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Histopathologic and molecular evaluation of the Organ Procurement and Transplantation Network selection criteria for intestinal graft donation

Anne Margot C. Roskott, MD,[a,*,1] *Wouter T. van Haaften, BSc,*[a,1] *Henri G.D. Leuvenink, PhD,*[a] *Rutger J. Ploeg, MD, PhD,*[a] *Harry van Goor, PhD,*[b] *Tjasso Blokzijl, BSc,*[c] *Petra J. Ottens, BSc,*[a] *Gerard Dijkstra, MD, PhD,*[c,1] *and Vincent B. Nieuwenhuijs, MD, PhD*[c,1]

[a] *Department of Surgery, University Medical Center Groningen, University of Groningen, The Netherlands*
[b] *Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, The Netherlands*
[c] *Department of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, The Netherlands*

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ABSTRACT

Background: The Organ Procurement and Transplantation Network (OPTN) has formulated criteria for the selection of donors for intestinal transplantation. To date, however, no study has correlated histologic findings of intestinal injury with the OPTN criteria. We aimed to describe histopathologic and molecular features of allograft injury in relation to donor conditions defined by the OPTN criteria.

Materials and methods: Graft histology (Park Score), Claudin-3 staining, systemic inflammatory markers (C-reactive protein/lipopolysaccharide-binding protein) and expression of heat shock protein 70, heme oxygenase 1, and interleukin 6 were evaluated in multiorgan deceased donors (donation after brain death [DBD] and donation after cardiac death [DCD]).

Results: Ninety-seven samples (52 jejunum/45 ileum) were recovered from 59 donors (46 DBD/13 DCD). The OPTN criterion cold ischemia time correlated with histologic injury (Park score) to which the jejunum appeared more susceptible than the ileum. Claudin-3 staining was higher, and heat shock protein 70 expression lower in donors meeting the OPTN criteria compared with donors not meeting the criteria and in DBD *versus* DCD. In DBD donors, interleukin 6 expression was higher compared with DCD donors and inversely related to C-reactive protein.

Conclusions: Our multiparameter analysis suggests that the OPTN criteria can be discriminative concerning intestinal graft quality. Our data suggest that DCD intestinal allografts are qualitatively inferior and that the jejunum is more sensitive to ischemia than the ileum.

* *Corresponding author*. Department of Surgery, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ, Groningen, The Netherlands. Tel.: +31 50 361 2283; fax +31 50 363 2796.
E-mail address: a.m.roskott@umcg.nl (A.M.C. Roskott).
[1] All these authors equally contributed.
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1. Introduction

Despite continued improvements in the field of intestinal transplantation (ITx) [1], the long-term survival of intestinal allograft recipients remains inferior compared with other forms of solid organ transplantation. This may be due to the susceptibility of the intestinal graft to warm and cold ischemia and immunologic injury as part of the so-called transplant injury cascade. This cascade starts during the process of brain death (BD) in the donor resulting in a systemic proinflammatory and procoagulatory environment that results in inflammatory, morphologic, and apoptotic alterations in transplanted organs [2–9]. Inflammation of the intestine causes profound structural deterioration and increased permeability [10–12]. This injury is exacerbated by warm ischemia and cold ischemia during the preservation phase [13]. Following engraftment into the recipient, reperfusion of the allograft completes the cascade. This process, termed ischemia-reperfusion injury is closely related to early postoperative complications such as sepsis and acute rejection [14–16]. Donor- and transplant-related components of this injury cascade are, therefore, likely to contribute to the outcome after ITx [17–20].

The number of deceased organ donors has plateaued or slightly decreased in the past 3 y [21]. Although the pool of ITx candidates is relatively small, donor allocation is challenging largely due to the inability to place matching donor organs from donation after brain death (DBD) donors for the appropriate recipient. The vulnerability of the intestine to injury and the strong relation between graft quality and outcome has lead transplant centers to be highly selective on accepting intestinal allografts for transplantation. A clear description of donor criteria to discriminate between acceptable and unacceptable intestinal grafts is unavailable. At present, recovery practices and intestinal graft acceptation vary between transplant centers worldwide. This could lead to the underutilization of intestinal grafts. A recent review by Fischer-Fröhlich *et al.* [22] detailed the absence of adequate studies to explore intestinal graft selection criteria; with the majority of studies being single-center and personal experiences. Donor age is the most studied donor variable with other donor variables being described inconsistently. Except for donor age (<50 y) and donor-recipient size match (donor smaller than recipient), valid criteria are unidentified. Fischer-Fröhlich *et al.* suggested the following criteria based on a retrospective analysis of their clinical results ($n = 39$, 2006–2011); age <50 y, intensive care unit stay <1 wk, no blunt abdominal trauma, most recent sodium <155 mmol/L, no severe ongoing transfusion requirements, standard donor therapy, and compatible size matching [22].

Organ donation after cardiac death (DCD) has increased in kidney and liver transplantation over the past decade [23]. Intestinal grafts from DCD donors are regarded as unacceptable due to the susceptibility of the intestine to ischemic injury [24,25]. However, the histopathologic quality of the human intestinal DCD graft and specific differences between grafts from different deceased donor types (DBD *versus* DCD) have not been described.

The USA Organ Procurement and Transplantation Network (OPTN) [21] has defined a set of empirical donor-based criteria (Table 1). Justification of these OPTN criteria and identification of crucial donor and transplant procedure based characteristics is needed to aid health professionals to select allografts for ITx, ensure optimal use of grafts and ultimately improve the outcomes of ITx.

Ideally, longitudinal assessment of intestinal grafts from human donors during the donor-, procurement-, preservation- and reperfusion phases is required to assess intestinal graft quality. However, this study design faces a number of ethical and logistical challenges. In addition, the modest size of intestinal clinical programs in most centers does not allow for an adequately powered study to use such a design. In this study, we have evaluated histopathologic and molecular features of allograft injury in relation to donor conditions (defined by the OPTN criteria) in a group of multi-organ donors (MOD). In particular, the validity of empirical OPTN selection criteria, differences between donor types (DBD/DCD), and regional intestinal vulnerability have been studied.

2. Materials and methods

2.1. Informed consent

Informed consent for intestinal biopsies was obtained from relatives of all donors together with consent for organ donation. In living kidney donors, informed consent was asked for control blood samples.

2.2. Establishment of a clinical donor data and biobank

A dedicated student team was trained to collect patient data, blood, and intestinal samples of the proximal (jejunum) and distal (ileum) small intestine during MOD procedures in the Northern Dutch region. Intestinal tissue samples were

Table 1 – OPTN donor criteria for acceptation of the intestinal graft.

Criteria	Number of donors not meeting criteria (%)
DBD	13 (22)
CIT < 9 h	6 (10)
Donor age <50 y	33 (56)
Other organs (except for intestine) retrieved	0
AST and ALT <500	1 (2)
Last serum sodium <170 meq/L	0
Serum creatinine <2 (if donor >1 y)/<1 mg/dL (if donor <1 y)	1 (2)
Negative virology (HIV, HBsAg/cAB, HCV AB)	0
Maximal 2 inotropes at recovery	1 (2)
Resuscitation <15 min if cardiac arrest after BD declaration	0

AST = aspartate aminotransferase; ALT = alanine aminotransferase; HIV = human immunodeficiency virus; HBsAg/cAB = hepatitis B serum antigen/core antibody; HCV AB = hepatitis C viral antibody.