Transplant International

REVIEW

Regulatory aspects of VCA in Eurotransplant

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SUMMARY

Vascularized composite allografts (VCAs) are a growing field within the area of transplantation. In 2014, the birth of a healthy baby after a successful uterus transplant from a living donor was reported in Sweden. VCAs are not specifically mentioned in any of the transplant acts of the Eurotransplant (ET) member states, which all belong to the European Union (EU). The Competent Authorities (CA) of the EU decided in 2012 that VCAs are to be regarded as organs. At the moment, there are no general guidelines in the ET area concerning wait list registration, allocation, procurement and transplantation, and also no regulations concerning reimbursement. To further develop this aspect, common policies and guidelines within the ET member states have to be developed.

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Introduction

Since the earliest times, the medical community has been looking for possibilities to replace important parts of the body. Arms and legs as well as parts of the skin were necessary for a normal life, and thus for being a respected part of society.

One very well-known replacement of a limb is described in the legend of the saints Cosmas and Damian. The twin brothers from Syria, who lived in the late 3rd century A.D. and died as martyrs in 303 A.D. in Turkey are said to have performed a restoration of a lower leg of a white merchant by a wondrous transplantation of the lower leg from a shortly deceased Moor (Fig. 1).

For the transplant community, this transplantation has always been a symbol for two aspects: the successful replacement of an important part of the body—even though not being regarded as an organ, and secondly full graft tolerance.

During World War II, there were attempts to transplant skin and composite tissue to badly burned pilots and sailors from U-boot attacks. Biologist Peter Medawar, together with plastic surgeon colleagues, started pioneering experiments for "composite tissue allografts" in Glasgow, where these soldiers were treated [1,2]. Rejection was still a major problem, immunosuppression no standard.

In 1954, Joseph E. Murray, John P. Merrill, and J. Hartwell Harrison performed in Boston the first successful human kidney transplantation between two identical twin brothers. As there was no adequate immunosuppression at this time, success was enabled by the identical human leukocyte antigen (HLA) and blood group [3,4].

The first successful human VCA three years later was the transplantation of an *en bloc* digital flexor tendon, conducted by Erle E. Peacock in 1957 in North Carolina in the absence of immunosuppression. This transplantation has nearly been forgotten, but it is a milestone in the era of transplantation. Peacock was the first who

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Figure 1 Regulatory aspects of VCA. A verger's dream: Saints Cosmas and Damian performing a miraculous cure by transplantation of a leg. Oil painting attributed to the Master of Los Balbases, ca. 1495 (http://www.wdl.org/en/item/3251/).

Table 1. Most common VCA and organs.

VCA (most common)*	Organs*
Hand	Heart
Arm	Lung*
Leg	Liver*
Face	Kidney*
Abdominal Wall	Pancreas
Uterus*	Small bowel
Trachea	
Penis	
Tendons	

*also living donation.

used the term "composite tissue allograft," to differentiate the complex nature of this kind of graft from solid organ transplantation [5].

It was not until 41 years later that the first successful (in terms of long-term graft survival) hand VCA transplant was performed by the team of Jean-Michel Dubernard in Lyon, France, in September 1998 [6]. The first bilateral hand transplant followed in January 2000 by the same team. [7]. It took five more years until another VCA was successfully transplanted—a face transplant was performed in France [8]. More VCA followed, larynx, trachea, abdominal wall, and uterus and in 2015, one successful penis transplantation in South Africa was reported [9] (Table 1). In 2014, the first baby from a successful uterus transplant (living donation) was born in Sweden, as reported by Mats Braennstroem [10].

Since the very beginning, more than 100 different VCA transplantations all over the world have been executed [11]. With many disabled soldiers from Iraq and Afghanistan—to name one special group of recipients—the need for this kind of transplantation is growing [12].

Eurotransplant and VCA

Eurotransplant International is a nonprofit organization, which is responsible for the allocation of deceased donor organs in eight different European countries, according to the respective national transplant laws, rules, and guidelines. This international collaborative framework includes not only the transplant centers in Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Slovenia, and the Netherlands, but also the respective tissue-typing laboratories, as well as the hospitals where organ donation takes place. Since 1967, more than 200.000 organ transplants from over 85.000 donors (deceased and living) have been performed in the Eurotransplant region [13].

The first documented and successful VCA in the ET area was a double hand transplant in March 2000 in Innsbruck, Austria, followed in January 2002 by a single hand transplant in Brussels, Belgium. In July 2008, the worldwide first double arm transplant in Munich, Germany, was reported, and a whole face transplant was performed in December 2011 in Ghent, Belgium.

Candidate organ recipients of the ET member states have to be listed on the national waiting list. When it comes to a VCA transplant candidates for a trachea transplantation were listed at ET a few years ago (2007), although ET was not involved in allocation. Wait list management, the selection of a suitable donor, and follow-up of VCA recipients are so far carried out according to the protocols of the respective transplant center, without involvement of ET.

Legal aspects within ET member states concerning European law

V*ascularized composite allografts* were initially classified as complex tissues. The member states of ET are European states, and therefore, the legal basis for all laws, guidelines, and regulations is the EU and her legal framework composed in the "Treaties of the European Union," originally signed in 1958, which describes the

consolidated treaties and documents forming the constitutional basis of the EU. In these documents, the "Treaty of the Functioning of the EU" in article 168, 4. (a), it is specified that the EU member states shall adopt measures to set "high standards of quality and safety of organs and substances of human origin,…". [14] High standard implies that there has to be a legal framework of rules that can be measured and audited.

In the *European Union tissue and cell directive* from 2004 (Directive 2004/23/EU), organs were defined as "a differentiated and vital part of the human body, formed by different tissues, that maintains its structure, vascularization, and capacity to develop physiological functions with an important level of autonomy" [15]. The definition of an organ as being a "vital part" of the body led initially to the conclusion by the national CA of the EU member states that VCAs are not included in this definition and should therefore be regarded as tissue. Tissues, on the other hand, fall under the regulation of the respective CA for tissues and drugs, and therefore, different standards concerning procurement, storage, use, and quality would have to be applied to VCA transplantation that would have made it impossible to further develop transplant programs and expertise. Furthermore, a transplant surgeon alone would not have been able to fulfill all the requirements that have to be adhered to when it comes to tissue procurement, processing, and transplantation [16].

In 2010, an updated *Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation* was released, in which the definition of an organ was modified in a slight but considerable way. The word "vital" from the former definition was removed due to the fact, that kidney and pancreas transplantation, both being organs, were not definitely covered by the "old" definition of an organ being a *vital* part of the body [17].

With this background, the national *CA on organ transplantation* and the *CA on tissue and cells* took the decision in September and December 2012 that *vascularized composite tissues* should be regarded as organs in every respect of the EU directive [18]. Consequently, the ET Board of Management decided in the same year to include VCA in the basic mandate of ET.

In another European state, France, an explicit equalization of VCA (greffe composites de tissus vascularisés) and organs was already introduced in the year 2004.

The VCA development was not only a European one. In July 2014, the National Organ Transplant Act (NOTA) in the United States (US) was adapted in such a way that the US Department of Health and Human Services recognized VCA per decree as organs [19]. The definition of a VCA was carried out in a general and abstract way, consisting of 9 criteria (Table 2):

As already mentioned, there are no strict definitions for VCA in the ET member state laws. The definition of an "organ" varies from a very general definition such as "part of the human body, excluding blood and reproductive cells" (the Netherlands) [20] to a more complex one such as "parts of the human body, composed of different tissues, which form a functional unit with regard to structure, blood supply, and ability to perform physiological function" (Germany) [21]. An overview is shown in Table 3. VCAs are not explicitly mentioned.

In one of the ET member states—Germany—with the renewal of the transplant act in 2012, there were already concerns that the transplantation of VCA might be compromised, if VCA would be regarded as tissue

Table 2. OPTN Policy 1.2: Definition of Vascularized Composite Allografts.

1.	Vascularized and requires blood flow by surgical connection of blood vessels to function after transplantation
2.	Containing multiple tissue types
3.	Recovered from a human donor as an anatomical/structural unit
4.	Transplanted into a human recipient as an anatomical/structural unit
5.	Minimally manipulated (i.e., processing that does not alter the original relevant characteristics of the organ relating to the organ's utility for reconstruction, repair, or replacement—examples of minimal manipulation include cutting, grinding, and shaping of VCA)
6.	For homologous use (i.e., the replacement or supplementation of a recipient's organ with an organ that performs the same basic function or functions in the recipient as in the donor, e.g., a hand from the donor is to be used as a hand in the recipient)
7.	Not combined with another article such as a device
8.	Susceptible to ischemia and, therefore, only stored temporarily (e.g., cold storage in preservation medium and intended for implantation in a recipient within hours of the recovery) and not cryopreserved
9.	Susceptible to allograft rejection, generally requiring immunosuppression that may increase infectious disease risk to the recipient

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Table 3. Organ definition transplant law ET member states.

ET member state	VCA	Definition of Organ
Austria	No	A differentiated part of the human body, consists of various tissues, which keeps through its structure and vascularization the competence to fulfill autonomous physiological functions
Belgium	No	A differentiated part of the human body, composed of various tissues, which keeps through its structure the competence to fulfill autonomous physiological functions
Croatia	No	A differentiated part of the human body, formed by different tissues, that maintains its structure, vascularisation, and capacity to develop physiological functions with a significant level of autonomy
Germany	No	Parts of the human body (excluding skin), composed of different tissues, which form a functional unit with regard to structure, blood supply, and ability for perform physiological functions
Hungary	No	Any part of the human body, composed of tissues of specialized structure, which, if removed entirely, cannot be renewed by the body
Luxemburg	No	Substances of human origin
the Netherlands	No	Part of the human body, excluding blood and reproductive cells
Slovenia	No	Body parts (organs and tissues), living donor: only restorable tissue, but also kidney and liver

[22]. Medical lawyer and law philosopher Thomas Gutmann discussed these concerns in 2014, namely that the existing definition of organs in the EU-directive 2010/53/EU and in the German Transplantation Act, summarized all aspects that are valid for both organs and VCA, and therefore, *de lege lata* there is legally no need to change the German Transplantation Act and mention VCA explicitly [23].

Regulatory aspects on wait list registration and donor consent in Eurotransplant

A patient in an ET member state, who is in need of an organ, has to be put on the waiting list of the respective ET member state. This is laid down in the different transplant acts as well as in the contracts that ET has concluded with the member states. As it is one of the main goals of ET to find the best suitable recipient for an organ, it is also necessary for ET to have all data that are needed for the allocation. But this implies that not only the data of the possible recipient are needed, but also all data of the donor. When it concerns a "traditional" organ allocation, these data include besides blood group and HLA also "external" aspects such as height and weight. For a VCA allocation, the same data are necessary. Furthermore special data have to be provided such as skin color, limb measurement, CT scans, and angiograms for bone and vessel architecture and morphometric information [24].

Evaluation of the donor has to be even more in-depth, because VCA transplantation is not a lifesaving procedure. This implies a careful examination of the donor for evidence of transmittable diseases, taking the Directive 2010/53/EU into account. Center specific protocols act at the moment as basis, but for the future, a common protocol within ET and Europe has to be agreed upon, to also facilitate cross-border organ exchange. A first step in this direction is FOEDUS (Facilitating exchange of organs donated in EU member states) [25], where common guidelines according to the Directive 2010/53/EU are developed.

Regarding the recipient, the transplant center has to evaluate every potential recipient very thoroughly. In particular, a physiological assessment is needed. Bearing in mind that a transplanted hand, arm, or face are not inside the body, but visible, the recipient must be able to judge and accept the impact, this transplantation entails for him and his family. Furthermore, as already mentioned, a VCA transplantation is not a lifesaving procedure. The consequences of the procedure are not only the regained functionality and visible improvement of the outer appearance. The patient has to follow a strict regime of regular follow-ups and a constant immunosuppressive medication, which can involve other organs (e.g., kidney) or even cause cancer. Thus, the recipient must be physiological stable and able and willing to support the necessary protocol [26].

VCAs are usually from postmortem donation (exception uterus allograft from living donor). Knowledge about this kind of donation is to date not wide spread in the population, as it is not a common transplant. The lack of knowledge might be an obstacle, as it could result in hesitation to give consent. There are limitations in living VCA donation, as only a uterus can be donated so far. All other VCA would "harm" the living donor (e.g., limb, face).

In the ET region, there are member states with a presumed consent for organ donation such as Belgium, Austria, Croatia, and Luxembourg [27,28,29,30]. There are countries with informed consent such as Germany (decision solution), the Netherlands, Slovenia, and Hungary [20,21,31,32]. In none of these countries is VCA so far a topic in transplantation acts. As mentioned above, VCAs includes all characteristics of an organ. No transplant act names the different organs explicitly, so it can be stated that there is also no need to mention VCA. As it is not a special topic in organ donation campaigns including donor cards, the general public may not be aware of the possibility of this special donation and a transplant coordinator cannot hence assume that if the deceased person did not object to organ or tissue donation, he or she would also be willing to donate VCA.

In countries with an informed consent or a decision solution in contrary to the countries with presumed consent in most cases, the will of the deceased person is unknown to the relatives. Surveys showed that only in about 35% of the population (depending of the member state) is the decision concerning organ donation known. The consent seeking person is faced with the situation to ask also for a VCA donation, thereby facing the risk of withdrawal of consent for complete organ donation. Furthermore, VCA transplantation is not a lifesaving procedure, thus making it more difficult to explain the positive aspect of VCA donation. The donation also has an impact on the "appearance" of the donor, which has to be explained. Every VCA donor gets the respective artificial limb, before the abdominal and thoracic organs are procured, and also the face has to be restored [26]. This has to be prepared in advance and must be communicated to the relatives in all countries, presumed or informed consent or decision solution.

A study in the United Kingdom showed a greater willingness to donate VCA if the donation was intended to help someone, who lost their limb or face in service of the country. If a soldier with combat trauma were to be the recipient, then people were more often willing to donate. The study has a certain bias concerning the "study cohort" and has an implication that the nature of the recipient was "revealed" [33]. This can put ethical or moral pressure on the decision-maker, which is not allowed in the ET member states.

On the other hand, if there are no patients on the waiting list for a VCA, there is no need to ask for consent. This implies that organ procurement organizations (OPO) should be regularly informed about the waiting list via the respective transplant center. As this can be performed in an anonymous way, there should be no conflict with regard to the privacy policy of the respective country.

At the moment, ET is not involved in organ allocation from living donors, as this is not in the basic mandate of ET. This has to be adapted and agreed upon in the different agreements with the member states of ET.

Legal aspects concerning allocation, transplantation, and follow-up

General

Within ET, approved allocation guidelines are basically the same for all member states, with special regard to urgency (high urgent patients at the top of the waiting list). At the moment, no waiting list exists in the ET area for VCA recipients.

ET is so far not involved in "allocation" of a hand, an arm, or a face. This takes place at the level of the OPO and the transplant center and is based on trusting communication. However, this also makes it difficult to learn from the outcome of these transplantations. ET does not know any details about recipient and donor, at least concerning the VCA specific parameter. The outcome of the recipient and the follow-up is also not known at the moment. The legal framework must ensure that there is a mandatory follow-up registry for these recipients.

In the United States, the *International Registry on Hand and Composite Tissue Transplantation* (IRHCTT) was founded in May 2002, now with 18 voluntary participating centers all over the world. All the centers report once a year to IRHCTT the follow-up of their recipients [34].

A mandatory registry for VCA transplants has to be part of a common future guideline on VCA in ET. A national and international exchange of these data is one important asset that ET can offer as a service to all its member states.

Aspects of VCA concerning reimbursement

At the moment, not all ET countries have already carried out VCA transplantations, only Austria, Belgium, and Germany have. Therefore, reimbursement is not regulated.

In Austria, all costs are covered by the insurance of the recipient. In Belgium, the costs for the first face transplant were fully covered by the transplant hospital.

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In Germany, the status of a VCA has not yet been officially discussed in the group of financiers. A possible reimbursement modus could be financing via a so-called fee for new diagnostics and therapies, which the hospital has to request from the insurers. At the moment, it is a case-to-case decision, financed via the insurance of the recipient.

In Croatia, one request has been discussed so far, the Ministry of Health has given permission to perform this kind of transplant, but it was not carried out. Here, the insurance of the recipient would have covered all the costs.

In Slovenia, a thorough discussion of the costs would take place between the Ministry of Health, the transplant center, and Slovenia Transplant. The reimbursement for the recipient would be taken over by the recipients' insurance. The procurement costs are covered by the governmental budget, which is negotiated yearly between the Ministry and Slovenia Transplant.

In the Netherlands, Hungary, and Luxemburg, no discussion about VCA and financing have been taken place so far.

In Spain, VCAs is considered to be an experimental procedure, which has to be authorized by the Transplant Committee of the Inter-Territorial National Health Council. The reimbursement is settled via the regional health care budget of the hospital.

In France, reimbursement is via a lump sum. The responsible organization—Agence de la Biomedicine—negotiates all lump sums concerning organ and tissue donation on a 2-year basis with the insurers [35].

In the UK, a new policy concerning VCA has been developed by the National Health Service (NHS) in July 2015 ("hand and upper limb reconstruction using vascularized composite allografts") on basis of strict protocols. NHS has funding responsibility for all with NHS insured patients, also for new treatment modalities such as VCA. For the following five years, reimbursement for up to four recipients per year is granted [36].

Development of VCA guidelines within ET

As already mentioned earlier, at the moment, there are no general guidelines or recommendations in the ET member states. In the transplant centers, where VCA transplantation has already taken place, center-specific protocols step in for the guidelines.

The process of developing a new guideline involves experts from every ET member state, is based on latest scientific finding, and has to be approved by all ET member states. Based on the experiences not only from Austria, Belgium, and Germany, but from the centers who contribute to IRHCTT, an ET-wide recommendation concerning wait list registration, necessary data for allocation, procurement, transplantation, and follow-up (allocation development) has to be developed in the coming years.

Every transplant center has to be licensed to execute VCA transplantation and follow-up, this is according to the standard of "normal" organ transplantation and is laid down in the respective transplant acts.

The procurement itself must be performed by a trained team that knows about the specific situation of the recipient. This will be one of the key factors for a successful transplantation. In this regard, guidelines for the VCA procurement teams have to include rules for cooperation with other traditional organ procurement teams and the procurement hospital. A strong cooperation with the transplant societies in the ET member states is necessary, as ET is not responsible for procurement.

Within ET, there are countries with a high number of procurement hospitals (Germany 1326 hospitals 2014) [37]. This number shows clearly that not every hospital is experienced in organ donation and that there is a need for standard operation procedures. The transplant centers within ET, that already perform VCA transplantation, have these standard operating procedures already in place. They can be used for national guidelines.

Concerning the specific VCA (e.g., skin color, limb measurement) donor and recipient profiles in the ET data base have to be adapted. On the other hand, these specific data should not be mandatory if there is no suitable VCA recipient. The special topic in that case is "data austerity," which is an important aspect in many EU data privacy laws, in contrast to the "get it all" policy for example in the US.

Another important allocation factor is cold ischemia time (CIT). That closely corresponds to transportation time (eight ET member states) and the question is whether VCA should always be allocated first local, then regional, then national, and then international. At the moment, there are very limited data concerning ischemia–reperfusion injury. In hand transplantation, there are data for a CIT between 2.5 and 13 h, but no threshold has been defined so far. The role of machine perfusion is at the moment unclear [38]. But with further development in this direction, the allocation scheme might change from a regional to an international one.

Conclusions

Vascularized composite allografts are not yet a general procedure, but an emerging field within the Eurotransplant area. In the eight different transplant acts of the ET member states, VCA are not explicitly mentioned. As the member states are a part of the EU, they must adhere to the EU directives. According to the EU-directive 2010/53/EU, the national *CA on organ transplantation* and the national *CA on tissue and cells* decided in 2012 that VCA have to be considered to be organs.

The first successful reports on transplantation of hands, arms, and face were reported in the last few years. Up-to-date, around 100 VCA transplantations have taken place. The outcome of the recipients is vital for the development of allocation rules and guidelines which are the legal backbone of any transplantation.

Possible recipients for a VCA transplantation have to be registered on the national waiting list at Eurotransplant. Clear rules and guidelines are the basis for an allocation of VCA based on the state of medical science. Procurement must be executed by a skilled team, according to national guidelines for procurement and transplantation of VCA, which still have to be developed.

Rules and guidelines according to state of science need data which have to come from the follow-up of the recipients of VCA. The follow-up must be mandatory in all ET member states, and a regular exchange of data between the national and ET-registry (international) should be made possible to further develop allocation procedures. A modification of an allocation scheme should always be grounded on solid data of the recipients, together with data from scientific studies.

With the birth of a baby from a transplanted uterus, VCA transplantation has stepped into another phase and we all should be more than willing to prepare the legal basis for a successful future. Eurotransplant together with experts in all ET member states is preparing for the future.

Conflicts of interest

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