Ten-year experience with cryopreserved vascular allografts in the Croatian Cardiovascular Tissue Bank

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Abstract The Croatian Cardiovascular Tissue Bank (CTB) was established in June 2011. Activities managed by CTB are processing of heart valves and blood vessels, as well as quality control, storage, medical release and distribution of allografts. The aim of this report is to present CTB's vascular tissue activities and retrospectively evaluate the outcomes of their use in the University Hospital Centre Zagreb. Between June 2011 and July 2021, 90 vascular allografts (VAs) from 55 donors after brain death were referred to CTB. Only 54% of VAs met the tissue quality requirements while 46% of tissues were discarded. The most frequent reasons for discard were unacceptable morphology and initial microbiological contamination. Altogether 42 VAs were released for transplantation and 37 of them were used in 27 surgical procedures. The most common indication for surgery was prosthetic graft or stent infection. According to the anatomic position of vascular reconstruction, patients were divided in the aortic and peripheral reconstruction group. A total of 23 patients were treated. In the aortic reconstruction group 58% of patients did not experience any graft-related complications. In the group of patients who underwent peripheral reconstruction significant incidence of reinfection was observed highlighting it as a major graft-related complication. Despite the small patient groups and limited duration of follow-up, presented clinical outcomes provide valuable information on the efficacy of vascular allografts. Additional clinical results collected on a larger patient groups and comparison to other reconstructive treatment options are necessary.

Keywords Tissue bank · Vascular allografts · Aortic reconstruction · Peripheral reconstruction

Introduction

Cardiovascular human allografts have been used since mid twentieth century. The first human aortic valve was implanted in 1956 by Gordon Murray (Murray 1956), whereas the first orthotopic allograft implantation was carried out in 1962 by Donald Ross (Ross 1962). The use of first allografts was limited by short-term storage and lack of proper sterilization methods. Therefore, further efforts in the field were initially focused on solving these issues. In 1964 Barratt-Boyes was first to use antibiotic-sterilized allografts (Barrat-Boyes 1964; Jashari et al. 2004) and in 1987 O'Brien introduced cryopreservation as a method for long-term

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storage of cardiovascular tissues (O'Brien et al. 1987; Jashari et al. 2004). These advancements led to rapid increase in the use of cryopreserved heart valves. On the other hand, the availability of adequate vascular synthetic prostheses and initial unsatisfactory long-term results delayed the same progress in the use of vascular allografts. In the early nineties Kieffer et al. (1993) published study on in situ replacement of infected infrarenal aortic prosthetic grafts with fresh vascular allografts emphasizing the advantages of their use in the treatment of prosthetic graft infection. Soon after, encouraged by the knowledge accumulated from the experience with the cryopreserved heart valves, many studies comparing fresh and cryopreserved vascular allografts (CVA) were initiated (Chiesa et al. 1998; Vogt 2011). These studies showed that the process of cryopreservation preserves the basic collagenous network of the blood vessels which prompted the use of CVAs but with caution and in limited indications (O'Brien et al. 1987; Vogt 2011; Guevara-Noriega et al. 2019). All these developments enabled establishment of cardiovascular tissue banks worldwide that could in an organized and structured way answer the increasing demands for heart valves and different types of blood vessels (Jashari et al. 2004; Goffin et al. 1998; Heng et al. 2013).

Although vascular allografts can be used in a variety of clinical situations, their most common application is in the setting of infected graft prostheses. Infection of aortic or arterial prosthetic graft occurs in 0.5–4% of cases following vascular intervention and presents one of the most challenging complications in vascular surgery (Lyons et al. 2016; Bisdas et al. 2010). The gold standard therapy for this condition is still not established and variable results for different treatment approaches have been reported each with its own advantages and disadvantages (Heinola et al. 2018; Debus and Diener 2017; Heo et al. 2017; Bisdas et al. 2010). The conventional surgical approach includes extirpation of the infected graft and thorough debridement of the surrounding infected tissue followed by surgical treatment chosen by the surgeon. One of the treatment options is extra-anatomical bypass which has been associated with complications such as poor outcome in graft patency, possible aortic stump blow-out and frequent reinfections all leading to high morbidity and 30-day mortality rates up to 28% (Lew and Moore 2011; Bossi et al. 2017; Lejay et al. 2017). In situ prosthetic

graft alignment is a more common option, but then again it brings further risks of infectious complications (Lejay et al. 2017). The usual grafts of choice in the setting of infection are prostheses made of synthetic materials such as silver-coated Dacron grafts or antibiotic-impregnated Dacron grafts since they are readily available and have shown good antibacterial effect. Biological alternatives such as autologous veins, primarily great saphenous vein, are also commonly used to reestablish arterial continuity. However, deep veins can sometimes be unavailable or unsuitable and their procurement prolongs the surgical procedure increasing the operative risk. On the other hand, CVAs have shown several advantages: intrinsic resistance to infection, good hemodynamic characteristics, better patency rate and low risk of thromboembolic complications (Harlander-Locke et al. 2014; Minga Lowampa et al. 2016). CVAs also have branch vessels that facilitate complex bypass procedures. However, vascular grafts have been associated with late degenerative changes such as development of aneurysms. In this regard, their long-term durability is still questionable and collecting the experiences from different centers that use CVAs for aortic and/or arterial reconstruction is an invaluable tool for assessment of vascular allograft transplantation success.

The Croatian Cardiovascular Tissue Bank (CTB) was established in June 2011. The first transplantations of heart valves and blood vessels that were processed and stored at CTB started one year after its establishment. The aim of this report is to present the CTB's vascular tissue banking activities and to demonstrate the single centre results in using CVAs.

Methods and patients

Donor assessment

The organ and tissue donation in Croatia is based on the system of presumed consent. However, if the family disagrees with the donation, tissue procurement will not proceed. All vascular tissues referred to CTB are procured from donors after brain death (DBD). The acceptable age of the vascular tissue donors is between 15 and 55 years. Donor evaluation is always performed by the clinical transplant coordinator who takes care that the procurement conditions are in

accordance with the national regulations. The evaluation includes physical assessment and evaluation of medical history and social/behavioural information including travel history. The clinical transplant coordinator performs haemodilution assessment, organizes collection of blood samples for serological and NAT testing for blood transmissible diseases and organizes samples' shipment to the accredited laboratory. The donor screening tests include serological tests for HBV, HCV, HIV and syphilis and NAT assays for HIV, HBV and HCV. According to the national epidemiological guidelines, from June to November NAT assay for West Nile Virus (WNV) must also be performed. In addition, since 2020 all donors need to be screened with SARS-CoV-2 PCR test within 72 h before procurement. All other data that are relevant for the donation are collected as well, such as results of additional microbiological testing and autopsy report. In some cases, transplant coordinator contacts CTB to inform about possible cardiovascular tissue exclusion criteria and then CTB's medical director makes a final decision about the eligibility of the referred donation.

Since June 2011 until July 2021, there were 67 DBD donations of cardiovascular tissues and 55/67 included donation of different types of blood vessels. In the first three years of CTB activity only four DBD donations included iliac arteries. The main reason for iliac arteries shortage was liver transplant surgeons' practice to recover iliac arteries along with the liver in case they are needed for revascularization or resolving complications after liver transplantation. For this reason, collaboration between CTB and liver transplant surgeons at University Hospital Centre Zagreb (UHC Zagreb) was initiated. The aim was to ensure that the vessels procured during liver recoveries performed by UHC hospital recovery team were referred to CTB where they were processed, decontaminated and cryopreserved according to CTB's standard operative procedures.

Tissue procurement

The procurement of the blood vessels from DBD is performed in the operating theatre by a trained surgical team. Types of blood vessels that have been referred to CTB include aortic arch and descending thoracic aorta, descending thoracic aorta, aortoiliac conduit, iliac arteries and femoral arteries. Aortoiliac conduit comprises at least 2 cm of abdominal aorta, abdominal

bifurcation and usually both iliac arteries. Femoral arteries are usually procured down to popliteal region together with some surrounding tissues including veins and nerves that need to be carefully removed during the processing in the tissue bank. During the procurement surgical team performs the evaluation of the vessel's morphology and decides whether it fulfils the initial tissue quality requirements. The procured tissues are stored in 500 ml of transport solution and placed in sterile triple layered package with wet ice. In most donations saline solution is used as a transport solution but if the blood vessels are procured during liver donation, tissues are stored in sterile perfusion solution such as histidine-tryptophan-ketoglutarate (HTK) or University of Wisconsin solution. Procured tissues packed in the described way and donor's blood samples are then placed in an Igloo PlaymateElite transport container (15 L; Igloo, USA) loaded with 2 L of double wrapped frozen sterile saline solution and shipped immediately to CTB. In this way the temperature during transport of vascular tissues remains + 4 °C ($\pm$ 2 °C) up to 12 h which is the time limit for the tissue delivery to the CTB.

Tissue processing and in-process quality controls

The processing of the cardiovascular tissues starts within 24 h from the tissue procurement and it takes place in a controlled environment of the safety laminar cabinet with an air quality equivalent to GMP Grade A with the background environment equivalent to GMP Grade B. The environmental microbiological monitoring is performed during all tissue processing steps.

Dissection

The dissection is performed carefully to avoid iatrogenic lesions. The surrounding tissue is removed from the arterial/aorta wall and collateral branches are cut at least 2 mm from the vessel wall. The aim is to preserve the maximum length of the vessel during dissection procedure. The morphology is thoroughly inspected and recorded. If deviations like atheroma patches in more than 30% of the vascular wall, diffuse calcifications and/or lesions are observed, the tissue is discarded for not meeting the tissue quality requirements. If the morphology is acceptable, the control tissue samples are taken and the diameter and length of

the blood vessel are determined. The diameter measurements are performed using Hegar's dilators.

Decontamination

Following dissection and morphology evaluation, tissue is decontaminated in an antibiotic solution at + 4 °C for 24–48 h. The antibiotic solution contains Vancomycin (50 µg/ml, Fresenius Kabi, Germany), Lincomycin (120 µg/ml, Pfizer, USA) and Polymyxin B (100 µg/ml, Caelo, Germany) in sterile Medium 199 (M199, Lonza, Switzerland). The decontamination solution does not contain antifungal agent like amphotericin B. This decision was made based on previous observations about its potential cytotoxic effect (Gall et al. 1995, 1998) and some reported cases of its ineffective fungal decontamination (Kuehnert et al. 1998). Therefore, CTB's list of contaminants that should result in tissue discard if detected at any stage of processing includes all fungi.

Cryopreservation

After decontamination procedure, tissue morphology is inspected again and the vessel length and diameter are recorded once more. Tissue is then rinsed three times in the sterile saline solution and finally immersed in cryoprotective solution comprised of 10% dimethyl sulphoxide (DMSO, Wak-Chemie, Germany) in M199. The tissue in the cryoprotective solution is transferred to inner Ethyl Vinyl Acetate transparent bag (Macopharma, France) and sealed with Hemofreeze sealer device (Fresenius HemoCare, Germany). This inner bag is then placed in an outer protective tri-laminated foil barrier bag (Kapak Corp., USA) that is sealed and labelled with the final product label. The allograft is then placed at + 4 °C for 30 min in order to allow DMSO to penetrate into the tissue thus preventing formation of intracellular ice crystals that could damage tissue during freezing procedure. The cryopreservation of the allograft is performed in the controlled rate freezer (Planer Limited, UK) in liquid nitrogen (LN2) vapour according to the validated protocol. Briefly, cooling rate is 1 °C/minute down to the − 40 °C and then 5 °C/minute down to − 100 °C. Cryopreserved vascular allograft is then transferred to quarantine vapour LN2 storage tank where it remains until the final decision about allograft suitability for clinical transplantation.

Quality control samples

The in-process control samples used for microbiological testing include initial tissue sample and transport solution, antibiotic solution, rinsed tissue sample taken after decontamination, cryoprotective solution and microbiological swabs of inner bag with allograft. For the microbiological testing of liquid samples, filtration through 0.45 µm filter membrane (Merck Millipore, USA) is performed and pieces of cut filter membrane are distributed equally in media for detection of microorganisms (BBL Thioglicollate Medium and BBL Trypticase Soy Broth, BD, USA). The collected samples are tested for the presence of aerobic and anaerobic bacteria, fungi and yeasts in the Department of Clinical and Molecular Microbiology at UHC Zagreb. The tissue samples taken from the margins of the arterial/aorta wall during dissection are fixed in formalin and represent in-process controls for histological analysis which is performed in the Department of Pathology and Cytology at UHC Zagreb.

Medical release

All information about the tissue donation, shipment and delivery to the CTB and all details of tissue processing, storage and medical release are documented in customized IT software and in handwritten forms. Once the results of donor testing and in-process controls are collected, final decision about CVA can be made. The CTB medical director reviews and verifies all test results and documentation related to donor and tissue donation and makes the final decision about allograft outcome.

If the vascular allograft (VA) is procured during liver donation, it is reserved for 30 days for liver recipient in the case of late vascular complications. After that period allograft is either discarded or released for clinical application.

Following medical release, allografts are moved to a cryogenic tank designated for storage of allografts suitable for clinical transplantation. Cryopreserved allografts are stored in LN2 vapour for up to 5 years.

Distribution and thawing procedure

The CVA selected by the transplant surgeon is transported to the operating theatre in the dry shipper at temperature below − 135 °C. The allograft thawing process begins at the moment of surgeon's approval. Briefly, double layered package with CVA is removed from the dry shipper, incubated for 5 min at room temperature and then immersed in the first water bath at temperature 37–40 °C for few minutes. After that outer protective bag is opened and sterile inner bag containing allograft is immerged in another sterile water bath. When all ice crystals are dissolved, inner bag is opened and thawed allograft in cryoprotective medium is transferred to another sterile container where stepwise dilution of DMSO with cold sterile saline is performed. Thawed allograft is once more rinsed with sterile saline and microbiological control samples of thawed tissue are taken. If the implantation of the allograft is not planned immediately, thawed tissue can be stored in cold sterile saline solution at + 4 °C for maximum of 6 h. If the result of allograft post-thaw microbiological testing is positive, the transplant surgeon is notified immediately so that an appropriate medical treatment can be administered if needed.

Patient population

The medical records of 23 patients that underwent surgical procedures involving use of CVAs in the period from June 2012 until July 2021 were reviewed. All patients were treated at the Department of Vascular Surgery at UHC Zagreb. Depending on the anatomic position of the vascular reconstruction, patients were divided in two groups; aortic reconstruction and peripheral reconstruction group. Collected data included preoperative patient data and intraoperatively detected microorganisms. The preoperative parameters included demographic data and risk factors like tobacco use or smoking history, hypertension, hyperlipidemia, diabetes mellitus, renal insufficiency and chronic obstructive pulmonary disease. In the case of patients who presented with the prosthetic graft infection and who were transferred from other hospitals, blood culture results and the duration of preoperative antibiotic treatment were incomplete. Therefore, these data were not included in this analysis. The results of intraoperative and postoperative microbiological analysis were reviewed. Different postoperative samples included surgical site swabs and/or blood culture, tracheal aspirate and drain fluid.

Follow-up

The follow-up data of the patients that underwent surgical procedures involving use of CVAs were collected from vascular transplant surgeons and hospital records. The follow-up period was defined as the time elapsed from surgical implantation of CVA until last clinical examination performed by vascular surgeon. The collected data included early (< 30 days) and late (> 30 days) postoperative mortality and morbidity. The results of postoperative microbiological analysis, complications related to implanted allograft and average length of hospital stay were additionally reviewed.

Results

Donors and allografts

Between June 2011 and July 2021, 90 vascular allografts from 55 DBD donations were referred to CTB from 14 different hospitals in Croatia (Tables 1 and 2). Procured VAs included aortic arch with descending thoracic aorta, descending thoracic aorta, aortoiliac conduit, iliac artery and femoral artery. The average time from procurement until the storage of the tissue was 55 h 54 min.

Only 49/90 VAs (54%) met the tissue quality requirements while 41 (46%) tissues were discarded (Table 2). The most frequent reasons for tissue discard were unacceptable morphology due to donor characteristics (20/41) and initial microbiological contamination (14/41) (Table 2). In the group of tissues discarded due to unacceptable morphology, 7/20 were procured during liver recovery. Initial microbiological contamination was a reason for discard of 14 tissues recovered from eight different donors. Transport solutions and tissues tested positive for following microorganisms: *Candida spp.*, *Enterococcus faecalis*, *Proteus mirabilis* and *Serratia marcescens*. According to the CTB protocol, the presence of these microorganisms at any stage of processing should

Table 1 Donors of vascular allografts

Cause of death	N = 55	Gender male/female	Average age/yrs (min–max)
Intracranial hemorrhage	34	16/18	42 (15–55)
Intracranial injury	14	9/5	34 (21–55)
Cerebral infarction	2	2/0	30 and 52
Stroke, not specified as hemorrhage or infarction	1	0/1	43
Carbon monoxide intoxication	1	0/1	17
Cardiac arrest	3	2/1	22, 40 and 50

Table 2 Number of processed tissues and reasons for discard of tissues

Processed Vascular Tissues	
Number of processed tissues	90
Discard rate of processed tissues	46% (41/90)
Reasons for Tissue Discard	N = 41
Morphology[a]	20
Microbiological contamination[b]	14
Medical contraindication	5
Technical error	1
Dissection error	1

[a] extensive atheroma and/or calcifications

[b] 8 Candida spp, 3 Enterococcus faecalis, 2 Proteus mirabilis, 1 Serratia marcescens

result in tissue discard. Additionally, five tissues procured from two different donors were discarded because of medical contraindications that were discovered following detailed investigation of donors' medical history.

Among 49 CVAs that fulfilled quality criteria, nine had initial microbiological contamination that was successfully resolved with decontamination procedure. Those tissues included seven femoral and two iliac arteries and they were procured from five different donors. The initial contamination detected in the transport solution and tissue samples in these cases included *Cutibacterium acnes, Corynebacterium sp., Staphylococcus epidermidis* and *Coagulase Negative Staphylococcus*. Taking into consideration the type of microorganisms detected and the order of the tissue procurement in the case of DBD donations, it is likely that the contamination occurred during procurement procedure.

The characteristics of 49 CVAs that fulfilled quality criteria for clinical transplantation are listed in Table 3. Altogether 42 CVAs were distributed for transplantation (Table 4) and 37 of them were transplanted. The remaining five CVAs were not used because the surgeons changed their decision in the operating theatre. Two CVAs were thawed before the decision was made and afterwards discarded. Three CVAs were reserved and distributed as backup tissues. These tissues were not removed from a monitored dry shipper and they were returned to CTB storage. Altogether 37 CVAs were used for 27 surgical procedures in 23 patients. The indications for surgical procedures and used CVAs are listed in Table 4. The most common indication for surgical procedure was prosthetic graft or stent infection.

The microbiological control samples collected during thawing procedures of CVAs in the operating theatre were sterile except in two cases where CVAs tested positive for *Coagulase Negative Staphylococcus* and *Staphylococcus warneri*, respectively. Both CVAs were used to prepare composite allografts in two separate procedures. In both cases patients recovered without complications.

Aortic reconstruction

A total of 13 in situ aortic reconstructions were performed in 12 patients (average age 61 years). The patient demographics are detailed in Table 5. Eleven patients were diagnosed with prosthetic graft or stent infection and one with aortoenteric fistula (Table 4). In ten patients with infection, aortic reconstruction was completed with the proximal anastomosis located in abdominal aorta and distal at the aortic, iliac or femoral position. One patient with infected Crawford type IV thoracoabdominal aortic aneurysm had

Table 3 Vascular allografts' characteristics

Vascular Allografts Released for Transplantation				
No. of VAs that met quality requirements		49/90 (54%)		
Dimensions of VAs (average ± sd)	N	Proximal diameter/mm (min–max)	Distaldiameter/mm (min–max)	Length/ mm(min–max)
Aortic arch with thoracic aorta	8	21 (17–24)	18 (14–22)	150[a] (110–180)
Thoracic aorta	11	17 (14–23)	15 (12–19)	132 (110–180)
Abdominal aorta (patch)[b]	1	13	13	40
Aortoiliac conduit	4	14 (14–15)	7 (6–8)	108 (100–120)/134 (105–170)
Iliac artery	9	7 (5–9)	5 (3–7)	110 (78–137)
Femoral artery	16	6 (2–9)	4 (2–6)	285 (175–430)

VA Vascular allograft

[a]Length of the thoracic aorta

[b]Piece of abdominal aorta for patch plastic

proximal anastomosis at supra-celiac aorta and distal in the abdominal aorta. In patient with aortoenteric fistula, proximal anastomosis was located in ascending and distal in descending thoracic aorta.

Altogether 18 CVAs were used in 13 surgical procedures. In nine cases only one CVA was used. In three procedures two CVAs and in one three CVAs were combined in order to obtain graft suitable for specific aortic reconstruction.

Early postoperative outcome

The 30-day mortality was 17% (2/12).

- The first patient underwent aortic reconstruction due to infection of aortobifemoral prosthesis. Intraoperative microbiological finding showed infection with *Staphylococcus sp.* (Table 6, patient No.1). Early postoperative microbiological findings of pharyngeal swab sample showed infection with *Candida glabrata* and tracheal aspirate with *Candida albicans*. The patient died of sepsis-related multiple organ failure (MOF) on postoperative day 9 (POD).
- The second patient underwent aortic reconstruction due to infection of aortoiliacofemoral prosthesis. Intraoperative microbiological finding showed infection with *Pseudomonas aeruginosa* (Table 6, patient No.3). The same microorganism was found in postoperative surgical site swab sample in addition to *Klebsiella pneumonia* ESBL

few days later. The patient died due to cardiorespiratory arrest on POD 15.

Late treatment outcome

In the case of the remaining nine patients the median follow-up was 24 months (range 2–99 months). The median length of postoperative hospital stay was 27 days (range 10–75 days).

One patient died during one-year follow-up period.

- The patient underwent aortic reconstruction due to infection of aortobiiliac prosthesis. Intraoperative microbiological sample showed infection with multiple microorganisms; *Enterococcus faecium VRE*, *Candida glabrata* and *Candida albicans* (Table 6, patient No.6). Early postoperative pharyngeal swab tested positive for *Candida glabrata* and *Candida albicans*. Patient received therapy according to microbiological findings. Following hospital discharge patient was controlled in the local hospital. The patient died on POD 120 due to ruptured graft.

When it comes to late events, there was one patient who underwent aortic reconstruction due to rupture of mycotic suprarenal aortic aneurysm. Five years later aneurysmal degeneration at the proximal anastomosis of previously implanted CVA was observed which was successfully resolved with EVAR. The remaining

Table 4 Indications for surgical procedures and types of VAs distributed for transplantation

Vascular Allografts Issued for Transplantation			
No. of VAs distributed for transplantation		42/49 (86%)	
No. of transplanted VAs		37/49 (76%)	
Aortic Reconstruction			
Indications for Surgical Procedures	*N = 13*	VAs Transplanted	*N = 18*
Prosthetic graft or stent infection	12	Aortic arch with thoracic aorta	6
		Thoracic aorta	6
		Aortoiliac conduit	2
		Femoral artery [a]	2
		Iliac artery [b]	1
Aortoenteric fistulae	1	Aortic arch with thoracic aorta	1
Peripheral Reconstruction			
Indications for Surgical Procedures	*N = 13*	VAs Transplanted	*N = 18*
Prosthetic graft or stent infection	11	Iliac artery	7
		Femoral artery	8
		Aortoiliac conduit	1
Femoral popliteal graft occlusion	1	Femoral artery	1
Mycotic pseudoaneurysm of the renal artery	1	Iliac artery	1
Peripheral Patch Plastic			
Indications for Surgical Procedures	*N = 1*	VAs Transplanted	*N = 1*
Prosthetic graft infection [c]	1	Aortoiliac conduit	1

VA Vascular allograft

[a] One patient with infected aortobifemoral bypass prosthesis. Composite graft was used for reconstruction (thoracic aorta and two femoral arteries)

[b] One patient with infected aortobiiliac prosthesis. Composite graft was used for reconstruction (aortic arch with thoracic aorta and iliac artery)

[c] One patient with infected aorto-bicarotid bypass

seven patients (58%) did not require any surgical reintervention during their available follow-up.

Intraoperative and early postoperative microbiological findings

Intraoperative microbiological samples were obtained from all 12 patients (Table 6). In the case of nine patients multiple microorganisms were detected, in two patients only one and in one case no microorganisms were detected.

Various postoperative microbiological samples were collected from 10 patients (Table 6). Postoperative infection was noted in all three patients who died and in one patient who had graft extirpation due do reinfection. However, multiple microorganisms were also detected in early postoperative microbiological findings in three patients who recovered successfully. None of these three patients had recurrence of the initial infection during their available follow-up (66 months in two cases and 99 months in one case).

Peripheral reconstruction

A total of 13 in situ peripheral reconstructions were performed in 10 patients (average age 64 ± 12 years). The patient demographics are detailed in Table 7. Nine patients were diagnosed with primary or secondary infection. They had either aortobifemoral (n = 4), femoropopliteal (n = 2), femorofemoral (n = 1) or iliac popliteal (n = 1) bypass infection and one patient presented with mycotic pseudoaneurysm (PSA) of the

Table 5 Pre-operative data and intraoperatively detected microorganisms in the group of patients that underwent aortic reconstruction

Variable	Patients (n)
Total	12
Demographics	
Male	11
Female	1
Mean age, years	61 (21–77)
Risk factor	
Tobacco use or smoking history	8
Comorbidities	
Hypertension	8
Hyperlipidemia	5
Diabetes mellitus	1
Renal insufficiency	1
COPD	2
Indications for aortic reconstruction procedure	
Total number of surgical procedures	13
Prosthetic graft or stent infection	12
Aortoenteric fistulae, St.post bypass aorto bifemoralis	1
Intraoperatively detected microorganisms	
No microorganisms detected	1
Monomicrobial	2
Polymicrobial	9
Staphylococcus sp.	4
Staphylococcus epidermidis	2
Staphylococcus pasteuri	1
Staphylococcus aureus	1
Staphylococcus warneri	1
Cutibacterium spp	1
Streptococcus anginosus	1
Streptococcus constellatus	1
Micrococcus luteus	1
Enterococcus faecium VRE	3
Pseudomonas aeruginosa	2
Acinetobacter Iwoffii	1
Escherichia coli	1
Klebsiella pneumoniae	2
Bacteroides spp	1
Candida glabrata	1
Candida albicans	3
Saccharomyces cerevisiae	1

COPD Chronic obstructive pulmonary disease

renal artery. One patient had femoral popliteal graft occlusion without infectious etiology (Table 4). All patients, except the patient with mycotic PSA of the renal artery, had the proximal and distal anastomoses located at the femoral and/or iliac arteries.

Altogether 18 vascular allografts were used in 13 surgical procedures. In eight cases only one CVA was used. In five procedures two CVAs were combined in order to obtain graft suitable for specific peripheral reconstruction.

Table 6 Intraoperative and early postoperative microbiologic findings and postoperative outcome in patients following aortic reconstruction with VAs

Patient	Intraoperative microbiologic finding	Early postoperative microbiologic findings	Outcome
1	*Staphylococcus sp.*	BC: sterile PS : *Candida glabrata* TA: *Candida albicans*	Died POD 9
2	*Staphylococcus sp., Bacteroides sp.*	NT	Recovered
3	*Pseudomonas aeruginosa*	SW: *Pseudomonas aeruginosa, Klebisella pneumoniae ESBL*	Died POD 15
4	*No microorganisms detected*	PS: normal flora UC: sterile	Recovered
5	*Streptococcus anginosus, Micrococcus luteus, Streptococcus constellatus*	PS: normal flora	Recovered
6	*Enterococcus faecium VRE , Candida glabrata, Candida albicans*	SW: sterile PS: *Candida glabrata, Candida albicans*	Died POD 120
7	*Cutibacterium spp., Staphylococcus species*	BC: sterile DF: *Dematiaceus fungi* PS: *Klebsiella pneumoniae ESBL* IC: *Staphylococcus sp.*	Recovered
8	*Acinetobacter lwoffii, Staphylococcus epidermidis, Staphylococcus pasteuri*	TA: *Candida spp., Neisseria saprophytic* SW: sterile	Recovered
9	*Escherichia coli, Klebsiella pneumoniae, Candida albicans*	PS: normal flora	Graft rupture and necrosis - partial graft extirpation on POD 5
	Partial allograft extirpation: Enterococcus faecium VRE, Klebsiella pneumoniae, Candida albicans	PS: *Candida albicans*	Graft necrosis and reinfection - extirpation of second graft on POD 8
	Second allograft extirpation: Streptococcus species, Enterococcus faecium VRE, Candida albicans	/	Extra-anatomical bypass
10	*Staphylococcus epidermidis, Pseudomonas aeruginosa*	NT	Recovered
11	*Staphylococcus aureus, Staphylococcus species*	BC: sterile TA: *Pseudomonas aeruginosa, Candida albicans*	Recovered
12	*Klebsiella pneumoniae, Enterococcus faecium, Stephylococcus warneri, Candida albicans, Saccharomyces cerevisiae*	PS: normal flora	Recovered

BC blood culture, *SW* surgical site swab, *TA* tracheal aspirate, *PS* pharyngeal swab, *UC* urine culture, *DF* drain fluid, *IC* intravascular catheter, *NT* not tested

Table 7 Pre-operative data and intraoperatively detected microorganisms in the group of patients that underwent peripheral reconstruction

Variable	Peripheral reconstruction	Peripheral patch plastic
	Patients (n)	
Total	10	1
Demographics		
Male	6	1
Female	4	0
Mean age, years	64 (40–82)	66
Risk factor		
Tobacco use or smoking history	4	1
Comorbidities		
Hypertension	10	0
Hyperlipidemia	4	0
Diabetes mellitus	2	0
Renal insufficiency	2	0
COPD	1	0
Indications for peripheral reconstruction procedure		
Total number of surgical procedures	13	1
Prosthetic graft or stent infection	11	1
Femoral popliteal graft occlusion	1	0
Mycotic pseudoaneurysm of the renal artery	1	0
Intraoperatively detected microorganisms in patients who presented with infectious etiology	**N = 8/9 (90%)**	
No microorganisms detected	1	0
Monomicrobial	5	1
Polymicrobial	3	0
Staphylococcus sp.	2	1
Staphylococcus epidermidis	1	0
Staphylococcus aureus	1	0
MRSA	1	0
Enterococcus faecalis	2	0
Cutibacterium sp.	1	0
Cutibacterium granulosum	1	0
Pseudomonas aeruginosa	1	0
Pseudomonas stutzeri	1	0
Candida albicans	1	0

COPD chronic obstructive pulmonary disease

MRSA methicillin-resistant Staphylococcus aureus

Early postoperative outcome

The 30-day mortality was 0%.

The 30-day morbidity was 10% (1/10).

- In the case of one patient various initial comorbidities existed that potentially influenced the treatment outcome (Table 8, patient No.5). This patient was a long term IV drug user and had hepatitis C infection. He developed focal segmental glomerulosclerosis and hypertension. Subsequently, he had a cadaveric kidney transplantation and one month later graphectomy. One month

following graphectomy, the patient underwent peripheral reconstruction due to femorofemoral bypass infection. Intraoperative microbiological finding showed infection with *Candida albicans*. The reinfection (*Candida albicans*) and necrosis of the implanted graft were observed on POD 14. The graft was extirpated and replaced with another femoral artery allograft. The reinfection and anastomotic disruption of the second graft occurred on POD 9 when the graft extirpation and limb amputation were performed.

Late treatment outcome

The median follow-up was 20 months (range 2–63). The median length of postoperative hospital stay was 29 days (range 14–91).

Three patients (3/10) died during one-year follow-up period.

- In the case of first patient peripheral reconstruction was performed due to infected iliac popliteal bypass. Intraoperative microbiological finding showed infection with *Pseudomonas aeruginosa* and *Staphylococcus sp.* (Table 8, patient No. 2). Three months following surgical procedure patient developed *Clostridium difficile* colitis and localized pustule at the surgical site that tested positive for *Pseudomonas aeruginosa*. Antibiotic therapy was administered and the patient was discharged from the hospital in stable condition. Six months later patient was administered in hospital due to recurrent abscess in the femoral region. The graft was extirpated and intraoperative microbiological findings showed reinfection with *Pseudomonas aeruginosa*. Due to complications during operative procedure, new peripheral reconstruction was not possible and the limb amputation was performed. Two days later, the patient died due to respiratory arrest.

- In the case of second patient various initial comorbidities existed including non-Hodgkin lymphoma, secondary cardiomyopathy, mitral valve insufficiency, hypertension and diabetes mellitus type II. This patient underwent peripheral reconstruction due to infection and PSA at distal anastomosis of aortobifemoral prosthesis. Intraoperative microbiological analysis did not detect any microorganism what is most probably result of prolonged use of antibiotics (Table 8, patient No. 9). One month following surgical procedure patient's blood culture tested positive for *Pseudomonas aeruginosa* and one month later graft reinfection occurred. The graft was extirpated and extra-anatomical bypass was performed. Intraoperative microbiological sample of extirpated graft showed infection with *Pseudomonas aeruginosa*. One month later limb amputation was performed due to gangrene and one day later patient died due to sepsis-related MOF.

- In the case of third patient peripheral reconstruction was performed due to disruption of infected distal anastomosis of aortobifemoral prosthesis. Intraoperative microbiological findings showed infection with *Pseudomonas stutzeri* and *Streptococcus sp.* (Table 8, patient No. 10). The graft reinfection occurred 6 months later. Graft was extirpated and replaced with another CVA. On the POD 24 s graft was ligated due to necrosis and thrombosis. Three days later limb amputation was performed. Two months later patient died due to sepsis-related MOF caused by complications following complete thyroidectomy and extirpation of mediastinal tumor.

During one-year follow-up period one graft-related complication was observed. In this case partial graft occlusion occurred six months after reconstruction of infected femoropopliteal bypass with two CVAs. New partial reconstruction was performed using two new CVAs and patient recovered without complications (available 13 months follow-up period).

When it comes to late events, there was one case of patient who underwent peripheral reconstruction with CVA due to infected PSA of distal anastomosis of aortobifemoral bypass. Five years and three months later, partial extirpation of the graft and reconstruction with interpositum Dacron graft was performed due to aneurysmatic degeneration of the implanted graft.

The remaining four patients did not require surgical reinterventions during their available follow-up period.

Table 8 Intraoperative and early postoperative microbiologic findings and postoperative course in patients following peripheral reconstruction with VAs

Patient	Intraoperative microbiologic finding	Early postoperative microbiologic findings	Postoperative course
PERIPHERAL RECONSTRUCTION			
1	*Staphylococcus species, Staphylococcus aureus*	SW: *Staphylococcus aureus*	Recovered
	Partial allograft extirpation: NT	SW: sterile	
2	*Pseudomonas aeruginosa, Staphylococcus species*	BC: sterile UC: *Enterococcus faecalis* SW: *Pseudomonas aeruginosa* Three months following reconstruction: Pustule: *Pseudomonas aeruginosa*	Graft extirpation on POD 274
	Allograft extirpation: Pseudomonas aeruginosa Serratia marcescens	PS: *Pseudomonas aeruginosa* UC: *Candida spp.*	Limb amputation on POD 2
3	*Enterococcus faecalis*	SW: sterile	Recovered
4	NT [a]	NT	Recovered
5	*Candida albicans*	BC: *Staphylococcus epidermidis* SW: *Candida spp.*	Graft reinfection and necrosis - graft extirpation on POD 14
	Allograft extirpation: *Candida albicans*	BC: sterile PS: *Klebsiella pneumoniae*	Graft necrosis and anastomotic disruption - extirpation on POD 9
	Second allograft extirpation: NT	BC: sterile PS: *Klebsiella pneumoniae* SW: *Staphylococcus epidermidis*	Limb amputation
6	*Enterococcus faecalis*	DF: *Enterococcus faecalis* SW: sterile	Recovered
7	*Staphylococcus aureus MRSA*	SW: sterile	Recovered
8	*Cutibacterium granulosum*	BC: sterile	Recovered
9	No microorganisms detected	BC: *Pseudomonas aeruginosa* SW: *Staphylococcus species, Enterococcus faecalis, Pseudomonas aeruginosa*	Graft reinfection – graft extirpation on POD 61
	Allograft extirpation: *Pseudomonas aeruginosa*	SW: *Pseudomonas aeruginosa* PS: *Candida albicans Candida dubliniensis*	Extra-anatomical bypass Limb amputation on POD 29 Died one day later
10	*Pseudomonas stutzeri, Streptococcus sp.*	SW: *Staphylococcus sp., Enterobacter sp., Enterococcus faecalis*	Graft reinfection – graft extirpation on POD 180
	Allograft extirpation: *Staphylococcus epidermidis, Cutibacterium sp.*	SW: *Pseudomonas aeruginosa, Proteus mirabilis, Enterobacter sp.*	Graft necrosis and thrombosis – allograft ligation on POD 24 Limb amputation on POD 3 Two months later patient died due to sepsis related MOF
PERIPHERAL PATCH PLASTIC			
1	*Staphylococcus sp.*	PS: normal flora SW: *Staphylococcus sp.*	Recovered

[a]Patient who presented with no infectious etiology

NT not tested, *BC* blood culture, *SW* surgical site swab, *TA* tracheal aspirate, *PS* pharyngeal swab, *DF* drain fluid, *UC* urine culture

Intraoperative and early postoperative microbiological findings

Intraoperative microbiological samples were obtained from all patients who presented with infectious etiology complications. In three patients multiple microorganisms were detected, in five patients only one and in one case no microorganisms were detected (Table 8). The collected postoperative microbiological samples are presented in Table 8. Postoperative infection was noted in all three patients who died and in one patient who had graft extirpation due do reinfection.

In addition to this group of patients, there was one patient who had a peripheral reconstruction at the carotid artery position and therefore needs to be presented separately. This particular patient had a patch plastic reconstruction of carotid arteries (ACC and ACI) with CVA due to infection of aortobicarotid bypass performed with Dacron prosthesis. In this case the reconstruction procedure was successful and patient did not require surgical reinterventions during available follow-up period (68 months).

Discussion

The interest of cardiac surgeons for cardiovascular allografts was a primary incentive for the establishment of Cardiovascular tissue bank at UHC Zagreb. This institution already had a crucial infrastructure needed to fulfill the tissue bank specific demands in regard of adequate premises and the equipment. The personnel that already had experience with the work in the cleanrooms were appropriately trained for cardiovascular tissue processing. Initial activities of the CTB in the first year of its existence were primarily focused on the processing of heart valves. However, first arteries and aortic conduits were soon stored as well which encouraged vascular surgeons to start with the use of cryopreserved vascular tissues.

The quality management system which covers the scope of all CTB's activities and ensures that the tissues comply with all technical and legal requirements has been put in place since CTB initiation in June 2011. The strict tissue selection criteria in accordance with the EU standards have been applied with the aim to ensure safe and efficient allografts for the recipients (Directive 2004/23/EC, Directive 2006/17/EC, Directive 2006/86/EC, EDQM 2019, Parker et al. 2000). These strict criteria resulted in the high vascular tissue discard rate. However, storage of only high-quality vascular allografts ensured their high implantation rate. Overall vascular tissue discard rate amounts 46%, with microbiological contamination and inadequate morphology being the most frequent reasons for discard. Altogether 16% (14/90) of procured vascular tissues were discarded due to initial microbiological contamination with highly virulent microorganisms that, according to the CTB protocol, if found at any stage of the processing should result in tissue discard. The discard rate due to inadequate morphology is quite high and amounts 22% (20/90). This high percentage can be partially attributed to the quality of the tissues procured during liver recoveries. The collaboration between CTB and Division of Hepatobiliary Surgery and Abdominal Organ Transplantation was initiated in November 2014 with the aim to increase the inflow of vascular tissues procured during liver donations. In these cases, the tissues were procured by the liver transplant teams. Although the presence of severe atherosclerosis is exclusion criteria for vessel procurement, it is not a contraindication for liver procurement (EDQM 2018). Taking into consideration that the liver transplant surgeons are primarily focused on the quality of the procured organ, it is clear why, in the beginning of this collaboration, some vessels harvested by liver transplant team had abundant atherosclerosis which subsequently resulted in the tissue discard during processing procedure at CTB. In time, the liver transplant surgeons started to perform initial assessment of the vessels' morphology in order to procure only vessels with acceptable initial morphology. At that point the incidence of procured vessels with poor morphology decreased. Therefore, despite the initial high discard rate of vascular tissues this program turned out to be efficient since all tissues procured in this setting that met quality criteria were subsequently transplanted.

The Department of vascular surgery at UHC Zagreb is a national refferal centre for complicated vascular cases including patients with infected vascular prostheses. For that reason, all transplantations of CVAs have been performed only at the tertiary centre UHC Zagreb where CTB is located as well. The CTB staff was involved in all tissue thawing procedures and ensured that CVAs were adequately manipulated

during thawing procedure. The immediate vicinity of CTB and transplant centre also enabled an easier communication with implanting surgeons regarding feedback about implanted tissue quality and patient follow-up.

In addition to presentation of CTB's vascular tissue banking activities, the aim of this report was also to retrospectively evaluate a single centre experience in using CVAs that were processed and stored in CTB. The most frequent indication for CVA use in our centre was prosthetic graft or stent infection and the choice to use CVA for vascular reconstruction was based on the patient's condition and the decision of the surgeon. Infection of aortic or arterial prosthetic graft following vascular intervention is one of the most challenging complications in vascular surgery (Lyons et al. 2016; Bisdas et al. 2010). Although several treatment options exist, the published reports show that revascularization with CVAs could provide better resistance to infection compared to conventional methods (Brown et al. 2009; Minga Lowampa et al. 2016). Previously published data indicate that recurrent infection following implantation of CVA is not very frequent. Large study performed by Harlander-Locke et al. (2014) that included 220 patients from different US centers reported this complication in only 4% of the treated patients. Similar rate of reinfection (3.7%) was observed in the study with 54 enrolled patients published by French group (Touma et al. 2014). The results published by Bisdas et al. (2011) are even more impressive with no cases of reinfection following use of CVAs in 22 patients with diagnosis of vascular infection. In this regard, it has to be emphasized that all previously mentioned studies included only patients with infection in the aortic position. In our report in this particular group of patients only one case of reinfection was confirmed which is a result comparable to the aforementioned outcomes. However, in the group of patients who underwent peripheral reconstruction procedure four cases of reinfection occurred highlighting the reinfection as a major complication in this group of patients. These circumstances in conjunction with various initial comorbidities mainly contributed to the unsatisfactory treatment outcomes in the group of patients with peripheral reconstruction. Additionally, it was previously observed that the CVAs resistance to bacterial colonization and subsequent infection is diminished in the presence of highly virulent microorganisms such as *Pseudomonas aeruginosa* (Couture et al. 2021; Bisdas et al. 2010) and *Candida* sp. (Lejay et al. 2017). This was confirmed with our findings in both patient groups as well. All patients who died and those who had complications due to persistent infection that resulted in extra-anatomical bypass or limb amputation had an infection that included *Pseudomonas aeruginosa* and/or *Candida sp.*

Other allograft-related complications described in the literature include allograft thrombosis, anastomotic or allograft disruption and aneurysmal degeneration. In our cohort of patients there were two cases of graft ruptures and one case of anastomotic disruption. Both graft ruptures occurred in the group of patients who underwent aortic reconstruction. In one case it was caused by an early reinfection while second patient had a fatal allograft rupture four months following implantation. This patient was treated due to infection of prosthesis with multiple highly virulent microorganisms and was subsequently controlled in the local hospital. In this case the reinfection might also be the cause of allograft rupture. However, this possibility was never investigated and therefore cannot be claimed as the cause of allograft-related complications. One case of anastomotic disruption was observed in a patient who underwent two subsequent peripheral reconstructions with CVAs due to recurrent infection.

When it comes to structural degeneration of the allograft as a consequence of the gradual weakening of the vessel's elastic tissue, two such cases were reported in our patients' groups; one in the aortic and one in the peripheral group of patients. Interestingly, in both cases the aneurysmatic dilatation of the allograft was observed as a late event five years following CVA implantation. Some authors speculate that structural degeneration could be a late consequence of the damage inflicted to the allograft by improper handling during thawing or it could be caused by implantation procedure (Minga Lowampa et al. 2016; Bisdas et al. 2010). Thawed tissue is indeed more fragile than native vessel and care should be taken that no firm pressure is applied to it during manipulation to avoid emergence of micro lesions in the vessel wall.

In conclusion, overall results presented in this study are consistent with previously published data and indicate that allograft-related complications following the use of CVAs in the setting of infection are common

but they do not outweigh the risks of conventional treatment approaches (O'Connor et al. 2006; Harlander-Locke et al. 2014; Minga Lowampa et al. 2016). This primarily refers to the use of CVAs in the aortic reconstruction procedures in the setting of infection where acceptable results have been accomplished. Altogether 58% of patients in this group did not have complications or need for surgical reinterventions during available follow-up. The patients included in the peripheral reconstruction group had various initial comorbidities that significantly contributed to their poorer treatment outcomes. Only 40% of patients in this group did not have complications or need for surgical reinterventions during available follow-up. These inferior results need to be further investigated in the larger group of patients.

Although the small number of patients and limited duration of follow-up are major limitations of this retrospective study, presented clinical outcomes provide valuable information on the efficacy of vascular allografts. Another shortcoming of the presented results is the lack of comparison of CVA implantation with other reconstructive treatment options. In this regard, comparison with the clinical outcomes of patients with similar preoperative characteristics who underwent other treatment options in our institution is warranted.

Ethics approval

All tissue donations reported in this study followed the procedure of acquiring the donor/family consent for tissue donation for clinical application in compliance with EU and national legislation. All procedures described in this study were performed in accordance with all applicable guidelines which aim to ensure the safety of the patients and ethical conduct according to the Declaration of Helsinki. The data sets generated and analysed during the current study are not publicly available due to protection of patients' and tissue donors' personal data but are available from the corresponding author on reasonable request.

Declarations

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