeks prior to esophagectomy. However, the SGAs, which, together with the LGA, participate consistently in the gastric fundus vascular supply [45], are technically difficult to embolize. In fact, most authors performing angiographic IGP describe a direct embolization of the splenic artery, potentially increasing spleen infarction risk [46]. As a result, we introduced a hybrid laparo-angiographic technique, in which IGP is achieved mainly angiographically, while the SGAs are divided laparoscopically, resulting in a minimization of the surgical manipulation. Indeed, the lack of adhesions at T21 laparotomy seems to support our hypothesis, which needs to be verified in humans.

No substantial difference was encountered in terms of perfusion between max- and min-IGP groups. An explanation might be that the majority of the gastric fundus blood flow is supplied by the SGAs and the LGA in humans [45]. This might be true in pigs as well, as a result the role of the LGEA (additionally embolized in max IGP) in terms of fundic perfusion could be minimal. However, the small sample size of our study could limit the significance of the results, therefore further studies with larger numbers are required in order to precisely understand the required extent of IGP. Nevertheless, min-IGP showed a higher safety profile than max-IGP, suggesting a better suitability for a potential clinical translation. Hybrid IGP might be an option for patients presenting resectable esophageal cancer and it could be performed in the context of the staging phase, which usually takes place at least 3 weeks before esophagectomy.

The merits of our study lie in the innovative approach, the survival design, and the robust methodology, implementing cutting-edge optical imaging technologies, allowing to quantify real-time perfusion.

The main downside is represented by limiting the surgical procedure to gastric conduit formation without esophagectomy and appraisal of the AL rate. This choice was taken considering that designing AL rate as primary endpoint, much larger groups would have been required to obtain a sufficiently powered study. Additionally, during preparation experiments preceding this work, we noticed a high intraoperative mortality in animals undergoing esophagectomy, possibly due to bradycardia triggered by extreme vasovagal sensitivity. This might justify the fact that, to our knowledge, no survival experiments have been published using a porcine esophagectomy model.

3. Conclusions

In conclusion, hybrid IGP improves mucosal and serosal blood flow of the future anastomotic region on the gastric conduit fundus. Our work suggests that the sole embolization of the LGA associated to the laparoscopic division of the SGAs (min IGP) would elicit an efficacious ischemic preconditioning effect improving gastric fundus perfusion. Those promising results need to be interpreted with caution and a clinical translation is necessary to demonstrate the validity of our protocol in humans undergoing esophageal resection.

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