DOI: 10.15825/1995-1191-2024-2-42-47

CARDIAC ALLOGRAFT VASCULOPATHY: CURRENT REVIEW

B.L. Mironkov, D.D. Uvarova, N.N. Koloskova, Yu.V. Sapronova, I.I. Muminov, A.A. Yusova, S.A. Sakhovsky

Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

Transplant coronary artery disease (TCAD) is one of the main causes of graft dysfunction and graft loss. Early diagnosis and treatment of cardiac allograft vasculopathy (CAV) can increase graft survival and improve the prognosis for heart transplant recipients. This review presents current data on the problem of CAV, its pathogenesis and the main factors influencing the course of this disease.

Keywords: cardiac allograft vasculopathy, heart transplantation.

About 6000 heart transplants are performed annually worldwide. In Russia, 308 heart transplants were performed in 2022, including 10 pediatric transplants [1]. Survival after heart transplantation is about 12.5 years [2 4]. Transplant coronary artery disease (TCAD) is a complex accelerated immune-inflammatory fibroproliferative disease of the transplant coronary bed. It is characterized by diffuse intimal hyperplasia in the early stages, which is followed by negative vascular remodeling. Ten percent of heart transplant recipients die within three years of receiving their transplant, with TCAD being the primary cause of death in these cases [3]. Recipients who experience rapidly progressive TCAD within the first year after transplantation have a significantly increased risk of death and/or retransplantation within 5 years.

The reasoning behind the prophylactic use of statins, immunosuppressants, and vigorous infection prevention against TCAD is based on current understanding of the pathophysiology of the disease [4].

TCAD RISK FACTORS

Immunological factors associated with TCAD are the initial link in the pathologic process. The interaction of "foreign" human leukocyte antigen (HLA) of allograft endothelial cells with the recipient's T lymphocytes initiates endothelial cell activation and inflammatory cell accumulation. This leads to production of cytokines (interleukins 2, 4, 5, and 6; interferon-gamma; tumor necrosis factor-alpha), proliferation, and activation of endothelial adhesion molecules. Activated macrophages accumulate in the intima and produce cytokines (interleukins 1 and 6, TNF-alpha) and growth factors. As a result, this causes smooth muscle cell migration into the intima, proliferation and deposition of the extracellular matrix. HLA class I antibodies promote endothelial and smooth muscle cell proliferation through activation of the mTOR pathway and induction of intracellular fibroblast growth factor receptor expression [5]. Even in the absence of pathogens, a variety of intracellular particles, including cytoplasm, mitochondria, and cell nuclei, which are also present in the extracellular matrix in transplanted organs, cause inflammatory processes [65]. Lin et al. showed the importance of this phenomenon by demonstrating that extracellular mitochondria are abundant in the blood of dead donor organs and that their abundance corresponds to rapid graft rejection [7]. Endothelial injury and activation induce the production of pro-inflammatory cytokines, chemokines and expression of adhesion molecules, which promotes immune cell recruitment and immune cell transmigration into the intima [8, 9].

Both innate and acquired immunity play an important role in both atherosclerosis and TCAD. Although the triggers of endothelial injury and endothelial dysfunction may differ in TCAD and atherosclerosis, once endothelial activation occurs, pathologic processes involved are similar in the two diseases.

Nonimmune factors associated with the risk of TCAD include advanced age (donors and recipients), male gender, infections, dyslipidemia, obesity, diabetes, coronary heart disease, cause of brain death in the donor, organ preservation and transportation conditions, surgical injury, and ischemia-reperfusion injury (IRI). Hyperlipidemia and insulin resistance are the most significant non-immune factors, occurring in 50–80% of heart transplant patients [10, 11].

An increased risk of TCAD has been linked to cytomegalovirus (CMV) infection [12]. By increasing the synthesis of nitric oxide synthase inhibitor, asymmetric dimethylarginine, CMV causes endothelial dysregulation and affects nitric oxide synthesis. The chemical similarity between CMV and endothelial cell surface may lead to cross-reactivity [7, 8]. However, recent studies have found no association between maximum intima-media thickening during the first year, assessed by intravascular

Corresponding author: Stepan Sakhovsky. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Phone: (926) 636-00-31. E-mail: milifolium@gmail.com

ultrasound (IVUS), and CMV infection [13]. The cause of brain death in the donor is relevant to the success of transplantation. Brain death causes severe cardiac injury due to increased catecholamine production, endocrine and hemodynamic disorders leading to organ hypoperfusion and subsequent IRI after transplantation. In addition, the mechanism of donor brain death has a significant impact on heart transplant outcomes, with traumatic brain death being associated with decreased mortality, rejection, allograft vasculopathy, and transmissible atherosclerosis [14]. Based on observations at Shumakov National Medical Research Center of Transplantology and Artificial Organs, donor brain death was associated with higher probability of transmitting coronary atherosclerosis from older donors and donors with stroke [15]. IRI caused by surgical injury leads to production of large amounts of reactive oxygen species (ROS), which directly cause vascular injury and endothelial activation [16].

It should be noted that, in terms of pathological anatomy, TCAD has a variety of morphologic manifestations. Wei-hui Lu et al. published a study [17] that evaluated the pathologic anatomic findings in the explanted heart of patients who underwent retransplantation for graft dysfunction. The study reviewed archival records and microscopic sections of hearts surgically explanted from 64 patients: 54 adults (18 to 70 years old) and 10 children (3 to 15 years old). 54 adults (18 to 70 years) and 10 children (3 to 15 years). Vascular lesions were categorized as showing intimal fibromuscular hyperplasia, atherosclerosis and/or inflammation. A total of 75% of hearts had signs of acute cellular rejection, predominantly mild. Intramyocardial arteries showed primarily intimal fibromuscular hyperplasia and inflammation with no atheroma present. Lesions in the epicardial coronary arteries presented as intimal fibromuscular hyperplasia, atherosclerosis, and/or inflammation affecting one or more vascular layers (intima, media and adventitia). Severe TCAD with >75% luminal narrowing was seen in at least one vessel in all hearts. Two hearts had severe narrowing of the left main coronary artery. Nineteen arteries had luminal thrombus. All hearts had narrowing of smaller epicardial coronary arteries that were often severe. Atheromas were present in arteries of adults and children; thus, not all atheromas could be considered pre-existing prior to transplantation. Both arteries and veins showed intimal hyperplasia and inflammation.

Thus, TCAD is a pathologically multifaceted disorder that affects large and small epicardial coronary arteries of adults and children, with different types of lesions: intimal fibromuscular hyperplasia; atherosclerosis; and/or inflammation (vasculitis).

According to pathoanatomical studies conducted at Shumakov National Medical Research Center of Transplantology and Artificial Organs, cardiac allograft vasculopathy (CAV) in the proximal coronary arteries was a combination of accelerated atherosclerosis and chronic rejection [18–23].

But despite the many manifestations of TCAD, the current classification used is the one developed by the International Society for Heart and Lung Transplantation (ISHLT), which is based mainly on angiographic criteria (Table 1) [24].

TCAD and coronary atherosclerosis of native arteries have both common and different features. Moreover, the presence of different risk factors leads to different types of vascular lesions in cardiac allografts. For example, hyperlipidemia, diabetes, and smoking are risk factors common to atherosclerotic disease and TCAD. With these risk factors, graft vessels develop atherosclerotic-like lesions. On the other hand, alloantigen-dependent risk factors (number of anti-HLA antibodies, number of rejection episodes) and CMV infection are more likely to be associated with changes such as endotheliitis and arteritis [17].

Although some of the risk factors (donor organ IRI, donor age, organ quality, recipient age, donor brain death, major histocompatibility mismatch) are unique to TCAD, many are in addition to the others (hyperlipidemia, diabetes, oxidative stress, hypertension, cytokine modulation, inflammation, C-reactive protein [CRP], infections and other environmental factors, smoking) [8, 25, 26]. Comparative characteristics of these diseases are presented in Table 2.

Table 1

Classification system for angiographic features of TCAD

Severity	Angiographic criteria
ISHLT CAV0 (Not significant)	No detectable angiographic lesion.
ISHLT CAV1 (Mild)	Angiographic left main (LM) <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction.
ISHLT CAV2 (Moderate)	Angiographic LM <50%; a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of 2 systems, without allograft dysfunction.
ISHLT CAV3 (Severe)	Angiographic LM ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology.

Table 2

Comparative characteristics of TCAD and atherosclerosis

Sign	TCAD	Atherosclerosis
Vascular involvement	Epicardial and intramural coronary arteries are affected.	Large epicardial coronary arteries are affected.
	Diffuse and very extensive vascular lesions in combination with epicardial localization.	Proximal epicardial coronary arteries are largely affected. Intramyocardial vessels and arteries under muscle bridges are usually intact.
	Veins may also be involved.	Veins are never involved.
	The media may be either unaffected or almost completely replaced by fibrous tissue. As intimal lesion progresses, fibrosis of the media and adventitia also increases.	All the vascular wall layers are involved.
Nature of lesion	Diffuse, concentric intimal thickening.	Focal, eccentric proliferative and degenerative intimal lesions in the proximal coronary vessels.
	Varies from concentric, diffuse intimal lesions to widespread fibrofatty plaques with degeneration.	Predominantly fibrofatty plaques with necrotic depressions and progressively thinned fibrous cap.
Onset and progression of the disease	Initially manifested by smooth muscle cell proliferation into the intima and extracellular lipid accumulation.	Initially manifested by fatty streaks.
	Accelerated progression of intimal proliferation and luminal stenosis at the early stage of the disease with the development of foam cells.	Slow progression of the lesion (decades) is characteristic.
	Superficial endothelial erosion is uncommon but may be a rare finding.	Endothelial erosion is characteristic.
	Fibrous capsule thinning and plaque rupture are rare.	Thin fibrous capsule and plaque rupture are often observed in moderate to severe lesions.

Other factors influencing the course of vasculopathy: Increased platelet aggregation is a well-recognized risk factor for sudden cardiac death and myocardial infarction in heart transplant patients [1]. A study of over 200 heart transplant recipients found that early aspirin therapy was associated with a significant (68%) reduction in the risk of cardiovascular events [27].

Statins are well-known hypolipidemic and anti-inflammatory drugs [28]. A recent meta-analysis confirmed the beneficial effects of statins in reducing graft rejection and increasing survival in heart transplant recipients [28]. Fang et al. studied antioxidant therapy with vitamins C and E to prevent endothelial dysfunction in TCAD. The authors found that antioxidant therapy delayed TCAD [29]. Calcineurin inhibitors (cyclosporine, tacrolimus) have historically been the therapy of choice for maintenance immunosuppression [30]. The development of agents such as everolimus and sirolimus has expanded therapeutic options for TCAD. Everolimus has been shown to significantly reduce TCAD progression when combined with immunosuppressants (cyclosporine, tacrolimus) at year 1 after transplantation compared to when combined with mycophenolate and azathioprine. On the other hand, later initiation of everolimus therapy does not increase vasculopathy incidence. Sirolimus therapy resulted in decreased incidence of acute graft rejection and vasculopathy compared to calcineurin inhibitors. There is evidence that sirolimus can inhibit TCAD, even when initiated after disease onset [31]. These drugs, however, need further evaluation when combined with newer immunosuppressants such as tacrolimus [4, 17]. It should be noted that their use may be limited in some patients due to the high incidence of side effects, such as infections, pericardial effusion and delayed wound healing [31].

Unfortunately, these measures have had little impact on the 5- and 10-year incidence of TCAD over the last 20 years of follow-up (32–30% and 52–49%, respectively) [16]. Furthermore, for recipients who develop TCAD within 3 years after transplantation, the 5-year survival rate remains virtually the same as 20 years ago (28–22%) [16]. These statistics highlight how the need for more sensitive techniques for early TCAD detection severely limits therapy options for heart transplant recipients at this stage. This is because effective treatment to prevent or delay TCAD must be initiated as soon as feasible.

There have been recent studies to identify potential targets for immunologic treatment, mainly using monoclonal antibodies, to eventually replace existing therapeutic immunosuppressants [32]. The main goal of immunomodulation in the context of TCAD has been to inhibit or suppress predominantly T-cell activity against the allograft [4].

CONCLUSION

Transplant coronary artery disease is one of the main factors limiting graft survival. Due to its intricate origins and multifaceted nature, this condition requires further study on both immune contribution to the pathogenesis of vasculopathy and the classical factors of atherogene-

sis. Infectious agents (CMV) deserve special attention as early detection and influence on them can improve the prognosis for this patient cohort. Even though CAV manifests 3–5 years after heart transplantation, the first signs may appear in the first year, which in turn is an unfavorable predictor. This necessitates prompt modifications to immunosuppressive medication and closer observation of the disease's progression. Even though modern immunosuppressive medications, such as everolimus, cannot be used in every patient, incorporating them more frequently into treatment plans could help cardiac recipients have better outcomes. Correcting the classical atherosclerosis factors is another crucial aspect of treatment for heart transplant patients.

The authors declare no conflict of interest.

REFERENCES

1. *Gautier SV, Khomyakov SM*. Organ donation and transplantation in the Russian Federation in 2022. 15th Report from the Registry of the Russian Transplant Society. *Russian Journal of Transplantology and Artificial Organs*. 2023; 25 (3): 8–30. https://doi.org/10.15825/1995-1191-2023-3-8-30.
2. *Khush KK, Cherikh WS, Chambers DC, Harhay MO, Hayes D Jr, Hsich E* et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: thirty-sixth adult heart transplantation report – 2019. *J Heart Lung Transplant*. 2019; 38 (10): 1056–1066. doi: 10.1016/j.healun.2019.08.004.
3. *Shah KS, Kittleson MM, Kobashigawa JA*. Updates on Heart Transplantation. *Curr Heart Fail Rep*. 2019 Oct; 16 (5): 150–156. doi: 10.1007/s11897-019-00432-3.
4. *Shetty M, Chowdhury YS*. Heart Transplantation Allograft Vasculopathy. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2023.
5. *Lee F, Nair V, Chih S.* Cardiac allograft vasculopathy: Insights on pathogenesis and therapy. *Clin Transplant*. 2020 Mar; 34 (3): e13794. doi: 10.1111/ctr.13794.
6. *Spitaleri G, Farrero Torres M, Sabatino M, Potena L.* The pharmaceutical management of cardiac allograft vasculopathy after heart transplantation. *Expert Opin Pharmacother*. 2020; 21 (11): 1367–1376.
7. *Spartalis M, Spartalis E, Siasos G.* Cardiac allograft vasculopathy after heart transplantation: Pathophysiology, detection approaches, prevention, and treatment management. *Trends Cardiovasc Med*. 2022 Aug; 32 (6): 333–338. doi: 10.1016/j.tcm.2021.07.002.
8. *Rahmani M, Cruz RP, Granville DJ, McManus BM.* Allograft vasculopathy versus atherosclerosis. Circ Res. 2006 Oct 13; 99 (8): 801–815. doi: 10.1161/01.RES.0000246086.93555.f3.
9. *Hu D, Yin C, Luo S, Habenicht AJR, Mohanta SK*. Vascular Smooth Muscle Cells Contribute to Atherosclerosis Immunity. *Front Immunol*. 2019 May 17; 10: 1101. doi: 10.3389/fimmu.2019.01101.
10. *Doulamis IP.* Editorial commentary: Cardiac allograft vasculopathy: Caveats and perspectives. *Trends Cardiovasc Med*. 2022; 32 (6): 339–340. doi: 10.1016/j.tcm.2021.07.007.
11. Bolezn' koronarnykh arteriy peresazhennogo serdtsa. Pod red. V.I. Shumakova. M.: MIA, 2008; 160. [Electronic resource]. https://www.centrmag.ru/catalog/product/bolezn-koronarnyh-arterij-peresazhennogo-serdca/ (accessed: 17.10.2023).
12. *Alyaydin E, Welp H, Reinecke H, Tuleta I.* Predisposing factors for late mortality in heart transplant patients. *Cardiol J*. 2021; 28 (5): 746–757. doi: 10.5603/CJ.a2020.0011.
13. *Guzik B, Szczepanek E, Niewiara Ł, Nosal M, Wierzbicki K, Krzanowski M et al.* Coronary revascularization after heart transplant – the search for prognostic factors. *Arch Med Sci*. 2020 Apr 18; 16 (4): 789–795. doi: 10.5114/aoms.2017.71847.
14. *Foroutan F, Alba AC, Guyatt G, Duero Posada J, Ng Fat Hing N, Arseneau E et al.* Predictors of 1-year mortality in heart transplant recipients: a systematic review and meta-analysis. *Heart*. 2018 Jan; 104 (2): 151–160. doi: 10.1136/heartjnl-2017-311435.
15. *Sakhovskiy SA, Izotov DA, Goncharova AYu, Koloskova NN, Mironkov BL.* Koronarnyy ateroskleroz donorskogo serdtsa. *Vserossiyskaya nauchno-prakticheskaya konferentsiya s mezhdunarodnym uchastiem "Kompleksnye problemy serdechno-sosudistykh zabolevaniy"*. 2021; S2: 166. https://cyberleninka.ru/article/n/koronarnyy-ateroskleroz-donorskogo-serdtsa (date of reference: 12.01.2024).
16. *Stehlik J, Kobashigawa J, Hunt SA, Reichenspurner H, Kirklin JK.* Honoring 50 Years of Clinical Heart Transplantation in Circulation: In-Depth State-of-the-Art Review. *Circulation*. 2018 Jan 2; 137 (1): 71–87. doi: 10.1161/CIRCULATIONAHA.117.029753.
17. *Lu WH, Palatnik K, Fishbein GA, Lai C, Levi DS, Perens G et al.* Diverse morphologic manifestations of cardiac allograft vasculopathy: a pathologic study of 64 allograft hearts. *J Heart Lung Transplant*. 2011 Sep; 30 (9): 1044–1050. doi: 10.1016/j.healun.2011.04.008.
18. *Mozheyko NP.* Patomorfologiya transplantirovannogo serdtsa: dis. … dokt. med. nauk. M., 2020; 171. [Electronic resource]. https://freereferats.ru/product_info.php?products_id=691983 (accessed: 17.10.2023).
19. *Muminov II, Koloskova NN, Poptsov VN, Zakharevich VM, Mozheiko NP, Sakhovsky SA, Shevchenko AO*. Experience of outpatient follow-up of heart transplant recipients at Shumakov center. *Russian Journal of Transplantology and Artificial Organs*. 2023; 25 (3): 68–75. https://doi.org/10.15825/1995-1191-2023-3-68-75.
20. *Sakhovskiy SA, Uvarova DD, Mironkov BL*. Techenie koronarnoy patologii u retsipientov serdtsa s gemodinamicheski ne znachimym transmissivnym ateroskleroz om. *Russian Journal of Transplantology and Artificial Organs*. 2023; 25 (S): 46.
21. *Sakhovsky SA, Koloskova NN, Izotov DA, Spirina EA, Goncharova AYu, Luchkin VM, Mironkov BL*. Life expectancy of heart recipients with donor-transmitted coronary atherosclerosis. *Russian Journal of Transplantology and Artificial Organs*. 2019; 21 (4): 14–19. https://doi.org/10.15825/1995-1191-2019-4-14-19.

22. *Chestukhin VV, Ostroumov EN, Tyunyaeva IYu, Zakharevich VM i dr.* Bolezn' koronarnykh arteriy peresazhennogo serdtsa. Vozmozhnosti diagnostiki i lecheniya. *Ocherki klinicheskoy transplantologii*. Pod red S.V. Gautier. M., 2009: 88–93.
23. *Gautier SV, Shevchenko AO, Poptsov VN.* Patsient s transplantirovannym serdtsem: rukovodstvo dlya vrachey po vedeniyu patsientov, perenesshikh transplantatsiyu serdtsa. M.–Tver': Triada, 2014; 144.
24. *Velleca A, Shullo MA, Dhital K, Azeka E, Colvin M, DePasquale E et al.* The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2023 May; 42 (5): e1–e141. doi: 10.1016/j.healun.2022.10.015.
25. *Raichlin E, Bae JH, Kushwaha SS, Lennon RJ, Prasad A, Rihal CS, Lerman A.* Inflammatory burden of cardiac allograft coronary atherosclerotic plaque is associated with early recurrent cellular rejection and predicts a higher risk of vasculopathy progression. *J Am Coll Cardiol*. 2009 Apr 14; 53 (15): 1279–1286. doi: 10.1016/j.jacc.2008.12.041.
26. *Pighi M, Gratta A, Marin F, Bellamoli M, Lunardi M, Fezzi S et al.* Cardiac allograft vasculopathy: Pathogenesis, diagnosis and therapy. *Transplant Rev (Orlando)*. 2020 Oct; 34 (4): 100569. doi: 10.1016/j.trre.2020.100569.
27. *Peled Y, Lavee J, Raichlin E, Katz M, Arad M, Kassif Y et al.* Early aspirin initiation following heart transplantation is associated with reduced risk of allograft vasculopathy during long-term follow-up. *Clin Transplant*. 2017 Dec; 31 (12). doi: 10.1111/ctr.13133.
28. *Vallakati A, Reddy S, Dunlap ME, Taylor DO.* Impact of Statin Use After Heart Transplantation: A Meta-Analysis. *Circ Heart Fail*. 2016 Oct; 9 (10): e003265. doi: 10.1161/CIRCHEARTFAILURE.116.003265.
29. *Fang JC, Kinlay S, Beltrame J, Hikiti H, Wainstein M, Behrendt D et al.* Effect of vitamins C and E on progression of transplant-associated arteriosclerosis: a randomised trial. *Lancet*. 2002 Mar 30; 359 (9312): 1108–1113. doi: 10.1016/S0140-6736(02)08154-0.
30. *Mallah SI, Atallah B, Moustafa F, Naguib M, El Hajj S, Bader F, Mehra MR.* Evidence-based pharmacotherapy for prevention and management of cardiac allograft vasculopathy. *Prog Cardiovasc Dis*. 2020 May-Jun; 63 (3): 194–209. doi: 10.1016/j.pcad.2020.03.007.
31. *Masetti M, Potena L, Nardozza M, Prestinenzi P, Taglieri N, Saia F et al.* Differential effect of everolimus on progression of early and late cardiac allograft vasculopathy in current clinical practice. *Am J Transplant*. 2013 May; 13 (5): 1217–1226. doi: 10.1111/ajt.12208.
32. *Bellumkonda L, Patel J.* Recent advances in the role of mammalian target of rapamycin inhibitors on cardiac allograft vasculopathy. *Clin Transplant*. 2020 Jan; 34 (1): e13769. doi: 10.1111/ctr.13769.

The article was submitted to the journal on 07.02.2024