Introduction

In organ transplantation, there is growing emphasis on the ethical, legal and psychosocial aspects. Every three years ELPAT organizes an international conference on the ethical, legal and psychosocial aspects of organ transplantation. ELPAT is a subdivision of the European Society for Organ Transplantation (ESOT). In April 2016 the 4th ELPAT congress was held in an ancient convent dating from 1600: the Angelicum Congress Center in Rome, Italy. This central locus for theological and philosophical debate and learning was an ideal setting for the ELPAT conference. Three hundred and seventy eight delegates from 44 countries participated. In total, 193 oral presentations and 54 poster presentations were held. Furthermore, two books were launched: *'Ethical issues in paediatric organ transplantation'* edited by Rebecca Greenberg, Aviva Goldberg and David Rodriguez-Arias (Springer, 2016) and *'Trafficking in human beings for the purpose of organ removal'* edited by Frederike Ambagtsheer and Willem Weimar (Pabst Science Publishers, 2016). Finally, we organized two parallel sessions on hot topics for physicians on living and deceased donation. In this proceedings book we present a collection of articles on topics that were presented during the congress.

'Global Challenges' was the theme of this congress. Whether performing transplantations in the United States, Europe, Asia or Africa, there are universal challenges we all face and these formed the back-bone of the programme. One such theme is financial incentives for living donation. It is illegal in all countries except Iran to financially or otherwise reward living donors. In reality we know that in some countries out of pocket costs for living donors are substantial [1] while the savings made for the health system due to avoidance of dialysis are significant. Why should donors not benefit in some way given their contribution to saving both lives and costs? While most would agree that we should try to remove disincentives for donation [2], we also need to consider how to define financial incentives. When does an expression of gratitude become a gift, when does a gift become an incentive? We can, and should, ask ourselves is it ethically justifiable to offer financial incentives to living donors [3], but also is it justifiable not to [4]? Therefore the first plenary debate considered the topic of incentives for living donation and how we may move beyond the current deadlock on the issue. Speakers were Elisa Gordon (USA), Allison Tong (Australia), and Sigrid Fry-Revere (USA).

One worldwide development influencing the search for living donors is the prolific integration of social media into modern life. While the civil war rages in Syria, a 7-year old girl tweets her experiences of daily life in Aleppo: a modern day Anne Frank. In science, as an author you can #presentyourpaper on Twitter, and using social media has been shown to be related to a significant increase in number of citations [5]. Patients too can harness the power of social media to tell their story online and solicit a living donor. This raises ethical, legal and psychological issues. Could this promote illegal trade in organs? Is it ethically justified to allocate organs in this way? Is it justifiable to limit patient autonomy and restrict this practice? [6, 7]. For this reason the second plenary debate was held on social media and transplantation. Speakers were Greg Moorlock (UK) and Emma Massey (The Netherlands).

Another timely topic that was discussed in the next plenary debate was heart donation after cardiac death: contradictio in terminis? In transplantation medicine, although we have become accustomed to regarding the absence of brain activity as the definition of death, nowadays the absence of heart

beat is considered an argument for an irreversible status leading to death. Therefore non-heart beating individuals are used as organ donors, and controversially even for heart transplant [8, 9]. So while the absence of the function of an organ is taken as a sign of death, the same non-functioning organ can be successfully transplanted into another individual. This might indeed feel like a contradiction in terms and raises questions on how to rhyme this with the dead donor rule [10]. Speakers were Stephen Large (UK) and Michael Nair-Collins (USA).

Finally, the desire to have children, to raise a family and continue the genetic blood line is universal and evolutionarily determined. For some, this is unfortunately a biological impossibility. In the final plenary debate we examined uterus transplantation [11, 12] and the worldwide trade in gametes from the perspective of whether it is a necessity or indulgence. Speakers were Niclas Kvarnström, Inez de Beaufort and Guido Pennings. Other 'global challenges' addressed in focus sessions and workshops included medication non-adherence, inequality in access to transplantation, ethical controversies in allocation of organs, engaging the general public in organ donation, psychosocial evaluation, support, education and informed consent of living donors, paired kidney exchange and anonymous living donation, organ trade and transplant tourism, paediatric donation and transplantation, and cultural and religious consideration in living and deceased donation.

Of course not all challenges are universal and context does matter. Laws, culture, and norms particular to each country or even regions determine the types of transplant that can be conducted, who can be a living donor, when someone can be considered to be a donor after death and how organs are retrieved and allocated after death. These nuances cannot be forgotten, but we can learn from them through exchange of experiences and development of ideas. And sharing solutions to global challenges can facilitate development of strategies to promote the best possible care for transplant recipients and donors.

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The role of ethics in the early history of transplantation

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Abstract

This article explores the early history of organ and tissue transplantation, in particular the period 1850 to 1940. In the pioneering years up to 1900, the focus was on grafting of animal tissues and cells, rather than on solid organs. Aim of these experiments was the attempt to rejuvenate the human organism. Transplantation of solid organs, especially the kidney, was taken up when around 1900 surgical techniques and skills in vascular anastomosis were developed. Animal experimentation, and also xenotransplantation in humans was undertaken, without clinical success, but adding to the understanding of the complexities of transplantation. In 1933, out of sight of the European medical community, pioneering work was undertaken by Ukrainian surgeon Voronoy, who performed the first successful kidney transplantations in humans. This article also focuses on the patients and donors who were involved, highlighting ethical aspects such as consent.

Introduction

In this article the early history of transplantation, from the 1850's to the 1930's, is explored, and in particular the role that animal and human experimentation have played in the emergence of transplant medicine, as well as evidence of ethical considerations concerning the recipients and donors of these early transplants. The work of a number of pioneers is described and the way humans and animals were involved in these experiments is highlighted.

The state of medicine around 1800

Up to the early 19th century the cause of illness in humans was commonly seen as a disturbance of the balance of essential bodily fluids (humours): blood, yellow bile, black bile and phlegm. This theory went back to Hippocrates and Galenus. Also the influence of the physical environment played a role (cold, heat, humidity). And although renaissance medical pioneers, e.g. Vesalius and Harvey, had started to explore and dissect the human body, the function of individual organs was largely unknown and seen as less important for the state of health than the holistic harmony of the body and the mind.

A new dawn in the development of medicine

Around 1850 there occurred a tremendous development in medicine, including new knowledge on virology, the role of bacteria and infections, and the development of antiseptic surgery. As a consequence, physicians are coming to see the human body as an interacting system of organs and tissues, each with specific functions. And this in turn had great influence on the development of surgical interventions and skills. The Viennese surgeon Theodor Billroth (1829-1894) stands out as a true pioneer of modern surgery and is commonly seen as the 'father of (abdominal) surgery'. He developed techniques for esophagectomy, laryngectomy and gastrectomy that are still relevant today. He worked in the Allgemeines Krankenhaus in Vienna, that was known as a centre of medical excellence and had many students all over Europe, which is, as will come out in this story, of decisive influence for the development of transplant medicine.

How the idea of transplantation originated

Although there have been early reports of clinical experiments in the field of autologous tissue transplantation in Indian history (Sushruta,1000 BC), and also in renaissance Europe (Tagliacozzi, 1557), the idea of transplanting human (and animal) body parts into patients did only arise in the middle of the 19th century, when medical knowledge and surgical skills made this feasible. There is evidence that an important source of inspiration to medicine has been Mary Shelley's Gothic novel 'Frankenstein, or, The modern Prometheus', published in 1818. This novel counts as the first example of science fiction, and is based on then popular vampire stories. The key story is about the creation by the weird scientist Frankenstein of a new perfect man (modern Prometheus) made up of body parts stolen from fresh corpses. However, when the new creature is not loved by society, he turns into a murdering monster. Making up this creature out of (fresh) human body parts, may be seen as an early example of allotransplantation [1].

The first clinical experiments in transplantation started towards the end of the 19th century and focused at first not on solid organs, but on cells and tissues. French neurologist Charles Édouard Brown-Séquard (1817-1894) developed an interest in the endocrine system, and started experiments around 1860. In an animal model he demonstrated that the adrenal function was essential for life; this led to the theory that injections with animal fluids (semen, testicular blood and gonadal extracts) could lead to rejuvenation and prolongation of human life. Brown-Séquard experimented on himself and at the age of 72 reported his findings to a scientific audience, saying that his injections enabled him to perform better physically and mentally (and even sexually!) Following this report, within a short time, several thousands of physicians all over Europe began to offer this 'therapy' to their elderly patients. These patients paid considerable sums of money, in fact being consenting human volunteers for a treatment that lacked robust evidence of efficacy.

From uncritical experiments to clinical application

Study into the function of endocrine tissue was further developed by the Swiss surgeon Emil Theodor Kocher (1841-1917). Kocher was a brilliant student of Billroth. During the years 1870-1885 he performed experiments with removal and implantation of thyroid tissue in order to treat thyroid deficiency (causing goiter and cretinism). His work contributed greatly to

the understanding of thyroid function, and led to the development of thyroid hormone replacement therapy. This earned him the Nobel Prize in Pathology and Surgery in 1909. Kocher did not make use of animal experiments, but his successful treatment of patients was based on careful clinical-pathological observation.

A milestone in modern surgery

The work on allo- and xenotransplantation using animal models was carried further by the Austrian surgeon Anton von Eiselsberg (1860-1939). Again, he was a student of Billroth in Vienna (who called him 'my best student').

Eiselsberg performed extensive animal experiments, transplanting pancreas, ovaries, testicles and adrenal gland. However, he saw no room for clinical application of the transplantation of endocrine tissue in man, and never performed any transplant experiment in a patient. After 1910 he switched his attention to neurosurgery and traumatology (following WWI experiences). Eiselsberg received honorary degrees from many European universities, including Athens, Budapest, Edinburgh, Leiden, Geneva, Paris and Vienna.

First clinical corneal transplant

Austrian-born ophtalmologist Eduard Zirm (1863-1944) got his medical education with Billroth in Vienna, and became chief of the new ophtalmology clinic that he helped to establish in Olomouc (Moravia) in 1892. He developed an interest in human corneal transplantation (keratoplasty), a procedure that had already been attempted with a disappointing measure of success since 1800, making use of both animal (rabbit) and human donor cornea. Zirm was in favor of using a full-thickness corneal graft, where others preferred partial-thickness grafts. In 1905, he was confronted with the patient Alois Glogar, a 45-year-old farm labourer, who had opaque corneas in both eyes, resulting from working with lime. At that same time, Zirm was trying to save the eyesight of an 11-year-old boy with penetrating trauma to both eyes, caused by metal particles. When the treatment proved unsuccessful, Zirm proposed to the father of the boy to have both eyes enucleated and use the intact corneas for transplantation into Alois Glogar. With the father's permission, both eyes were removed and the corneas transplanted. Complications affected the result in one eye, but the other graft survived, enabling Glogar to return to work [2]. Although Zirm at the time had no microscope and microsurgical instruments at his disposal, his technique became the basis for repairing corneal damage later on. He performed similar corneal operations in 1906, but without success. Zirm stated that corneas from animal species should not be used (although other attempts at human corneal transplantation did use xenografts, because tissue from a live donor was seen as essential). The success of this first corneal transplant was remarkable, in view of the fact that suitable surgical equipment for this operation was lacking, and infection control and antibiotics were not yet developed. The success is to be explained by the skill that Zirm developed doing numerous animal experiments, and the availability of a young live donor. In later years Zirm performed many successful corneal transplants using deceased donors. In fact, the 1905 corneal transplant was the first successful allotransplant in a human being of any organ. Zirm was also a gifted violin player and poetry writer.

Development of solid organ transplants

Around the beginning of the 20th century, medical interests (especially in surgeons) shifted from transplanting tissues and cells to solid organs. The outstanding pioneers at this time were Alexis Carrel in France and Hungarian-born Imre Ullmann in Vienna. Carrel devoted much of his early career to developing vascular surgical techniques, enabling blood vessel anastomosis and vascular reconstruction. Later on (after 1904) he became involved in organ transplantation, including renal transplantation. Working together with Charles Guthrie in Chicago, they performed numerous animal experiments, placing the kidney of a dog in different locations in the same animal, as well as transplants between different animal species. Gaining an understanding of biologic incompatibility, that made allotransplants in animals fail, Carrel and Guthrie did never perform transplants in humans, nor ever used human organs.

Imre Ullmann (1861-1937) was a student of Billroth in Vienna, and also worked with Pasteur in Paris (studying bacteriology and working on antisera against rabies (becoming himself a healthy subject to test the effectiveness of the sera). Being skilled in (vascular) surgery, Ullmann started out on a series of experiments with renal transplantation in animal models [3]. In 1902, he started with allogeneic kidney transplants in dogs, followed by implantation of a canine kidney in the neck of a goat. For five days this kidney functioned, producing a quantity of urine. Not yet able to perform vascular anastomosis, Ullmann used metal cylinders to join the kidney to the vessels in the neck. This successful experiment was published in 1902 in the renowned medical journal Wiener klinische Wochenschrift, and attracted wide interest [4]. Following this break-through, Ullmann next attempted to transplant a pig's kidney in a young women with serious uraemia. The graft however, was acutely rejected, and the patient died. After this failure, Ullmann terminated his experiments in transplantation for – in his words – ethical reasons. He also believed that – in his life time – the immunologic barriers could not be overcome.

The pioneering work of Ullmann was carried on by the German physician Ernst Unger, who received his medical training in Berlin, and there continued Ullmann's experiments in transplantation in 1909-10. Unger has performed around 100 kidney transplants in dogs, and between animal species (pig to dog, dog to goat, cat to dog) both auto- and allotransplants. Gaining confidence from these experiments, in 1909 he went a step further by transplanting the kidney of a still-born child in a monkey, followed in 1910 by the grafting of two monkey kidneys in a 21-year-old uraemic woman (who died on day 2). Finally he did an en-bloc transplantation of monkey kidneys in the thigh of a young woman (who died after 32 hours). This step towards xenotransplantation involving human patients was likely undertaken because in those years biologists had stressed the close relationship between monkeys and humans, making it seemingly feasible to overcome the immunologic incompatibility. After these pioneering transplants, Unger became involved in setting up a blood transfusion/donation service in Germany (1932). However, because of his jewish background, he was forced to give up his medical practice in 1936 and died in 1938 in a road accident.

Around the same time, in France, the gifted surgeon Mathieu Jaboulay (1860-1913), who was the teacher of Carrel in Lyon, developed surgical techniques for performing arterial anastomosis. In his first experiments he connected human kidneys to the arm of two uraemic patients, but there was

no visible function. Next, he implanted pig and goat kidneys in two other patients, which led to acute destruction of these kidneys (Jaboulay was the first to describe the process of acute rejection response in xenografts). He died in 1913, in a railway accident near the town of Melun. It is not reported if permission was asked from patients to perform these xeno-transplants.

Standstill during the inter-bellum years

The devastating effects of WWI had great influence on medical research in the years after 1918. German medical scientists were shunned from the international medical community and most renowned medical centres, such as Vienna and Berlin, were in ruins. French and British medical establishments were at that time more devoted to caring for the many wounded soldiers than with medical research and innovation, and the pre-WWI work in transplantation was not taken up again. The pioneering role in medicine was, for the time being, taken over by the United States.

During the 1920s, there was a short-lived interest in the grafting of sex glands, but serious work on renal transplantation had come to a standstill, and would not resume in Europe and the US until the 1950s.

The forgotten work of Yurii Voronoy

In the relative isolated political climate of Stalinist Russia, the Ukranian surgeon Yurii Voronoy (1895-1961) had already been doing research on blood transfusion, based on the new knowledge on blood-group differences, deriving from the work of Karl Landsteiner. In the late 1920s he performed testicle and kidney transplants in a dog model, and had observed the important role of complement as a host defence to destroy foreign cells [5]. He was also aware of the technique for vascular anastomosis developed by Jaboulay and Carrel. By 1930 he was able to perform successful heterotopic kidney transplants in dogs, placing the kidney in the neck. Then, on April 3, 1933, Voronoy did what turned out to be the first human allograft kidney transplantation, when he was confronted with a 26-year-old woman who had attempted suicide taking mercury chloride, and who developed acute renal failue as a consequence. In a rescue operation, Voronoy transplanted a kidney from a 60-year-old man, having died from head trauma, in the upper thigh of the patient, who was unconscious at the time. The exposed kidney was covered with skin grafts. Since the patient and donor had different blood types, a partial-exchange transfusion was also performed. After the transplant operation, the kidney showed function and started to execrete urine. However, on day two the condition of the patient deteriorated, the urine excretion stopped and the patient died in the evening.

After this first kidney transplant, Voronoy performed five more transplants using the same approach: grafting the kidney from a cadaveric (DCD) donor in a heterotopic position in the patient. From his report to the Ukranian Academy of Medical Sciences in Kiev in 1950, it becomes clear that he

did not attempt to finally cure the renal insufficiency of the patient by transplanting a kidney, but that he saw the transplant as a temporary 'bridging' intervention, until the native kidney of the patient started to function again. Voronoy in his report decribes two cases where the transplanted kidney was removed after the native kidneys of the patients had resumed functioning. Both patients were discharged from hospital after two months and survived.

Technique employée par Voronoy, pour la première greffe de rein humain (1933)

In the period following this first series of transplants, Voronoy's work was officially supported by the Soviet Medical establishment and his work was reviewed in an official journal in 1934., but later ignored. Voronoy however, published his pioneering work in a Spanish medical journal in 1936, but this received wider attention only in 1973 [6]. After WWII Voronoy resumed his transplants, using refrigerated cadaver kidneys from donors who had died nine to twenty day earlier. When none of these transplants succeeded, he abandoned this work and turned his attention and research to traumatology.

Discussion and conclusions

From this short overview of early attempts at organ transplantation, leading up to – what is now known to be – the first successful kidney transplant by Voronoy in 1933, a number of observations and conclusions can be derived.

1) In the period 1850-1870 the first pioneering attempts at transplantation are performed using animal tissues and cells. Experiments are done in animal models using both an autologous and allograft (xenotransplant) approach. The main aim of these experiments is to explore to possibility of using animal tissues and cells in humans for rejuvenation (restoring the physical, mental and sexual function). Although there is no scientific evidence-base to bolster up this approach, this 'therapy' is given to (healthy) volunteers, who give their consent and often have to pay considerable sums to undergo the treatment. Some of the pioneers test the procedure on themselves (Brown-Séquard).

2) The second period, 1870-1910, is characterized by both a better scientific understanding of the function of human organs in general, and the development of surgical skills to enable explantation and grafting of organs, and vascular anastomosis. Clinical transplantation in humans is performed with endocrine tissue (e.g. thyroid tissue); in animal models also kidney transplants are explored. This period also sees the first successful clinical corneal transplant, using corneal tissue from a live donor. Consent for this procedure in a minor was asked from and given by the parent. Several clinical experiments were also done (by Ullmann, Unger, and Jaboulay) with implanting animal organs in human patients (xenotransplants), all of which failed. Due to the lack of knowledge concerning immunological response/rejection, ABO blood-group incompatibilities, and immunosuppressive treatment, clinical transplantation remains a trial and error approach. Because of this, these transplants involving humans are abandoned. There is almost no information on the issue of (informed) consent for these experimental procedures from the patients: in almost all cases the xenotransplant is performed as a last resort (rescue operation) in an unconscious patient, where permission is given by the relatives.

3) The third period, 1910-1940, sees a lot of focused activities: development of surgical technique, anastomosis, animal experimentation, and xenotransplants in the years up to WWI. But during

the war and in the inter-bellum years, medical research and clinical efforts on transplantation in the former centres of excellence in Germany and France came to a stand-still. However, a breakthrough development in clinical renal transplantation, making use of cadaveric donors, took place in Ukraine, part of the inaccessible Soviet Union. These transplants were performed in patients with acute renal failure, with the aim of bridging the period of renal insufficiency until the native kidneys regained their function. Patients were mostly unconscious at the time of operation and no details about consent are known.

These developments have all contributed to the final pioneering work that was done between 1947 and 1954 in Boston (USA) and Paris (France), leading up to the successful kidney transplants by Murray and co-workers in December 1954.

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1.
Ethical, Legal and Cultural Aspects

Summary of Workshop 2: 'Common problems and national approaches to death and deceased donation'

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National transplant systems – their legal and organizational frameworks and their specific 'cultures' – feature different strengths, weaknesses, blind spots and even 'taboos'. Many of the problems we face at home have found acceptable or even convincing solutions abroad. There are best practices and less convincing ones. The workshop, moderated by *Medard Hilhorst* (Netherlands) and *Thomas Gutmann* (Germany) served as one step in a learning process on the European level which ELPAT and ESOT are aiming at: 'Why exactly don't we discuss what others are discussing? Why exactly don't we learn from the reasonable and successful policies and practices of our neighbours? What are the main obstacles (legal rules, practices, habits) for an efficient and justifiable deceased donation policy in our countries?' The list of topics comprised legal definitions of death, practices in the determination of death, the dead donor rule, legal frameworks for deceased organ donation, organisational models of the organ transplantation system, legal and practical rules concerning the 'moment of asking' the relatives, rules and practices concerning ante mortem preparatory measures, and the question as to how far organ donation is perceived as an integral part of end-of-life-care and of patient autonomy at the end of life.

Five invited speakers presented some preliminary results from an ELPAT research project dealing with these issues, complemented by two abstract speakers. *Tanja Krones* (Switzerland) sketched 'The Swiss approach' to the topics mentioned above, focusing on experiences with controlled donation after circulatory determination of death (cDCD), on the brain death criterion in DBD and on some blind spots in the Swiss discussion. She demonstrated that the Swiss transplant system, which – at least in its legal dimension – might still be called the European gold standard – faces some serious issues, e.g. in its dealing with donation by and transplantation of mature newborns, and the respective procedures for brain death diagnosis. In their talk on 'The Spanish approach', *Pablo de Lora* and *Alicia Pérez Blanco* (Spain) focused on pressing questions relating to controlled donation after circulatory determination of death (cDCD) and presented the results of a study on the Spanish public's attitude about disregarding the dead donor rule in cDCD. *Antonia Cronin* (United Kingdom) gave an overview on 'The United Kingdom approach' to the definition of death (including English case law and evolving medical approaches) and on the current dynamics in deceased organ donation in the UK, focusing on the field of DCD and on the increasing number of organs from higher risk donors which are being used for transplants. *Thomas Gutmann* (Germany) asked what went wrong with 'The German approach' after actual deceased organ donor rates in Germany hitted rock bottom with constant 10 ppm. He pointed at institutional factors, including the fact that the main actor in the German organ transplantation system is not a public body but a network of private stakeholders, at a lack of political and legal oversight, a lack of learning and steering potential in

the system and a culture of distrust. *Marco Vergano* (Italy) presented 'The Italian Approach' (see the article in this volume), showing that the legal and practical definition of clear pathways for end-of-life decision making and the shortening of the hands-off period for the declaration of cardiac death (which currently is 20 minutes) could be the basis for a successful implementation of nationwide DCD programmes in Italy.

The workshop was completed by two complementary short presentations, the first by Elvira Santiago (Spain) on 'Abandoning the dead donor rule: insights from an exploratory survey in Spain', the second by *Anne Dalle Ave* (Switzerland) on 'The use of the brain death criterion in organ donation after the circulatory determination of death'.

Common problems and national approaches to death and deceased donation: the Italian approach

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Abbreviations

CNT	National Transplant Centre
cDCD	controlled Donation after Cardiac Death
DBD	Donation after Brain Death
DCD	Donation after Cardiac Death
DDR	Dead Donor Rule
ECLS	Extracorporeal Life Support
ECMO	Extracorporeal Membrane Oxygenation
EoLC	End-of-Life Care
ICU	Intensive Care Unit
nRP	normothermic Regional Perfusion
uDCD	uncontrolled Donation after Cardiac Death
WIT	Warm Ischemia Time
WLST	Withdrawal of Life-Sustaining Treatments

Abstract

Italy is among the first European countries in terms of number of deceased donors. However, the striking majority of donated organs comes from donations after brain death, and experience with donation after cardiac death (DCD) is still limited to few institutions. Implementation of a comprehensive approach to organ donation for the patients dying in the ICU has been advocated both globally and nationally. The lack of an open debate about end-of-life care issues, together with the absence of exhaustive legislation about end-of-life decision making, may be responsible for the high variability in the practice of withdrawal of life-sustaining treatments among the Italian intensive care units. Also, the long (20 minutes) hands-off period required for the declaration of cardiac death may unreasonably prolong the warm ischemia time during DCD, and compromise the viability of retrieved organs. The definition of clear pathways for end-of-life decision making and the shortening of the hands-off period for the declaration of cardiac death could be the basis for a successful implementation of nationwide DCD programmes in Italy.

Keywords: DCD, end-of-life care, WLST, declaration of death, DDR

Organ donation in Italy

The Italian Transplant Coordination Network is currently organized at three different levels, represented by local hospitals, regional networks and a National Transplant Centre (CNT). The CNT coordinates all activities concerning donation, allocation and transplantation of organs, together with fixing parameters for transplant quality assessment and promoting information campaigns for the general public. On a local basis, hospital procurement coordinators (mainly anesthetists or critical care physicians), supported by specially trained nurses, are in charge of the donation process. In 2013, Italy was the third European country in terms of absolute numbers of deceased donors (n = 1,323) and the ninth country in terms of deceased donors per million population (pmp, n = 21.7) [1]. In 2014, a slight increase in both absolute (n = 1,384) and relative (22.7 ppm) numbers of deceased donors was recorded [2]. Still, a 30.6 percent family refusal rate for donation was reported with significant regional differences, the higher refusal rates being observed in Southern Italy [3]. Excluding transplants from living donors, virtually all the transplanted organs came from donations after brain death (DBD) [4]. Only two donations after cardiac death (DCD) were reported, leading to a single double-lung transplant [5].

At present, the number of donations after brain death is still greatly outweighed by the number of patients on a waiting list [3]. Donations after cardiac death can potentially increase the number of organs available for transplantion, and implementation of DCD protocols in the Intensive Care Unit (ICU) has been advocated [1].

According to the Maastricht classification [6], revised in 2013 [7], uncontrolled DCD (uDCD) follows an unexpected cardiac arrest, and death is confirmed using circulatory criteria after resuscitation efforts have proved ineffective. In Italy, a single institutional protocol for uDCD has been implemented since 2007 [8], and new Extracorporeal Life Support (ECLS) centres are being established [5], potentially leading to an increase in the number of uDCD in the next future. However, experience is still scarce and confined to a few institutions.

Experience with controlled DCD (cDCD), which occurs after the planned withdrawal of life-sustaining treatments (WLST), is even more limited. The lack of an open debate about end-of-life pathways and the legal requirement of a 20-minute hands-off period for the declaration of cardiac death are the two major problems currently hindering the nationwide implementation of successful DCD programmes in Italy.

End-of-life care issues

Multiple guidelines on End of Life Care (EoLC) and WLST in the Intensive Care Unit (ICU) have been released [9-11], and international consensus on key issues of EoLC in the ICU has been gathered to provide a worldwide standard of practice [12]. In Italy, national guidelines on EoLC and WLST have been issued more than a decade ago [13, 14], but a specific legal framework for end-of-life decision making and medical advance directives is still lacking. In the absence of exhaustive legislation, low agreement rates on EoLC practices have been reported among Italian doctors [15].

Also, although palliative care is now recognized as a key component of critical care medicine [16], high variability in EoLC and WLST practices has been observed globally [17] and among the Italian ICUs. In a prospective observational study on 84 ICUs, treatment limitations anticipated 62 percent of deaths [18]. However, nearly half of the limitations (45%) consisted in a do-not-resuscitate order; 25 percent of patients underwent withholding of a life-sustaining measure and 27 percent under-

went active WLST. Terminal weaning of mechanical ventilation with or without terminal extubation was performed in a minority of cases. Interestingly, ICUs less prone to limit treatments (odds ratio < 0.77) exhibited higher overall standardized mortality ratios (1.08; 95% confidence interval: 1.04-1.12). Accordingly, limitation of treatments does not appear to be against the patient's best interest, and may indicate a better quality of care in the ICU.

Implementation of institutional protocols on EoLC and WLST could help the prevention and management of distressing symptoms during WLST, particularly when discontinuation of mechanical ventilation is performed [16, 19]. Also, open communication among healthcare team members, patients and patients' families is an essential feature of any EoLC pathway [10, 11], as improved communication can significantly reduce the psychological morbidity in family members after a death in the ICU [20]. In parallel, an intensive communication strategy has proved successful in reducing the burden of stress on the healthcare staff [21]. This included unrestricted visiting hours, dedicated time and space for daily meetings between families and caregivers, availability of a staff psychologist for consultation and continuing medical education training in end-of-life ethics.

These considerations apply even more strikingly to controlled DCD scenarios, where complex ethical, legal, psychological and clinical issues may intertwine.

Ethical and legal implications of the hands-off period

Documentation of the complete cessation of cardiac electrical activity through a 20-minute electrocardiographic monitoring is currently required in Italy for the declaration of cardiac death [22]. This legal obligation imposes a long (20-minute) hands-off period between the loss of cardiac function and the declaration of death, which has no parallel in other Western countries [23]. Although this time interval does not have a clear scientific basis, it ensures that an irreversible ischemic brain damage has occured after such period of no-flow, and that the dead donor rule (DDR) is fully respected. However, in the context of DCD, this long hands-off period may unnecessarily prolong the warm ischemia time (WIT), and potentially compromise the organ viability.

A shortening of the 20-minute hands-off period has recently been advocated [22, 23], and the ethical meaning of the dead donor rule has been questioned in the context of heart donation after circulatory death [24, 25]. According to several observational studies, autoresuscitation (defined as the spontaneous, unassisted return of effective circulation), is not possible after a time interval between two and five minutes since the last heartbeat [26-28]. As such, without external interventions, the process of dying will progress towards an irreversible ischemic organ damage. While most Western countries rely on circulatory criteria (i.e., loss of cardiac mechanical function) for the declaration of cardiac death, waiting for the complete cessation of cardiac electrical activity (as is the case in Italy) necessarily places the declaration of death at a much more advanced time in the dying process.

By significantly prolonging the WIT, the long hands-off period could hamper the successful transplantation of retrieved organs. Under a moral perspective, this could impede the full completion of the donor's wish to donate vital organs. At the same time, when a vital organ is offered to a recipient, the patient's right to receive the best possible organ should be warranted [23]. The use of normothermic Regional Perfusion (nRP) via extracorporeal membrane oxygenation (ECMO), together with ex-vivo organ perfusion, can partially overcome these issues, and successful organ transplants (almost exclusively from uDCD) have been reported despite a prolonged hands-off period [5, 8]. Still, organizational and economic concerns are currently limiting the availability of these techniques.

Adoption of new, circulatory-based criteria for the declaration of cardiac death, with a shortening of the hands-off period from 20 to 5 minutes (as in most European countries) could potentially increase the number of DCDs in Italy. Provided that the donor is always considered as an end in itself, and not merely as a means, any action that is directed at improving the outcomes of transplanted organs could be considered as a moral obligation aiming to promote the donor's dignity and final wishes [22, 29].

Conclusions

Together, the implementation of current recommendations on EoLC and WLST, the adoption of intensive communication strategies in the ICU and the revision of current requirements on declaration of cardiac death could successfully increase the number of controlled (and uncontrolled) DCDs in Italy in the next future. A formal, open debate on key ethical and legal issues of end-of-life care is necessary to provide a common framework for WLST practice and ensure that the individual's wishes are fully respected.

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