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LEFT VENTRICLE MODIFICATION AFTER ENDOVASCULAR AORTIC REPAIR – DOES EVAR AFFECT THE HEART?

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ABSTRACT

INTRODUCTION

EndoVascular Aortic Repair (EVAR) nowadays represent the first line treatment for aortic pathologies and largely replaced open repair (OR) due to its lower invasiveness and better short-term results. Based on a meta-analysis performed on the four most important EVAR Trials (EVAR 1 from UK, DREAM from the Netherlands, OVER from the US and ACE from France) a tendency towards long-term cardiac deaths is apparent in patients treated with endovascular therapy. Endograft deployment is a well-known cause of arterial stiffness increase as well as arterial stiffness increase represent a recognized cardiovascular risk factor.

For this reason, a harmful effect on cardiac function induced by the endograft deployment should be considered and investigated. Aim of this study was to evaluate the impact of endograft deployment on the arterial stiffness and cardiac geometry of patients treated for aortic aneurysm in order to detect modifications that could justify an increased cardiac mortality at follow-up.

MATHERIALS AND METHODS

Over a period of 3 years, patients undergoing elective EVAR for infrarenal aortic pathologies in two university centers in Emilia Romagna were examined. Patients who met inclusion criteria were selected and enrolled in a prospective electronic database. All patients underwent pre-operative and six-months post-operative Pulse Wave Velocity (PWV) examination using an ultrasound-based method performed by vascular surgeons together with trans-thoracic echocardiography examination performed by cardiologist of the two centers in order to evaluate cardiac chambers geometry before and after the treatment.

RESULTS

Between December 2018 and December 2021, 69 patients were enrolled in the study. After 36 months, 36 patients (52%) completed the 6 months follow-up examination and were taken into consideration for the statistical analysis (Bologna/Parma 19/17; 52,7%/ 47,3%). Male patients were 27 (75%), mean age was 74,8 years old (Min-Max 61 – 87; SD 6,20). The mean follow-up was 8,2 months (Min-Max 6,4 – 14; SD 5,89). Ten out of 69 patients initially recruited for the study died during follow-up (14,5%). The cause of death was SARS-Cov-2 infection in 6 cases (60%), cardiac infarction in 2 cases (20%) and unknown in 2 cases (20%). The ultrasound-based carotid-femoral PWV measurements performed preoperatively and 6 months after the procedure revealed a significant postoperative increase of cf-PWV (11,6±3,6 m/sec vs 12,3±8 m/sec; p.value: 0,037). Postoperative LVtdV (90±28,3 ml/m2 vs 99,1±29,7 ml/m2; p.value: 0.031) LVtdVi (47,4±15,9 ml/m2 vs 51,9±14,9 ml/m2; p.value: 0.050), IVStd (12±1,5 mm vs 12,1±1,3 mm; p.value: 0,027) were significantly increased if compared with preoperative measures. Postoperative E/A (0,76±0,26 vs 0,6±0,67; p.value: 0,011), E' lateral (9,5±2,6 vs 7,9±2,6; p.value: 0,024) and A' septal (10,8±1,5 vs 8,9±2; p.value 0,005) were significantly reduced if compared with preoperative measurements. No significant correlation was found between preoperative cardiovascular comorbidities and/or cardiovascular medications and/or type of endograft used; and postoperative cf-PWV and transthoracic echocardiographic parameters modifications.

CONCLUSION

The endovascular treatment of the abdominal aorta causes an immediate and significant increase of the aortic stiffness. This increase reflects negatively on patients' cardiac geometry inducing left ventricle hypertrophy and mild diastolic disfunction after just 6 months from endograft's

implantation. Further investigations and long-term results are necessary to access if this negative remodeling could affect the cardiac outcome of patient treated using the endovascular approach.

PREMISE

The following study was carried out between 2019 and 2022. The SARS-CoV2 global pandemic seriously affected both the surgical and outpatient clinic activities of the Vascular Surgery and Cardiology Departments involved in the study causing both a reduced number of patients treated and consequently enrolled in the study and a reduced follow-up.

INTRODUCTION

The endovascular treatment of the aorta

In the last 20 years[1,2] the endovascular aortic repair (EVAR) largely replaced open repair (OR) as the first line treatment for aortic pathology and particularly aneurysm. EVAR represents a less invasive procedure characterized by lower surgical trauma, earlier return to daily activities, reduced mortality and lower morbidity if compared with open repair[2-4].
The aim of the endovascular approach is the deployment of these endografts at the level of the aorto-iliac segment in order to exclude the aortic lesion from the blood stream and consequently from hemodynamic forces[5].

Endografts are highly technological tools generally composed by two components: a metallic self-expandable stent made of bio-compatible metal alloys such as Nitinol (Nickel and Titanium) or stainless steel characterized by high radial force able to guarantee stability and fixation; and a synthetic polymeric fabric tube made of polyester (Dacron) or polytetrafluoroethylene (PTFE) responsible for aneurysm exclusion. Infrarenal aortic endografts can have a straight, bifurcated and aorto uni-iliac configuration despite nowadays bifurcated endografts represent the preferred and most used configuration. Different materials and characteristics make each typology of commercially available endografts specifically indicated for different anatomical conditions. The endograft's choice represent one of the most delicate part the endovascular approach and must follow a meticulous pre-operative planning performed by physician's expert in endovascular treatment.

The endograft implantation is performed using radioscopic guidance and iodinated or non-iodinated contrast medium. The access to the patient's vasculature is performed with small groin incisions or

percutaneously using the Seldinger's technique through the femoral arteries[6]. Hydrophilic metallic guidewires and catheters are used to deliver the endograft inside the infrarenal aorta. The endograft is then deployed at the level of the infrarenal aortic neck (a healthy portion of the infrarenal aorta) keeping both renal arteries patent. In case of bifurcated endografts the implant is completed with distal extensions that seal in both iliac arteries possibly maintaining hypogastric arteries patency. In case of inadequate distal iliac sealing zone due to aneurysmal degeneration the implant can be completed using specific iliac branch devices (smaller bifurcated endografts specifically designed to spare hypogastric arteries and preserve their patency) that requires a femoro-femoral through and through technique to be deployed.

The effectiveness of the endovascular approach and its results compared with OR have been widely reported in literature in four well established national EVAR Trials (EVAR 1 from UK[7], DREAM from the Netherlands[8], OVER from the US[9] and ACE from France[10]). The analysis of the data from randomized EVAR Trial 2 showed that, despite the absence of statistical significance, cardiac events rate in patients underwent EVAR is slightly higher if compared with patients discharged from treatment because considered unfit for OR[11]. Understandably the authors hypothesized for the first time a negative effect of EVAR on cardiac function. A recent meta-analysis of the data from the above-mentioned trials published in the British Journal of Surgery, analyzed and compared the long-term results of both EVAR and the OR[12]. Data from the meta-analysis, as data from each single trial, testify as the reduced invasiveness of EVAR can guarantee better immediate, 30 days and short terms (30 days to 6 months) results in terms of mortality if compared with OR[12]. Figure 1.

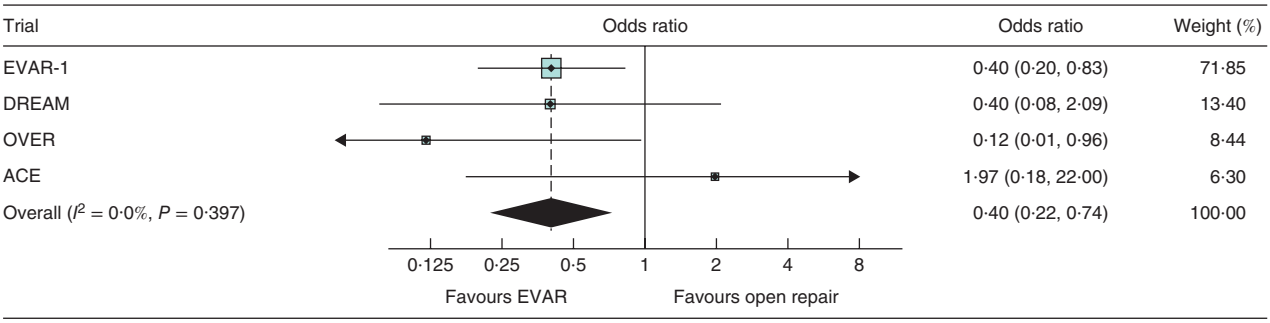

Figure 1) 30-Days results from Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, Greenhalgh RM; EVAR-1, DREAM, OVER and ACE Trialists. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg. 2017 Feb;104(3):166-178. doi: 10.1002/bjs.10430. Erratum in: Br J Surg. 2018 Aug;105(9):1222. PMID: 28160528; PMCID: PMC5299468.[12]

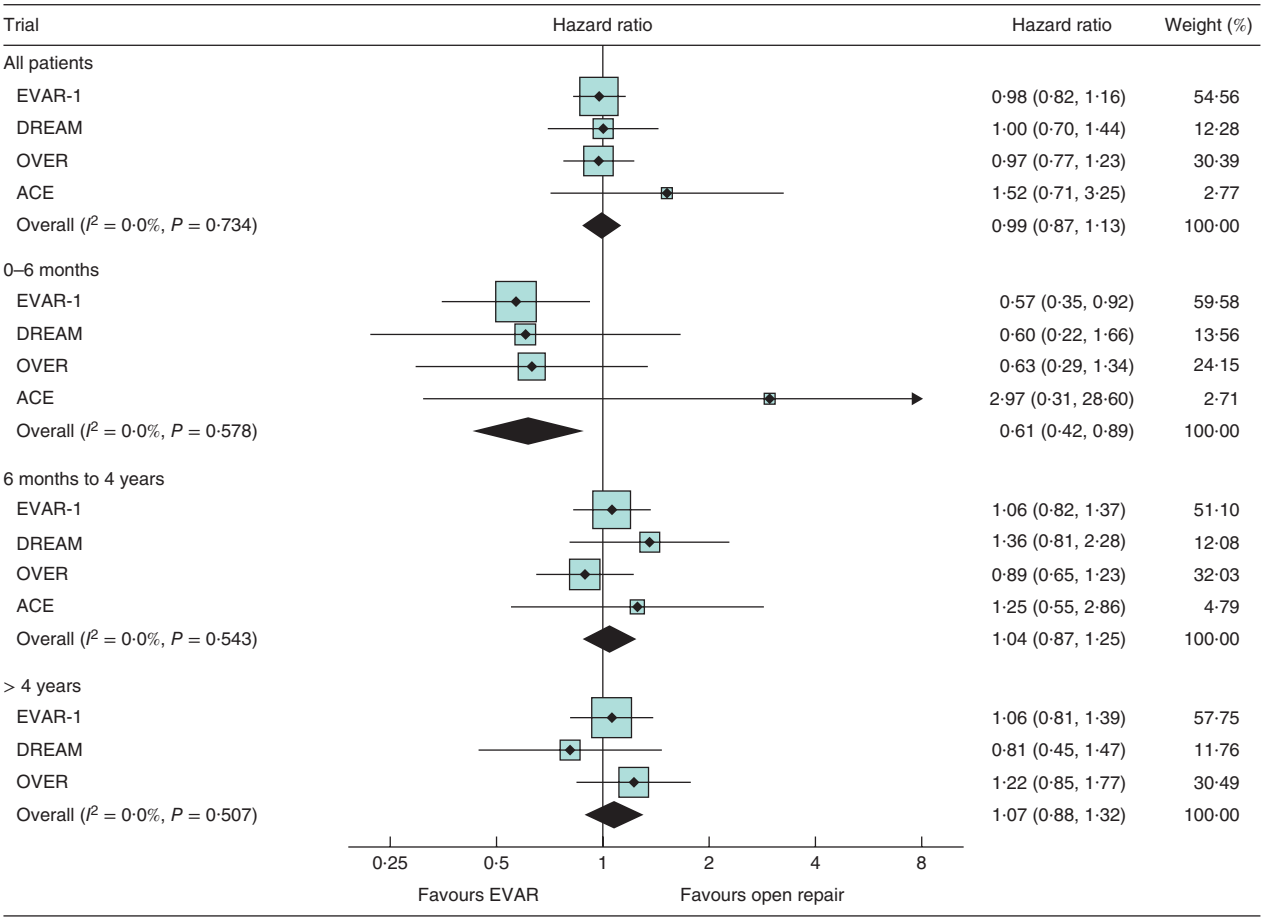

Figure 2) Mid-term and long-term results from Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, Greenhalgh RM; EVAR-1, DREAM, OVER and ACE Trialists. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg. 2017 Feb;104(3):166-178. doi: 10.1002/bjs.10430. Erratum in: Br J Surg. 2018 Aug;105(9):1222. PMID: 28160528; PMCID: PMC5299468.[12]

Being said that, moving forward with the follow-up, a convergence in all-cause mortality between EVAR and OR both at mid and long-term emerged balancing the mortality rate of the two approaches at the final general results. Going deep into the meta-analysis shows as, despite an absence of statistical significance, cardiac deaths at follow-up are higher in the EVAR group if compared with the OR group. Figure 2.

In author opinion the consideration we can line out from this meta-analysis are two:

- A non-significant tendency toward cardiovascular deaths in the endovascular groups was apparent within the most important EVAR Trials at follow-up
- A harmful effect on cardiac function induced by the endograft deployment should be considered and investigated.

Arterial stiffness express arterial wall rigidity. Physiologically it occurs as a consequence of biological aging and arteriosclerosis. Arterial stiffness has been correlated with long-term cardiovascular outcomes independently from traditional cardiovascular risk factors (systemic arterial hypertension, dyslipidaemia, diabetes, obesity, smoke habit, exc); and has been confirmed to be associated with an increased risk of cardiovascular events such as myocardial infarction, hypertension, stroke and heart failure[13].
An increased arterial stiffness can be measured using Pulse Wave Velocity (PWV) that represents the speed of the pulse wave generated by the heart travelling through an arterial vessel. Pulse wave velocity can be measured with different invasive and non-invasive techniques.

EVAR is demonstrated to affect vascular stiffness and to induce PWV modifications, left ventricle (LV) hypertrophy and left atrium (LA) enlargement without elevating systemic blood pressure in the early post-operative and mid-term period and that these modifications persist for at least one

year after treatment[14]. Although these modifications have been shown in animal models[15,16], the impact of aortic endografting in humans undergoing EVAR remains unclear and poorly investigated.

Aim of this study was to evaluate the impact of endograft deployment on arterial stiffness and cardiac geometry of patients treated for abdominal aortic aneurysm in order to detect modifications that could justify an increased cardiac mortality at follow-up.

The arterial structure

The arterial wall is composed by three layers, tunica intima, tunica media and tunica adventitia. While intima or the endothelial layer comprises of a single layer of endothelial cells. The tunica media is the thickest layer and composed of circumferentially arranged elastic fibres, smooth muscle cells, and collagen fibres. Adventitia comprises of large diameter collagen fibres oriented longitudinally as wavy containing bundles. The mechanical behaviour of an artery is based mainly on the thickness of the tunica media layer and its main structural components (elastin and collagen), which differ significantly in their elastic modulus (elastin = 0.6–1 MPa, collagen = 1 GPa)[17]. Aorta, together with common carotids, subclavian and pulmonary arteries, is an elastic artery. Elastic arteries are constituted by a tunica media characterized by a very well represented elastin component. The elastic component gives to elastic arteries the specific capability to stretch in response to each cardiac cycle. This elasticity also gives rise to the so called Windkessel Effect, which helps maintaining a relatively constant pressure in the arteries despite the pulsating nature of blood flow. From a histological point of view, moving caudally along the aorta the number of elastin fibres within the tunica media progressively decrease (abdominal aorta - 40% if compared with descending thoracic aorta)[18] leaving to ascending aorta, aortic arch and descending aorta the major role in terms of “pressure manager” acting as an elastic reservoir. Despite a reduced number

of elastin fibres, the abdominal aorta also represents and works as an elastic artery within the close circuit of the human vasculature.

The elastic modulus

The elastic modulus is a quantity that measures a material or substance's resistance to elastic deformation (i.e. non permanently) when a stress is applied to it. The elastic modulus of an object is defined as the slope of its stress-strain curve in the elastic deformation region. The stiffer the material the higher elastic modulus it has[19]. Many different types of elastic moduli have been described based on how stress and strain are measured and on the direction these are applied. The Young's modulus (E) describes tensile elasticity or the tendency of an object to deform along its axis when opposing forces are applied along the same axis. This modulus is defined as the ratio between tensile stress and tensile strain and represent the most appropriate to describe the forces applied to a conduit such the aorta and an endograft. The elastic modulus is usually expressed in Pascals (Pa), a derived unit of pressure used to quantify, among others, internal pressure, stress and tensile strength.

Based on previous published experiences, the elastic modulus of the thoracic aorta in a middle-aged patient is 0.44 MPa while the elastic modulus of a typical endograft is 55,2 MPa[20]. We can then assume that the endograft deployment can increase arterial stiffness[21].

The ventricular-arterial coupling

The cardiovascular system is composed by a four chambers pump and pipes, respectively represented by the heart and arteries. The ventricular-arterial coupling (VAC) represents a well-known physiological concept[22]. It emerges from the logical notion that the heart and the arterial system are inherently related as they are anatomically and functionally linked structures constituting

a closed system. Coupling refers to the pumping action of the heart when connected to the load opposed by the arterial system[23].

Age-dependent increased in vascular stiffening is a known physiological phenomenon and the consequence of the widening of arterial pulse pressure in the elderly[24]. Because of the VAC, this age-related increase in vascular stiffening is associated with a compensatory change in left ventricular (LV) structure at rest, which maintains the normal coupling between the heart and the arterial system but with a decreased cardiovascular reserve during exercise[25]. If the vascular stiffness increase is maintained, as it happens in patients with uncontrolled hypertension, diabetes and kidney diseases, LV's structure alterations can become chronic, leading to LV disfunction.

MATERIALS AND METHODS

Inclusion criteria

Between December 2018 and December 2021 all the patients treated in the elective setting using an endovascular approach for infrarenal aortic aneurysm (AAA) in two University Centers for vascular and endovascular surgery in Emilia Romagna (Italy) and respecting the following inclusion criteria:

- intention to treat after receiving computed tomography angiography (CTA) diagnosis of AAA
- age between 18 and 99 years old

were enrolled in a prospective electronic database (Microsoft Excel. Microsoft Corporation, Redmond, WA, USA).

Exclusion criteria

Exclusion criteria of the study were:

- Intention to treat after diagnosed aortic dissection
- Previous aortic endovascular treatment
- Previous open aortic replacement
- Significant valve disease
- Significant congenital heart diseases
- Significant pre-operative left ventricle regional wall motion abnormality
- History of open-heart operation

- Heart transplant history

The following demographic information were collected:

- date of birth
- age
- sex
- date of admission
- date of treatment
- date of discharge
- in-hospital stay

The following pre-operative clinical characteristics and cardiovascular risk-factors were collected:

- hypertension
- dyslipidaemia
- diabetes
- current smoke habits
- former smoke habits
- chronic obstructive pulmonary disease (COPD)
- chronic renal failure (CRF)
- coronary artery disease (CAD)
- atrial fibrillation (AF)
- previous history of cardiac failure (CF)
- obesity

- American Society for Anaesthesiology (ASA) Score

together with the following preoperative chronic cardiovascular medications:

- Angiotensin Converting Enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Beta-Blockers
- Calcium channel blockers
- Diuretics
- Oral anticoagulants
- Antiplatelet therapy
- Digoxin
- Amiodarone

All the patients underwent pre-operative thoraco-abdominal CTA examination.
The morphological characteristics of the aorto-iliac anatomy were collected after post-processing evaluations (multiplanar three-dimensional, central lumen-line reconstructions) and elaborated by a dedicated software for vessel analysis (3Mensio; Vascular Imaging, Bilthoeven, The Netherlands) in order to determine the feasibility of an endovascular treatment.

Aortic Stiffness Measurement

The measurement of the carotid-femoral pulse wave velocity (cf-PWV) was performed by experienced vascular surgeons using a non-invasive ultrasound-based method widely described in literature[26,27]. A pulsed Duplex ultrasound machine (MyLab Twice, Esaote, Firenze, Italy) equipped with a linear array (6,6 MHz) probe coupled with 3-lead ECG connected to the Duplex machine

was used pre-operatively and 6 months after the procedure to perform the examinations. The patients were supine in a silent and calm room and underwent the examination after a 15 minutes rest time. The right carotid artery was located using B-mode at the supraclavicular level (1-2 cm of the bifurcation). The Doppler's wave maximum velocity was measured, and the measurement was repeated three times. Each recording involved two or three cardiac cycles. In order to measure the transit time (TT), we measured the time (in milliseconds) from the R wave of QRS to the foot of the waveform using the digital caliper function of the Duplex ultrasound machines. The process was repeated three times also at the level of the right common femoral artery. (Figure 3) The average Doppler's wave maximum velocity was calculated out of the three previous measurements both at the level of the common carotid artery and common femoral artery. To measure the carotid-femoral distance we measured the distance between the sternal notch and pubic symphysis using an inextensible measuring tape. The measure was in centimetres (cm) and the cf-PWV in meters/seconds (m/sec).

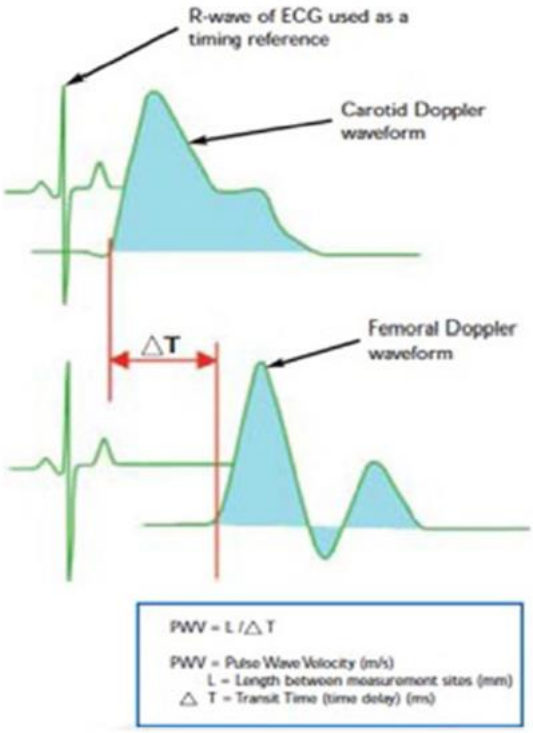

Figure 3) Ultrasound Based cf-PWV measurement scheme. cf-PWV was measured in m/seconds

Cardiological and Transthoracic Echocardiography Evaluation

Transthoracic echocardiography examination was performed by experienced cardiologists pre-operatively and 6 months post-operatively using (Philips) in dedicated echocardiography outpatient-clinic rooms.

The echocardiographic parameters taken into consideration and analysed for the purpose of the study were:

- Body Surface Area (BSA)
- Left Ventricular end diastole Volume (LVtdV)
- Left Ventricular end diastole index (LVtdVi)
- Ejection Fraction (EF)
- Left Ventricular end diastoleDiameter (LVtdD)
- Interventricular septal end diastole (IVStd)
- Interventricular septal end systole (IVSts)
- Posterior Wall Tickness end diastole (PPtd)
- Posterior Wall Tickness end systole (PPts)
- Relative Wall Tickness (RWT)
- Left Ventricle Mass (LVmass)
- Left Ventricle Mass Index (LVmass index)
- LAAP (mm)
- Left Atrium Volume (LA vol)
- Left Atrium Volum index (LA vol index)
- E wave

- A wave
- E/A ratio (E/A)
- E wave deceleration (EDT)
- S septal
- S lateral
- E septal
- E lateral
- A septal
- A lateral
- Ee septal
- Ee lateral
- Aortic root diameter (mm)
- Ascending aorta diameter (mm)
- Inferior Vena Cava diameter VCI (mm)
- Systolic Pulmonary Artery Pressure (PAPs)

Systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and heart rate (beats/min) were measured pre-operatively and 6 months post-operatively together with EKG.

The Endovascular Procedures

All the patients signed an informed consent before the treatment. The endovascular procedures were performed under general (GA) or spinal anaesthesia (SA) in an Allura Clarity Hybrid Room

(Philips, Amsterdam, Netherlands) or in standard operative room using a portable a Zihem Vision RFD C-Arm (Ziehem Imaging Inc. GmbH, Nurnberg, D).

Systemic heparinization was obtained using Sodium Heparin (50UI/kg) after the first access to the femoral artery and maintained through the monitoring of Activated Coagulation Time (ACT) during the procedure (target value >200 sec). Both suprarenal fixation and infrarenal fixation standard bifurcated aortic endografts commercially available were used. In case of inadequate distal sealing zone due to common iliac artery or hypogastric artery aneurysm hypogastric commercially available branched endografts were used.

Technical aspects such operative time (minutes), fluoroscopy time (minutes), contrast medium volume (cc) used during the procedure, type of endograft used were recorded.

Postoperative renal function impairment was considered as ≥30% reduction of the glomerular filtration rate calculated with the Cockcroft-Gault formula compared with pre-operative values.

Pre-operative cf-PWV and echocardiographic were compared with 6 months follow-up data of patients alive and with valid follow-up by a multidisciplinary team composed of vascular surgeons and cardiologists expert in echocardiography examination.

Statistical Analysis

Statistical analysis was performed with SPSS software Edition 23.0 for MacBook (IBM, Armonk, NY, USA). Categorical and continuous variables were evaluated in terms of frequency, valid percentage and statistical mean, range and standard deviation respectively. Non-parametric Wilcoxon signed-rank test for not normally distributed related samples was used. The statistical hypothesis test chosen to evaluate significance comparing different groups was Fischer exact chi-squared test because the sample was ≤100. Difference was considered significant with a P-value < 0,05.

RESULTS

Between December 2018 and December 2021, 273 patients were treated in the University of Bologna Vascular Surgery Unit and 180 patients in the University of Parma Vascular Surgery Unit, using commercially available standard bifurcated aortic endografts. Sixty-nine patients fit the inclusion criteria and were enrolled in the study. After 36 months, 36 patients (52%) completed the 6 months follow-up examination and were taken into consideration for the statistical analysis (Bologna/Parma 19/17; 52,7%/ 47,3%).

Male patients were 27 (75%). Mean age was 74,8 years old (Min-Max 61 – 87; SD 6,20).

Preoperative characteristics, risk factors and chronic cardiovascular medications are listed in Table 1 and 2 respectively.

Preoperative Cardiovascular Risk Factors		
	N	**%**
Current Smoker	14	38,9
Former Smoker	13	36,1
Hypertension	32	88,9
Dyslipidemia	25	69,4
Diabetes Mellitus	8	22,2
COPD	11	30,6
CAD	9	25
CRF	11	30,6
AF	4	11,1
Previous cardiac failure	-	-
Obesity (BMI ≥30)	9	25

ASA Score 2	7	19,4
ASA Score 3	22	61,1
ASA Score 4	7	19,4

Table 1) Preoperative cardiovascular risk factors. COPD: Chronic Obstructive Pulmonary Disease; CAD: Coronary Artery Disease; CRF: Chronic Renal Failure; AF: Atrial Fibrillation; BMI: Body Mass Index; ASA: American Society for Anaesthesiology

Preoperative Chronic Cardiovascular Medications		
	N	**%**
Angiotensin Converting Enzyme (ACE) inhibitors	7	19,4
Angiotensin receptors blockers (ARBs)	11	30,6
Beta Blockers	20	55,6
Calcium channel blockers	7	19,4
Diuretics	8	22,2
Oral anticoagulants	4	11,1
Antiplatelet therapy	30	83,3
Digoxin	-	-
Amiodarone	-	-

Table 2) Preoperative Chronic Cardiovascular Medications

Suprarenal fixation endografts were used in 20 patients (55,6%) while infrarenal fixation endografts in 16 patients (44,4%). Gore Excluder (W.L. Gore & Associates, Flagstaff, AZ, USA) was used in

16 patients (44,4%), Medtronic Endurant II (Medtronic, Minneapolis, MI, USA) was used in 3 patients (8,3%) and Cook Zenith Alpha Abdominal (Cook Medical, Bloomington, IN, USA) was used in 17 patients (47,2%). Hypogastric branch devices were used in 3 patients (8,3%). Gore Excluder Iliac Branch Endoprosthesis (W.L. Gore & Associates, Flagstaff, AZ, USA) was used in 2 patients (5,5%) while Zenith Branch Endovascular Graft (Cook Medical, Bloomington, IN, USA) was used in 1 patient (2,7%).

Mean procedural and fluoroscopy time was 168 min (range 70 - 420) and 35 min (range 5 - 90), respectively. Mean contrast medium volume injected was 86.5 cc (range 22 - 210).

Intra-operative and 30-days mortality, morbidity and aortic related reintervention rate was 0%. None of the patients suffered postoperative renal function impairment.

The mean follow-up was 8,2 months (Min-Max 6,4 – 14; SD 5,89). Ten out of 69 patients initially recruited for the study died (14,5%). The cause of death was SARS-Cov-2 infection in 6 cases (60%), cardiac infarction in 2 cases (20%) and unknown in 2 cases (20%).

Pre-operatory cf-PWV and transthoracic echocardiography parameters are listed in Table 3.

Preoperative Cardiovascular Parameters			
	Median	**Min - Max**	**Standard Deviation**
Cf-PWV (m/sec)	11,6	4,8 – 20,38	3,6
BSA (m2)	1,8	1,36 – 2,28	0,2
LVtdV (ml/m)	90	52 - 208	28,3
LVtdVi (ml/m2)	47,4	29,6 - 120	15,9

Ejection Fraction (%)	62	50 – 74	7
LVtdD (mm)	46	38 - 65	5,7
IVStd (mm)	12	8 – 14	1,5
IVSts (mm)	16	13 - 19	1,7
PPtd (mm)	11,2	6 - 14	1,6
PPts (mm)	14,5	12 - 18	1,6
RWT	0,47	0,1 – 0,6	0,10
LV mass (g)	210	101 – 310	48,6
LV mass index (g/m2)	104,3	63,7 – 159,7	26,4
LA AP (mm)	40	32 - 66	7,9
LA vol (ml)	63,9	29 – 116	21,7
LA vol ind (ml/m2)	31,4	19 – 61,2	11,2
E wave (cm/sec)	66	36 - 195	36,1
A wave (cm/sec)	100	48 - 122	24
E/A	0,76	0,39 – 1,6	0,26
EDT (ms)	250	150 – 350	54,2
S' septal	7,15	5,5 – 9,1	0,87

S' lateral	8,8	5,8 – 12	1,8
E' septal	6,4	3,2 – 11	1,7
E' lateral	9,5	4,6 – 15,7	2,6
A' septal	10,8	8 – 12,6	1,5
A' lateral	12,6	4,6 - 19	4
E/e' septal	10,34	5 - 19	3,6
E/e' lateral	7,05	4,3 – 11,2	2,2
Aortic root diameter (mm)	34	30 - 47	4,8
Ascending aorta diameter (mm)	37,5	30 - 45	4,3
VCI (mm)	10	5 – 20	4,2
PAP s (mm/Hg)	35	25 – 45	6,2

Table 3) Preoperative Echocardiographic Parameters

Post-operatory cf-PWV and transthoracic echocardiography parameters at 6 months are listed in Table 4.

Postoperative Cardiovascular Parameters			
	Median	**Min - Max**	**Standard Deviation**

Cf-PWV (m/sec)	12,3	5,8 – 45,8	8
BSA	1,89	1,2 – 2,2	0,21
LVtdV (ml/m)	99,1	52 - 207	29,7
LVtdVi (ml/m2)	51,9	30 – 118	14,9
Ejection Fraction (%)	61	35 – 72	7,4
LVtdD (mm)	45,7	34 - 65	5,8
IVStd (mm)	12,1	10 – 14,9	1,3
IVSts (mm)	16,4	13,6 – 19,1	1,6
PPtd (mm)	11	0,9 – 14,4	2,2
PPts (mm)	14,5	2,19 – 19,4	3,6
RWT	0,5	0,04 – 0,6	0,1
LV mass (g)	210,7	108 – 343	56,9
LV mass index (g/m2)	105,8	67,2 – 196,1	29,8
LA AP (mm)	40	29 – 54	6,5
LA vol (ml)	65	22 – 157	28
LA vol ind (ml/m2)	34,6	17,3 – 71,6	13,2
E wave (cm/sec)	62	39 – 192	37,2

A wave (cm/sec)	85	22 – 130	27,6
E/A	0,6	0,4 – 4,2	0,67
EDT (ms)	222	103 – 430	81,4
S' septal	6,8	3,5 – 8,9	1,3
S' lateral	7,2	6 – 11	1,7
E' septal	5,4	3,1 – 11,6	1,7
E' lateral	7,9	3,5 – 14	2,6
A' septal	8,9	5,2 – 12,7	2
A' lateral	10,1	3,8 – 17,5	3,3
E/e' septal	10,5	5,12 – 30,3	6,7
E/e' lateral	7,7	4 – 21,5	4,2
Aortic root diameter (mm)	34	39 – 46	10,5
Ascending aorta diameter (mm)	36	37 - 45	11,1
VCI (mm)	12	5 – 23	4,9
PAP s (mm/Hg)	25	15 – 55	9,6

Table 4) Preoperative Echocardiographic Parameters

The Duplex based carotid-femoral PWV measurements performed preoperatively and 6 months after the procedure revealed a significant postoperative increase of cf-PWV (11,6±3,6 m/sec vs 12,3±8 m/sec; p.value: 0,037).

Postoperative LVtdV (90±28,3 ml/m2 vs 99,1±29,7 ml/m2; p.value: 0.031) LVtdVi (47,4±15,9 ml/m2 vs 51,9±14,9 ml/m2; p.value: 0.050), IVStd (12±1,5 mm vs 12,1±1,3 mm; p.value: 0,027) were significantly increased if compared with preoperative measures.

Postoperative E/A (0,76±0,26 vs 0,6±0,67; p.value: 0,011), E' lateral (9,5±2,6 vs 7,9±2,6; p.value: 0,024), A' septal (10,8±1,5 vs 8,9±2; p.value 0,005) and E/e' mean (9,59±4,12 vs 8,7±4,6; p.value: 0,037) were significantly reduced if compared with preoperative measurements.

Any significant correlation was found between preoperative cardiovascular comorbidities and/or cardiovascular medications and/or type of endograft used; and postoperative cf-PWV and transthoracic echocardiographic parameters modifications.

Comparison between post-operatory cf-PWV and transthoracic echocardiography parameters at 6 months are listed in Table 5.

	Preoperative		**Postoperative**		
	Median	**Standard Deviation**	**Median**	**Standard Deviation**	**p.value**
Cf-PWV (m/sec)	11,6	3,6	12,3	8	**0,037**
BSA	1,8	0,2	1,89	0,21	0,071
LVtdV (ml/m)	90	28,3	99,1	29,7	**0,031**

LVtdVi (ml/m2)	47,4	15,9	51,9	14,9	**0,050**
Ejection Fraction (%)	62	7	61	7,4	0,294
LVtdD (mm)	46	5,7	45,7	5,8	0,734
IVStd (mm)	12	1,5	12,1	1,3	**0,027**
IVSts (mm)	16	1,7	16,4	1,6	0,118
PPtd (mm)	11,2	1,6	11	2,2	0,537
PPts (mm)	14,5	1,6	14,5	3,6	0,276
RWT	0,47	0,10	0,5	0,1	0,651
LV mass (g)	210	48,6	210,7	56,9	0,561
LV mass index (g/m2)	104,3	26,4	105,8	29,8	0,658
LA AP (mm)	40	7,9	40	6,5	0,742
LA vol (ml)	63,9	21,7	65	28	0,940
LA vol ind (ml/m2)	31,4	11,2	34,6	13,2	0,886
E wave (cm/sec)	66	36,1	62	37,2	0,897
A wave (cm/sec)	100	24	85	27,6	0,572
E/A	0,76	0,26	0,6	0,67	**0,011**
EDT (ms)	250	54,2	222	81,4	0,223

S' septal	7,15	0,87	6,8	1,3	0,256
S' lateral	8,8	1,8	7,2	1,7	0,151
E' septal	6,4	1,7	5,4	1,7	0,304
E' lateral	9,5	2,6	7,9	2,6	**0,024**
A' septal	10,8	1,5	8,9	2	**0,005**
A' lateral	12,6	4	10,1	3,3	0,959
E/e' septal	10,34	3,6	10,5	6,7	0,427
E/e' lateral	7,05	2,2	7,7	4,2	0,477
Aortic root diameter (mm)	34	4,8	34	10,5	0,255
Ascending aorta diameter (mm)	37,5	4,3	36	11,1	0,384
VCI (mm)	10	4,2	12	4,9	0,236
PAP s (mm/Hg)	35	6,2	25	9,6	0,112

Table 5) Comparison between post-operatory cf-PWV and transthoracic echocardiography parameters at 6 months

DISCUSSION

A negative effect of aortic endografts deployment on aortic stiffness and consequently on cardiac function have been widely investigated and described in literature after thoracic aorta treatment[15, 28-31]. The deployment of a stent-graft inside the aorta can intuitively affect arterial elasticity as the materials it is made are less elastic if compared with the native aortic wall in particular at the level of the descending thoracic aorta that, following the ascending aorta and the aortic arch, represent the most elastic segment of the human circulatory system and responsible for the so called Windkessel effect which helps maintaining a relatively constant pressure in the arteries despite the pulsating nature of blood flow. The effects of thoracic endograft deployment on arterial stiffness have been described since TEVAR introduction[15, 28-31], while the same effects have been scarcely described after abdominal endovascular repair[32-35].

Arterial stiffness has been correlated with long-term cardiovascular outcomes independently from traditional cardiovascular risk factors (systemic arterial hypertension, dyslipidaemia, diabetes, obesity, smoke habit, exc). Arterial stiffening results in increased pulse pressure leading to left ventricular hypertrophy, subendocardial ischemia, endothelial dysfunction and cardiac fibrosis.

EVAR is demonstrated to affect vascular stiffness and to induce PWV modifications, left ventricle hypertrophy and left atrium enlargement without elevating systemic blood pressure in the early post-operative and mid-term period and that these modifications persist for at least one year after treatment[14]. Although these modifications have been shown in animal models[15,16], the impact of aortic endografting in humans undergoing EVAR remains unclear and poorly investigated.
Aim of this study was to evaluate the impact of endograft deployment on arterial stiffness and cardiac geometry of patients treated for abdominal aortic aneurysm in order to detect modifications that could justify an increased cardiac mortality at follow-up.

Performing preoperative and postoperative PWV measurements and echocardiography Takeda Y. et al firstly demonstrated as EVAR can increase vascular stiffness and induce cardiac geometry modifications causing left ventricle hypertrophy and diastolic dysfunction without elevating blood pressure nor in acute or chronic phase[14]. These results can be explained by the decreased aortic compliance caused by EVAR that result in an increased left ventricle afterload that predispose to left ventricle hypertrophy. This induced hypertrophy in turn can cause a left ventricle diastolic filling deterioration that worsen subendocardial blood flow. All these elements, in the long term, can cause heart failure and worsen cardiac morbidity and mortality[32]. In a recent study, Marketou M. et colleagues evaluated the same modifications after EVAR and confirmed as the endovascular repair of abdominal aneurysms leads not only to an increase in aortic stiffness (measured by the increase in PWV), but also to a reduction in cardiac systolic function testified by Global Longitudinal Strain (GLS) deterioration[34]. The same author correctly suggested the need for a stricter postoperative cardiac surveillance specifically tailored for patients undergoing abdominal endovascular repair; and for further investigations in order to define if these cardiac modifications may translate into long-term cardiovascular complications.

In our experience, patients treated using EVAR experienced a significant cf-PWV increase 6 months after the implantation (11,6±3,6 m/sec vs 12,3±8 m/sec; p.value: 0,037). This result testifies as, despite the lack of agreement in recent literature[36,37], aortic stiffness is affected also by abdominal endografts. The abdominal aorta seems then play a role in pressure management and cardiac-arterial coupling despite being characterized by -40% elastin fibers if compared with thoracic aorta[18]. As a result of endograft implantation (and the consequent aortic stiffness increase) the pulse wave generated by the heart is reflected prematurely and return to the heart during systole increasing the systolic pressure (namely increasing cardiac workload). Consequently, the heart is forced to increase its work in order to maintain the same stoke volume, leading to the development of left ventricular hypertrophy and ventricular geometry remodeling. Post-operative transthoracic

echocardiography examinations at 6 months demonstrated a significant increase in LVtdV (90±28,3 ml/m2 vs 99,1±29,7 ml/m2; p.value: 0.031), LVtdVindex (47,4±15,9 ml/m2 vs 51,9±14,9 ml/m2; p.value: 0.050) and IVStd (12±1,5 mm vs 12,1±1,3 mm; p.value: 0,027). Left ventricle end diastolic volume represent the amount of blood in the left ventricle just before the systole (the so-called preload). To allow comparison among individuals with different body size and features, chambers measurements can also be reported indexed to BSA. Interventricular septal end diastole represents the diameter of the interventricular septum that divides the left ventricle from the right ventricle[38]. Both an increased LVtdV or LVtdV index and a IVStd are markers of left ventricle concentric hypertrophy that could be reasonably motivated by the increased arterial stiffness secondary to endograft implantation.

Another parameter that significantly highlighted a postoperative left ventricle function modification in our series was a reduction in the E/A ratio (0,76±0,26 vs 0,6±0,67; p.value: 0,011). This parameter represents the ratio between the E wave (the measure of the peak blood flow velocity from the left ventricle during early diastole relaxation) and the A wave (the measure of the peak blood flow velocity during late diastole caused by atrial contraction). E/A ratio is used as an echocardiographic marker of mild diastolic dysfunction (namely an inefficient left ventricle filling)[39]. Left ventricle hypertrophy is characterized by ventricular walls stiffening that, increasing back pressure during ventricular diastolic filling, can lower the E/A ratio. Left ventricle concentric hypertrophy induced by endograft implantation could again reasonably be the cause of this modification and confirm this study hypothesis. Similarly, E' lateral, defined as lateral early diastolic mitral annular velocity and A' septal, defined as septal late diastolic mitral annular velocity were significantly reduced postoperatively confirming a mild diastolic disfunction that could reflect left ventricle concentric hypertrophy. (E' lateral: 9,5±2,6 vs 7,9±2,6; p.value: 0,024; A' septal: 10,8±1,5 vs 8,9±2; p.value 0,005).

Taken together, these findings confirm how abdominal aorta endovascular repair have a relevant and possibly negative effect on left ventricle geometry, inducing left ventricle concentric

hypertrophy and mild diastolic disfunction after just few months from the procedure. A longer follow-up and further echocardiographic investigation after 12 months and thereafter will help determining the impact of such modifications on patients' cardiac function and will help understanding if EVAR worse the cardiac outcome in the long term.

In authors opinion the limitation of this study was mainly four:

- The limited number of patients enrolled that can bias the study from a statistical point of view. As anticipated, this was mainly motivated by the historical period the study was performed as SARS-Cov-2 pandemic drastically affected our national health system, particularly the elective/non urgent surgical and outpatient clinic activities.
- The limited follow-up that could have affected some parameters that are known to variate in more than just 6 months and biased some other parameters that could reflect an hyperacute response to the aortic endograft implantation.
- Duplex Ultrasound and Echocardiography were the only diagnostic tools in this study and are by their very nature highly operator dependent so the authors cannot guarantee the results to be repeatable despite all the examinations were performed by experienced vascular surgeons and cardiologists.
- The absence of a control group.

CONCLUSION

The endovascular treatment of the abdominal aorta causes an immediate and significant increase of the aortic stiffness. This increase reflects negatively on patients' cardiac geometry inducing left ventricle hypertrophy and mild diastolic disfunction after just 6 months from endograft's implantation. Further investigations and long-term results are necessary to access if this negative remodeling could affect the cardiac outcome of patient treated using the endovascular approach.

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