Strategies to improve donation after circulatory death kidneys for transplantation

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CHAPTER 2

Factors that complicated the implementation of a program of donation after unexpected circulatory death (uDCD) of lungs and kidneys. Lessons learned from a regional trial In the Netherlands.

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ABSTRACT

Background

Organ shortage remains a problem in transplantation. An expansion of the donor pool could be the introduction of unexpected donation after circulatory death (uDCD) donors. The goal of this study was to increase the number of transplantable kidneys and lungs by implementing a uDCD protocol.

Methods

A comprehensive protocol for uDCD donation was developed and implemented in the emergency departments (ED) of three transplant centres. All out of hospital cardiac arrest (OHCA) patients were screened for uDCD donation. Inclusion criteria were declaration of death in the ED, age (< 50y kidneys, < 65y lungs), witnessed arrest, and basic and advanced life support started within 10 min and 20 min, respectively.

Results

A total of 553 OHCA patients were reported during the project of which 248 patients survived (44.8%). A total of 87 potential lung and 42 potential kidneys donors were identified. A broad spectrum of reasons resulted in termination of all uDCD procedures. Inclusion and organ-specific exclusion criteria were the most common reason for not proceeding followed by consent. None of the potential donors could be converted into an actual donor.

Conclusion

Although uDCD potential was shown by successful recognition of potential donors in the ED, we were not able to transplant any organs during the study period. The Dutch EMS guidelines to stop futile OHCA in the pre-hospital setting and the strict use of in–and exclusion criteria like age and witnessed arrest hampered the utilization. A pre-hospital uDCD protocol to bring all OHCA patients who are potential uDCD candidates to an emergency department would be helpful in creating a successful uDCD program.

INTRODUCTION

Donor and subsequent organ shortage remain a major problem worldwide. The availability of organs for transplantation depends on two key factors: first, the recruitment of donors and second, the utilization rate of organs from these donors.[1]

The availability of donation after brain death (BDB) donors is decreasing due to epidemiological factors such as improved road safety and improved neurosurgical techniques after cerebrovascular bleeding.[2] For this reason, many countries implemented donation after circulatory death (DCD). DCD can be classified in five different categories (Table 1).[3]

The type of DCD donors that are utilized in different countries mainly depends on local legislation, cultural and ethical considerations and as well on organizational infrastructure.[4] Currently, 50% of all deceased donors in the Netherlands are controlled DCD donors.[5] Similar trends are seen in the United Kingdom and Belgium.[6] Spain, on the other hand, pioneered with uncontrolled DCD donors since the 1980s and only recently started with the use of controlled DCD donors.[7] Nevertheless, organ shortage is not resolved by one measure alone. Therefore, other strategies for expanding the donor pool have been implemented. Examples of such strategies are the use of expanded criteria donors (ECD) and implementation of the Eurotransplant Senior Program (ESP).[8] The most obvious reflection of the globally failing donor system is the usage of living donors, which leads worldwide to approximately 30,000 kidney transplantations.[9] General consensus on living donation is that the risks for the donor are minimal. A recent study however, indicates lower life expectancies and higher risks of end stage renal disease in this population.[10] Therefore, it would be preferable to find the organ shortage solution in deceased donors instead of aiming for living donors.

The DCD category 2 donor also referred to as unexpected donation after circulatory death (uDCD) is a DCD donor type that has not been implemented in many countries.[11] Although DCD category 3 donation rates are increasing throughout Europe, only a minority developed uDCD protocols and make use of this potential group of organ donors.[12] One could wonder why, since France and Spain have shown promising results with uDCD donors, leading to considerable numbers of successful kidney and liver donations-and transplantations.[13–18] Positive results are published with lungs donated from uDCD donors as well, however, the numbers are scarce.[18–21] There are several reasons why uDCD donors

are not widely utilized yet. These reasons include concerns regarding organ quality because of possible prolonged warm ischemia, complicated logistical protocols in combination with demanding organ preservation techniques, legal requirements and ethical issues.

The combination of organ shortage and the possible potential of uDCD donors has resulted in a regional collaboration to introduce a project for uDCD kidney- and lung donation in the Netherlands. The availability of machine perfusion techniques, such as normothermic regional perfusion (NRP), hypothermic kidney perfusion (HMP) and ex vivo lung perfusion (EVLP) in all participating centres, was deemed crucial to provide confidence in organ quality. The Maastricht University Medical Center (MUMC) has 35-years' experience with donation of uDCD kidneys and effectuate an average of three uDCD kidney donors yearly.[22] Therefore, this local uDCD initiative has proven to be a source for kidneys and/or potential other organs. This all together resulted in a protocol for kidney and/or lung donation from uDCD donors.

The ultimate purpose of this study was to increase the number of transplantable kidneys and lungs by the implementation of a regional uDCD protocol.

Table 1. The Maastricht categories of donation after circulatory death.

Category	Definition	Type
DCD 1	Dead in the out-of-hospital setting	Uncontrolled
DCD 2	Unsuccessful resuscitation	Uncontrolled
DCD 3	Awaiting circulatory arrest	Controlled
DCD 4	Circulatory arrest while brain death	Controlled
DCD 5	Euthanasia	Controlled

DCD = donation after circulatory death

PATIENTS AND METHODS

This prospective study was conducted at the emergency departments (ED) of the University Medical Center Groningen (UMCG), University Medical Center Nijmegen (UMCN), and Maastricht University Medical Center (MUMC) between October 2014 and April 2016. All centres are university transplant hospitals in middle-sized cities with a population of 200.336, 170.681 and 122.397, respectively. Emergency medical services (EMS) are locally organised. Groningen has the largest region (2960 km^2, total inhabitants of region; 530.000), followed by Nijmegen (1040 km^2, 583.581) and Maastricht (203 km^2, 183.000).

The medical ethical committee of the MUMC reviewed the protocol and concluded that, considering the Dutch donor legislation, no additional consent was required.

Potential donors

Potential eligible participants in this project were patients that suffered an out of hospital cardiac arrest (OHCA) prior to presentation to one of the participating EDs. All resuscitations were performed according to standard protocols. For this study the dedicated uDCD transplant coordinator was notified to screen for donation potential at time of arrival in the hospital. Inclusion and exclusion criteria are outlined in Table 2. If a patient seemed eligible for donation, the Dutch donor registry was consulted to verify permission for donation. In case of an unsuccessful resuscitation relatives were approached for consent when donation criteria were met. Relatives were entitled to withdraw consent and stop donation preparations or donation at any time.

Professionals involved

A dedicated team with a project manager, transplant coordinator, ED physician, thoracic, vascular and procurement surgeon was installed to execute the project.

Preparations for organ donation

Actions of preparations were carefully applied and taken in accordance with the Dutch legislation on organ donation. After withdrawal of resuscitation and declaration of death, five minutes of 'no touch' was observed before invasive interventions took place to ensure organ quality. For potential lung donors, thoracic drains were placed to enable in situ cooling of the thoracic cavity. For potential kidney donors, the femoral artery and vein were cannulated to initiate NRP of the abdomen. A balloon catheter was inserted to prevent blood flow towards the heart and brain.

Organ retrieval and preservation

Organ retrieval was performed following standard protocols [23], with the distinction of possible lung procurement before termination of the NRP. Furthermore, for lungs EVLP would be applied for quality assessment of the organ prior to transplantation. Kidneys would be preserved by non-oxygenated HMP.

Allocation

Within Eurotransplant and the Dutch Transplant Foundation, both responsible for the allocation of organs donated by donors in the Netherlands, arrangements were made to optimize the allocation of organs donated within the project. Lungs donated were first offered to the UMCG, the only centre with a lung transplant program within the project area. Kidneys were first offered to the participating centres before entering the Eurotransplant Kidney Allocation System (ETKAS).

Table 2. In- and exclusion criteria uDCD protocol

Inclusion criteria		
General	Witnessed arrest	
	Basic life support (BLS) started within 10 minutes after collapse	
	Advanced life support (ALS) started within 20 minutes after collapse	
Organ specific	Lung: donor age (years)	Kidney: donor age (years)
	Between 18 and 65	Between 18 and 50
Exclusion criteria		
General	Unknown patient identity	
	Unnatural death*	
	Negative registration in the Dutch donor registry	
	Untreated sepsis prior to death	
	Malignancy	
	Positive serological HIV test result	
	Unknown cause of death	
	No suitable recipient	
Organ specific	Lung	Kidney
	Resuscitation time: >120 minutes	Resuscitation time: >90 minutes
	Warm ischemic time:> 60 minutes	Warm ischemic time: >30 minutes
	Pre-existing lung pathology**	Pre-existing kidney disease**
	Aspiration	

*If there are any concerns that the patient died because of a unnatural death: “Every death that is NOT exclusively the result of a spontaneous disease, including a complication of a medical treatment performed” donation is only possible with permission of a municipal coroner and public prosecutor. ** Pre-existing lung- and kidney pathology are defined as a disease in which a decreased capacity/function is seen that would have a negative impact on function in the recipient.

RESULTS

Study group

During the 19-month study period, a total of 553 OHCA patients were admitted to the participating EDs. The median age and interquartile range of this population was 63± 23 with 71.4% male patients. The initial survival rate was 57,3% (n=317). These patients were admitted to the intensive care unit (ICU) or ward. 248 were discharged alive, the other 69 deceased at the hospital. The remaining 42.7% (n=236) deceased in the ED.

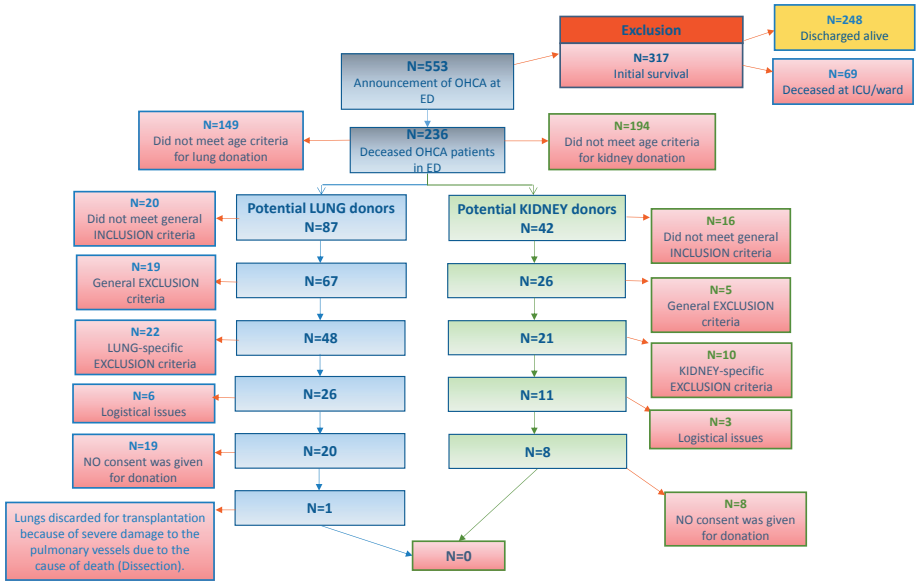
Lung donation

No uDCD lung donation took place during the study period. In 149 cases (26.7%) the age criteria were not met. That leaves 87 patients (15.7%) eligible as potential lung donor, based on age criteria and location of death (ED). 20 of them (23%) did not meet the remaining predefined general inclusion criteria. In 19 (21.8%) cases general exclusion criteria were the reason to stop the procedure. In 22 (25.3%) lung-specific contraindications made donation impossible. Consent for donation was not given in 19 (21.8%) cases, and in 6 (6.9%) logistical issues were the reason not to continue. In one case, the donor was taken to the operating room (OR) but during procurement the lungs were deemed unsuitable for transplantation, due to a severe aortic dissection. Figure 1 shows a flow chart of the OHCA population and the summarized reasons for not utilizing a potential uDCD lung donor. A more detailed overview of reasons to terminate the procedure is given in supplemental figure 1.

Kidney donation

No uDCD kidney donation took place during the project. A total of 194 (35%) potential donors did not meet the stricter age criteria for kidney donation. This resulted in 42 (7,6%) potential kidney donors based on age criteria and location of death (ED). 16 patients (38%) did not meet the other predefined general inclusion criteria. In 5 (11.9%) of the cases general exclusion criteria were the reason to stop the procedure prematurely. In 10 (23.8%) kidney-specific contraindications made donation impossible. Refusal for donation occurred in 8 (19 %), and in 3 (7.1%) of cases logistical issues were the reason for not proceeding with the donation procedure (Figure 1). In one case cannulation was performed, but NRP could not be initiated within 30 minutes after ending resuscitation and the procedure was therefore terminated. All specified reasons for exclusion are depicted in supplemental figure 2.

Figure 1. Flow chart OHCA population and the summarized reasons for not proceeding the donation procedure. All specified reasons are depicted in Appendix A and B.



DISCUSSION

The implementation of a uDCD protocol in the three participating centres was a major effort. A dedicated multidisciplinary team of professionals prepared the protocol. The protocol was successfully utilized, with every potential donor, indicating that awareness for organ donation in the ED is possible, and was created without significant problems. However, despite major commitment, the net result of this study is negative since no potential donors were effectuated into an actual donation and subsequent transplantation procedure. Given our goal to increase the number of transplantable organs, we need to conclude that this uDCD program was unsuccessful. We will discuss factors in the study set up that led to this negative result but also factors related to informed consent, the way the Dutch emergency services are organized, and the factor of population density.

During the study period no uDCD donors were effectuated in the MUMC too. A possible explanation could be that the in- and exclusion criteria were too strict during this study. Convincing data in favor of uDCD kidney donation, available at the time of the preparation of the protocol (before October 2014)[11,14,22,24,25], was significantly scarcer and less convincing than nowadays.[2,12,26–29] Furthermore, the use of NRP was a relatively unknown technique for the transplant specialists in the UMCG and UMCN. Therefore, adaptations to the MUMC protocol were made because concerns regarding kidney quality were present. This resulted in in- and exclusion criteria that provided confidence to all parties involved. Therefore, a maximum warm ischemic time of 30 minutes, a maximum resuscitation duration of 90 minutes, and a maximum age of 50 year for kidney donation was chosen for this project. An important twofold decrease in potential kidney donors was seen in this cohort because of this adaptation and 42 potential kidney donors were left. Age criteria for lung donation was set between 18 - 65 years and we identified 87 potential lung donors based on location of death (in ED) in combination with age. Changing age subsequently results in an altered potential. Changing inclusion criteria, however, is not the only possible explanation for any effectuated donors.

National and regional quality improvement in EMS services have led to higher survival rates in the case of a OHCA then before.[30] For example, in the region of Maastricht the survival for patients of 70 years or younger was 31% in 2013. In comparison, survival rates during the mid-nineties were approximately 9% in the Netherlands[31] so this major improvement in OHCA survival has subsequently led to a lower number of potential donors.

The uDCD potential presented by others, using similar inclusion criteria, vary between 0.7 and 19 % of the total OHCA population. This is in-line with our finding of 15.7% and 7.6% for potential lung and kidney donors.[32–34] However, these were studies with calculated potentials based on EMS data. There was no actual intention to include donors. Within our project, potential donors were actually screened for donation with the intention to utilize them as donors, which provides a range of exclusion reasons beyond usual EMS data collection. The existence of this range of additional reasons to not proceed with donation and subsequent transplantation is important to know when setting up a uDCD program and are highlighted in the supplemental figures 1 and 2.

ROSC after OHCA in the pre-hospital setting or ROSC in the ED in 57.3% was the most important factor that lowered the uDCD potential. Age criteria accounted for 26.8 %, absence of a witnessed arrest for 3.3% and negative donation consent for 2.7%. We used witnessed arrest as inclusion criteria since it was common in uDCD protocols from other centres procuring uDCD kidneys.[13,17,22,35] However, for lung donation, a witnessed arrest could be considered less obligatory. Preclinical data shows that pulmonary tissue seems to withstand warm ischemia better than other organs, with measurable lung function still present after two hours of warm ischemic time.[36,37] Furthermore, lung quality could also be secured through evaluation by means of EVLP when lungs have been procured from a uDCD donor. With a more lung-focused protocol, and with a less strict threshold on witnessed arrest, a potential 18 more lung donors could have been implemented (Supplemental figure 1). However, one needs to be aware of the fact that these 18 potential extra lung donors were not further screened for donation. If they would have been screened, additional causes to exclude these donors might have emerged.

In our cohort 27 potential organ donors were excluded because there was no consent for donation. In 15 of these cases, the family did not give permission to proceed. This was contrary to our expectations which were based on a Dutch study from the MUMC [38] that demonstrated that family consent rates for donation can be significantly higher in the uDCD setting (53%) compared to controlled DCD settings (29%). It can be assumed that the ED physicians in the MUMC were more exposed because of their years of experience with uDCD donors. However, no significant differences were found in family refusal rates between the three centres in this project. Furthermore, prior to start of the project special attention was paid in training the ED physicians in communication regarding donation. The family approach was therefore, with some minor exceptions, similar in the

participating hospitals. This was in line with family refusal rates found in other cohorts.[39–41] Voluntary consent for organ donation is very important to respect individual autonomy. There are two different ways of establishing consent, depending on a countries legislation: “opt-in” requires explicit consent from the patient or its relatives for the removal of organs and “opt-out” is any system that does not make that requirement and presumes consent when it is not specifically given.[42] One of the reasons for our high family refusals might be the Dutch opt-in system as refusals are seen less in opt-out systems.[43] However, even in an opt-out consent country like France, family refusal rates up to 75% are reported in the uDCD setting.[39] So, it seems that organizational factors are also important and not only a countries legislation with regard to donation. In Spain family refusal rates in the uDCD setting are low ranging from 0 up to 15%.[2,15,16,44] The key success factor proved to be that the transplant coordination network operates on national, regional and hospital level and that the communication lines are kept short between all three.[45] Therefore, the decision making process is efficient. Furthermore, in Spain much effort and attention are paid to inform the Spanish inhabitants on organ donation and transplantation. This in combination with great effort in continuous medical teaching for every step of the process, including family approach, has resulted in their excellent outcomes in terms of consent for organ donation. In addition, an adequate legal, economic, ethical, medical and political background are present in Spain to support all efforts. With all these measures, the organ donation rates increased from 14 in 1989 to 32.5 organ donors per million people in 2001.[45,46] Their approach, referred to as “The Spanish model”, demonstrates that organ shortage is not only present because there are too few potential donors, but rather due to a failure to convert a potential donor into an actual one.

A good example of how a potential donor has more chance to become an actual donor is to see an OHCA as an event creating potential for donation. Therefore, we need to handle OHCA patients differently. The handling of patients in Spain is in some crucial aspects distinct compared to the Netherlands. In Spain all OHCA patients that could be potential donors are transported to the ED or directly to the ICU, even if treatment of the OHCA is deemed futile.[44] In contrast, in the Netherlands EMS crew can independently stop a futile OHCA resuscitation. As a result, multiple resuscitations are terminated at the site of collapse without transferring the patient to an ED. This explains the high initial ROSC rate of 57.3% after resuscitation in the ED in our study population. When reviewing our regional EMS data, 38.8% of OHCA patients are not transported to the ED but are directly transferred to a morgue. Changing this practice similar to the Spanish system

might increase the Dutch uDCD potential. The local EMS were aware of the project but not actively involved. The reason for this was because our potential calculation, based on EMS data of patients that were transferred to the hospital, was positive (13% of the total OHCA population). Starting this uDCD program in three transplant centres in the Netherlands was already a major challenge. Also changing prehospital OHCA protocols would have given significant logistic and ethical obstacles for the project.

Finally it appears that successful uDCD programs need dense populated areas with large cities.[14,15,40,16–18,20,24,25,35,36] This project was realized in an rural region with middle-sized cities. There are, however, examples from Spain in which uDCD programs were successful in cities from comparable size.[2,47] The difference with our protocol is that patients were directly transferred to the ICU after an unsuccessful resuscitation in these programs. The ICU is a department in which organ donation from other donor types is a common procedure in contrast to the ED. The experiences and subsequent results from Santander[2] and Granada[47] are therefore less comparable with our situation.

In summary, we failed in our goal to increase the number of transplantable organs by implementing a uDCD protocol. This study showed that there were many factors that contributed to this result, some of which are outside the influence of protocols, such as regional feasibility, a countries ethical dynamics and donor legislation. However, it could be possible that a pre-hospital approach to transfer deceased OHCA patients towards the ED for the sole purpose of donation, in combination with the use of new preservation techniques to test organ function[48–54], creates a potential for uDCD donation in the Netherlands that is not being utilized at the moment.

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SUPPLEMENTARY MATERIAL

Supplemental figure 1. Specified reasons for exclusion potential lungs donors.

Exclusion reason	Number (n=)	Percentage (%)	Cumulative percentage (%)	Categorization exclusion reason
Initial survival OHCA	317	57.3	57.3	Did not meet inclusion criteria
• Discharged alive	248	78.2	78.2	
• Deceased at ICU/ward	69	21.8	100	
Age	149	26.7	84	Did not meet inclusion criteria
No witnessed arrest	18	3.3	87.3	Did not meet inclusion criteria
No family consent	15	2.7	90.0	Consent
Negative registration	7	1.3	91.3	General exclusion criteria
Trauma	4	0.7	92.0	Organ-specific exclusion criteria
Resuscitation > 120 min	3	0.55		Organ-specific exclusion criteria
No family present	3	0.55		Consent
Chronic obstructive pulmonary disease (COPD)	3	0.55		Organ-specific exclusion criteria
No announcement TC	3	0.55	94.2	Logistical
Aspiration	2	0.37		Organ-specific exclusion criteria
Blood in breathing tube	2	0.37		Organ-specific exclusion criteria
No BLS < 10 min	2	0.37		Did not meet inclusion criteria
No suitable recipient on waiting list	2	0.37		General exclusion criteria
Malignancies in medical history	2	0.37		General exclusion criteria
Sarcoidosis	2	0.37	96.4	Organ-specific exclusion criteria
Actalysis	1	0.19		Organ-specific exclusion criteria
End stage heart lung failure	1	0.19		Organ-specific exclusion criteria
No EVLP capacity	1	0.19		Logistical
Drug abuse	1	0.19		General exclusion criteria
Duration canulation NRP	1	0.19		Logistical
Congestion pulmonary vessels	1	0.19		Organ-specific exclusion criteria
Leukaemia	1	0.19		General exclusion criteria
Body not released by coroner	1	0.19		Consent
Lung carcinoma	1	0.19		Organ-specific exclusion criteria
Lung emboli	1	0.19		Organ-specific exclusion criteria

Supplemental figure 1. Continued.

Unnatural death	1	0.19		General exclusion criteria
Unknown cause of death	1	0.19		General exclusion criteria
Unknown identity	1	0.19		General exclusion criteria
Waiting list lung transplantation	1	0.19		Organ-specific exclusion criteria
Excessive smoking	1	0.19		Organ-specific exclusion criteria
Refractory shock	1	0.19		General exclusion criteria
Terminal liver failure	1	0.19		General exclusion criteria
No transplantation capacity	1	0.19		Logistical
Dissection of pulmonary vessels	1	0.19	100.0	Organ-specific exclusion criteria
TOTAL	**553**		**100**	

* Trauma was not an absolute contraindication but in these cases the trauma was too severe for proceeding donation.

Supplemental figure 2. Specified reasons for exclusion potential kidney donors.

Exclusion reason	Number (n=)	Percentage (%)	Cumulative percentage (%)	Categorization exclusion reason
Initial survival OHCA	317	57.3	57.3	Did not meet inclusion criteria
• **Discharged alive**	248	78.2	78.2	
• **Deceased at ICU/ward**	69	21.8	100	
Age	194	35.0	92.3	Did not meet inclusion criteria
No witnessed arrest	15	2.7	95.0	Did not meet inclusion criteria
No family consent	6	1.1	96.1	Consent
Resuscitation > 90 min	6	1.1	97.2	Organ-specific exclusion criteria
Negative registration	2	0.37		General exclusion criteria
Excessive bleeding	2	0.37		Organ-specific exclusion criteria
No family present	2	0.37		Consent
No announcement TC	2	0.37	98.7	Logistical
***Trauma**	1	0.19		Organ-specific exclusion criteria
No BLS < 10 min	1	0.19		Did not meet inclusion criteria
Failed canulation NRP	1	0.19		Logistical
Prolonged ischemic time	1	0.19		Organ-specific exclusion criteria
Unknown cause of death	1	0.19		General exclusion criteria
Refractory shock	1	0.19		General exclusion criteria
Terminal liver failure	1	0.19	100.0	General exclusion criteria
TOTAL	**553**		**100**	

*Trauma was not an absolute contraindication but in these cases the trauma was too severe for proceeding donation.