

Original Research

## Is Donation after Circulatory Determination of Death in Japan Uncontrolled or Controlled?

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### Abstract

Using donation after circulatory determination of death (DCD) donors has been shown to be a potential means of increasing the number of donors for organ transplantation. The purpose of this study was to examine the published practice of DCD in Japan to properly define their practice as controlled or uncontrolled. Through the Web of Science database, we systematically searched articles describing uncontrolled DCD, controlled DCD or Maastricht classification. A total of 12 articles (ten articles related to kidney, one to pancreas, another to islet transplantation), which were published between 1999 and 2023 from Japanese institutes, were eligible for our study. Systematic review revealed that most DCD in Japan occurs when a terminally ill patient undergoes an expected cardiac arrest without rapid discontinuation from a ventilator, and in some cases with premortem interventions such as cannulation to the femoral vessels. Surprisingly, these DCD donors in Japan have been categorized as uncontrolled DCD. This categorization confuses the donation and transplantation community globally because the international consensus is that uncontrolled DCD occurs after an



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unexpected cardiac arrest. Further clear definition of terminology would be required within Japan as well as other countries practicing uncontrolled DCD.

### **Keywords**

Donation after circulatory determination of death; uncontrolled DCD; Maastricht classification; kidney transplantation; withdrawal of life-sustaining treatment

## **1. Introduction**

Shortage of organ donors continues to be a serious problem for patients waiting for transplants. Using donation after circulatory determination of death (DCD) donors has been shown to be a potential means of increasing the number of organ donors [1]. DCDs have been traditionally divided into two types according to the Maastricht classification: controlled DCD (mostly Maastricht category III) and uncontrolled DCD (mostly category Maastricht II) [2]. Controlled DCD refers to donation after an expected or anticipated death typically accompanied with a planned removal of life-sustaining therapy in the face of catastrophic illness. Uncontrolled DCD refers to donation following an unexpected or unanticipated death typically accompanied with an unsuccessful resuscitation attempt. Globally, the majority of DCD donors are controlled DCD, primarily Maastricht category III [3]. Countries that utilize uncontrolled DCD donors are limited partially because of logistical difficulties [4]. For example, a system supporting uncontrolled DCD requires a rapid transition from resuscitation to organ preservation. It also needs an organ procurement team and operation room to be available anytime.

Literature search suggests that Japan is one of the limited countries utilizing uncontrolled DCD [4, 5]. Domiguez-Gil, et al. published recommendations and guidance for the optimization of development of uncontrolled DCD [5]. Four studies including two Japanese studies [6, 7] were selected to evaluate the optimal age of uncontrolled DCD donors. However, careful review of these two studies suggests that uncontrolled DCD in Japan is different from Western countries in terms of definition and practice.

Consistent usage of definitions around deceased donor categorization is important in order to enable the international transplant community to compare and contrast graft and patient outcomes. We sought to examine the published practice of DCD in Japan to properly define their practice as controlled or uncontrolled.

## **2. Materials and Methods**

We systematically searched articles describing uncontrolled DCD, controlled DCD or Maastricht classification using the Web of Science database. We employed all field strategy with the following terms: “transplantation” and “donor” and [“non-heart-beating” or “circulatory death” or “circulatory arrest” or “cardiac death” or “cardiac arrest” or “DCD”]. We limited our search to articles published between 1999 and 2023, as well as to articles from Japanese institutes. We further refined articles by document types including “article”. Review articles and book chapters were excluded. The article selection was conducted independently by two of the authors, and any disagreements were resolved by achieving consensus through discussion.

We identified 171 articles after the initial search. After excluding 81 non-clinical articles based on title and abstract, we assessed 90 full-text articles for eligibility and excluded 60 articles not describing DCD type in the context of Maastricht classification. Sixteen articles were further excluded because of publication by the same institute or group with an overlapped study period. One article was excluded as it was a review, and another one was excluded due to low quality data presentation. A total of 12 articles remained for our review.

We collected information on (1) DCD type (uncontrolled or controlled), (2) attempt of cardiopulmonary resuscitation (CPR) (distinct from cardiac compression with the goal of preserving organs), (3) Maastricht classification category I through V, (4) withdrawal of life-sustaining treatment (WLST) (5) premortem cannulation, (6) premortem heparinization, and (7) warm ischemia time (WIT). When the term “uncontrolled setting” or “uncontrolled cardiac arrest” was used in the articles, we deemed that these terms were used to express uncontrolled DCD.

There is wide variability in methods and practices of WLST between countries, institutes, and physicians. The methods may include, but are not limited to, terminal extubation, gradual decrease in mechanical cardiopulmonary support, or gradual weaning of inotropic agents. In this paper, we use the term WLST as rapid discontinuation from a ventilator or circulatory mechanical support unless specified.

### **3. Results**

In Table 1, the twelve articles included in our systematic review are listed: ten articles were related to kidney transplantation [6-15]; one to islet transplantation [16]; and another one to pancreas transplantation [17]. All twelve were retrospective studies.

**Table 1** Articles included in the study.

First author, Year published	Study period	Description of DCD type	Attempt of CPR	Description of Maastricht classification	WLST	Premortem cannulation	Premortem heparinization	Mean WIT (range), minutes
Mizutani 2001 [6]	1987-1997	All uncontrolled DCD	NR	NR	NR	Performed but % NR	100%*	9.2**
Koyama 2002 [8]	NR	All uncontrolled cardiac arrest	NR	III or IV	NR	0% (0/23)	NR	27.3
Hattori 2003 [7]	1986-2000	All uncontrolled DCD	NR	NR	NR	Performed but % NR	NR	NR
Nishikido 2004 [9]	1983-2003	Most controlled DCD	NR	III (n = 3), IV (n = 53), unknown (n = 4)	100% (60/60)	0% (0/60)	NR	18.6
Tojimbara 2007 [10]	1975-2004	Uncontrolled or controlled setting	NR	III or IV	25% (18/73)***	84% (61/73)***	100%*	6.3***
Morozumi 2010 [11]	After 2007	Group A: standard DCD Group B: uncontrolled DCD	Group A: NR Group B: Yes	NR	NR	Group A: 100% (5/5) Group B: 0% (0/2)	Unclear	Group A: 6.4 Group B: 41.0
Matsuno 2010 [12]	NR	Uncontrolled DCD	Yes	NR	NR	Performed but % NR	Unclear	7.8** (0-16)
Kusaka 2019 [13]	1983-2011	NR	NR	III (n = 20), IV (n = 251)	0%****	Performed but % NR	NR	11.7 (1-71)
Tojimbara 2019 [14]	2008-2017	NR	NR	III or IV	0% (0/8)	75% (6/8)	NR	8.3 (1-24)
Aida 2022 [15]	2000-2018	Most uncontrolled DCD	NR	Most IV	NR	NR	NR	NR

Saito 2010 [16]	2004-2007	All uncontrolled DCD	NR	All V	NR	Performed but % NR	NR	7.6 (0-37)
Tojimbara 1999 [17]	1990-1994	Uncontrolled or controlled setting	NR	NR	27% (3/11)	82% (9/11)	NR	3.3 (0-14)

\* Exact values not reported, \*\* Calculated from the reported values, \*\*\* Data for year 2000-2004 are shown, \*\*\*\* The hospital does not permit WLST.  
DCD: donation after circulatory determination of death, CPR: cardiopulmonary resuscitation, WLST: withdrawal of life-sustaining treatment, NR: not reported, WIT: warm ischemia time.

Uncontrolled DCD is a predominant DCD type in Japan according to the descriptions in the articles listed in Table 1. Among studies dealing with uncontrolled DCD, only two studies reported that CPR with the goal of life saving was attempted to potential donors [11, 12]. Other studies claiming uncontrolled DCD did not report anything about CPR.

Regarding Maastricht classification, the majority of DCDs were indicated as category IV in many studies. One study [16] indicated category V, but this was based on modified classification not widely used [18], where category V is defined as unexpected cardiac arrest in intensive care.

WLST was conducted in 100% of donors [9], 25% [10], 27% [17], in three studies where organ procurements were performed prior to 2004. In more recent studies, WLST seems not to be performed. Two studies indicated that WLST was not performed [13, 14]. The remaining studies did not explicitly cite if WLST was performed or not. One study used the term “uncontrolled setting” to express that WLST was not performed and “controlled setting” to express that WLST was performed [17].

Four studies reported the number of donors who underwent pre-mortem cannulation to the femoral vessels [10, 11, 14, 17]. The frequency of the procedures was as high as 84% [10]. Most other studies indicated that either pre-mortem or post-mortem cannulation was done, but the actual number of the procedures for each was not clearly stated [6, 7, 12, 13, 16]. Pre-mortem heparinization was conducted in two studies as a part of the protocol [6, 10]. The other two studies described intravenous injection of heparin, but whether it was administered at pre-mortem or post-mortem was not clear [11, 12]. Nothing was described regarding heparin injection in the remaining articles.

Nine studies reported WIT which was generally defined as time between cardiac arrest and initiation of organ perfusion with cold solution. In seven studies, mean WIT was reported as being shorter than 12 minutes with some donors being reported as 0 minutes [12, 16, 17]. Two centers where pre-mortem cannulation was not performed at all reported a longer WIT (27.3 and 18.6 minutes) [8, 9]. The longest mean WIT (41.0 minutes) was reported by Morozumi, et al. [11]. The authors' group continued mechanical chest compression using an automated device to potential donors (n = 2) who experienced sudden cardiac arrest at the emergency department while consent for organ donation was obtained from donor family.

#### **4. Discussion**

It is apparent from the current global point of view that the most DCD donors are misclassified as uncontrolled DCD donors in Japan. There are several factors leading to this misclassification.

When the original Maastricht classification was published in 1995 [3], the term “controlled” was meant for circumstances leading to the short ischemia time. The nine of twelve Japanese articles were published prior to 2016 [2] when the current Maastricht classification was published in which controlled/uncontrolled DCD was clearly defined. The timing of publications would be one of the factors of misclassification regarding uncontrolled vs controlled.

WLST at the end-of-life care is rarely performed in Japan [19]. There are various factors, for physicians not to perform WLST, including the lack of an open discussion about the end-of-life care, the lack of sociocultural acceptance, anxiety over assisted dying, and legal challenges. However, gradual decrease of inotropic agents and/or reduction of fluid support is not a rare practice at the end-of-life care in Japan, as described in some DCD articles [15, 20]. This activity might be seen as a

non-aggressive version of withdrawal. As mentioned in the Materials and Methods section, a wide variability exists in methods of withdrawal [21]. This circumstance surrounding the end-of-life care in Japan should be recognized by the organ donation and transplant community.

Further discussion can be made regarding “WLST”. According to the Maastricht classification, category III DCD includes “those patients for whom circulatory death occurs after a planned WLST, *mainly* cardiopulmonary support” [2]. This implies “WLST” does not have to be limited to rapid discontinuation from a mechanical ventilator. In fact, Kootstra, et al. pointed out that not all category III DCD donors are ventilator dependent [3]. Thus, as long as withdrawal is planned, regardless of its method, and cardiac arrest is expected, then a potential DCD donor may be categorized as III (or controlled IV). Unfortunately, the most recent Maastricht classification does not define “WLST” in detail although many other terms related to DCD are defined [2]. We all tend to assume that “WLST” in the context of DCD means rapid discontinuation from a ventilator or circulatory mechanical support. This assumption may be the reason for relatively less cases of Maastricht category III in Japan.

In an article published in 1998 by a group from Tokyo Women’s Medical University in Japan [22], the authors used the terms “controlled” for DCD with WLST and “uncontrolled” for DCD without WLST. Many other transplant surgeons in Japan seem to follow this concept to express their DCD type (no WLST indicates “uncontrolled”) in their published articles. Temporal constraints for the procurement process would be controlled in some degree by a means of WLST. For example, initiation of WLST can be scheduled based on availability of a procurement team and an operation room. In contrast, it is hard for Japanese physicians, who do not perform WLST, to control temporal constraints when death is expected anytime. For example, it is not rare to take a few weeks to complete the process from donation decision to organ retrieval in Japan [13].

We found that most DCDs in Japan are categorized to Maastricht IV. Maastricht IV DCD includes controlled or uncontrolled cardiac arrest after brain death diagnosis. In Japan, physicians are legally authorized to declare brain death only in certified hospitals [19]. Conversely, physicians cannot declare brain death to any patients in non-certified hospitals even when it is sufficiently believed that they are brain dead. Therefore, many articles dealing with DCD in Japan use the term “clinical” brain death to distinguish it from legal brain death when DCD occurs in a non-certified hospital (which are much higher in number than the number of certified hospitals in Japan). With this bear in mind, it is ambiguous to distinguish between Maastricht III and controlled IV in Japan. Typical DCDs in Japan would not fit well to any of Maastricht category I through V because of too unique situations in Japan.

In Japan, typical DCDs are those patients for whom expected cardiac arrest occurs. WLST is not performed, but non-aggressive withdrawal may be involved for the dying process. Premortem interventions are performed when possible. Despite these, many donors in Japan are categorized as uncontrolled DCDs because it is difficult to control temporal constraints for the procurement process. Japanese physicians’ view might be that “timing of cardiac arrest” is unexpected (or unpredicted) for DCD without WLST, resulting in labelling “uncontrolled” to such donors. On the other hand, the current international consensus is that uncontrolled DCD is donor after unexpected cardiac arrest. WLST does not matter when distinguishing between controlled and uncontrolled DCD.

The transplantation community in Japan is recommended to avoid using the term “uncontrolled DCD” to their typical donors to avoid confusion and misconception at the international level. At the same time, the Maastricht classification has been ignoring or misunderstanding the unique

circumstances in Japan. Further modified classification or clear definition, especially to WLST, would benefit to the donation and transplant community.

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TK drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, read and approved the final manuscript.

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### **Competing Interests**

The authors have declared that no competing interests exist.

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