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Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
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ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

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«ΕΝΔΑΓΓΕΙΑΚΕΣ ΤΕΧΝΙΚΕΣ»

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ: Cardiac Function Alteration after Thoracic Endovascular Aortic Repair based on Echocardiography: A systematic review and meta-analysis

ΜΕΤΑΠΤ. ΦΟΙΤΗΤΗΣ: ΠΑΠΑΚΩΝΣΤΑΝΤΙΝΟΥ ΚΩΝΣΤΑΝΤΙΝΟΣ

ΑΘΗΝΑ

ΙΟΥΝΙΟΣ 2021

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Η Επιτροπή **διαπίστωσε** ότι η Διπλωματική Εργασία του **Παπακωνσταντίνου Κωνσταντίνου** με τίτλο **«Cardiac Function Alteration after Thoracic Endovascular Aortic Repair based on Echocardiography: A systematic review and meta-analysis»** είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη.

Η εξεταστική επιτροπή αφού έλαβε υπόψιν το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους ..... προτείνει την απονομή στον παραπάνω Μεταπτυχιακό Φοιτητή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's).

Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους ....., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ..... και για τον βαθμό «ΚΑΛΩΣ» ψήφους ..... Κατά συνέπεια, απονέμεται ο βαθμός «.....».

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CONTENTS

Abstract

Background: Thoracic Endovascular Aortic Repair (TEVAR) is widely recognized as an alternative treatment to open surgery when considering thoracic aortic diseases. Evidence suggests that there is an increase in arterial stiffness post-TEVAR, as documented by an augmentation in Pulse Wave Velocity and certain biochemical markers, such as NT-proBNP, which signifies potential cardiac chamber stretching. However, the effect of the documented stiffness post-TEVAR on cardiac function has not been extensively studied.

Objective: To unveil potential alterations in cardiac function post-TEVAR based on certain Ultrasonographic markers [Left Ventricle Mass (LVM), Left Ventricle Mass Index (LVMI), Left Ventricle Ejection Fraction (LVEF), Left Ventricle End-Diastolic Diameter (LVEDD), Left Ventricle End-Systolic Diameter (LVESD), Interventricular Septal Thickness (IVST), Left Ventricle Posterior Wall Thickness (LVPWT)].

Data sources: A thorough literature search was applied using MEDLINE and CENTRAL bibliographic databases in March 2021. Free text terms, along with controlled vocabulary thesaurus ("MeSH" database) were used and reference lists of certain articles were evaluated for relevant information. No language or date restrictions were applied.

Study Selection: Non-Randomised Studies of Interventions of TEVAR in specified diseases [Thoracic Aortic Aneurysm, Thoracic Aortic Dissection (Type A, Type B, Non – A Non -B), Blunt Thoracic Aortic Injury], which examine cardiac function with ultrasonography encompassing the pre-specified parameters. Case reports, case studies and experimental studies were excluded. Patients with abdominal, or juxtarenal aortic aneurysms were also excluded.

Data extraction: Independent extraction of articles by two authors using pre-specified criteria.

Data synthesis: Four studies met the inclusion criteria and were included in the meta-analysis. Random- effects model was applied due to heterogeneity between the studies. Data were analyzed on mean values of LVM, LVMI, LVEF, LVEDD,

LVESD, IVST, LVPWT and standard deviation (SD) pre- and post-TEVAR from each individual study and the pooled standardized difference in means and 95% confidence interval (CI) were calculated. The between-study heterogeneity was examined with the combination of the Cochran's Q ($\chi 2$) test and the I^2 statistic. The meta-analysis results were non-significant for all parameters examined. However, LV mass showed borderline significance. In particular, for LVEF, non-significant differences were found pre- and post-TEVAR (SMD=-0.53, 95% CI=-1.8 to 0.728, P=0.406, I^2= 96%, P<0.0001). IVST results also were non-significant (SMD= -0.79, 95%CI= -3.25 to 1.66, P= 0.52, I^2=98%, P<0.0001). Concerning LVEDD, no significant alteration was documented (SMD= -0.10, 95%CI= -0.48 to 0.28, P= 0.60, I^2= 72%, P=0.0013). Regarding LVESD, no significant difference was found (SMD= -0.66, 95%CI= -2.35 to 1.02, P= 0.44, I^2=97%, P<0.0001). LVPWT did not differ significantly post-TEVAR (SMD= -2.20, 95%CI= -5.89 to 1.47, P= 0.24, I^2=99%, P<0.0001). Concerning LVM, a trend towards an increase was documented post-implantation (SMD= 0.28, 95%CI= -0.03 to 0.60, P= 0.08, I^2=0%, P=0.335), but not for LVMI (SMD = 0, 95%CI= -0.195 to 0.195, P=1, I^2=0%, P=1).

Conclusion: The present study's results did not show a trend towards cardiac function alteration after treatment with TEVAR, based on the echocardiographic parameters examined. A borderline significant increase in LV mass was documented, without other markers of LV geometry being affected. Despite the increase in arterial stiffness, LVEF and cardiac dimensions were not affected. Overall, the impact of TEVAR on heart physiology seems to be negligible.

ΠΕΡΙΛΗΨΗ

Υπόβαθρο: Η ενδαγγειακή αποκατάσταση της θωρακικής αορτής αναγνωρίζεται ευρέως ως μια εναλλακτική θεραπεία του ανοιχτού χειρουργείου σε ό,τι αφορά τις παθήσεις της θωρακικής αορτής. Υπάρχουν δεδομένα που υποδεικνύουν μια αύξηση στην αρτηριακή δυσκαμψία μετά την εμφύτευση του μοσχεύματος. Πράγματι, αυτό υποστηρίζεται από μια παρατηρούμενη αύξηση της Ταχύτητας Παλμικού Κύματος, καθώς και υπέρβαση των φυσιολογικών ορίων σε ορισμένους βιοδείκτες, όπως το NT-proBNP, το οποίο σηματοδοτεί μια δυνητική διάταση των καρδιακών κοιλοτήτων. Παρ'όλα αυτά, η επίδραση της δεδομένης αρτηριακής δυσκαμψίας μετά την ενδοαυλική αποκάτασταση στην καρδιακή λειτουργία δεν έχει επαρκώς μελετηθεί.

Σκοπός: Να ανακαλύψουμε δυνητικές αλλαγές στην καρδιακή λειτουργία μετά την ενδοαυλική αποκατάσταση της θωρακικής αορτής βασιζόμενοι σε συγκεκριμένα υπερηχογραφικά κριτήρια (Μάζα αριστερής κοιλίας, Δείκτης Μάζας αριστερής κοιλίας, Κλάσμα Εξώθησης αριστερής κοιλίας, Τελοδιαστολική Διάμετρος αριστερής κοιλίας, Τελοσυστολική Διάμετρος αριστερής κοιλίας, Πάχος Τοιχώματος Μεσοκοιλιακού Διαφράγματος, Πάχος Τοιχώματος Οπισθίου Τοιχώματος αριστερής κοιλίας).

Πηγές Πληροφόρησης: Πραγματοποιήθηκε μια ενδελεχής βιβλιογραφική αναζήτηση στις βιβλιογραφικές βάσεις δεδομένων PUBMED και CENTRAL τον Μάρτιο του 2021. Χρησιμοποιήθηκαν ποικίλλοι όροι σε διάφορους συνδυασμούς, η βάση "MeSH", καθώς και οι παραπομπές από συγκεκριμένα άρθρα. Δεν υπήρχαν γλωσσικοί ή χρονολογικοί περιορισμοί.

Επιλογή Μελετών: Μη τυχαιοποιημένες μελέτες ασθενών που υποβλήθηκαν σε ενδοαυλική αποκατάσταση παθήσεων της θωρακικής αορτής [θωρακικό αορτικό ανεύρυσμα, διαχωρισμός αορτής (τύπου Α, τύπου Β, Non – A Non -B), Αμβλύ Τραύμα Θωρακικής Αορτής) και που εξετάστηκαν με υπέρηχο καρδιάς (συμπεριλαμβανομένων των προαναφερθέντων παραμέτρων). Αναφορές περιστατικού/περιστατικών, πειραματικές μελέτες, καθώς και ασθενείς με κοιλιακό ή παρανεφρικό αορτικό ανεύρυσμα αποκλείσθηκαν από τη συστηματική

ανασκόπηση και μετα-ανάλυση μας.

Εξαγωγή δεδομένων: Ανεξάρτητη εξαγωγή δεδομένων από δυο συγγραφείς χρησιμοποιώντας συγκεκριμένα κριτήρια.

Σύνθεση δεδομένων: 4 μελέτες πληρούσαν τα κριτήρια συμμετοχής αι συμπεριλήφθηκαν στη μετα-ανάλυση. Το μοντέλο τυχαίων παραγόντων χρησιμοποίηθηκε λόγω ετερογένειας μεταξύ των μελετών. Τα δεδομένα αναλύθηκαν χρησιμοποιώντας την μέση τιμή των προαναφερθέντων παραμέτρων (Μάζα αριστερής κοιλίας, Δείκτης Μάζας αριστερής κοιλίας, Κλάσμα Εξώθησης αριστερής κοιλίας, Τελοδιαστολική Διάμετρος αριστερής κοιλίας, Τελοσυστολική Διάμετρος αριστερής κοιλίας, Πάχος Τοιχώματος Μεσοκοιλιακού Διαφράγματος, Πάχος Οπισθίου Τοιχώματος αριστερής κοιλίας) και υπολογίστηκε η τυπική απόκλιση πριν και μετά την επέμβαση για κάθε μια μελέτη και η συνδυασμένη τυπική διαφορά στις μέσες τιμές (ΣΤΔΜ), καθώς και τα 95% Διαστήματα Εμπιστοσύνης (ΔΕ). Η ετερογένεια μεταξύ των μελετών εξετάστηκε χρησιμοποιώντας το τεστ του Cochran Q (χ^2) και το τεστ I^2.Τα αποτελέσματα της μετα-ανάλυσης ήταν μη στατιστικά σημαντικά για όλες τις παραμέτρους που εξετάστηκαν. Ωστόσο, παρατηρήθηκε μια οριακά στατιστικά σημαντική διαφορά για τη Μάζα αριστερής κοιλίας. Πιο συγκεκριμένα, δεν παρατηρήθηκαν στατιστικά σημαντικές διαφορές για το Κλάσμα Εξώθησης αριστερής κοιλίας (ΣΤΔΜ=-0,53, 95% ΔΕ=-1,8 έως 0,728, P=0,406, I^2= 96%, P<0.000), το Πάχος Τοιχώματος Μεσοκοιλιακού Διαφράγματος (ΣΤΔΜ=-0,79, 95% ΔΕ=-3,25 έως 1,66, P=0,52, I^2= 98%, P<0.0001), την Τελοδιαστολική Διάμετρο της αριστερής κοιλίας (ΣΤΔΜ=-0,10, 95% ΔΕ=-0,48 έως 0,28, P=0,60, I^2= 72%, P=0.0013), την Τελοσυστολική Διάμετρο της αριστερής κοιλίας (ΣΤΔΜ= -0,66, 95%ΔΕ= -2,35 έως 1,02, P= 0,44, I^2=97%, P<0.0001) και το Πάχος Οπισθίου Τοιχώματος αριστερής κοιλίας (ΣΤΔΜ= -2,20, 95%ΔΕ= -5,89 to 1,47, P= 0,24, I^2=99%, P<0.0001). Όσον αφορά την Μάζα της αριστερής κοιλίας, παρατηρήθηκε μια τάση για αύξηση αυτής μετεπεμβατικά (ΣΤΔΜ= 0,28, 95%ΔΕ= -0,03 έως 0,60, P= 0,08, I^2=0%, P=0.335), χωρίς ωστόσο να ισχύει το ίδιο για τον Δείκτη Μάζας αριστερής κοιλίας (ΣΤΔΜ = 0, 95%ΔΕ= -0,195 έως 0,195, P=1, I^2=0%, P=1).

Συμπεράσματα: Τα αποτελέσματα της παρούσας μελέτης δεν έδειξαν κάποια τάση για μεταβολή της καρδιακής λειτουργίας μετά από ενδοαυλική αποκατάστασης παθήσεων της θωρακικής αορτής, βάσει των υπερηχογραφικών

παραμέτρων που εξετάστηκαν. Σημειώθηκε μια οριακά στατιστικά σημαντική αύξηση της Μάζας αριστερής κοιλίας, χωρίς όμως να επηρεάζονται άλλοι δείκτες της γεωμετρίας της αριστερής κοιλίας. Παρά την τροποποίηση της αρτηριακής δυσκαμψίας, το κλάσμα εξώθησης και οι διαστάσεις της αριστερής κοιλίας δεν επηρεάστηκαν. Συνολικά, η επίδραση της ενδοαυλικής αποκάταστασης της αορτής στη φυσιολογία της καρδιάς φαίνεται να είναι αμελητέα.

Rationale

Thoracic Endovascular Aortic Repair (TEVAR) tends to become the mainstay of treatment for patients with Thoracic Aortic Diseases. The number of procedures, since the first reported implantation of thoracic stent grafts(1), shows an ever-growing trend(2). Though useful, however, Endovascular Repair has been associated with adverse effects in terms of hemodynamics.

Evidence shows that Endovascular Aortic Repair may induce aortic stiffness. This has been shown in various studies through Pulse Wave Velocity (PWV) augmentation(3-7). PWV serves as a reliable reference point to arterial stiffness and an independent risk factor for cardiovascular morbidity and mortality(3, 8, 9). The reason for the observed phenomenon may be the attenuation of the Windkessel effect(10). Indeed, the stent graft and the aorta do not possess the same mechanical properties. As a result, the stented segment does not exhibit the same volume storage capacity during diastole as the native counterpart.

Concerning the heart, there seems to be a relation between Left Ventricle Hypertrophy and increased Arterial Stiffness (11). Endovascular Aortic Repair has also been associated with elevation of biochemical markers indicative of cardiac function, such as (NT-pro-BNP)(7). Those two parameters, taken together, reflect the increased hydraulic load to the heart after the intervention.

However, the exact impact of TEVAR on cardiac function (mainly the left ventricle) postoperatively and subsequent outcomes have not been thoroughly examined. In addition, risk factors for cardiac events in TEVAR patients have not been studied extensively(12, 13). So, in the context of guiding future health policies, one way to quantify the TEVAR-heart relationship characteristics is through Echocardiography, an easily reproducible technique with documented probability of adverse events based on its marker findings(14-16).

Anatomy

The aorta is the first and largest artery in the body. It starts from the aortic valve of the left ventricle of the heart (Aortic Root) and ends in the proximal iliac bifurcation at the level of the L4 vertebra. Based on location, it is divided in 2 subsets: Thoracic aorta and Abdominal aorta. The thoracic aorta is further subdivided in the following segments: The ascending aorta, the aortic arch and the descending aorta(17).

The ascending aorta refers to the portion extending from the aortic valve and up to T4 vertebral level. Its length approximates 5cm and normal diameter is 22-35mm. Its branches are the coronary arteries, the very first branches of the aorta.

The aortic arch is the part right after the ascending aorta as it traverses posteriorly and to the left in the thoracic cavity. As its name implies, it forms a curve, such that its proximal and distal portions are at the same level, T4 vertebra. It has 3 major branches: the brachiocephalic trunk (divided to the right subclavian artery and right common carotid artery supplying blood to the right arm and head respectively), the left common carotid artery (supplying blood to the head) and the left subclavian artery (supplying blood the left arm). Its normal diameter is 22-35mm. The final section of the aortic arch is just distal to the origin of the left subclavian artery and is known as the aortic isthmus. There is a mild narrowing of the aorta that occurs at the site of the ligamentum arteriosum, which is a remnant of the ductus arteriosus(18).

The descending aorta begins at the end of the curve of the aortic arch, at T4 vertebral level. It continues inferiorly in the posterior mediastinal cavity, lying left to the vertebral column. Then, it courses medially and, up to the level of the T12 vertebra, it transitions to the abdominal aorta through the aortic hiatus in the diaphragm.

The descending thoracic aorta gives rise to certain branches, including pericardial, bronchial, esophageal and mediastinal branches.

The main function of the aorta is to transmit oxygenated blood to the systemic circulation following ejection from the left ventricle of the heart. The heart acts as a pump based on pressure gradients between its chambers and the vessels attached to it.

During systole, when pressure in the left ventricle rises above the pressure in the aorta, the aortic valve opens and blood is ejected from the left ventricle to the ascending aorta. After the pressure in the left ventricle reaches a peak, it gradually starts dropping. When it becomes lower than the pressure in the aorta (diastolic phase), then the aortic valve closes, thus preventing blood from returning in the left ventricle(19).

Histologically, the aorta consists of three distinct layers: tunica intima, tunica media and tunica adventitia(20).

Tunica intima is the inner layer which is composed by epithelium (called endothelium), a basement membrane and subendothelial connective tissue (mainly fibroblasts, collagen and elastic fibers). This is the site where atherosclerosis develops gradually through multiple mechanisms, leading to arterial stiffening.

Tunica media is the middle layer of the aortic wall, mainly consisting of elastin, collagen fibers, and smooth muscle cells. These are arranged in such a way that the aorta may expand and distend, relative to the pressure enforced by the left ventricle of the heart.

Tunica adventitia is the outer layer of the aorta and comprises loose connective tissue, nervi vasorum (the innervation of the aorta), vasa vasorum (the vessels supplying the aortic wall) and lymphatics.

Windkessel effect

The normal heart pump acts by exerting contractions of the myocardium at a regular pace, thus ejecting a certain amount of blood (called stroke volume) with every beat. This kind of periodic movement creates a pulsatile flow transmitted to the systemic circulation during systole. The pressure applied to the aortic wall by the left ventricle during systole causes the aorta to extend to a certain limit, based on its elastic properties. This extension stores approximately 50% of the stroke volume generated with each beat during systole. During diastole, the elastic recoil of the extended aorta pushes the stored volume to the peripheral circulation, such that the pulsatile flow mentioned before tends to become an almost continuous flow. The clinical

significance of this process, called Windkessel effect, is that it augments the volume of blood transmitted to the systemic circulation, as well as coronary perfusion, and it reduces afterload (the load against which the heart must contract in order to eject the blood volume). Specifically, the aortic arch is vigorously involved in this phenomenon, as it contributes almost 50% of total arterial compliance(10).

Definitions

Aneurysm (or true aneurysm)(21): a permanent localized dilatation of an artery, having at least a 50% increase in diameter compared with the expected normal diameter of the artery in question. Although all 3 layers (intima, media, and adventitia) may be present, the intima and media in large aneurysms may be so attenuated that they are undetectable in some sections of the wall.

Pseudoaneurysm (or false aneurysm)(21): contains blood resulting from disruption of the arterial wall with extravasation of blood contained by periarterial connective tissue and not by the arterial wall layers. Such an extravascular hematoma that freely communicates with the intravascular space is also known as a pulsating hematoma.

Aortic dissection (AoD)(21): disruption of the media layer of the aorta with bleeding within and along the wall of the aorta. Dissection may, and often does, occur without an aneurysm being present. An aneurysm may, and often does, occur without dissection. The term “dissecting aortic aneurysm” is often used incorrectly and should be reserved only for those cases where a dissection occurs in an aneurysmal aorta.

Blunt Thoracic Aortic Injury (BTAI)(22): BTAI is defined as a tear in the aorta that is a result of a combination of shear and stretch forces, rapid deceleration, increased intravascular pressure and compression of the aorta between the anterior chest wall and vertebrae. Injury can occur along the entire length of the aorta, essentially from the ascending aorta to the iliac bifurcation, although the injury typically occurs in areas of aortic tethering, notably the aortic isthmus.

Pulse wave Velocity (PWV)(23): Contraction of the left ventricle generates a pulse wave which is propagated throughout the arterial tree. The PWV is the time taken for

the arterial pulse to propagate from the common carotid artery (CCA) to either the radial or the femoral artery. To calculate PWV, the distance between the two sites at which the pulse wave is being recorded is divided by the time of travel of the wave from the first to the second site. Conventionally, carotid-femoral PWV is used for assessment of the central arterial stiffness. Another way is to measure Branchial-Ankle PWV. In the measurement of the carotid-femoral PWV, the pulse wave is detected by tonometry, Doppler, or oscillometry, and the path length is measured superficially. In the case of the brachial-ankle PWV, the pressure wave is detected by oscillometry after tying pressure cuffs around the four extremities, as shown in Figure 1. The calculation methods for PWV are depicted in Figure 2(24).

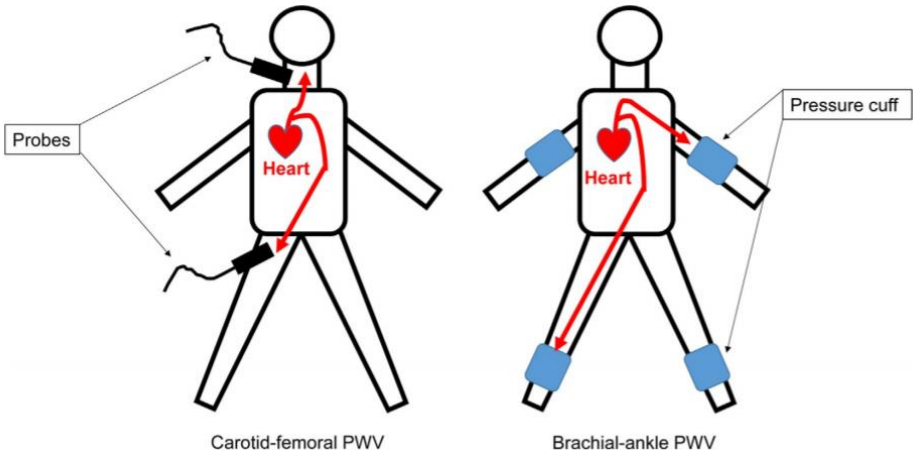


Figure 1: Carotid – Femoral and Brachial – ankle PWV measurement technique

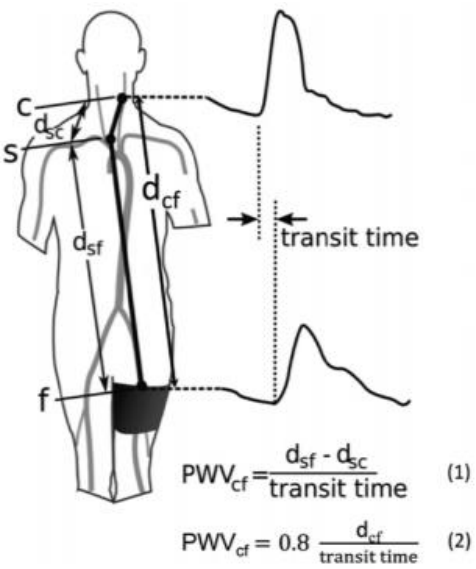


Figure 2: Distances for calculation of carotid–femoral pulse wave velocity (PWVcf) from the pulse transit time registered between carotid artery (C) and femoral artery (f) recording sites. PWVcf can be calculated using the subtraction method (Equation 1) or direct distance method (Equation 2). In the subtraction method, the distance between the carotid artery and suprasternal notch (S) (d_{sc}) is subtracted from the distance between the suprasternal notch and femoral artery (d_{sf}). This is also described as the 3-point method. A variation of this is the 4-point method where the distance d_{sf} is the sum of the distance between the suprasternal notch and umbilicus and distance between umbillicus and femoral site. In the direct distance method, the path length is 80% of the direct distance between carotid and femoral sites.

Echocardiographic parameters

Left Ventricle Internal End-Diastolic and End-Systolic Diameter (LVEDD, LVESD): Linear measurements of the Left Ventricle are carried out in the parasternal long-axis view, measured immediately below the mitral valve leaflet tips. The measurement angle should be perpendicular to the Left Ventricle long axis and the cursor must be positioned on the interface between the myocardial wall and cavity and the interface between the wall and the pericardium (orange arrows), as seen in Figure 3. Normal values are depicted in Table 1(25).

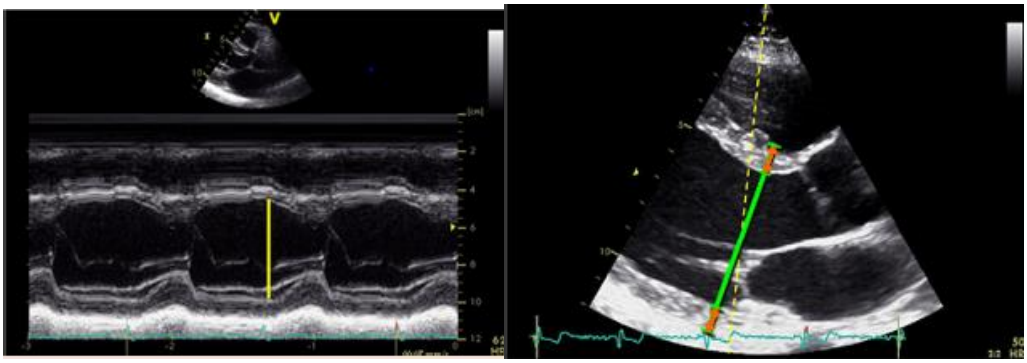


Figure 3: Right side: Linear measurements in the parasternal long axis view. Left side: The same view using M-Mode modality.

Normal values for 2D echocardiographic parameters of LV size and function according to gender

Parameter	Male		Female	
	Mean ± SD	2-SD range	Mean ± SD	2-SD range
LV internal dimension				
Diastolic dimension (mm)	50.2 ± 4.1	42.0–58.4	45.0 ± 3.6	37.8–52.2
Systolic dimension (mm)	32.4 ± 3.7	25.0–39.8	28.2 ± 3.3	21.6–34.8

Table 1: Normal values of LVEDD and LVESD.

Left Ventricle Ejection Fraction (LVEF) (26): It is calculated based on the blood volume that exits the left ventricle (stroke volume) divided by the left ventricle end-diastolic volume (**EDV**, the volume of blood in the left ventricle measured at end-diastole). It is a pure number and the result is expressed as a percentage. To quantify stroke volume, we extract the volume of blood in the left ventricle at end-systole (**ESV**, left ventricle end-systolic volume) from the EDV.

SV= EDV – ESV

LVEF: [SV/EDV] x 100

Normal values of LVEF for men include:

- 52% to 72%: normal range
- 41% to 51%: mildly abnormal
- 30% to 40%: moderately abnormal
- Less than 30%: severely abnormal

Normal values of LVEF for women include:

- 54% to 74%: normal range
- 41% to 53%: mildly abnormal
- 30% to 40%: moderately abnormal
- Less than 30%: severely abnormal

The most used clinical classification derived from the American College of Cardiology depicts the following categories:

- Hyperdynamic = LVEF greater than 70%
- Normal = LVEF 50% to 70% (midpoint 60%)
- Mild dysfunction = LVEF 40% to 49% (midpoint 45%)
- Moderate dysfunction = LVEF 30% to 39% (midpoint 35%)
- Severe dysfunction = LVEF less than 30%

Measurement Technique: The methods applied to obtain the LVEF are based both on the type of the echocardiographic image viewed (M-mode, two-dimensional, three dimensional) and on the mathematical models used to derive end-diastolic volumes. For the former, two-dimensional echocardiography is mostly used and for the latter, the biplane method of disks (modified Simpson's rule) is the currently recommended two-dimensional method.

Specifically, the 2D tomographic images used to derive the EDV and ESV are the apical four- and two-chamber views. Volumetric measurements are usually based on measurements of the interface between the compacted myocardium and the LV cavity by tracing the endocardial border in both the apical four-chamber and two chamber views in end-systole and end-diastole, as shown in Figure 5. At the mitral valve level, the contour is closed by connecting the two opposite sections of the mitral ring with a straight line.

Prerequisites include(27):

- Non oblique standard image planes or image planes of known orientation relative to the long and short axis of the LV
- Inclusion of the apex of the LV
- Adequate endocardial definition
- Accurate identification of the endocardial borders

Concerning the mathematical models used, the calculation of ESV and EDV are based on geometrical assumptions of the left ventricle, such as an ellipsoid, complex hemicylindrical of hemiellipsoid shapes. In this context, the Teichholz method (based on short axis measurements of the left ventricular inner diameter using M-mode) and Quinones method (single measurements of the LV cavity in the mid-ventricle in both end-diastole and end-systole either with M-mode or two-dimensional imaging), which calculate LV volumes based on LV linear dimensions are no longer recommended for clinical use, since they rely on the assumption of a fixed geometric LV shape such as a prolate ellipsoid, which is incorrect when cardiac anatomy is deformed.

The Simpson's rule, or method of discs, which is currently used, calculates ventricular volume as the sum of a series of parallel "slices" from apex to base(28). In particular, after tracing the endocardial borders as mentioned above, the LV cavity is divided in a pre-specified number of parallel ellipsoid discs (usually 20), as shown in Figure 5. Each disk is characterized by a specific volume, based on the tracings measured. Inbuilt software in all the echocardiography machines would automatically divide this LV area into twenty equal divisions once the LV LAX has been marked from the apex to the middle of the line joining the mitral annulus. The Simpson's rule is also termed "apical biplane method", as it is obtained in four-chamber and two-chamber views in end-diastole and end-systole. The method is universally recommended because it is accurate even when cardiac geometry is distorted.

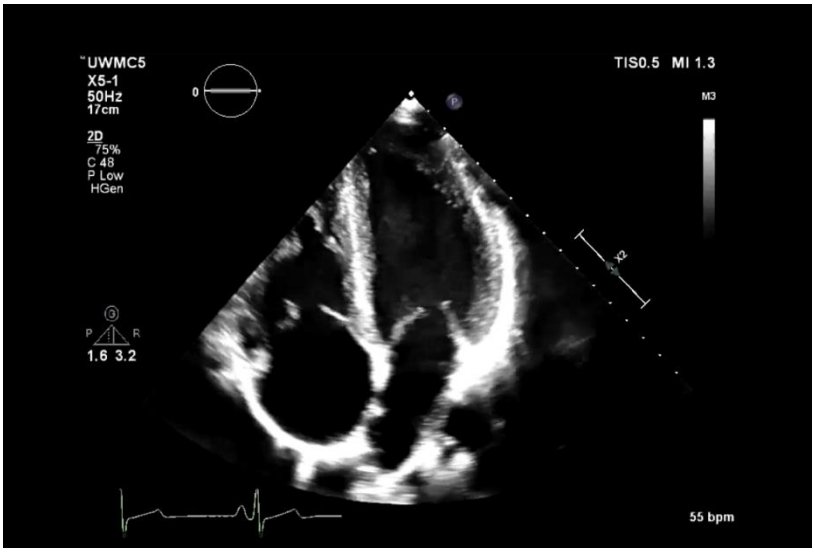


Figure 4: Typical apical four-chamber view

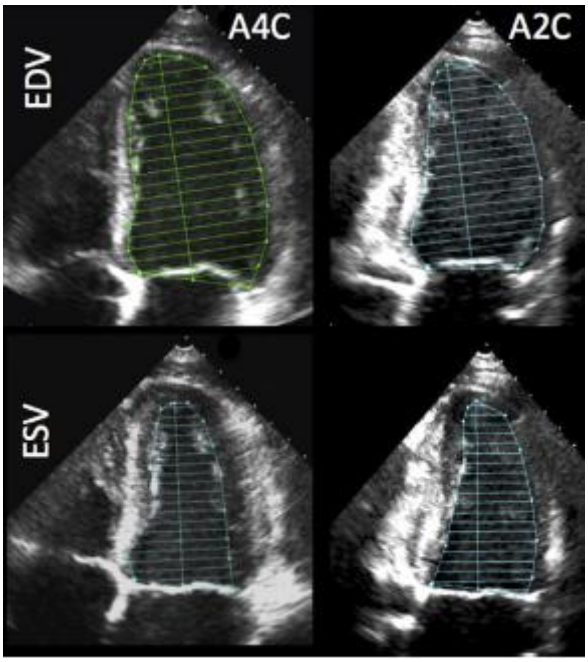


Figure 5: Typical measurements of End-diastolic Volume (EDV) and End-systolic volume (ESV) using the Simpson's method

Left Ventricle Mass (LVM): Left Ventricle Mass is the total weight of the myocardium, calculated by multiplying the volume of myocardium by the specific density of cardiac muscle (approximately 1,05g/ml). There are several methods that effectively calculate LV mass from M-mode echocardiography, 2DE, and 3DE. LVM calculation from 3D may be measured directly. For M-mode and 2D, the approaches include the linear method, and 2D- based formulas (truncated ellipsoid and area-length).

Most studies and reports with a significant prognostic value for LV mass have been performed using the linear method, which uses M-mode dimensions of Interventricular Septal Thickness (IVST), Left Ventricle Posterior Wall Thickness (LVPWT) and LVEDD. In particular, the linear measurements are obtained from the parasternal LV long axis view, perpendicular to the long axis of the ventricle and measured at the level of the mitral valve leaflet tips. The M-mode measurements should be acquired from a LV Short-axis view and from a parasternal long axis view.

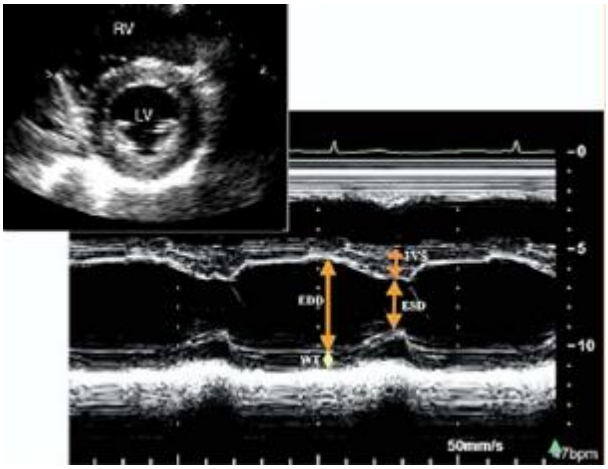


Figure 6: LV short-axis view and M-mode measurements

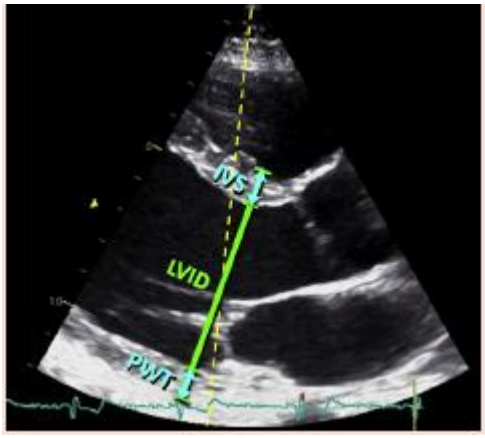


Figure 7 : LV parasternal long axis view measurements. LVID = LVEDD

It is a fast, widely used method, which is fairly accurate for normally shaped ventricles, such as in aortic stenosis or in systematic hypertension. The mathematical formula (also termed cubed formula or Devereux formula (29)) is depicted below:

Left Ventricular Mass= $0.8 \times [1.04 (LVEDD + LVPWT + IVST^3) – (LVEDD^3)] + 0.6g$

It is understood that even slight measurement inaccuracies may lead to significant errors, since they are cubed. In addition, the method does not yield accurate results when there is asymmetrical hypertrophy or dilated ventricles. However, it is subject to less measurement variability and is applicable to screening large populations compared to the other techniques.

Unlike the linear dimension or M-mode method, the 2D echocardiographic methods can accommodate for the shape of the ventricle and account for changes in LV size that might occur along the long axis of the chamber. These methods include the truncated ellipsoid method and the area-length method.
The truncated ellipsoid uses specific measurements of the left ventricle in an apical two chamber view and is based on the current formula:

$$\text{LV mass} = 1.05\pi\left\{(b+t)^2\left[\frac{2}{3}(a+t)+d-\frac{d^3}{3(a+t)^2}\right]-b^2\left[\frac{2}{3}a+d-\frac{d^3}{3a^2}\right]\right\}$$

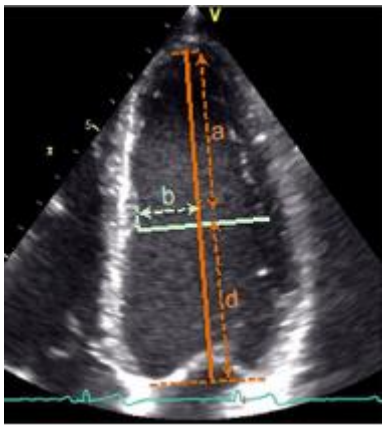


Figure 8: Truncated ellipsoid measurements in two chamber view

In the Area-length method, LV mass can theoretically be determined by tracing epicardial borders to calculate the total ventricular volume (wall plus chamber), then subtract the volumes determined from endocardial border tracing and then multiply the specific density of the myocardium. However, since epicardial definition seldom is adequate for this approach, the method demands mean wall thickness calculations from epicardial (A1) and endocardial (A2) cross-sectional areas in a short-axis view at the papillary muscle level (Figure 6), based on the current formula:

LVM = 1.05 (LV epicardial volume – LV endocardial volume) = LV myocardial volume ● 1.05

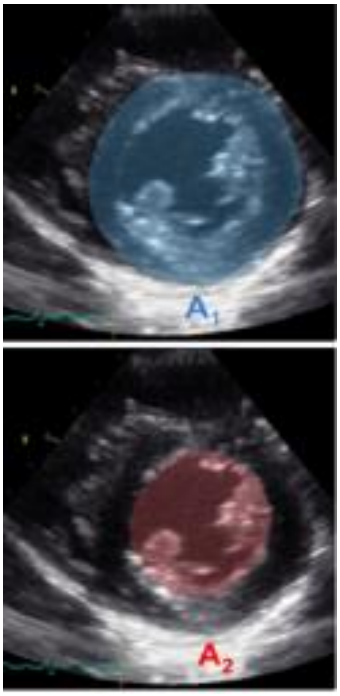


Figure 9: LV short axis views (papillary muscle level) measurements (area-length method). A1 = LV epicardial volume , A2 = LV endocardial volume

Left Ventricle Mass Index (LVMI): The values for LV mass vary according to gender, age, body size, obesity, and region of the world. As a result, there does not exist a uniform definition of cutoff values. Also, LV mass is higher in men and increases with body size. Thus, indexing for Body Surface Area (BSA) is a prerequisite to study subjects with different body sizes. Reference upper limits of normal LV mass by linear measurements are 95 g/m2 in women and 115 g/m2 in men. Reference upper limits of normal LV mass by 2D measurements are 88 g/m2 in women and 102 g/m2 in men with 2D methods. The reference limits are summarized in Table 2.

Interventricular Septal Wall Thickness (IVST) and Left Ventricle Posterior Wall Thickness (LVPWT): The diameter of the interventricular septum and of the posterior wall of the left ventricle, respectively. They are measured using the same views, as for LV mass. Normal values for IVST include 6-9mm for women and 6-10mm for men when linear methods are used. The reference limits are summarized in Table 2.

Left Ventricle Stroke Work (LVSW): It is a measure of the work produced by the left ventricle in order to generate forward blood flow and pressure. It is derived from

Ventricular Pressure-Volume loops. In particular, stroke work is the area enclosed by the loop, as seen in figure 10 and 11 (30).

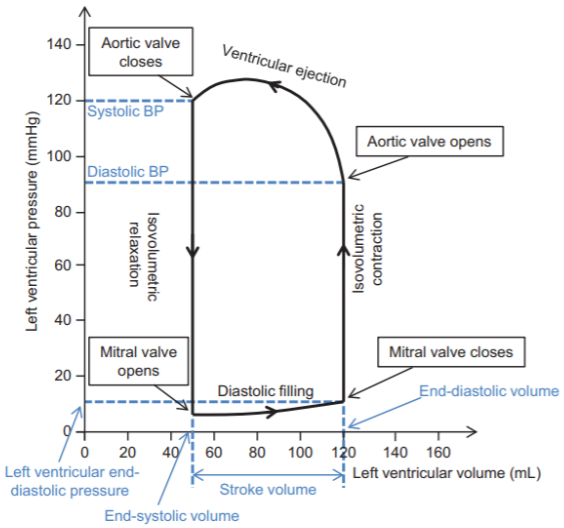


Figure 10: A pressure–volume loop (BP = blood pressure; EDPVR = end-diastolic pressure–volume relationship; LVEDP = left ventricular end-diastolic pressure).

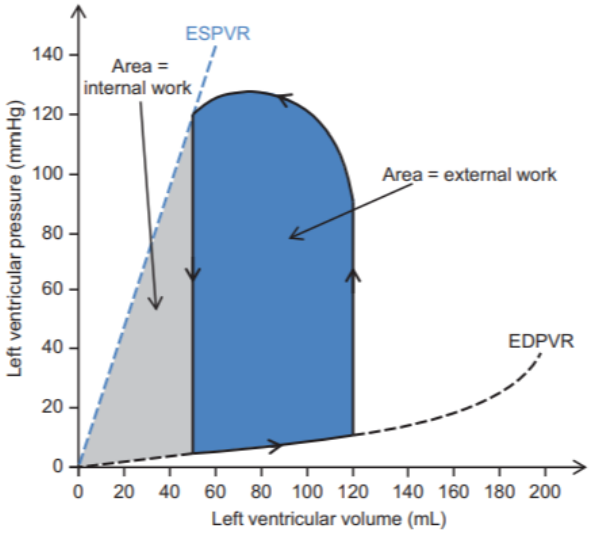


Figure 11: External work (or stroke work) is the kinetic energy expended when blood is ejected under pressure from the ventricle. The area enclosed by the ventricular pressure–volume loop (i.e. pressure volume) represents the external work done during a single cardiac cycle.

LV Hypertrophy (LVH) (25): The increase in left ventricle mass, secondary to an increase in wall thickness, an increase in cavity size, or both. Pathogenesis relates to a significant increase in the number and/or size of sarcomeres within each myocardial

cell. The cutoff values to define LVH depend on the method used to quantify LV mass, as shown in Table 2. LVH is diagnosed when the upper normal limits are exceeded.

Normal ranges for LV mass indices

	Women	Men
Linear method		
LV mass (g)	67–162	88–224
LV mass/BSA (g/m²)	***43–95***	***49–115***
Relative wall thickness (cm)	0.22–0.42	0.24–0.42
Septal thickness (cm)	***0.6–0.9***	***0.6–1.0***
Posterior wall thickness (cm)	***0.6–0.9***	***0.6–1.0***
2D method		
LV mass (g)	66–150	96–200
LV mass/BSA (g/m²)	***44–88***	***50–102***

Bold italic values: recommended and best validated.

Table 2: Reference values for LVM, LVMI, LVPWT, IVST based on the imaging method

Relative wall thickness (RWT)(29): a measure of ventricular geometry in LVH patients that correlates left ventricle wall thickness compared to the chamber size. Relative wall thickness (RWT) is measured in clinical studies both as: 2 * posterior wall thickness divided by LV diastolic diameter or, septal wall thickness + posterior wall thickness divided by LV diastolic diameter. Normal cutoff values are <0,42 (as seen in table 2), irrespective of which formula is used to calculate the parameters. Based on LV mass the following geometric models may be assumed for the left ventricle:

- Normal geometry: Normal LVM and normal RWT
- Concentric Hypertrophy: Increased LVM and increased RWT
- Eccentric Hypertrophy: Increased LVM and normal RWT
- Concentric Remodeling: Normal LV mass and increased RWT

Some examples include:

Concentric Hypertrophy: typical in patients with aortic stenosis, where the increased afterload leads to significant pressure overload in the left ventricle and thus, to thick walls with a small chamber. This happens to the parallel replication of sarcomeres.

Eccentric Hypertrophy: typical in patients with chronic volume overload, such as in aortic or mitral regurgitation, where there is a dilated chamber with increased total weight of the ventricle, but with normal LVM. This is due to the series replication of sarcomeres.

Concentric Remodeling: typical in patients with arterial hypertension, where walls become thicker, but there is normal total weight and mass of the left ventricle.

Clinical Significance of the Echocardiographic Parameters examined

Concerning LVEDD and LVESD, it has been acknowledged for almost thirty (30) years that these diameters are associated with adverse cardiovascular outcomes in both sexes(31). These include coronary disease, stroke, transient ischemic attack, claudication, heart failure and deaths from cardiovascular disease. When used in conjunction with LVEF, dilated left ventricles along with low LVEF appeared to have greater odds of sudden cardiac death(16). The pathophysiologic mechanism of sudden cardiac death in a dilated left ventricle relates to the incurring arrhythmogenic substrate, where re-entrant ventricular arrythmias may occur.

On the other hand, LVEF alone is a widely known indicator of adverse cardiovascular events in patients with and without history of cardiovascular disease. Indeed, this parameter served as potent predictor of risk of multiple outcomes, such as total mortality, cardiovascular death, cardiovascular hospitalizations and heart failure hospitalizations. This also applies to acute hospitalizations for noncardiac causes and in ambulatory surgery patients(32).

Left Ventricular Hypertrophy has been acknowledged as a significant marker of cardiovascular morbidity and mortality(14, 29). Although it may be beneficial at first, reflecting a compensatory mechanism to chronic pressure or volume overload, it portends a remarkably high prevalence of morbid cardiovascular events, including myocardial ischemia and myocardial infarction(33)(29). Indeed, it decreases coronary flow reserve (the ability of the coronary arteries to augment blood flow when subjected to stress), as the coronary vascular bed is not increased proportionately to

the LV mass. It has also been documented that increased LVM and LVH are independent risk factors for a subsequent decrease in LVEF(15). In addition, as the disease progresses, myocardial fibrosis is developed, which induces diastolic as well as systolic dysfunction. Also, premature and complex ventricular arrythmias may occur, increasing the risk of sudden cardiac death. In addition, atrial fibrillation is more frequent in patients with LVH(15).

It is known that LVH correlates to blood pressure, since one of the most common pathophysiologic mechanisms of the disease is essential hypertension. The heart becomes hypertrophied to compensate for the increased afterload. Other parameters associated with LVH is sex (women present a greater hypertrophic response and are more prone to death 5-fold compared to men when indexed to body size), obesity (the increase in LV mass maybe is more than a mere physiologic adaptation), age (the mass increases with aging, both in normotensive and in hypertensive patients), as well as diabetes mellitus and metabolic syndrome(29).

Concerning IVST and LVPWT, higher values of these two parameters may be caused by increased blood pressure values, even if the latter are within the upper normal limits. This may indicate patients at greater risk for LVH development. Vice versa, IVS thickening, even in the presence of normal LVM, is associated with systolic hypertension(34). In addition, using these parameters in conjunction with LVM specifies LV geometry, which seems to carry a separate cardiovascular risk burden compared to that of LVMI(14, 29).

Treatment options

There are three main options to treat thoracic aortic diseases: Medical therapy (conservative treatment), Open Surgery and Thoracic Endovascular Aortic Repair (TEVAR). In this Thesis, we will focus on TEVAR.

The procedure is generally performed under general anesthesia, though it may be accomplished with conscious sedation and/or using local anesthetics. TEVAR technique includes the following(35):

The first step is to gain femoral access for placement of the sheath required for TEVAR. This may be done either through an "open" technique, in which the artery is surgically exposed through an incision in the groin (or retroperitoneally), or percutaneously, with the use of special closure devices. If there is the need for additional access, this may be accomplished from either the arm or the contralateral groin to allow for control angiography. The next step entails using various wires to be able to deliver and implant the device in the inside of the vessel. To track the wire and properly position the stent graft, a device called C-arm is positioned in the right posterior oblique position to maximally splay out the arch. Once the device is positioned, angiography is performed and respiratory arrest to allow for precise graft positioning. Additional techniques to minimize graft movement during deployment include induced hypotension, rapid pacing, and adenosine-induced cardiac arrest. Once the graft is deployed, ballooning may be needed at the seal zones and at any overlap zones to ensure full cooptation to the aortic wall. In dissection cases, it is a contraindication to perform ballooning of the endograft, as there is a significant risk of creating fenestrations or causing aortic rupture. Completion angiography is then performed to assess for endoleak, the sheath and device are removed, and the arteriotomy is closed.

Zones of attachment

The original zone attachment proposal by Ishimaru divided the thoracic aorta to the ascending aorta, arch, and proximal descending aorta (zones 0-4), as seen in figure 12 (36). It refers to the attachment of the proximal end of the endograft. In particular:
Zone 0: the proximal edge of the endograft is proximal to the innominate artery origin
Zone 1 : distal to the innominate but proximal to the left common carotid artery (LCCA) origin
Zone 2 : distal to the LCCA but proximal to the subclavian artery
Zone 3 : distal to the left subclavian artery up to the level of Thoracic Vertebra 4 (proximal descending thoracic aorta)
Zone 4: distal to Thoracic Vertebra 4 (mid-descending thoracic aorta) up to end of the descending thoracic aorta (diaphragm)

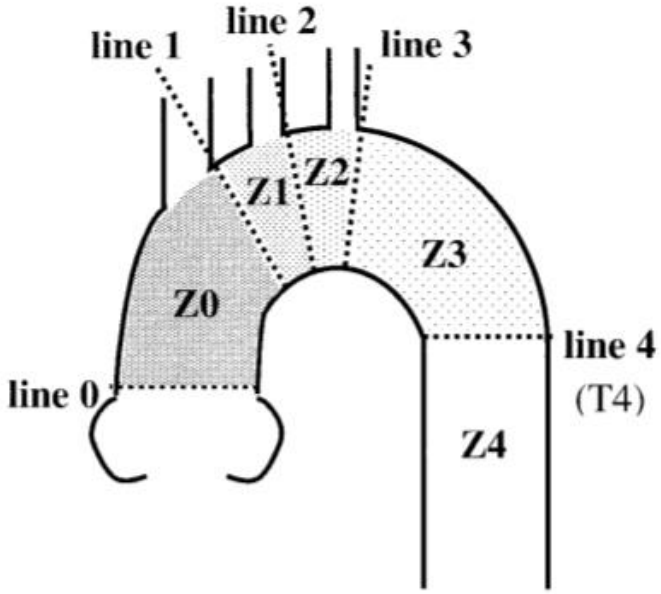


Figure 12: Ishimaru zones of attachment

Objective

The aim of this meta-analysis is to delineate the possible negative effects of Thoracic Stent grafting in the long-term period after Thoracic Endovascular Aortic Repair (TEVAR) in patients with thoracic aortic diseases (Thoracic Aortic Aneurysm, Aortic Dissection, Blunt Thoracic Aortic Injury), based on certain ultrasonographic markers.

Methods

Review Design: The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines(37).

Eligibility Criteria

Types of Studies: Non-Randomised Studies of Interventions examining Cardiac Function with Echocardiography pre- and post-TEVAR in patients with Thoracic Aortic Diseases. Case reports, case series and experimental studies were excluded.

Types of Participants: Patients with Thoracic Aortic Diseases [Thoracic Aortic Aneurysm, Thoracic Aortic Dissection (Type A, Type B, Non – A Non -B), Blunt Thoracic Aortic Injury]. Patients with abdominal, or juxtarenal aortic aneurysms were also excluded. No rules in terms of age or gender were applied.

Type of Intervention: Thoracic Endovascular Aortic Repair for Thoracic Aortic Aneurysm, Thoracic Aortic Dissection and Blunt Thoracic Aortic Injury, with no restrictions regarding endovascular repair in an acute or elective setting, deployment zones, types of endografts used, or treatment length.

Types of Outcome Measures: Outcome Measures include findings in the Following Ultrasonographic Criteria: Left Ventricle Mass (LVM), Left Ventricle Mass Index (LVMI), Left Ventricle Ejection Fraction (LVEF), Left Ventricle End-Diastolic Diameter (LVEDD), Left Ventricle End-Systolic Diameter (LVESD), Interventricular Septal Thickness (IVST), Left Ventricle Posterior Wall Thickness (LVPWT).

Information Sources and Search Strategy

An electronic search of the literature was carried out by two authors (Papakonstantinou K., Antoniou G.) in March 2021. The search strategy was applied to MEDLINE and CENTRAL databases. “MeSH” terms were used in groups, along with free text terms, to encompass all relevant information. There were no constraints concerning language, publication date or publication status. The reference lists of certain research articles were also assessed for other potential studies relevant to the topic. The literature search strategy for PUBMED is depicted below.

Search strategy

- ((aorta, thoracic[MeSH Terms]) AND (ventricular remodeling[MeSH Terms])) AND (endovascular procedures[MeSH Terms])
- ((thoracic aorta) AND (ventricular remodeling)) AND (endovascular procedure)
- (("thoracic aorta") AND ("endovascular repair")) AND ("Cardiac function")
- ((thoracic-aorta*) AND (endovascular procedure)) AND (echocardiography*)
- ((endovascular procedure[MeSH Terms]) AND (aorta, thoracic[MeSH Terms])) AND (cardiac function tests[MeSH Terms])

- ((aorta, thoracic[MeSH Terms]) AND (ventricular remodeling[MeSH Terms])) AND (endovascular procedures[MeSH Terms])
- ((blood vessel prosthesis implantation[MeSH Terms]) AND (aorta, thoracic[MeSH Terms])) AND (cardiac function tests[MeSH Terms])
- (((heart ventricles[MeSH Terms]) AND (endovascular procedures[MeSH Terms]))) AND (aorta, thoracic[MeSH Terms])
- ((ventricular remodeling[MeSH Terms]) AND (aorta, thoracic[MeSH Terms])) AND (blood vessel prosthesis implantation[MeSH Terms])
- ((echocardiography[MeSH Terms]) AND (aorta, thoracic[MeSH Terms])) AND (endovascular procedure[MeSH Terms])
- ((left ventricular hypertrophy[MeSH Terms]) AND (aorta, thoracic[MeSH Terms])) AND (endovascular procedures[MeSH Terms])
- (((aneurysm, dissecting[MeSH Terms]) AND (aorta, thoracic[MeSH Terms])) AND (endovascular procedures[MeSH Terms])) AND (cardiac function tests[MeSH Terms])
- (((aortic aneurysm[MeSH Terms]) AND (aorta, thoracic[MeSH Terms])) AND (endovascular procedures[MeSH Terms])) AND (echocardiography[MeSH Terms])
- (((aorta, thoracic[MeSH Terms]) AND (aneurysm[MeSH Terms])) AND (endovascular procedures[MeSH Terms])) AND (cardiac function tests[MeSH Terms])
- ((aorta, thoracic[MeSH Terms]) AND (heart ventricles[MeSH Terms])) AND (endovascular procedures[MeSH Terms])
- (((echocardiography*) AND (aorta, thoracic[MeSH Terms])) AND (endovascular procedures[MeSH Terms])) AND (heart ventricles[MeSH Terms])

Study Selection and Data Extraction

Eligibility assessment was performed by two authors (Papakonstantinou K. Antoniou G.), based on the pre-specified criteria.

The following types of data were extracted from the selected studies:

- *Study related data*: First author, Year of Publication, Country of Origin, Journal of Publication, Study type, Recruitment Period, Mean duration of Follow-up, Timing of Transthoracic Echocardiography (TTE)
- *Baseline Demographics*: Sex, age, Diabetes Mellitus, Hypertension, Coronary Artery Disease, Hyperlipidemia, History of Smoking, Currently Smoking, COPD, Cerebral Vascular Disease, Chronic Kidney Disease, Peripheral Arterial Disease
- *Type of Intervention*: TEVAR landing zones, Types of Endografts used, Treatment Length
- *Outcome data*
- *Data related to Risk of Bias Assessment*

Assessment of risk of bias in included studies

The NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group was used to assess the risk of bias in the selected studies(38). The evaluation was performed by two review authors (Papakonstantinou K. Antoniou G.). The GRADE approach was also used to evaluate the quality of the evidence(39).

Data synthesis

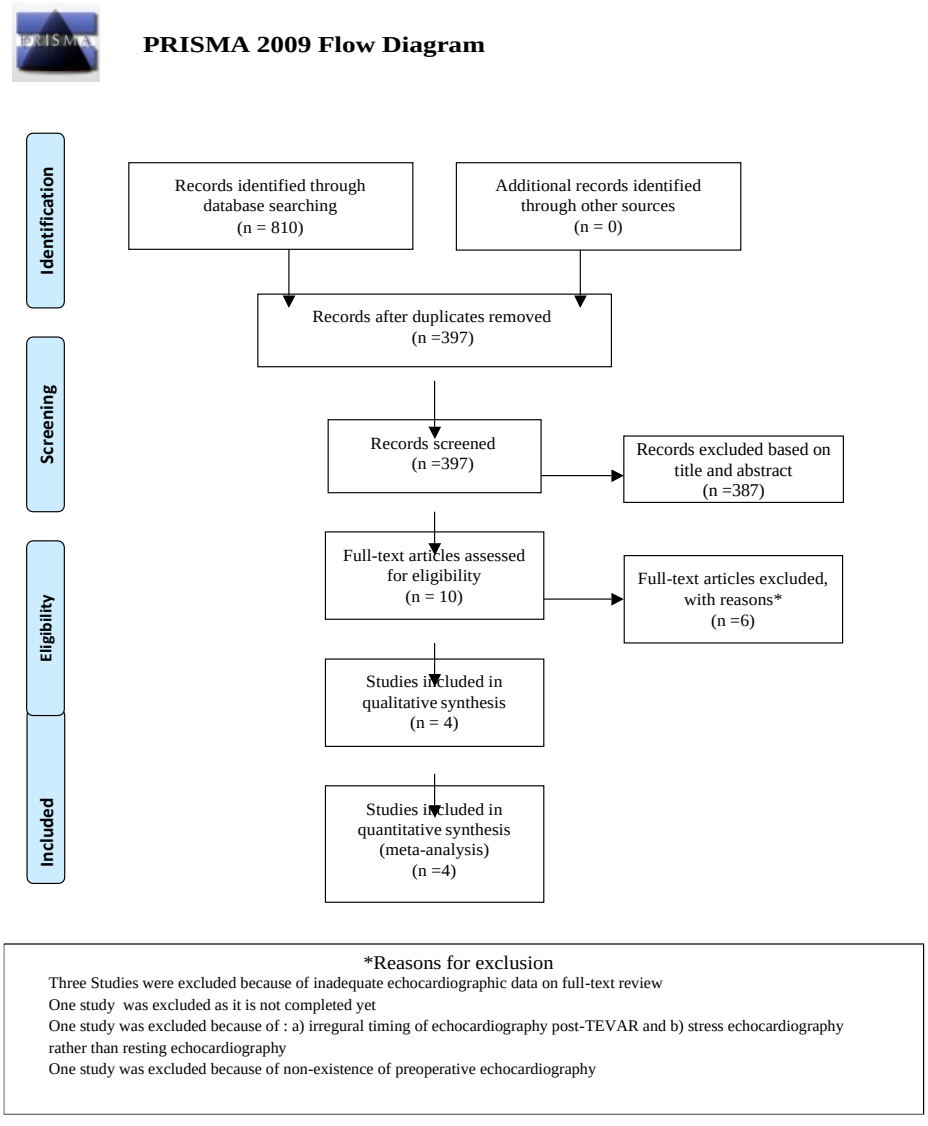
A meta-analysis was performed to assess the impact of TEVAR on cardiac function as indicated by changes in Left Ventricle Mass (LVM), Left Ventricle Mass Index (LVMI), Ejection Fraction (EF), Left Ventricle End-Diastolic Diameter (LVEDD), Left Ventricle End-Systolic Diameter (LVESD), Interventricular Septal Thickness (IVST), Left Ventricle Posterior Wall Thickness (LVPWT). Data were collated on mean values of LVM, LVMI, LVEF, LVEDD, LVESD, IVST, LVPWT and standard deviation (SD) pre- and post-TEVAR from each individual study and the pooled standardized difference in means and 95% confidence interval (CI) were calculated(40). Because the studies do not report pre/post correlation, a range of pre/post correlations for the scores was tested and the most conservative approach was selected. The between-study heterogeneity was examined with the combination of the Cochran's Q ($\chi 2$) test and the I^2 statistic. Because of conceptual heterogeneity (the

etiology of the treatment was different among study populations), random-effects models of meta-analysis were employed. The Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ, USA) was used for the statistical analyses.

Results

Search results

The literature search initially resulted in *n*= 810 items. After removing duplicates and extraneous data, the full-text articles included for qualitative synthesis were *n*=5. One cohort study remains to be completed(41). The study selection process and the reasons for exclusion of certain studies are summarized below.



Description of Studies

There were 4, single – center, retrospective studies identified. All were published from 2018 and after, while the study recruitment period spanned from 2004 to 2020. Three of them were uncontrolled before-after studies(42-44) and one study(45) matched healthy controls with the TEVAR patients post-intervention, due to missing pre-TEVAR echocardiographic data. The studies reported a sum of 216 patients. The inclusion and exclusion criteria were dependent on the available data of each center. The timing of TTE varied between the studies, as well as the duration of follow-up**.** Each study measured specific echocardiographic markers and did not include the total of the outcome measures examined in this review. Baseline characteristics were similar for three of the four studies. Concerning intervention parameters, there were cases for each one of the Ishimaru zones, depending on the condition treated. Treatment length varied accordingly, as well as types of endografts used. The study characteristics, baseline demographics, Intervention data, Inclusion-Exclusion criteria and outcomes data are summarized in the tables below.

Author	**Study year**	**Country, Journal**	**Study type**	**Recruitment period**
Kreibich et al.	2019	Germany, Interactive CardioVascular and Thoracic Surgery	Uncontrolled Before-After	Jan 2005- Dec 2018
Youssef et al.	2020	Germany, Vasa	Retrospective Study	Nov 2009 - Nov 2019
Du et al.	2018	China, International Journal of Cardiology	Uncontrolled Before-After	May 2004 - Jan 2016
Van Bakel et al.	2019	USA, European Journal of Cardiothoracic Surgery	Uncontrolled Before-After	2013-2016

Table 3: Characteristics of the included studies

Author	Follow – up (months)		Timing of TTE (months)	
	Mean	SD	Mean	SD
Kreibich et al.	29	28	24	29
Youssef et al.	63,6	21,6	63,6	21,6
Du et al.	48 (31,84)*		48 (31,84)*	
Van Bakel et al.	15,2 (12,4 , 18,7)*		15,2 (12,4 , 18,7)*	

Table 4: Intervention data of the included studies, *median (IQR)

Author	Total number of patients	Number of patients with aneurysm	Number of patients with dissection	Number of patients with Blunt Thoracic Aortic Injury
Kreibich et al.	31	19	12	
Youssef et al.	14			14
Du et al.	163		163	
Van Bakel et al.	8	8		

Table 5: Baseline demographics of the included studies

Author	Age (years)		Male	Diabetus Mellitus	Hypertension
	mean	SD			
Kreibich et al.	69	9	22 (71%)	7 (23%)	26 (74%)
Youssef et al.	35,1	8,7	12 (86%)	0	0
Du et al.	51,06	10,79	136 (83.4%)	7 (4.3%)	122 (74.8%)
Van Bakel et al.	68 (25,73)*		2 (25%)	NR	6 (75%)

Table 6: Baseline demographics of the included studies (continued), *median (IQR), NR = not reported

Author	Coronary Artery Disease	Hyperlipidemia	Previous smoker	Cerebral Vascular Disease
Kreibich et al.	11 (35%)	15 (48%)	14 (45%)	2 (6%)
Youssef et al.	0	0	0	0
Du et al.	24 (14.7%)	33 (20.2%)	NR	26 (16.0%)
Van Bakel et al.	NR	NR	NR	NR

Table 7: Baseline demographics of the included studies (continued), NR = not reported

Author	COPD	CKD	PAD	Currently Smoking
Kreibich et al.	2 (6%)	5 (16%)	NR	NR
Youssef et al.	0	NR	0	0
Du et al.	NR	12 (7.4%)	NR	52 (31,9%)
Van Bakel et al.	1 (12,5%)	1 (12,5%)	NR	NR

Table 8: Baseline demographics of the included studies (continued), NR = not reported

Author	Patient Sample	Deployment Zone				
	n	Zone 0	Zone 1	Zone 2	Zone 3	Zone 4
Kreibich et al.	31	0	2	7	12	10
Youssef et al.	14	0	0	14	0	0
Du et al.	163	0	0	46	117	
Van Bakel et al.	8	NR	NR	NR	NR	NR

Table 9: Intervention data (continued), NR = not reported

Author	Treatment Length(mm)	
	mean	SD
Kreibich et al.	163	66
Youssef et al.	variation: 100-250	
Du et al.	150.95	120.41
Van Bakel et al.	NR	

Table 10: Intervention data (continued), NR = not reported

Author	Types of endografts						
	Gore cTAG	Valiant	Relay	Talent	TX2	Endurant II	Ankura
Kreibich et al.	NR	NR	NR	NR	NR	NR	NR
Youssef et al.	10	3				1	
Du et al.				108			55
Van Bakel et al.	NR	NR	NR	NR	NR	NR	NR

Table 11: Intervention data (continued), NR = not reported

Author	Inclusion Criteria	Exclusion criteria
Kreibich et al.	TEVAR procedures, available Pre- and Post-TEVAR echocardiographic data	Previous replacement of thoracic aorta (ascending, arch, descending)
Youssef et al.	Patients aged > 18 years and up to a maximum age of 50 years with polytrauma as a cause of admission and diagnosed aortic rupture as a blunt thoracic injury in the descending thoracic aorta, treated by TEVAR with the stent graft located in Ishimaru zone 2	Patients with relevant cardiovascular risk factors (past or current smoking status, diabetes mellitus, arterial hypertension before treatment with TEVAR, and hypercholesterolemia), those with comorbidities (atherosclerotic or inflammatory cardiovascular disease and known connective tissue disease) with a potential impact on arterial stiffness, and those with prior aortic surgical or endovascular interventions
Du et al.	Patients with Acute Type B Aortic Dissection who underwent TEVAR	Patients who had congenital heart disease, severe valvular heart disease, thoracic aortic pseudoaneurysm, or traumatic aortic injury, or who had undergone a previous aortic surgical procedure

Van Bakel et al.	Descending aortic aneurysms, available pre-TEVAR and post-TEVAR echocardiography and CTA data	Aortic dissection, prior surgical or endovascular aortic repair, prior open-heart surgery, atrial fibrillation and echocardiographic ejection fraction of <50%.

Table 12: Inclusion – Exclusion Criteria of the included studies

Author	**Left Ventricle Mass (g)**						**Left Ventricle Mass Index (g/m^2)**					
	before TEVAR			after TEVAR			before TEVAR			after TEVAR		
	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n
Kreibich et al.	217,00	84,00	31	237,00	102,00	31	NR	NR	NR	NR	NR	NR
Youssef et al.	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Du et al. §	NR	NR	NR	NR	NR	NR	129.60	3.55	93	115.79	3.62	93
Van Bakel et al.	109,38	30,09	8	128,38	30,78	8	54,00	50,03	8	68,00	54,50	8

Table 13: Outcome data. NR = not reported, §= Mid-term results only

Author	Ejection Fraction (%)						Left Ventricle End- Diastolic Diameter (mm)					
	before TEVAR			after TEVAR			before TEVAR			after TEVAR		
	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n
Kreibich et al.	55,00	0,00	31	53,33	3,88	31	49,00	11,00	31	51,00	9,00	31
Youssef et al.	62,86	2,57	14	57,14	2,57	14	46,86	4,00	14	46,43	4,69	14
Du et al. §	58.01	0.55	93	58.57	0.83	93	49.47	0.56	93	49.19	0.67	93
Van Bakel et al.	NR	NR	NR	NR	NR	NR	31,10	29,93	8	33,80	26,53	8

Table 14: Outcome data (continued). NR = not reported, §= Mid-term results only

Author	**Left Ventricle End - Systolic Diameter (mm)**						**Interventricular Septal Thickness (mm)**					
	before TEVAR			after TEVAR			before TEVAR			after TEVAR		
	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n
Kreibich et al.	NR	NR	NR	NR	NR	NR	11,00	3,00	31	12,00	2,00	31
Youssef et al.	31,64	4,40	14	31,71	3,12	14	9,43	1,22	14	10,93	1,00	14
Du et al. §	27.41	0.58	93	26.03	0.67	93	11.59	0,14	93	10.82	0.15	93
Van Bakel et al.	20,36	9,56	8	24,23	19,38	8	7,06	6,52	8	9,43	6,34	8

Table 15: Outcome data (continued). NR = not reported, §= Mid-term results only

Author	Left Ventricle Posterior Wall Thickness (mm)					
	before TEVAR			after TEVAR		
	mean	SD	n	mean	SD	n
Kreibich et al.	11,00	2,00	31	11,00	2,00	31
Youssef et al.	8,64	0,74	14	10,14	1,51	14
Du et al. §	10.89	0.11	93	10.02	0.11	93
Van Bakel et al.	NR	NR	NR	NR	NR	NR

Table 16: Outcome data (continued). NR = not reported, §= Mid-term results only

Risk of bias in included studies

The NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group assesses the risk of bias through a 12-item questionnaire and judges the overall quality of evidence as “good”, “fair”, or “poor”, based on study design (Supplementary data, Appendix 3). Three of the studies were determined to provide good quality of evidence(43-45) and the rest (42, 46) were labeled as “fair”. The reason for the former(42) study was that it did not mention the TEVAR landing zones, which may act as a confounder. For the latter(46), loss to follow – up and echocardiographic data missing accounted for over 20%. The GRADE evidence approach indicated the certainty of evidence for each of the parameters examined as very low. The NIH tool summary is depicted below.

Components	Van Bakel et al	Kreibich et al	Du et al	Youssef et al§
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes	Yes	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	No	No	Yes	No

6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No$^{\infty}$	Yes	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No	No	No
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes	Yes	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p	Yes	Yes	Yes	Yes

values for the pre-to-post changes?				
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	No	Yes	No
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Not applicable	Not applicable	Not applicable	Not applicable
Quality Rating	Fair	Good	Good	Good
∞The TEVAR landing zones are not mentioned in the supplementary material, which may act as a confounder §The matched individuals are considered the pre-intervention group				

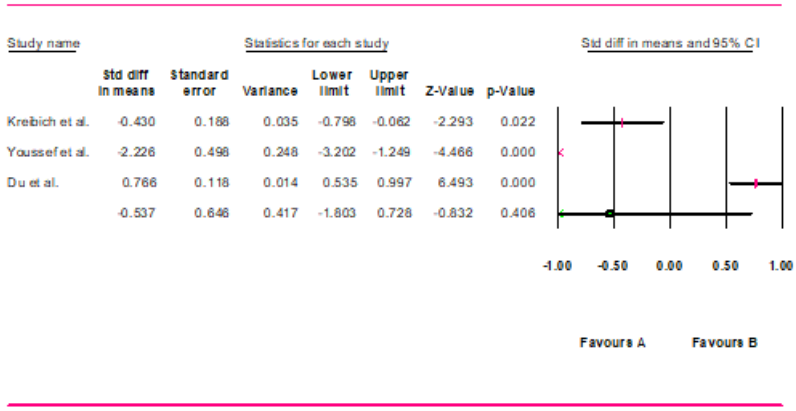
Table 17: The NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group summary

Effects of Intervention

Outcomes

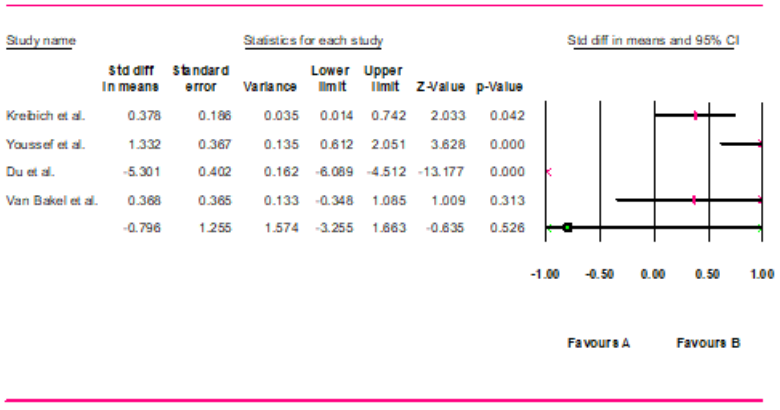
a. Three studies(43-45) reported data concerning Ejection Fraction (208 patients). Non-significant differences were found pre- and post-TEVAR (SMD=-0.53, 95% CI=-1.8 to 0.728, P=0.406). There was considerable heterogeneity between the studies (I^2= 96%, P<0.0001). (GRADE: very low quality of evidence)
b. Data concerning Interventricular Septal Thickness were derived from four studies(42-45) (216 patients). The measurements before and after the intervention did not differ significantly (SMD= -0.79, 95%CI= -3.25 to 1.66, P= 0.52). Again, there was considerable inner- study heterogeneity (I^2=98%, P<0.0001). (GRADE: very low quality of evidence)
c. Four studies(42-45) yielded results on Left ventricle end-diastolic diameter (216 patients). There was no significant difference in measurements before and after TEVAR (SMD= -0.10, 95%CI= -0.48 to 0.28, P= 0.60). Heterogeneity was lower, although substantial (I^2= 72%, P=0.0013). (GRADE: very low quality of evidence)
d. Left Ventricle End systolic diameter measurements were extracted from three studies(42, 43, 45) (185 patients). No significant differences were found pre- and post- TEVAR (SMD= -0.66, 95%CI= -2.35 to 1.02, P= 0.44). Heterogeneity was deemed considerable (I^2=97%, P<0.0001). (GRADE: very low quality of evidence)
e. Left ventricle mass measurements were extracted from two studies(42, 44) (39 patients). Although not statistically significant, a borderline trend towards left ventricle mass increase was documented (SMD= 0.28, 95%CI= -0.03 to 0.60, P= 0.08). Heterogeneity was negligible (I^2=0%, P=0.335). (GRADE: very low quality of evidence)
f. Left ventricle Mass index data were derived from two studies (42, 43)(171 patients.) The measurements before and after the implantation did not differ significantly (SMD = 0, 95%CI= -0.195 to 0.195, P=1). Heterogeneity was negligible (I^2=0%, P=1) (GRADE: very low quality of evidence)
g. Left ventricle posterior wall thickness data were derived from three studies(43-45) (208 patients). The measurements before and after the intervention did not differ significantly (SMD= -2.20, 95%CI= -5.89 to 1.47, P= 0.24). Heterogeneity was deemed considerable (I^2=99%, P<0.0001). (GRADE: very low quality of evidence)

Meta-analysis tables



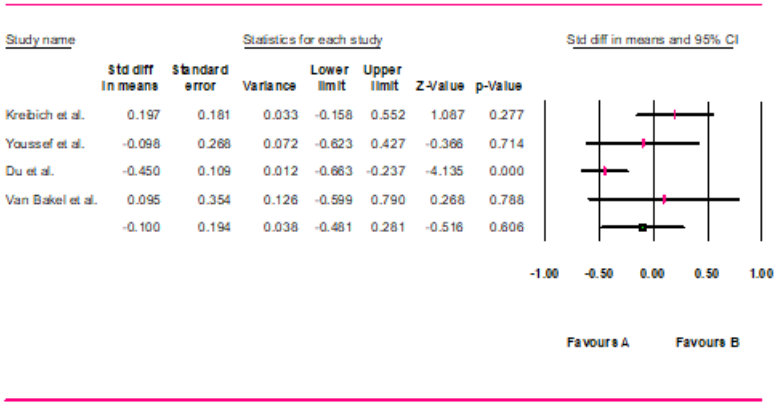
Ejection fraction, A: decrease, B: increase

Heterogeneity: P<0.0001, I^2=96%



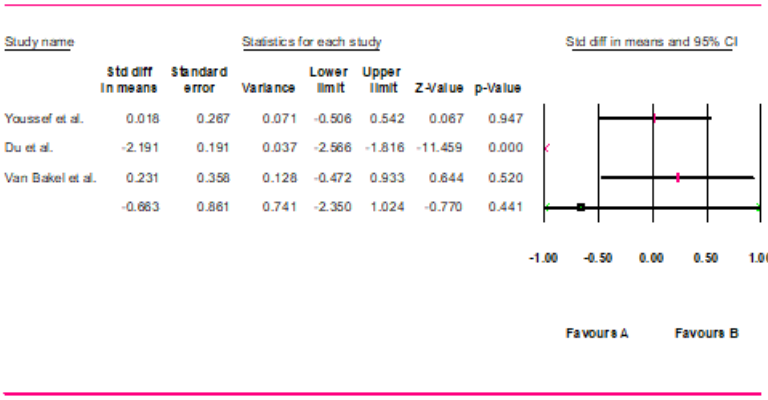
Interventricular septal thickness, A: decrease, B: increase

Heterogeneity: P<0.0001, I^2=98%



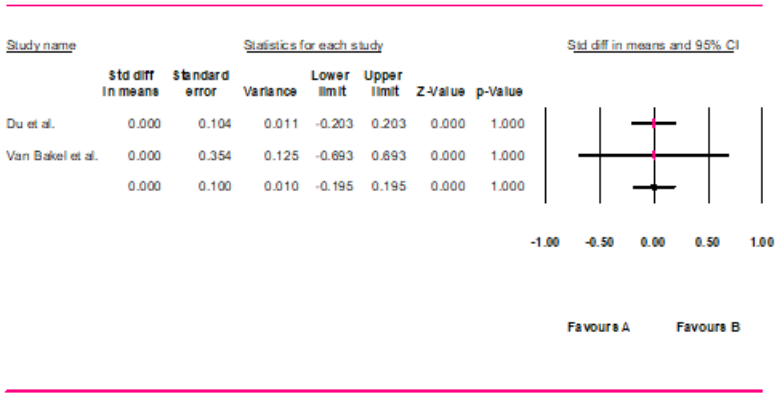
Left ventricle end-diastolic diameter, A: decrease, B: increase

Heterogeneity: P=0.013, I^2=72%



Left ventricle end-systolic diameter, A: decrease, B: increase

Heterogeneity: P<0.0001, I^2=97%

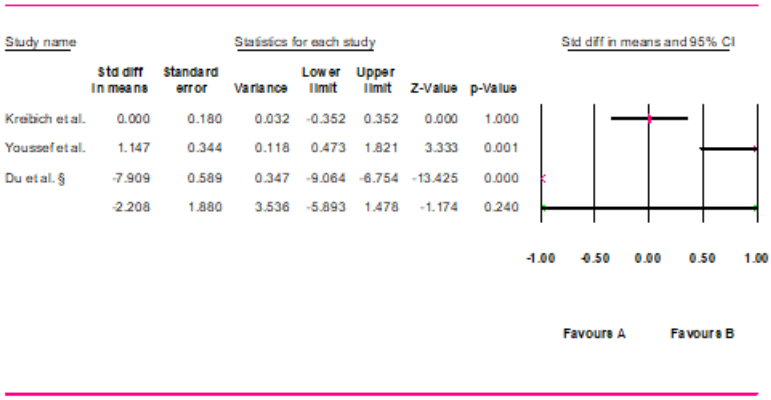


Left ventricle mass index, A: decrease, B: increase

Heterogeneity: P=1, I^2=0%

Left ventricle mass, A: decrease, B: increase

Heterogeneity: P=0.335, I^2=0%



Left ventricle posterior wall thickness, A: decrease, B: increase

Heterogeneity: P<0.0001, I^2=99%

Discussion

The goal of this systematic review and meta-analysis was to elucidate whether TEVAR alters cardiac systolic function post-implantation and whether it induces certain morphological changes in the left ventricle. It has been acknowledged that TEVAR augments PWV, which is a potent indicator of cardiovascular mortality and morbidity, and that NT-proBNP levels, are also increased 6 months post-TEVAR (7). One speculation is that the heart strain implicated by those two parameters could have a negative effect on cardiac systolic function, as well as induce cardiac remodeling (probably concentric remodeling), to counterbalance the arterial stiffness mismatch because of the endograft.

However, our findings suggest otherwise. The meta-analysis did not yield a statistically significant change in the echocardiographic parameters examined. Concerning LVM, there was borderline significance, which should be interpreted with caution.

Regarding LVEF, LVEDD and LVESD, the hydraulic load imposed to the heart post-TEVAR would be an indicator for change in the long-term. Indeed, although there was a documented increase in NT-proBNP levels in two of the fourteen patients in the

study of Youssef et al.(45), as well as an increase in LVSW(42) post-TEVAR, this was not translated to systolic function impairment. It would be implied that, for younger patients(45), who are healthy, do not present any co-morbidities and have a greater cardiac function reserve, we would not expect these factors to change compared to older individuals. Indeed, in this latter cohort of patients, one study(44) showed a significant difference in LVEF and TAPSE, suggesting global heart remodeling. Nevertheless, the clinical significance of this alteration is debatable since the mean values of LVEF remained above 50% and mean values of TAPSE remained within normal limits. Overall, the meta-analysis results were non-significant.

Concerning LVH, our meta-analysis yielded non-significant results for IVST and LVPWT. However, they showed borderline significance towards an increase in LV mass, but not LVMI. Indeed, there has been an increase in LVSW and LVMI and a positive correlation between them in one study (42), while there was a documented significant decrease in LV geometry parameters (IVST,LVPWT,LVMI) post-TEVAR in another study(43), indicating LVH regression. These results are contradictory. In particular, the population studied where LVH regression took place were exclusively acute Type B Aortic Dissection (TBAD) patients. The author states that the high prevalence of LVH in patients with TBAD is due to multiple hemodynamic changes incurring post-dissection, such as increased pressure gradient between ascending and descending aorta and false lumen pressure exceeding true lumen pressure in distal dissection. Thus, with TEVAR, the author suggests that he obliterates all causes of LVH by occluding the primary tear and overcoming the pressure load from within the false lumen. As a result, LV unloading occurs, reflected on echocardiographic parameters. This may be true; however, it would be mostly applicable in patients with chronic dissection since there is a compulsory interval for left ventricle adaptation to chronic stressors. Consequently, we cannot deduce that TBAD patients present LVH regression post-TEVAR, as the meta-analysis yielded different results.

There are some issues that should be considered. First, the timing of TTE is important, as alterations in the parameters examined need a significant amount of time to accommodate cardiac remodeling. However, this was not an issue in our study, as the follow-up period was quite extensive in all studies included. Secondly, the study samples (except for one(45)) are representative of the general TEVAR population,

where co-morbidities, such as Diabetes Mellitus, Hypertension, Coronary Artery Disease, Dyslipidemia, are most frequent. Thus, external validity is ensured.

Concerning hypertension, this disease acts as a confounder, since it relates to both the exposure (TEVAR for aneurysm, dissection) and to the outcomes (all of the echocardiographic parameters examined). Indeed, most of the TEVAR patients in our studies were hypertensive and there was an incremental increase in the anti-hypertensive regimen post-TEVAR in almost all studies included. Arterial hypertension's effect on cardiac function is known and well documented, as it induces LVH. However, the increase in blood pressure in the TEVAR population seems not to have an influence on the echocardiographic markers examined, as documented from the meta-analysis results. Even in the study where LVH regression occurred, the author states that the results were not affected by the strict blood pressure control(43). However, except for this study, we do not know blood pressure goals and patient compliance to treatment, neither do we know any lifestyle modifications (such as salt intake reduction, exercise, smoking cessation), which would have an impact on overall cardiac function. Nevertheless, the echocardiographic parameters remained unchanged.

Pulse Wave Velocity was augmented in two studies(45, 46), which reflect the already known increased arterial stiffness imposed by the endografts. Despite this fact, however, it did not seem to alter cardiac function post-TEVAR, as implied by the attenuation of the Windkessel effect.

Limitations

This meta-analysis has certain limitations. First, the study sample is small, as all studies had specific inclusion and exclusion criteria. Secondly, there is a great degree of heterogeneity between study measurements. Third, the studies included are uncontrolled before-after studies and the overall certainty of evidence is very low, as documented by GRADE. Therefore, our results should be interpreted carefully.

Conclusion

TEVAR does not seem to alter cardiac function post-implantation, except for a borderline increase in LV mass. Even though there is a documented compliance

mismatch (through PWV) as well as arterial hypertension development, the heart does not seem to be greatly affected. Further studies with greater sample size are needed to elucidate potential effects of TEVAR on cardiac physiology.

Bibliography

1. Dake MD, Miller DC, Semba CP, Mitchell RS, Walker PJ, Liddell RP. Transluminal placement of endovascular stent-grafts for the treatment of descending thoracic aortic aneurysms. N Engl J Med. 1994 Dec 29;331(26):1729-34.
2. Chen Z, Brown C, Khurshan F, Kreibich M, McCarthy F, Bavaria JE, et al. Thoracic Endovascular Aneurysm Repair Trends and Outcomes in Over 27,000 Medicare Patients for Descending Thoracic Aneurysms. Ann Thorac Surg. 2020 Jun;109(6):1757-64.
3. Gray C, Goodman P, Badger SA, O'Malley MK, O'Donohoe MK, McDonnell CO. Endovascular Aneurysm Repair Increases Aortic Arterial Stiffness When Compared to Open Repair of Abdominal Aortic Aneurysms. Vascular and Endovascular Surgery. 2016;50(5):317-20.
4. Moulakakis K, Mylonas S, Kakisis J, Kadoglou N, Papadakis I, Sfyroeras G, et al. Arterial Stiffness Alterations and Inflammatory Response Following Endovascular Aortic Repair. Aorta. 2018;03(02):75-80.
5. Yamashita Y, Oishi Y, Matsuyama S, Ushijima T, Fujita S, Kimura S, et al. Determinants of Changes in Arterial Stiffness after Thoracic Endovascular Aortic Repair. Annals of Vascular Surgery. 2021;70:474-80.
6. Tzilalis VD, Kamvysis D, Panagou P, Kaskarelis I, Lazarides MK, Perdikides T, et al. Increased Pulse Wave Velocity and Arterial Hypertension in Young Patients With Thoracic Aortic Endografts. Annals of Vascular Surgery. 2012;26(4):462-7.
7. Moulakakis KG, Kadoglou NPE, Antonopoulos CN, Mylonas SN, Kakisis J, Papadakis I, et al. Changes in Arterial Stiffness and N-terminal pro-brain natriuretic peptide Levels after Endovascular Repair of Descending Thoracic Aorta. Annals of Vascular Surgery. 2017;38:220-6.
8. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010 Mar 30;55(13):1318-27.
9. Cavalcante JL, Lima JAC, Redheuil A, Al-Mallah MH. Aortic Stiffness: Current Understanding and Future Directions. Journal of the American College of Cardiology. 2011 2011/04/05/;57(14):1511-22.
10. Kanzaki H. Aortic Compliance and Left Ventricular Diastolic Function. Circulation Journal. 2014;78(2):307-8.
11. Toprak A, Reddy J, Chen W, Srinivasan S, Berenson G. Relation of Pulse Pressure and Arterial Stiffness to Concentric Left Ventricular Hypertrophy in Young Men (from the Bogalusa Heart Study). The American Journal of Cardiology. 2009 2009/04/01/;103(7):978-84.
12. Acheampong DO, Paul P, Boateng P, Leitman IM. Predictors and Outcomes of Cardiac Events following Thoracic Endovascular Aortic Repair in Descending Thoracic Aortic Aneurysm and Dissection. Aorta. 2020;08(01):006-13.
13. Ganapathi AM, Englum BR, Schechter MA, Vavalle JP, Harrison JK, McCann RL, et al. Role of cardiac evaluation before thoracic endovascular aortic repair. Journal of Vascular Surgery. 2014;60(5):1196-203.
14. Tsao CW, Gona PN, Salton CJ, Chuang ML, Levy D, Manning WJ, et al. Left Ventricular Structure and Risk of Cardiovascular Events: A Framingham Heart Study Cardiac Magnetic Resonance Study. Journal of the American Heart Association. 2015;4(9).
15. Artham SM, Lavie CJ, Milani RV, Patel DA, Verma A, Ventura HO. Clinical Impact of Left Ventricular Hypertrophy and Implications for Regression. Progress in Cardiovascular Diseases. 2009;52(2):153-67.
16. Narayanan K, Reinier K, Teodorescu C, Uy-Evanado A, Aleong R, Chugh H, et al. Left Ventricular Diameter and Risk Stratification for Sudden Cardiac Death. Journal of the American Heart Association. 2014;3(5).

17. White HJ BS, Borger J. Anatomy, Abdomen and Pelvis, Aorta. [Updated 2020 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537319/.
18. Kelley JD KC, Ashurst JV. Anatomy, Thorax, Aortic Arch. [Updated 2020 Aug 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499911/.
19. Collins JA, Munoz J-V, Patel TR, Loukas M, Tubbs RS. The anatomy of the aging aorta. Clinical Anatomy. 2014;27(3):463-6.
20. Zafar MA, Peterss S, Ziganshin BA, Elefteriades JA. Chapter 3 - Histology of Aortic Disease and Progression of Aortic Dissection From Acute to Chronic. In: Ţintoiu IC, Ursulescu A, Elefteriades JA, Underwood MJ, Droc I, editors. New Approaches to Aortic Diseases from Valve to Abdominal Bifurcation: Academic Press; 2018. p. 41-59.
21. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease. Circulation. 2010;121(13).
22. Mouawad NJ, Paulisin J, Hofmeister S, Thomas MB. Blunt thoracic aortic injury - concepts and management. J Cardiothorac Surg. 2020 Apr 19;15(1):62.
23. Tomiyama H, Yamashina A. Ankle-Brachial Pressure Index and Pulse Wave Velocity in Cardiovascular Risk Assessment. 2018:111-22.
24. Avolio A, Zuo J, Tan I, Butlin M. Pathway for Elimination of Distance Measurement in Studies of Pulse Wave Velocity. Hypertension. 2018;71(5):819-21.
25. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2015;28(1):1-39.e14.
26. Kosaraju A, Goyal A, Grigorova Y, et al. Left Ventricular Ejection Fraction. [Updated 2021 May 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459131/
27. Catherine M. Otto, Textbook of Clinical Echocardiography, 6th Edition. Elsevier, ISBN Number:9780323480482
28. Chengode S. Left ventricular global systolic function assessment by echocardiography. Annals of Cardiac Anaesthesia. 2016;19(5):26.
29. Foppa M, Duncan BB, Rohde LEP. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy? Cardiovascular Ultrasound. 2005;3(1).
30. Chambers D HC, Matthews G. Cardiac Pressure–Volume Loops. Basic Physiology for Anaesthetists. 2nd ed. Cambridge: Cambridge University Press; 2019. p. 136–40.
31. Galderisi M, Lauer MS, Levy D. Echocardiographic determinants of clinical outcome in subjects with coronary artery disease (the Framingham Heart Study). Am J Cardiol. 1992 Oct 15;70(11):971-6.
32. Angaran P, Dorian P, Ha ACT, Thavendiranathan P, Tsang W, Leong-Poi H, et al. Association of Left Ventricular Ejection Fraction with Mortality and Hospitalizations. Journal of the American Society of Echocardiography. 2020;33(7):802-11.e6.
33. Bornstein AB, Rao SS, Marwaha K. Left Ventricular Hypertrophy. [Updated 2021 Mar 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557534/
34. Eliakim-Raz N, Prokupetz A, Gordon B, Shochat T, Grossman A. Interventricular Septum and Posterior Wall Thickness Are Associated With Higher Systolic Blood Pressure. The Journal of Clinical Hypertension. 2016;18(7):703-6.
35. Nation DA, Wang GJ. TEVAR: Endovascular Repair of the Thoracic Aorta. Semin Intervent Radiol. 2015 Sep;32(3):265-71.
36. Mitchell RS, Ishimaru S, Ehrlich MP, Iwase T, Lauterjung L, Shimono T, et al. First International Summit on Thoracic Aortic Endografting: Roundtable on Thoracic Aortic

Dissection as an Indication for Endografting. Journal of Endovascular Therapy. 2002;9(2_suppl):II-98-II-105.
37. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLOS Medicine. 2009;6(7):e1000100.
38. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
39. Schünemann H BJ, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook.
40. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology. 2014;14(1).
41. Nauta FJ, Kamman AV, Ibrahim EH, Agarwal PP, Yang B, Kim K, et al. Assessment of CardiOvascular Remodelling following Endovascular aortic repair through imaging and computation: the CORE prospective observational cohort study protocol. BMJ Open. 2016 Nov 17;6(11):e012270.
42. van Bakel TMJ, Arthurs CJ, Nauta FJH, Eagle KA, van Herwaarden JA, Moll FL, et al. Cardiac remodelling following thoracic endovascular aortic repair for descending aortic aneurysms. Eur J Cardiothorac Surg. 2019 Jun 1;55(6):1061-70.
43. Du Y, Aizezi M, Lin H, Xie X, He J, Qi B, et al. Left ventricular remodeling in patients with acute type B aortic dissection after thoracic endovascular aortic repair: Short- and mid-term outcomes. Int J Cardiol. 2019 Jan 1;274:283-9.
44. Kreibich M, Morlock J, Beyersdorf F, Berger T, Allweier S, Kondov S, et al. Decreased biventricular function following thoracic endovascular aortic repair. Interact Cardiovasc Thorac Surg. 2020 Apr 1;30(4):600-4.
45. Youssef A, Kalaja I, Alkomi U, Abt T, Hoffmann RT, Reeps C, et al. Aortic stiffness and related complications after endovascular repair of blunt thoracic aortic injury in young patients. Vasa. 2020 Jun;49(4):295-300.
46. Hori D, Yuri K, Kusadokoro S, Shimizu T, Kimura N, Yamaguchi A. Effect of endoprostheses on pulse wave velocity and its long-term outcomes after thoracic endovascular aortic repair. Gen Thorac Cardiovasc Surg. 2020 Oct;68(10):1134-41.