Potential options to expand the intestinal donor pool: a comprehensive review

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Abstract *(199 words; max 200)*

Purpose of review

Intestinal donation is currently restricted to “perfect” donors, as the intestine is extremely vulnerable to ischemia. With generally deteriorating donor quality and increasing indications for intestinal transplantation, the potential to safely increase the donor pool should be evaluated.

Recent findings

Increasing awareness on intestinal donation (often forgotten) and cautiously broadening the strict donor criteria (increasing age, resuscitation time, and intensive care unit stay) could expand the potential donor pool. Donors after circulatory death (DCD) have so far not been considered for ITx, due to the particularly detrimental effect of warm ischemia on the intestine. However, normothermic regional perfusion might be a safe strategy to render the use of DCD intestinal grafts feasible. Furthermore, machine perfusion is under continuous development and might improve preservation of the intestine and potentially offer a platform to modulate the intestinal graft. Lastly, living donation currently represents only a minority of all intestinal transplantations performed worldwide. Various studies and registry analysis show that it can be performed safely for the donor and successfully in the recipient.

Summary

Several potential strategies are available to expand the current intestinal donor pool. Most of them require further investigation or technical developments before they can be implemented in the clinical routine.

Key words
Intestinal transplantation, Living donation, Machine Perfusion, Normothermic Regional Perfusion, Organ Donation

MAIN BODY TEXT *(2299 words)*

Introduction

The intestine remains the most challenging organ to transplant. To safeguard the outcome, only “perfect” donors are generally considered for intestinal donation. Despite the limited number of patients being evaluated for intestinal transplantation (ITx), the waiting time is relatively long with a concomitant waitlist mortality(1,2). With increasing ITx indications and overall worsening of the donor quality, expansion of the donor pool might be warranted in the near future(3). In this review, we summarize the recent findings on potential strategies to safely expand intestinal donation.

Increasing awareness on intestinal donation

According to recent data of the International Intestinal Transplant Registry (ITR), only 50% (46/97) of all historical ITx centers have performed an ITx recently (unpublished data, presented during CIRTA PARIS, June 2019). Several small volume centers ceased their activity or started a multi-center collaboration, improving their experience. As a consequence of this scarcity of the ITx programmes, intestinal donation is often “forgotten”. However, it has been shown that increasing awareness on intestinal organ donation can expand the potential intestinal donor pool. In the UK, new prioritization of the national pediatric donor allocation, favoring the intestine, resulted in a significant increase in the number of intestines being offered. Subsequently, the number of transplants performed increased from 2.6 to 7.7 mean transplants per year(4).

Extended donor criteria

In the past, ITx teams remained very strict in the acceptance criteria of donor organs. As the intestine is very vulnerable to ischemia, hemodynamically stable donors have been preferred so far. For many other solid organs, transplant centers were forced to expand donor criteria based on an increasing organ shortage and therefore, to accept extended-criteria donors as well (more advanced age, longer intensive care unit stay, vasopressor need, higher body mass index, …). Unlike for other solid organs, there is no clear definition of extended donor criteria for the intestine. Standard intestinal donor criteria, like the Organ Procurement and Transplantation Network (OPTN) and other single-center published criteria are currently used(5–7). However, more extended intestinal criteria could be safely considered – on a case-by-case evaluation – and based on the criteria effectively applied by different centers which have proven to result in good outcome (*Table 1*)(8). Most criteria for which a safe extension has been used are size mismatch, donor age, body mass index (BMI), intensive care unit (ICU) stay, and duration of cardiopulmonary resuscitation (CPR).

Firstly, size matching is important in ITx as most of the recipients have a compromised abdominal domain due to short bowel syndrome and previous surgical procedures(9). As such, weight is an important factor in donor selection and it has been advocated that the donor should be 25-50% smaller in size than the recipient(10–14). Graft-reduction – both in isolated ITx and combined liver-ITx – have been shown possible in individual cases(15). Alternatively, the implementation of several techniques to expand the abdominal wall after transplantation (e.g. (non-) vascularized fascia or full-thickness abdominal wall transplant) also allows the use of larger grafts(16,17). Especially in case of multivisceral transplantation or chronic pseudo-obstruction, size-mismatch has safely been performed, because of the preserved abdominal domain in these patients(15). Secondly, maximal donor age has been set arbitrarily at 50

years(6). However, in the meantime, several centers have reported successful outcome after ITx with donors up to 65 years(1,6,15,18). Thirdly, a BMI of 25kg/m² is usually used as an upper limit, since it is known that a higher BMI is associated to a thicker mesentery, which becomes rigid after cold storage and might adversely impact graft mismatch. However, the use of intestinal donors with a BMI up to 28kg/m² has been reported(5). In selected cases, BMI up to 30kg/m² was used without impacting graft quality(19). Donor ICU stay is usually limited to 1 week. However, ICU stay of up to 2 weeks have been shown non-inferior(20,21) at the condition that infection is avoided and that hemodynamic stability is maintained. One of the most important measures to take is to start enteral nutrition as early as possible on the ICU, to prevent bacterial overgrowth and translocation and keep the integrity of the villi(15,22). Another discriminative factor is donor hemodynamic instability since the intestine is extremely sensitive to ischemia. Donors with prolonged cardiopulmonary arrest, sustained hypotension or on high doses of vasopressors were generally excluded. However, comparative analysis between donors with and without cardiac arrest could not show a negative correlation with survival and rejection (21). Cautious consideration of these hemodynamic criteria should always be on a “case-by-case” basis. Serum sodium values are another important donor criterium and values exceeding 155mEq/L are usually associated to edematous tissues resulting in a more complex transplant procedure and reperfusion phase(6,20). Furthermore, high sodium values might also reflect inferior donor management.

Finally, cold ischemia time for intestinal graft preservation is generally limited to 9 hours. Again, this is due to the extreme vulnerability of the intestine to ischemia, in particular the mucosa, since mucosal breakdown might result in more bacterial translocation after reperfusion. However, successful cases of ITx after longer cold

storage preservation have been described. Nevertheless, all attempts should be made to keep cold ischemia time as short as possible, in particular in case of an extended donor(15).

Table 1: Proposed standard and extended criteria donors.

Donor	Standard criteria	Extended criteria
D/R size match	Compatible	Adapted graft
Age	0 - 50 years	50 - 65 years
BMI	< 25kg/m²	25 – 30kg/m²
ICU stay	< 1 week	1 - 2 weeks
CPR	< 15min	> 15min
Sodium	< 155mEq/L	155 - 170mEq/L
Blood group compatibility	Identical	Compatible
Cold Ischemia Time	0 - 9 hours	> 9 hours

BMI: Body Mass Index; CPR: CardioPulmonary Resuscitation; D/R: Donor/Recipient; ICU: Intensive Care Unit

Donation after circulatory death

Another type of extended criteria donors, which are nowadays increasingly used in lung, liver and kidney transplantation, are donors after circulatory death (DCD). Mainly, controlled DCD procedures (Maastricht category 3) or euthanasia DCD procedures (Maastricht category 5 in Belgium and The Netherlands), are being performed(23,24). In these settings, the donor is declared death after cardiac arrest and a no-touch period of 3-5 minutes is respected, according to the national legislation. Procurement is initiated after this no-touch period and following rapid aortic cannulation, organs are flushed with a cold preservation solution. Compared to other organs, the small intestine is more vulnerable to warm ischemia and intestines from these donors have - for this reason - not been used for clinical ITx(25).

Normothermic regional perfusion

A potential modality to increase organ donation from DCD is regional perfusion. Before 2005, literature on this strategy was scarce and mainly oriented towards hypothermic regional perfusion(26). Since then, crucial developments in normothermic regional perfusion (NRP) have been reported (*fig. 1*). Via NRP, circulation and oxygenation is restored after cardiac arrest, potentially limiting (and even reversing) the detrimental effects of warm ischemia on organ viability(27). Preliminary results show survival figures after NRP DCD liver and kidney transplantation that are substantially superior compared to classically procured DCD organs (rapid recovery technique), and even equivalent to matched Donation after Brain Death (DBD) transplantation(27). This reversal of warm ischemic injury before transplantation is potentially due to partial restoration of adenosine triphosphate (ATP) content. In addition, an "ischemic preconditioning effect" –shown protective in various ischemia-reperfusion injury studies(27)– might also play a role. In a porcine model of intestinal preservation, 1 hour of NRP was effective to improve the ATP content and viability of the bowel. However, the integrity of intestinal mucosa was gradually deteriorated when duration of extracorporeal support time increased up to 3 and 5 hours(28). The same research group showed that intestinal grafts exposed to 1 hour of NRP, had better absorptive function and decreased ischemia-reperfusion injury, in contrast to DCD grafts not exposed to NRP. Decreased mucosal apoptosis seemed to be one of the main operating mechanisms(29).

Furthermore, NRP provides the possibility to inspection donor organs in detail and to perform blood analysis to assess organ function and quality. Lastly, the risk of involuntarily damaging procured organs is decreased due to the change from an ultrarapid procurement technique to a more controlled "DBD-like" procedure(27).

Implementation of NRP has also resulted in an increased rate of organ utilization for liver, kidneys and pancreas and it has had a major impact in the field of heart transplantation(27,30–32).

In ITx, assessing organ function is less crucial than for kidneys and livers. However, NRP may create a window for macroscopic and microscopic assessment of the donor intestine. Also, an ischemic preconditioning effect might be beneficial for the intestinal graft. Therefore, NRP might result in the future in the consideration of DCD donors for intestinal and multivisceral donation, but more research is needed.

Machine perfusion

The first notification of machine perfusion (MP) of a single organ dates back to 1849 by Loebel(33). In 1967, the possibility to prolong hypothermic storage by using oxygenated cryo-precipitated plasma and pulsatile perfusion was shown(33). Despite the clinical usage of MP for kidneys in the 1970s, this preservation strategy virtually disappeared in the 1980s due to the development of adequate preservation solutions for simple static cold storage and the simplicity of this preservation technique(33). Recently, supported by the technical innovations and the interest of the industry, MP became of increasing interest in solid organ transplantation once more(34). These developments were also initiated by the deteriorating profile of the donor organs that could no longer be adequately preserved by simple cold storage. Over the last decade, kidney hypothermic MP has become standard in several countries(35). For liver transplantation, a short period of hypothermic MP after simple cold storage has recently been shown efficient in improving outcome(35). Lung and heart MP are also increasingly performed pre-clinically and clinically(36). MP is currently used to better asses the quality and function of extended-criteria donor organs and/or to safely

prolong preservation time (long-distance transportation, combined organ transplantation, etc..)(36–38). However, MP is an unfinished product, and many parameters still need to be studied. For example, whether hypothermic, subnormothermic or normothermic perfusion is superior, still needs to be determined(39). The search for reproducible and prognostic organ viability markers is a work in progress(40,41).

In contrast to other solid organs, only preclinical experience is available on MP of the isolated intestine. Compared to other organs, the small intestine has a luminal compartment and this needs to be taken into account. By this route, it is possible to more rapidly cool the small intestine and/or to expose the mucosa to potentially beneficial compounds(42–44). However, clinical practice of combined organ-pumping for liver-intestine or multivisceral blocs is still far from reality(45). However, it can be expected that, as the small intestine is so vulnerable to ischemia, MP can exert a crucial role. Prolonged (24h) oxygenated preservation of the small intestine was already proven successful in canine studies in 1973 and even then, immunomodulation during MP was discussed as a potential application(37,41). In a porcine intestinal preservation model, normothermic perfusion was shown not to be superior in comparison to static normothermic or hypothermic preservation(47). Recently, the team of Yale developed a fully integrated, transportable, hypothermic machine MP device for intestinal preservation(48). In this setup, oxygenation was not foreseen but could be implemented, as well as (sub)normothermic perfusion. However, despite these developments, MP has not found its way yet into the clinical field of ITx, mostly due to several remaining uncertainties, the lack of a clear indication and a high cost for an orphan organ(49).

Living Donation

Since dr. Joseph Murray successfully transplanted a kidney between identical twins in Boston in 1954, the field of living donation and transplantation continuously evolved(50). Living donation for transplantation is currently a successful strategy, mainly used for kidney and liver transplantation. In kidney transplantation, living donation has unequivocally shown superior graft and patient survival rates over deceased donation, so far(51). Due to surgical and anatomical challenges, living donation is less common in lung, pancreas, and intestinal transplantation. According to a recent analysis from our group on behalf of the scientific committee of the ITR (unpublished data), only 78 ITx out 4,156 (1.9%) were reported as living donors, between 6 April 1985 and 14 September 2019(52). North America and in particular The Minnesota and Chicago groups (R Gruessner and E Benedetti) have been the frontrunner with 58% of the cases, followed by Asia-Australia (24%), and Europe (17%). Most procedures were isolated ITx (95%), and some were combined liver-ITx (5%). Adult/pediatric recipient ratio was 49%/51%. One- and 5-year graft survival rates were 62% and 44% after living donation, which is comparable to deceased donation (67% and 46%, respectively). Patient survival rates after living donation were 74% and 52% at 1- and 5-year respectively, which is comparable to survival rate after deceased donation (including combined liver-intestine and multivisceral transplantation) (*table 2*). With only 1.9% of all ITx procedures performed worldwide being living donors, it is reasonable to speculate that there is a potential to increase this procedure for specific cases (e.g., high titers of donor-specific antibodies, long waiting time, high mortality risk in small infants, countries with no or limited deceased donation activity)(53).

In the living donor procedure, 150-200cm of terminal ileum is being procured, while paying attention to preserve at least two-thirds of the remaining small intestine, as well as the ileocecal valve with 20-30cm of the terminal ileum, to ensure sufficient vitamin B12 uptake(54–56). No perioperative donor death has been reported so far(19,53,54). However, there is a 1-5% theoretical lifetime risk of small bowel obstruction in the donor and the later is associated to a mortality risk of 1-2%(19). Of note, a more favorable and potentially protective lipid profile has been seen after intestinal resection in living donors. This is an indirect "bonus", which however should not be seen as an argument in favor of living donation(57).

Table 2: Data on living and deceased donation ITx, by the ITR between 6 April 1985 and 14 September 2019.

In courtesy of the ITR and the Scientific Committee of IRTA.

	Living donation	Deceased donation
Numbers (%)	78 (1.9%)	4,078 (98.1%)
Adult / Pediatric recipients (%)	49% / 51%	48% / 52%
Transplant type		
Isolated ITx	73 (95%)	1.452 (36%)
cLi-ITx	5 (5%)	1.052 (26%)
MMvTx	0 (0%)	184 (5%)
MvTx	0 (0%)	681 (17%)
Graft survival		
1-year	62%	67%
5-year	44%	46%
Patient survival		
1-year	74%	74%
5-year	52%	54%

cLi-ITx: combined Liver-Intestinal Transplantation; ITR: International Intestinal Transplant Registry; ITx: Intestinal Transplantation; MMvTx: Modified Multivisceral Transplantation; MvTx: Multivisceral Transplantation

Conclusion

The intestine is often a “forgotten” organ to procure and increased awareness is needed. Criteria for intestinal organ donation are currently arbitrarily strict and moderate extension of these criteria should be cautiously considered on a case-by-case basis. The field of DCD is expanding for all organs, and like for the heart, NRP might open a new avenue for intestinal donation. MP has become a clinical reality for all solid organs and should be further investigated in intestinal preservation, due to its anticipated benefit in terms of improved and potentially longer preservation. Finally, living donation currently represents a very small percentage of the ITx activity worldwide and expansion of living donor programs for specific indications could be cautiously considered.

Key points

- Many potential intestinal donors are not identified and referred and increased awareness is crucial.
- Intestinal organ donation is currently limited to “perfect” donors. With increasing indications, strategies to increase the organ donor pool should be considered.
- Slight extension of donor criteria should be considered on a case-by-case approach.
- Susceptibility of the intestine to ischemia precludes the use of intestinal grafts from classically procured DCD donors. However, normothermic regional perfusion, by reversing the warm ischemic injury, might render intestinal procurement from DCD possible and should be further studied.
- Whether machine perfusion will allow to preserve intestinal grafts better and longer, and possibly evaluate and modulate them is still to be studied.

- Living donation ITx is rarely performed and could be expanded in certain indications.

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Conflicts of interest

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Figure 1: Multi-organ donor being prepared for thoraco-abdominal normothermic regional perfusion (above). Thoraco-abdominal regional perfusion with selective canulation and drainage of the supra-aortic vessels (under).