International Journal of Cardiology 290 (2019) 129–133

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Association between aortic telomere length and cardiac post-transplant allograft function☆,☆☆,☆☆☆

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ARTICLE INFO

Article history:
Received 26 September 2018
Received in revised form 15 March 2019
Accepted 2 May 2019
Available online 7 May 2019

Keywords:
Telomere length
Aortic tissue
DNA
Heart transplantation
Cellular rejection

ABSTRACT

Background: In patients having undergone orthotopic heart transplantation, a number of complications exist that are known to be connected to both telomerase activity and telomere length. The aim of this study was to determine how telomere length in aortic DNA correlates with the subsequent post-transplantation development of the patients.

Materials and methods: Between 2005 and 2015, we collected aortic samples from 376 heart recipients (age 50.8 ± 11.8 years) and 383 donors (age 38.6 ± 12.2 years). Relative telomere length in aortic tissue DNA was determined using quantitative PCR.

Results: Shorter telomere length was detected in heart allograft recipients compared to donors ($P < 0.0001$). Patients suffering acute cellular rejection had significantly shorter telomere length ($P < 0.01$) than patients without rejection. Shorter telomere length was observed in patients with implanted mechanical circulatory support before heart transplantation ($P < 0.03$), as well as in subjects with cardiac allograft vasculopathy ($P < 0.05$). Overall survival time after heart transplantation was associated with shorter donor telomeres ($P < 0.004$).

Conclusions: Telomere length differed between donors and recipients independent of the sex and age of the patients. Our findings suggest a potential new linkage between the aortic telomere length of recipients and post-heart transplant complications. Further studies focusing on epigenetic modifications and gene regulation involved in telomere maintenance in transplanted patients should verify our results.

1. Introduction

Heart failure (HF) is a complex and highly prevalent condition, one in which the heart undergoes substantial molecular, cellular and histologic changes, a process known as "cardiac remodelling" [1]. Triggered by a wide range of disease-related cues, HF pathophysiology is governed by both genetic and epigenetic events. The accumulation of DNA damage and telomere attrition increases cellular senescence and apoptosis and decreases the number of cells and influences their function, which, in turn, contributes to overall tissue and organ dysfunction [2]. Telomeres are non-coding structures located at each end of eukaryotic chromosomes. Their functional role is to maintain genomic stability. Telomeres consist of a large number of tandem repeats (TTAGGG in humans), and telomere length (TL) is an important determinant of telomere function [2,3]. TL depends on many factors, including inheritance, cellular replicative history and the activity level of telomerase and reverse transcriptases [4]. Shorter leukocyte TL has been previously detected in subjects with different cardiometabolic diseases [5–8]. Telomere dysfunction and increased susceptibility to apoptosis in cardiac myocytes have been acknowledged as underlying mechanisms of HF [9]. In humans, endomyocardial biopsies (EMB) from patients with HF

Abbreviations: ABMR, antibody mediated rejection; ACR, acute cellular rejection; ArTL, aortic relative telomere length; CAV, cardiac allograft vasculopathy; CGD, chronic graft dysfunction; DNA, deoxyribonucleic acid; EMB, endomyocardial biopsy; HF, heart failure; LVAD, left ventricular assist device; MCS, mechanical circulatory support; OHT, orthotopic heart transplantation; PCR, polymerase chain reaction; SCG, single copy gene; ST, survival time; TL, telomere length; VAD, ventricular assist device; VSMCs, vascular smooth muscle cells.

☆ None of the authors have a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

☆☆ This work was supported by the Ministry of Health of the Czech Republic – conceptual development of research organizations (Institute for Clinical and Experimental Medicine – IKEM, IN 00023001).

☆☆☆ DD designed and performed the experiments, analysed the data, and wrote the article. JH contributed to the design of experiments and the interpretation of results and edited the article. JV performed the clinical aspects of the project, contributed to the interpretation of the results and edited the article. VL performed statistical analyses. IM conceived and directed the study.

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https://doi.org/10.1016/j.ijcard.2019.05.006
0167-5273/

have revealed shortened telomeres, increased cellular senescence and cell death. In aged hearts with mild hypertrophy and biventricular failure, shorter average telomere length has been found [10].

The implantation of mechanical circulatory support (MCS) improves survival and quality of life for HF patients not responding to medical therapy and is, along with heart transplantation, a leading therapeutic option for these patients. Although MCS technology is improving, heart transplantation remains the preferred treatment for many patients because of major complications in MCS, such as stroke, bleeding and infection, and due to the limited quality of life-related drivelines and battery change requirements [11]. Unfortunately, there are still many short-term (primary graft failure, infection, graft rejection) and long-term (neoplasm, cardiac allograft vasculopathy) complications that can lead to heart failure and patient death after orthotopic heart transplantation (OHT) [12].

Most previously reported studies that have compared recipient/donor TL, and the transplantation outcomes have been assessed in kidney, lung and liver transplant subjects. Moreover, TL has been measured in different types of tissues, mostly in leukocytes [13–15], lymphocytes [16–18], lung tissues [18], and hepatocytes [19], with dissimilar results. There is a paucity of studies that have focused on TL in cardiovascular tissues .[20,21].

Whether there is a link between telomere dynamics measured in leukocytes or lymphocytes and those in cardiovascular tissue is still unclear. Recently, Marques et al. [22] detected a correlation between leukocyte TL and cardiac TL in hypertrophic rat hearts. Furthermore, Yin et al. [23] used multi-tissue assessments from patients who underwent cardiovascular surgery and determined that the cardiac atrium-leukocyte telomere length difference could predict post-operative complexity. In our study, we examined aortic telomere length (ArTL) in a large group of heart allograft recipients and donors in order to determine the relationship between telomere shortening and accelerated immunosenescence of the arterial system. Our hypothesis was that telomere length in aortas is associated with post-transplant complications such as acute cellular rejection (ACR) and cardiac allograft vasculopathy (CAV).

2. Materials and methods

2.1. Clinical study

2.1.1. Subjects

Samples of aortic tissue were collected from January 2005 to December 2015 at the Institute for Clinical and Experimental Medicine in Prague. A total of 797 tissue samples were obtained during OHT (406 donors and 391 recipients). Subjects with repeated OHT ($N = 3$) and samples with low-quality DNA ($N = 35$) were excluded from the analysis. ArTL was measured in 376 heart recipients and 383 donors. The protocol of this study was carried out according to the principles of the Declaration of Helsinki [24]. All examined individuals provided their informed consent, which, together with the study protocol, was approved by the institution's ethics committee.

EMB was used for surveillance of cardiac allograft rejection and for the diagnosis of unexplained ventricular dysfunction. On the same day, transthoracic echocardiography was also performed. Multiple myocardial biopsy samples were examined for evidence of rejection by trained pathologists according to updated international classification criteria. ACR was defined according to Revision of the 1990 Working Formulation for the Standardization of Nomenclature in the Diagnosis of Heart Rejection [25]. Antibody-mediated rejection (ABMR) was defined according to the most recent recommendations of the pathology task force of the ISHLT as follows: pAMR0: no features of ABMR; pAMR1: suspicious ABMR subdivided into pAMR1(H+) – histopathology-positive and immunohistochemistry-negative – and pAMR1(I+) – histopathology-negative and immunohistochemistry-positive; pAMR2: histopathology and immunohistochemistry (both positive); pAMR3: severe ABMR [26]. Diagnostic coronary angiography was used for examination of CAV.

2.1.2. DNA analysis

Genomic DNA was isolated from a maximum of 100 mg of the aortic samples using the modified "salt out" method [27] after cell lysis by Proteinase K (Fermentas).

The quantity and purity of isolated DNA were examined by standard spectrophotometry using a Nanodrop 2000 spectrophotometer (Thermo Scientific, USA). DNA integrity was tested on 1.0% agarose gel (Bio Rad Power Pac 300) after visualization using ethidium bromide.

2.1.3. Measurement of telomere length

Relative telomere length was analysed as described previously [28] with slight modifications [8,29]. Briefly, the relative telomere length was calculated as the ratio of telomere repeats to single-copy gene (SCG) copies (T/S ratio). The acidic ribosomal phosphoprotein PO (36B4) gene was selected as the SCG. For each sample, the quantity of telomere repeats and the quantity of SCG copies were determined compared to a reference sample. Identical reference DNA was used in all runs to allow comparisons of the results in different runs. All PCRs were performed in triplicate on the Rotor-Gene 3000 (Corbett Research Ltd). The raw data from each PCR were analysed using comparative quantification analysis. The second derivative of the amplification curve was considered in order to identify the peak of the exponential amplification and to determine the take-off of the reaction. The take-off was estimated by finding the first point to be 80% below the peak level. Based on the take-off point and the amplification, the method calculated the relative quantity of telomere repeats or SCG copies in each sample compared to the reference sample. Oligonucleotide sequences were as follows: telomere analysis 5′ GGT TTT TGA GGG TGA GGG TGA GGG TGA GGG TGA GGG T and 5′ TCC CGA CTA TCC CTA TCC CTA TCC CTA TCC CTA TCC CTA; single copy gene 5′ CAG CAA GTG GGA AGG TGT AAT CC and 5′ CCC ATT CTA TCA TCA ACG GGT ACA A. To examine the measurement stability of telomere length by qPCR analysis, both intra-assay (1.9–6.9%) and inter-assay reproducibility were evaluated (3.4–14.8%) [29]. Inter-plate calibration was performed to quality-control each run.

2.2. Statistical analysis

Analysis was carried out using JMP 10 statistical software. Normal (Gaussian) distributions of ArTL data were examined using the Shapiro-Wilk W test. Continuous data are expressed as the means ± SD and as median and interquartile range when non-normally distributed. Non-parametric Spearman's correlation was performed to determine the strength of association between age and telomere length. Student's or nonparametric Mann-Whitney tests were used for differences between groups. P values <0.05 were considered significant.

3. Results

The basic characteristics of the study group are described in Table 1.

As expected, allograft recipients were older than donors (50.8 ± 11.8 vs. 38.6 ± 12.2 years; $P < 0.0001$) and had significantly shorter ArTL (0.84 ± 0.28 vs. 0.99 ± 0.31, $P < 0.0001$). In contrast with donors, the age of recipients did not correlate with relative telomere length (Fig. 1). Gender proportions (Table 1) were similar in both groups, without impacting ArTL.

Donor ArTL was neither associated with ACR nor ABMR, chronic graft dysfunction (CGD), or CAV development in our study.

Recipient ArTL was identical in patients with ischaemic and non-ischaemic HF aetiology (0.83 ± 0.29 vs. 0.82 ± 0.26). Relative telomere length differed between groups of patients with congenital heart defects and cardiac causes of HF (0.93 ± 0.31 vs. 0.83 ± 0.28; $P < 0.03$), but the differences disappeared after age adjustment.

Table 1
Basic characteristics of patients included in the study. Age, ArTL and survival time are expressed as the means ± SD.

	N
Recipients (males/females)	376 (302/74)
Donors (males/females)	383 (288/95)
Recipient age (years)	50.8 ± 11.8
Donor age (years)	38.6 ± 12.2
Recipient ArTL (T/S ratio)	0.84 ± 0.28
Donor ArTL (T/S ratio)	0.99 ± 0.31
Aetiology of heart failure (N)	
Dilated cardiomyopathy	154
Coronary artery disease	156
Congenital heart defects	59
Other	7
LVAD before heart transplantation (N)	99
Rejection (N)	
ACR/repeated ACR	135/25
ABMR	32
Cardiac allograft vasculopathy	56
Chronic graft dysfunction	55

Overall, ACR developed in 135 subjects. The majority ($N = 96$) of patients were affected during the first 6 months after OHT. Shorter recipient ArTL was associated with the occurrence of ACR ($P < 0.006$ and $P < 0.01$* after age adjustment) but not with ABMR ($N = 32$; Table 2).

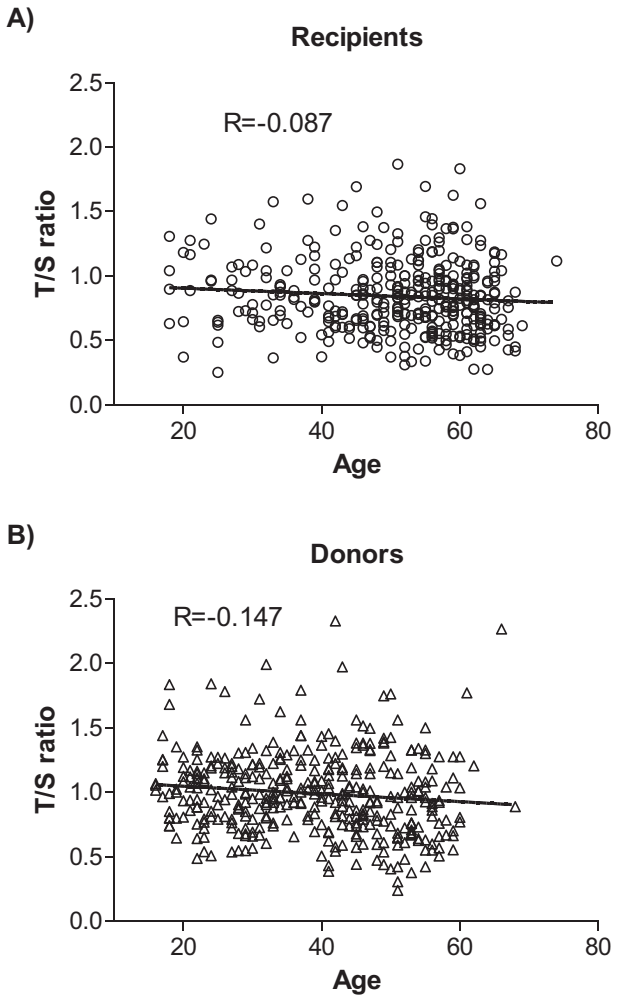

Fig. 1. Correlation between aortic telomere length and age. Panel A for recipients ($N = 376$; R = -0.087; $P = 0.09$) and panel B for donors ($N = 383$; R = -0.147; $P < 0.01$). ArTL is expressed as T/S ratio. Correlation coefficients were calculated for the respective data sets, and their values are plotted in the graphs denoted as R. The lines in the graphs represent simple linear regression.

Pronounced relationships between recipient ArTL and ACR were observed, especially during the first 6 months after OHT ($P = 0.001$ and $P < 0.01$* after age adjustment; Table 3). Moreover, a subgroup of patients with repeated ACR occurrence ($N = 25$) exhibited the shortest recipient ArTL (0.69 ± 0.20).

CGD affected 55 patients, while there was no difference in recipient ArTL between patients with or without CGD ($P < 0.42$; Table 2).

CAV was detected in 56 heart recipients. In nearly 40% of affected subjects, CAV occurred within the first year after OHT. A borderline association ($P < 0.05$) between the shorter ArTL of recipients and CAV was detected, but it disappeared after age adjustment ($P = 0.08$*; Table 2).

Patients with implanted left ventricular assist devices (LVAD; $N = 99$) exhibited reduced recipient ArTL (0.79 ± 0.26 vs. 0.86 ± 0.29; $P < 0.03$* after age adjustment), without any significant effects of VAD type on ArTL (Fig. 2). The median duration of LVAD implantation was 201 days (interquartile range 81 to 413 days). The LVAD duration was not associated with ArTL, nor did it influence the survival time (ST) of patients. In recipients who had implanted LVADs and who were affected by CAV ($N = 14$), we found shorter ArTL compared to subjects ($N = 111$) without CAV and previous mechanical circulatory support (0.66 ± 0.18 vs. 0.86 ± 0.26; $P < 0.03$). Subjects with LVAD ($N = 31$) who were affected ACR showed insignificantly shorter ArTL (0.74 ± 0.25 vs. 0.81 ± 0.27; $P = 0.22$).

The follow-up (FU) time ranged from 0 to 12.2 years, with a median (interquartile range) of 5.3 (2.4 to 8.3 years). During FU, 83 transplanted patients died. The median ST was 339 days (interquartile range 41 to 1098 days). Shorter donor ArTL was found in surviving recipients (0.97 ± 0.30 vs. 1.10 ± 0.34; $P = 0.003$). The worst post-transplant survival outcomes bore no association with the ArTL of recipients but, surprisingly, were significantly associated with longer telomere length in donors (RR = 2.8, 95% CI = 1.4–5.4; $P < 0.004$* after age adjustment).

4. Discussion

There is a scarcity of studies focused on the association between telomere length and complications after heart transplantation. Most of the previously reported studies have focused on the telomere length measured in leukocytes as a relative non-invasive source of samples, although there is different correlation linkage with the length of telomeres in different tissues [23,29]. Our large retrospective study is the first to investigate the connection between differences in aortic telomere length among donors and recipients of heart allograft, with a special focus on post-transplant complications.

First, we detected significantly shorter ArtL in patients with HF compared to healthy donors without a correlation between age and telomere length in recipients. These findings probably reflect HF disease status, which alters vascular ageing, and they are in an agreement with previous studies, which have reported shorter telomere lengths in aortic tissues among patients with atherosclerotic lesions [30] and reduced telomere length and telomerase expression in patients exhibiting aortic abdominal aneurisms [31,32]. Vascular smooth muscle cells (VSMCs), which make up the muscular middle layer of arteries, unlike cardiac and skeletal muscle cells, are capable of modulating their phenotypes in response to vascular injury or environmental cues [33]. The proliferation of VSMC closely correlates with increased telomerase activity. VSMC senescence in atherosclerosis is associated with loss of telomeric repeat-binding factor 2 [34], while decreasing telomere length in arteries probably reflects vascular ageing [35]. Our finding of shorter ArTL in HF subjects was also in agreement with previously reported studies [36,37] in which the telomere length of circulating leukocytes and cardiomyocytes were compared. Moreover, we observed no difference in ArTL between patients with ischaemic and non-ischaemic causes of HF. The similar telomere length in aortic tissue in both groups was probably caused by local factors associated with

Table 2
Association between ArTL and secondary post-transplantation outcomes. The mean ArTL ± SD for events and non-events. ACR – acute cellular rejection; ABMR – antibody mediated rejection; CAV – cardiac allograft vasculopathy; CGD – chronic graft dysfunction.

	Recipients				Donors		
	Events	Non-events	*P* value		Events	Non-events	*P* value
ACR	0.78 ± 0.27 (*N* = 135)	0.87 ± 0.28 (*N* = 241)	<0.01*	ACR	0.98 ± 0.29 (*N* = 140)	0.99 ± 0.33 (*N* = 243)	0.75
ABMR	0.85 ± 0.29 (N = 32)	0.84 ± 0.28 (*N* = 344)	0.75	ABMR	0.98 ± 0.29 (N = 34)	0.99 ± 0.32 (*N* = 349)	0.92
CAV	0.77 ± 0.26 (*N* = 56)	0.85 ± 0.26 (*N* = 320)	0.08*	CAV	1.00 ± 0.36 (N = 56)	0.97 ± 0.28 (*N* = 327)	0.77
CGD	0.83 ± 0.33 (*N* = 55)	0.84 ± 0.27 (*N* = 321)	0.42	CGD	1.03 ± 0.34 (N = 57)	0.98 ± 0.31 (*N* = 326)	0.41

* *P value* after age adjustment.

haemodynamics, atherosclerosis, increased apoptosis and DNA damage in aortic walls induced by cardiac disease.

Second, we demonstrated a relationship between the shorter ArTL of heart recipients and ACR. Rejection of the transplanted heart is a major cause of morbidity and mortality in the first year after transplantation. ACR is a T-cell-mediated response involving infiltration of lymphocytes and macrophages and resultant myocytolysis. Shorter aortic telomeres that were already present before OHT in patients affected by ACR could be a result of chronic oxidative and biomechanical stresses and inflammation in these subjects. Inflammation and heart failure are strongly interconnected. Accelerated cellular senescence together with telomere attrition in aortas probably contribute to the development of ACR and worse post-transplant outcomes for patients. In a direct comparison with studies performed on another organ tissue, Domanski et al. [38] found, similar to our results, a correlation between shorter telomeres in biopsy specimens of kidney allografts and delayed graft function, acute rejection and chronic allograft dysfunction. In contrast, Courtwright et al. [18] found no association between recipient lung tissue telomere length and ACR in a study cohort of 54 subjects. ABMR, also called vascular rejection, occurs days to weeks after OHT and is much less common than ACR. Initiated by antibodies as opposed to T cells, alloantibodies are directed against donor HLA or endothelial cell antigens [39]. Recently, an association between ABMR and graft loss, cardiac allograft vasculopathy and death was reported [40–42]. In our study, we found no linkage between ArTL and ABMR in recipients affected by chronic graft dysfunction, which could be influenced by small sample size ($N = 39$ resp. $N = 57$).

Third, we found reduced telomere length within aortic tissue in relation to the post-transplant CAV occurrence. CAV is one of the major causes of post-transplant morbidity and mortality, occurring as early as the first year after OHT (in the case of approximately 10% of subjects), and it affects nearly 40% of patients within 5 years after OHT. CAV typically involves a combination of accelerated atherosclerosis and chronic rejection. The aetiology of CAV is not clear since the influence of immunological factors is assumed.

Additionally, we found significantly shorter ArTL in patients with implanted LVADs before OHT, without a relationship between VAD type, support duration or telomere length. The implantation of LVADs improves survival and quality of life for HF patients who do not respond to medical therapy; it is also commonly used as a bridge to heart transplantation. However, some studies of patients with LVAD have demonstrated changes in the structure, composition, compliance and stiffness of the aortic wall [43–45], factors that are associated with vascular ageing and that can be present before the clinical manifestation of cardiovascular disease [46]. Briefly, smooth muscle and elastic fibre degeneration [47] and the development of vascular inflammation have all been reported [48], which could support our results. Our findings of shorter aortic telomeres in LVAD patients affected by CAV could suggest accelerated senescence of aortic tissue leading or contributing to post-transplant complications. Due to the small number of affected individuals ($N = 14$), the result needs to be further verified.

Interestingly, we detected a relationship between shorter donor aortic telomere length and overall survival in patients after OHT. In contrast, it was previously reported that there was no association between donor telomere length and survival in transplanted subjects [15,18], or worse post-transplant outcome with shorter donor telomeres was described [49]. In almost all mentioned studies, leukocyte telomere length was analysed. However, there are doubts about the relevant correlations between telomere length measured in leukocytes and in different tissues. In our previous study, we found an inverse correlation between leukocyte and aortic telomere length in recipients of heart allografts [21]. Whether the negative correlation is the consequence of severe heart failure or if there is a potential influence of immunosuppressive treatment after OHT remains unclear. Unfortunately, it

Table 3
Recipient aortic telomere length and the occurrence of acute cellular rejection. The occurrence of acute cellular rejection (ACR) within the period of 0 to 6 months, 7 to 12 months and >1 year after OHT. Recipients with ACR have generally shorter ArTL than others. The mean ArTL± SD for events and non-events.

Rejection	Events		Non-events		*P* value
ACR	N	Mean ± SD	N	Mean ± SD	
0–6 M	96	0.77 ± 0.27	219	0.87 ± 0.28	<0.01*
7–12 M	21	0.73 ± 0.21	209	0.88 ± 0.28	0.03
>12 M	45	0.79 ± 0.27	206	0.88 ± 0.28	0.07

* *P value* after age adjustment.

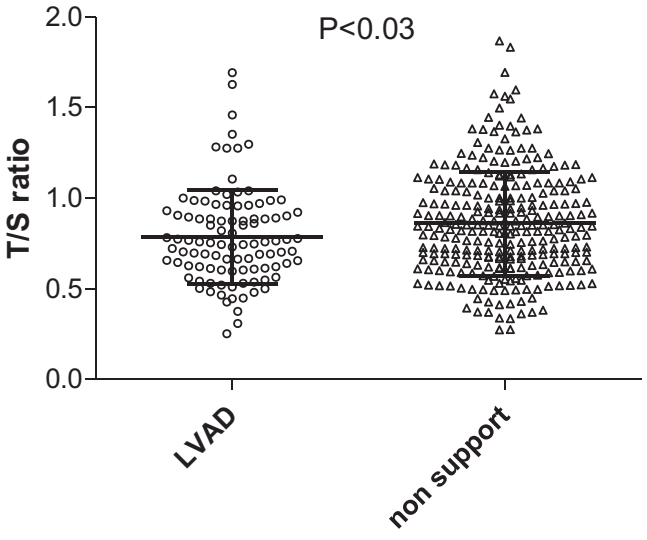

Fig. 2. Comparison of telomere length between groups of patients with or without implanted LVAD before OHT. Significantly shorter ArTL in subjects with LVAD ($N = 99$; 0.79 ± 0.26) compared to non-supported patients ($N = 275$; 0.86 ± 0.29); $P < 0.03$*. Data are shown as the means ± SD. ArTL is expressed as T/S ratio. * *P value* after age adjustment.

was not possible to obtain donor leukocyte samples to verify this linkage in the present study. Our findings suggest that shorter donor ArTL could result in lower response to heart allograft.

5. Conclusions

ArTL differed between donors and recipients independent of the sex and age of patients. Our findings suggest a potential new linkage between the aortic telomere length of recipients and post-heart transplant complications. Further studies focusing on epigenetic modifications and gene regulation involved in telomere maintenance in transplanted patients should verify our results.

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