New insights in intestinal ischemia-reperfusion

Valorisation addendum

The aim of this chapter is to audit this doctoral thesis in terms of scientific, social and economic value that can lead to societal benefits. It is a critical look upon the return of investment that the world community may receive from the knowledge gathered during the studies in this dissertation [1].

Scientific relevance

Acute intestinal ischemia is a disease caused by occlusion (e.g. thrombosis) of the intestinal blood flow which often leads to death (60-80%), because it is difficult to diagnose intestinal ischemia at an early stage and adequate treatment lacks. Furthermore, intestinal ischemia is often responsible for a complicated course after major (cardio-) vascular or abdominal surgery, trauma and in patients with systemic inflammatory response syndrome (SIRS) and/or sepsis in the intensive care unit [2]. Results of this thesis will add to a better understanding of the pathophysiology of intestinal ischemia-reperfusion (IR). The knowledge gained in this thesis on biomarkers for detecting intestinal ischemia and differentiating between mucosal and transmural intestinal damage are essential in the development of effective diagnostic and therapeutic strategies. This will aid in the early detection of intestinal ischemia and its serious consequences. It was found that plasma levels of smooth muscle protein of 22 kDa (SM22) are potentially useful for the detection of transmural intestinal damage. SM22 in combination with intestinal fatty acid binding protein (I-FABP), as marker for the early diagnosis of mucosal intestinal ischemia, may help us in daily clinical practice to gain a more complete picture of the level of intestinal injury. This will identify patients with transmural ischemia in need of emergency surgery, from patients with only mucosal ischemia which can be treated using endovascular revascularization techniques and a more intestinal preserving strategy.

Knowledge on intestinal IR is of importance for surgeons, anesthetists, intensive care physicians, cardiologists, pulmonologists, gastroenterologists and pediatricians. Furthermore, all researchers, pharmaceutical companies and physicians involved in intestinal transplantation or dealing with patients with intestinal ischemia-related injuries will benefit from results of this thesis. The knowledge obtained in the search of new biomarkers to detect intestinal ischemia will also support the search of biomarkers to diagnose other ischemic organ diseases like acute ischemic heart disease, ischemic kidney injury or ischemic cerebrovascular disease.

The new insights in the pathophysiology of intestinal ischemia will be the start of a new research line aiming to develop treatment strategies improving the outcome of patients suffering from intestinal IR. Using the present unique model to study the consequences of intestinal ischemia without any risk for patients during major surgery, the present group will try to further elucidate why patients with intestinal ischemia develop such

severe inflammation and illness. The hypothesis is that measurement of digestive enzymes (proteases) in plasma enables clinicians to early detect whether the intestine is functionally damaged. Inhibition of these proteases will potentially lead to a new treatment, approaching the cause of the disease instead of its symptoms [3]. This hopefully will result in enhanced (postoperative) recovery and less admissions in the intensive care unit. In line, society costs for hospital stay and intensive treatment will decrease.

Economical relevance of the results

Although acute mesenteric ischemia accounts for less than 1% of the patients seen at the emergency department with acute abdominal complaints, this number increases exponentially with age resulting in an incidence of 10% in patients with acute abdominal pain aged over 70 years [4]. Next, intestinal ischemia or splanchic hypoperfusion is a frequently occurring phenomenon during major surgery, trauma and shock. It often leads to systemic inflammatory response syndrome (SIRS), sepsis and multiple organ failure (MOF), important causes of death in critically ill patients. Moreover, patients suffering from chronic heart failure and chronic obstructive pulmonary disease (COPD) are known to experience intestinal ischemic episodes during daily activities, resulting in bacterial translocation, which can trigger SIRS [5]. This underlines the economical issues related to intestinal ischemia, since many (older) patients have cardiovascular diseases, COPD, IBD, pancreatitis or undergo major surgery or trauma, which increasingly leads to intensive care admissions for SIRS, sepsis and MOF. Given the aging population, the number of patients suffering from intestinal ischemia will increase with time. This eventually leads to increased (healthcare) costs.

As described in this thesis, intestinal ischemia is notorious difficult to diagnose. An inaccurate or delayed diagnosis leads to an impaired therapeutic management causing catastrophic complications.

When diagnosed in an early state, mortality rates are between 0-40% and intestinal ischemia can mostly be treated by restoring the mesenteric circulation with minimally invasive endovascular techniques, before irreversible intestinal injury develops [5]. After this intervention the patients will be admitted to the ICU for observation. This therapy plan will cost approximately €12,000. When the intestinal ischemia is diagnosed 12-24 h after the onset of the clinical symptoms, mortality steps up to 60-70% and transmural infarction has already occurred. In these patients intestinal revascularization still should be performed to reduce the extent of damage and facilitate healing of the potential intestinal anastomoses, followed by an exploratory laparotomy to resect unsalvageable parts of the intestine [5]. After the bowel resection is done, the decision has to be made whether the patient is stable enough to create primary bowel reconstructions and finish the initial operation or the patient needs to be stabilized in the ICU with open abdomen and the anastomoses are performed later as a planned second-look operation. This therapeutic strategy is accompanied with increased costs up to €30,000. Delayed

diagnoses not only leads to dramatically increasing mortality rates, but it will also lead to increased healthcare costs. Using the proposed new biomarkers the diagnosis for intestinal ischemia could be made in an earlier state, potentially resulting in less patients with transmural intestinal damage and thereby reducing healthcare costs in the short-term and costs for society on the long-term.
In addition, the current new biomarkers could contribute in monitoring intestinal graft viability in patients suffering from intestinal failure. Small bowel transplantation is the ultimate life-saving therapy for patients with intestinal failure. The main complication in intestinal transplantation is graft rejection. Around 50-75% patients undergoing small bowel transplantation experience acute rejection leading to serious morbidity and mortality rates [6]. Monitoring the graft viability is crucial in these patients. Unlike other types of transplantation, there is no non-invasive or reliable marker to predict rejection in small bowel transplantation. The rejection reaction must be detected at a stage when immunologic therapy could salvage the intestinal graft. The current diagnosis of rejection is made with protocol biopsies taken by invasive endoscopy. Besides the complications of taking biopsies, it is time-consuming and expensive. This delay in diagnosis results in loss of the intestinal graft [7]. Biomarkers, like I-FABP, detecting graft rejection early in the process would allow for the timely diagnostic detection when pharmacologic therapy can still save the intestinal graft, leading to increased graft survival. Together with the reduced costs to perform these diagnostic tests, these biomarkers will also result in lower healthcare costs in patients who undergo small intestinal transplantation because of better graft survival.

Societal relevance

Elucidation of the mechanisms involved in the transition of mild inflammation towards severe inflammation following human intestinal IR, is of major importance since intestinal IR causes critical illness in multiple pathologies. Moreover, new strategies to treat intestinal IR and its sequelae would be of importance to many clinical fields. Patients suffering from intestinal ischemia are admitted in hospital for long time and their mortality rate is high. This leads to diminished quality of life (QoL). Part of the patients with intestinal ischemia in need of surgical exploration will end up with an ileostomy or colostomy after resection of nonviable bowel. The decision for an ostomy versus primary anastomosis depends upon the patient's general condition and assessment of the transected ends of the intestine. Potential reversal of the ostomy should be postponed for about six months [8]. Given a majority of the patients with intestinal ischemia is older and likely more frail with higher risk for subsequent surgery, a substantial part will end up with an ostomy. Up to two thirds of the above mentioned patients never proceed to reversal of the ostomy because of comorbid conditions [9]. These patients are also exposed to common ostomy complications including poor ostomy location, high output, skin irritation, retraction and prolapse. Due to this major change in physical appearance

and bodily function, an ostomy has a considerable impact on a patient's QoL afterwards. Patients with an ostomy have a poorer QoL caused by fear of leakage and they also have to deal with a certain stigma that deeply impacts them psychologically. Furthermore, their difficulties also extend to an altered body image and sexual malfunctions [10]. Next, extensive bowel resections as a result of intestinal ischemia are still the leading cause of short-bowel syndrome [11]. This again has a major impact on patient's QoL as short-bowel syndrome is accompanied with high mortality and morbidity rates. Therefore, modern treatment of intestinal ischemia is focused on intestinal preserving management. The goal of treatment for patients with acute intestinal ischemia is to restore intestinal blood flow as quickly as possible instead of an early surgical laparotomy. Accurate diagnosis is essential in this regard to avoid the potential for intestinal infarction and to differentiate between patients eligible for revascularisation and those in need for acute surgical exploration. Using the knowledge of the diagnostic biomarkers presented in this thesis, treatment options and strategies can be more personalized and improve the chance of survival. Next, resection of bowel should ideally be delayed until endovascular mesenteric arterial revascularization can be performed to salvage as much bowel as possible. This approach remains somewhat controversial as direct visualization of the bowel is not an option during percutaneous intervention but it leads to a lower frequency of bowel resection and death rates [12]. Using plasma values of I-FABP and SM22 to monitor the intestinal viability, the above mentioned treatment strategy can be improved with better results in patient's mortality and morbidity.

Last, for long time only animal studies were reported on intestinal IR. These animal models are indispensible for the understanding of the different mechanisms contributing to the development of IR-induced organ damage. The use of animal models however, is also considered to be one of the main reasons that no effective clinical treatment for intestinal IR was developed and the associated high morbidity and mortality rates are unchanged the last 70 years [13]. With the development of the current human experimental IR model, of which the safety evaluation is presented in this thesis, a basis is formed to obtain the knowledge essential to develop new effective therapeutic means. Secondly, the place of the animal models in modern societies is often debated, particularly the right to use animals to benefit human purposes, with the possibility that animals are harmed. The present human IR model will reduce the number of animals used for scientific purposes. This is in line with the statement of the European commission aiming at replacing animal methods as much as possible.

Potential knowledge utilization

In life sciences and medicine knowledge utilization be characterized as effective translation of the newly obtained knowledge by basic science research into state-of-the-art approaches for the prevention, diagnosis, and treatment of disease. This has the

potential to transform research from "bench-to-bedside", delivering new medical options for patients. For this area of research, the end point is the production of a new diagnostic tool or a promising new treatment that can be used clinically or commercialized.

Before the proposed biomarkers can enter the daily clinical practice a phase four diagnostic study needs to be preformed, assessing the effectiveness of these new markers in large surveillance cohort studies. Therefore the creation of a rapid test for the proposed biomarkers with good diagnostic performance (low detection limit, clinical relevant cut-off points) is imperative. However, the limited availability of financial resources, scientific staff and laboratory capabilities to efficiently develop such tests and to perform these kind of studies are major obstacles for public research institutes and universities.

Public-private partnerships for innovation are an important part of the answer to such challenges. One of the most important weaknesses of the current innovation system is an inadequate interaction between science and industry. Scientists must continue to build partnerships with the industry to combine the strengths of both parties. Together, a unifying goal should be embraced: to act on behalf of patients and provide solutions to unsolved clinical problems. To aid in this field between science and biomedical companies the Dutch government and European Union (EU) face a couple of challenges. First, the incentives and the institutional frameworks for co-operation between public and private actors of innovation need to be improved. Second, the public support schemes for innovation and the complex innovation governance systems need to be streamlined lowering the administration burden. Last, the interdepartmental co-ordination needs to be improved causing research to work together side-by-side instead of against each other back-to-back [14].

To strengthen the position of public labs the government and EU stimulates the financing mechanisms of university research by increasing the available funding for public-private partnerships. Also more performance-based criteria (including applicability of research for innovation) in the allocation of institutional funding were introduced, stimulation future innovations. The exchange of researchers between universities and business enterprises is another way to enhance knowledge utilization. It is still rare for university researchers to spend time at the research and development departments of industrial partners companies. This is a lost opportunity for academic researchers to get better acquainted with industrial needs and market-oriented research, and may reflect the fact that university researchers do not feel a sense of competition for translating research into the daily clinical practice. It is noticed that academic investigators lack the knowledge assessing issues affecting the potential success of their translational research in the daily clinical practice. This shortcoming needs to be resolved by additional training [14].

The presented studies will also open new opportunities to develop therapeutic interventions directed at key aspects of the pathogenomic process. Especially new therapies directed at the inhibition of the pancreatic enzymes or the subsequent PAR-receptor activation by these proteases, which were successfully applied in animals undergoing intestinal ischemia and recently in a septic patient with Fournier's gangrene [15].

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