Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

UNIVERSITÀ
DEGLI STUDI
DI MILANO

Trattamento Endovascolare della Malattie Aortiche

Nuove conoscenze in materia di stiffness aortica e simulazione computazionale

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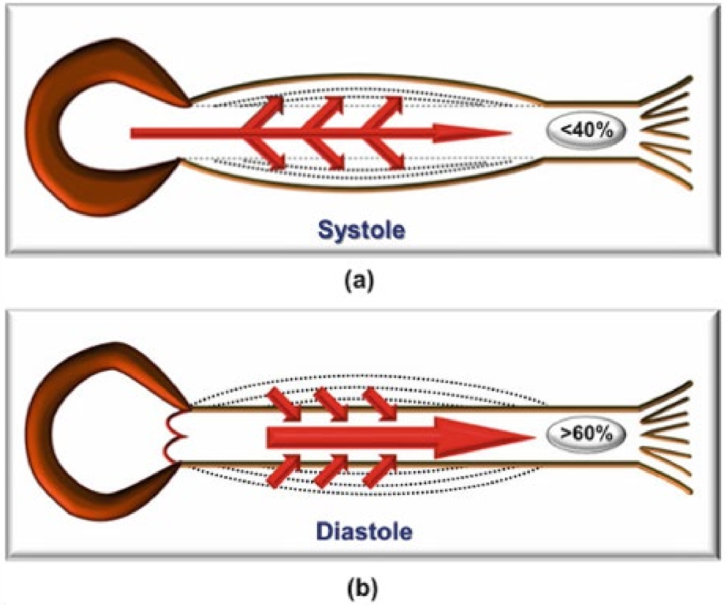
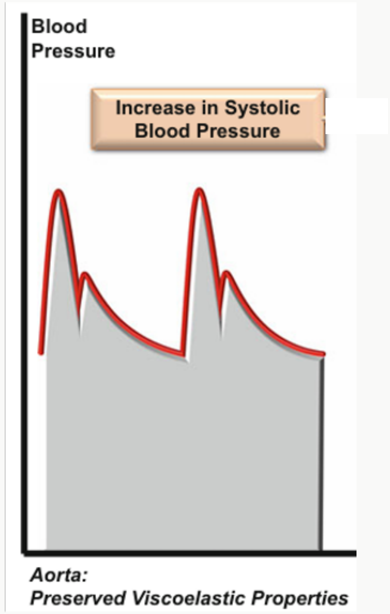
Dipartimento Cardio Toraco Vascolare
Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milano

Arterial Stiffness



Physiologic aortic distensibility



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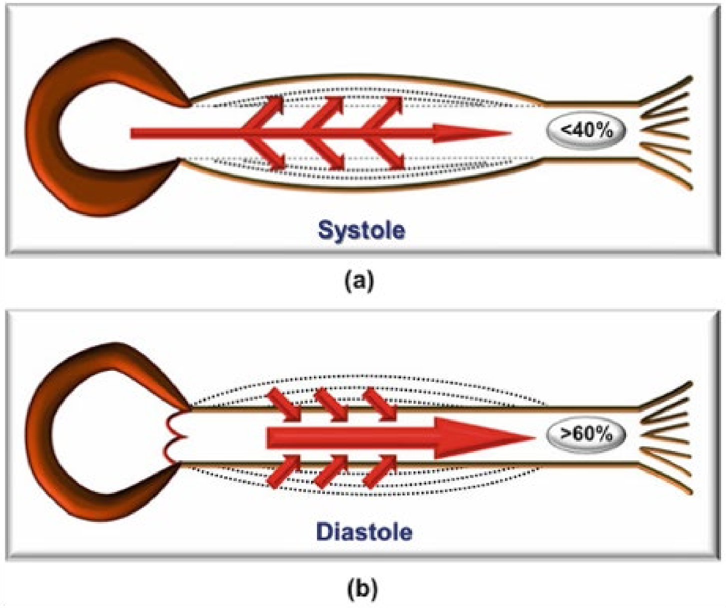

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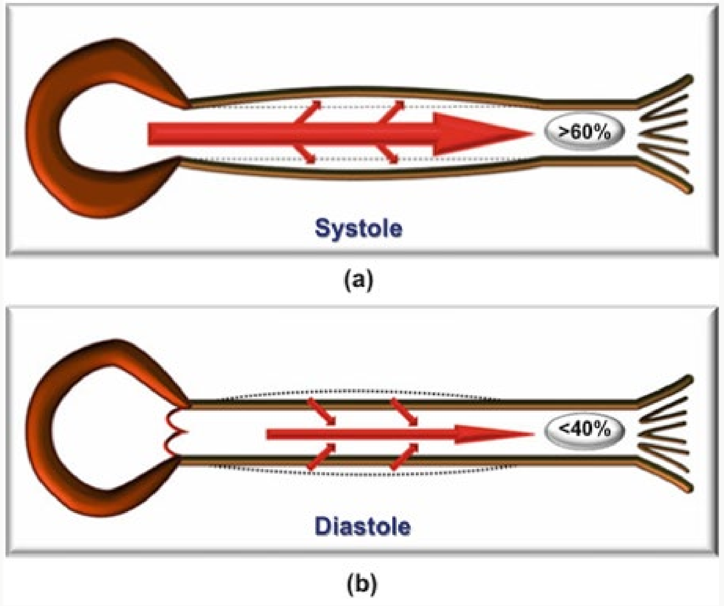
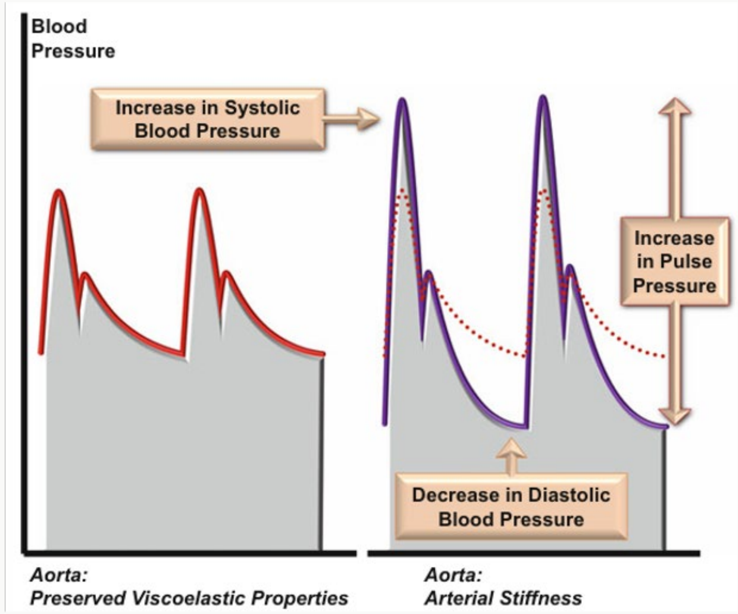
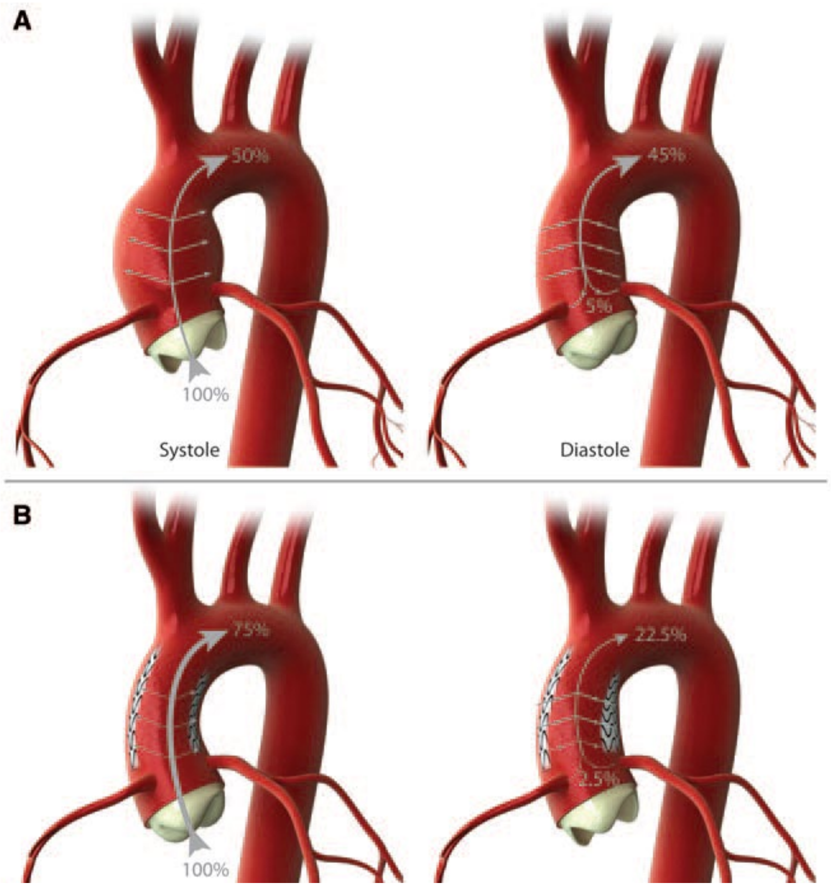


Reduced aortic distensibility



Aortic Stiffness

- Impairs the aortic cushioning function, known as the **Windkessel effect**



Impact of thoracic endovascular aortic repair on radial strain in an *ex vivo* porcine model

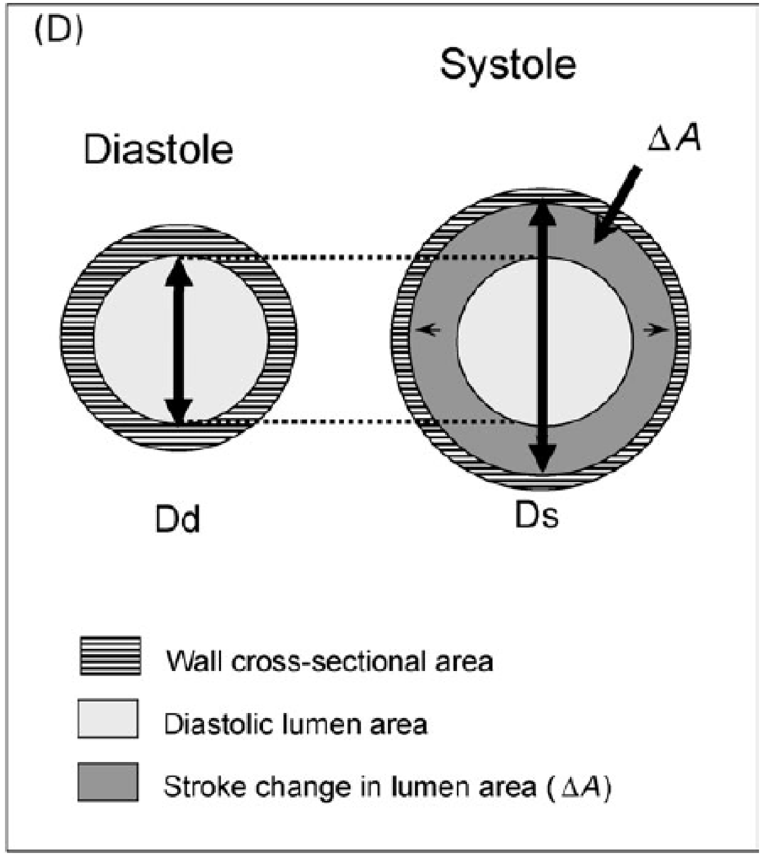
Foeke J.H. Nauta[a,b,*], Hector W.L. de Beaufort[a,b], Michele Conti[c], Stefania Marconi[c], Arnoud V. Kamman[a,b], Anna Ferrara[c], Joost A. van Herwaarden[b], Frans L. Moll[b], Ferdinando Auricchio[c] and Santi Trimarchi[a,d]

European Journal of Cardio-Thoracic Surgery 51 (2017) 783–789

Arterial Stiffness

- Arterial stiffness is the **resistance** offered by vascular walls **to deformation** powered by a propulsive force (such as the cardiac pump).

- It **can be modified** by several factors including cardiac status, vessel compliance, and peripheral resistance.



European Heart Journal (2006) 27, 2588–2605
doi:10.1093/eurheartj/ehl254

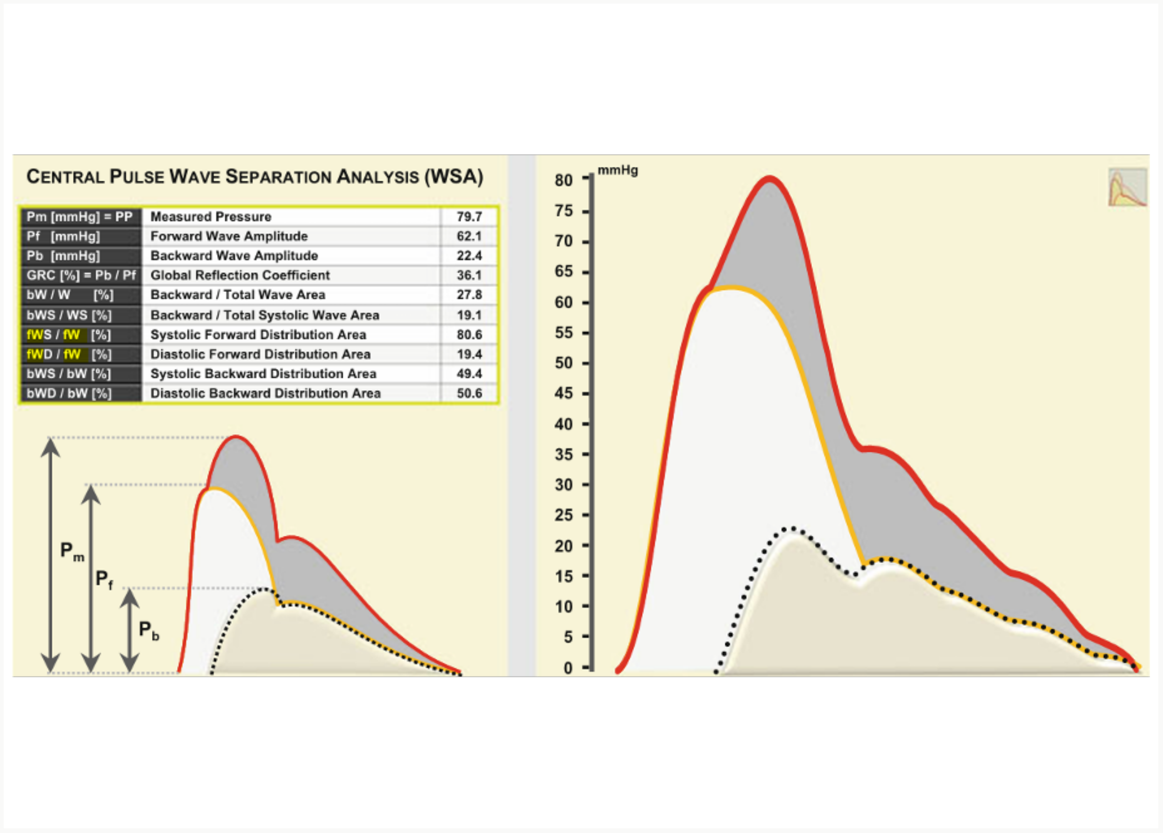
Special article

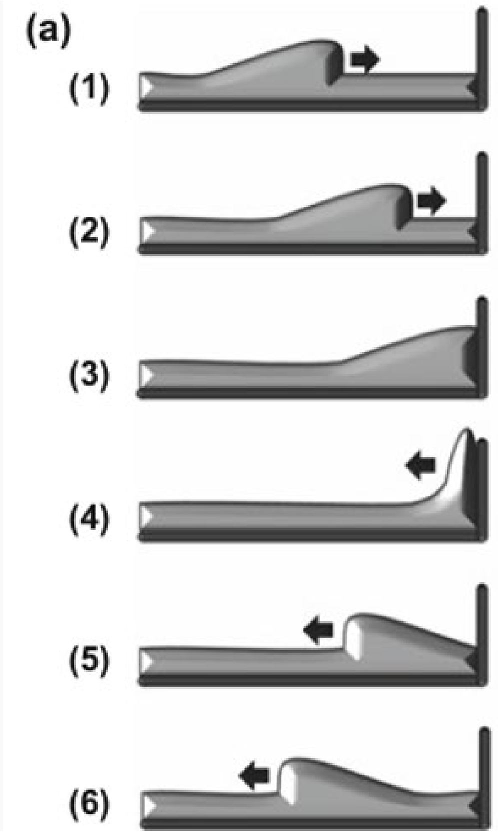
Expert consensus document on arterial stiffness: methodological issues and clinical applications

Stephane Laurent[1]*, John Cockcroft[2], Luc Van Bortel[3], Pierre Boutouyrie[1], Cristina Giannattasio[4], Daniel Hayoz[5], Bruno Pannier[6], Charalambos Vlachopoulos[7], Ian Wilkinson[8], and Harry Struijker-Boudier[9] on behalf of the European Network for Non-invasive Investigation of Large Arteries

Arterial Stiffness

PRESSURE WAVE = ANTEGRADE WAVE + RETROGRADE WAVE





Arterial Stiffness

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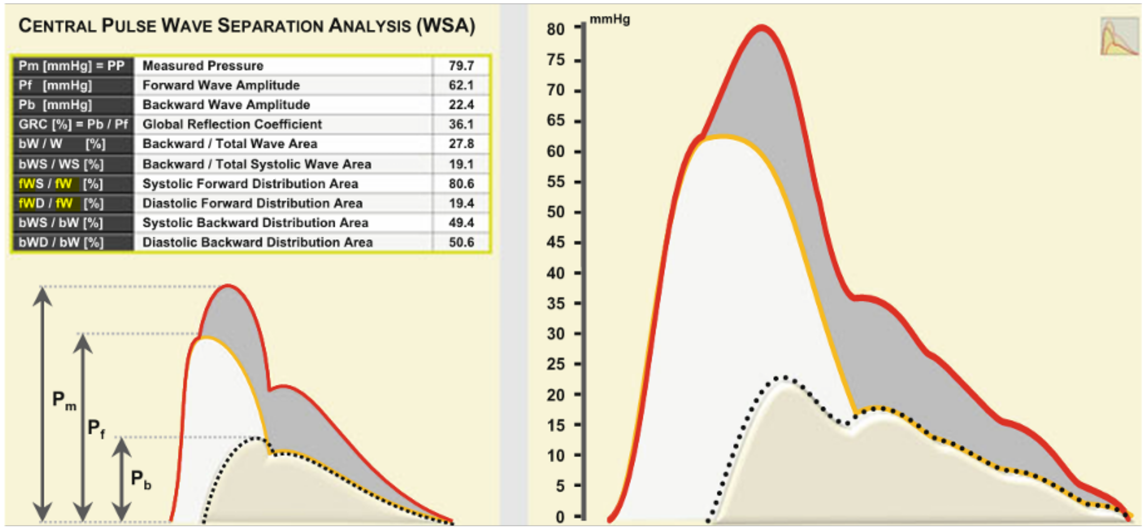
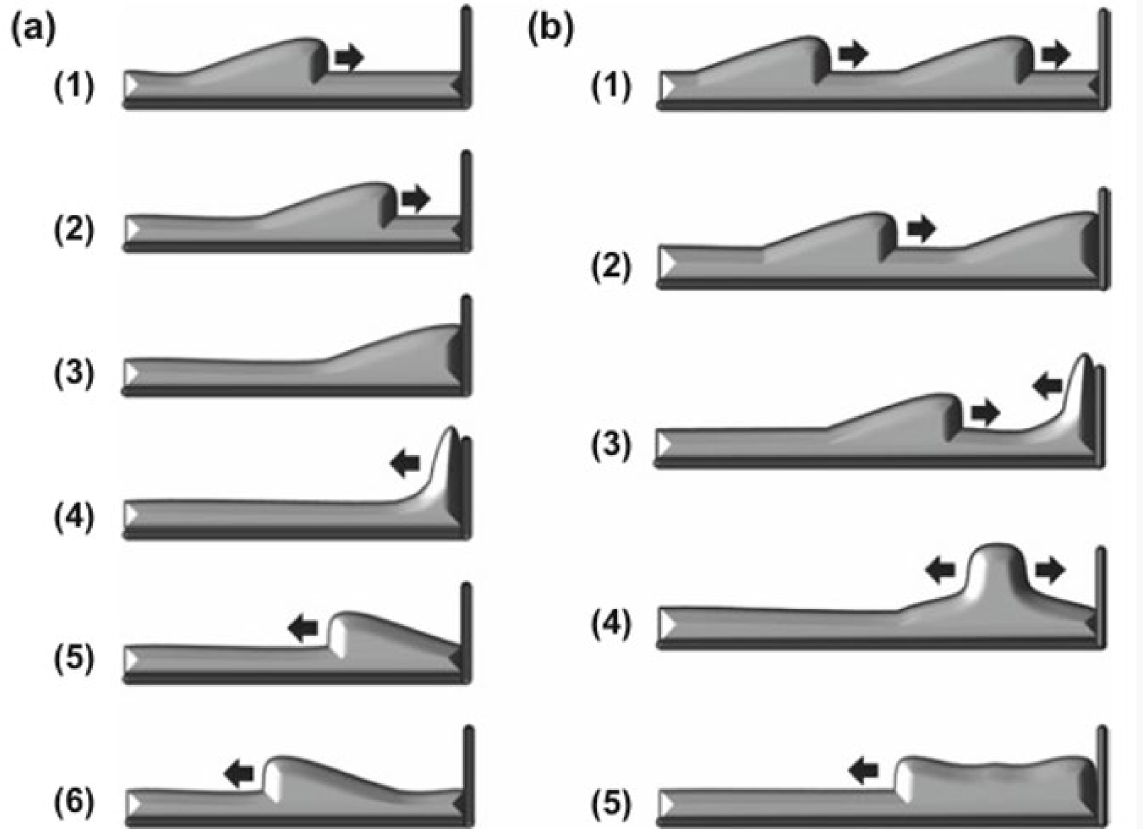
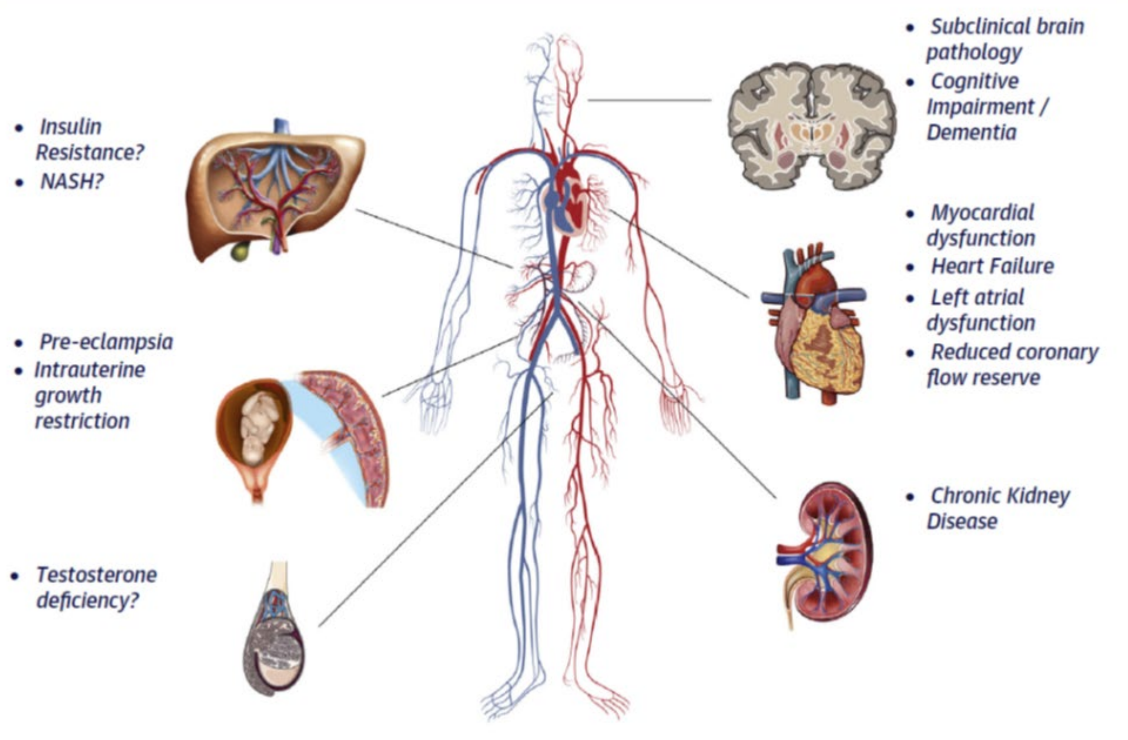




Aortic Stiffness

- Determines isolated systolic hypertension and abnormal ventricular-arterial interactions that promote left ventricular remodeling, dysfunction, and failure, and other **target organ damage**

FIGURE 4 Potential Consequences of LAS on Target Organs



Large-Artery Stiffness in Health and Disease

JACC State-of-the-Art Review

VOL. 74, NO. 9, 2019

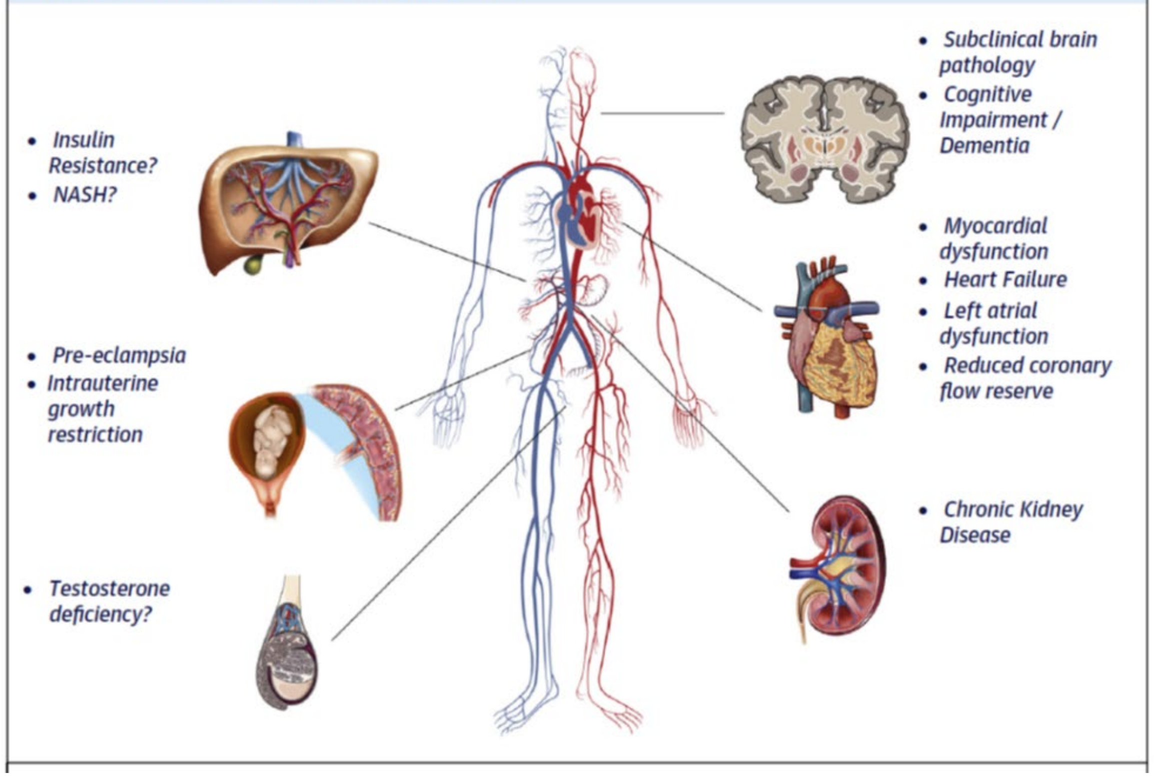
Julio A. Chirinos, MD, PhD,[a,b] Patrick Segers, PhD,[c] Timothy Hughes, PhD,[d] Raymond Townsend, MD[b,e]

Aortic Stiffness

- Determines isolated systolic hypertension and abnormal ventricular-arterial interactions that promote left ventricular remodeling, dysfunction, and failure, and other **target organ damage**

Such aspects predict cardiovascular risk and may represents a high-priority therapeutic target to ameliorate the global burden of cardiovascular disease.

FIGURE 4 Potential Consequences of LAS on Target Organs



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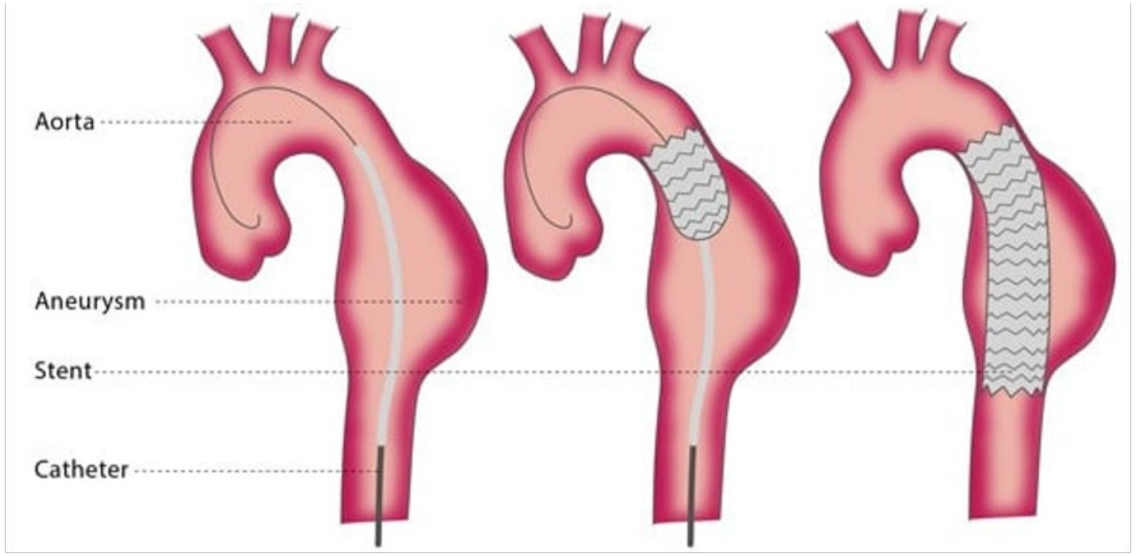
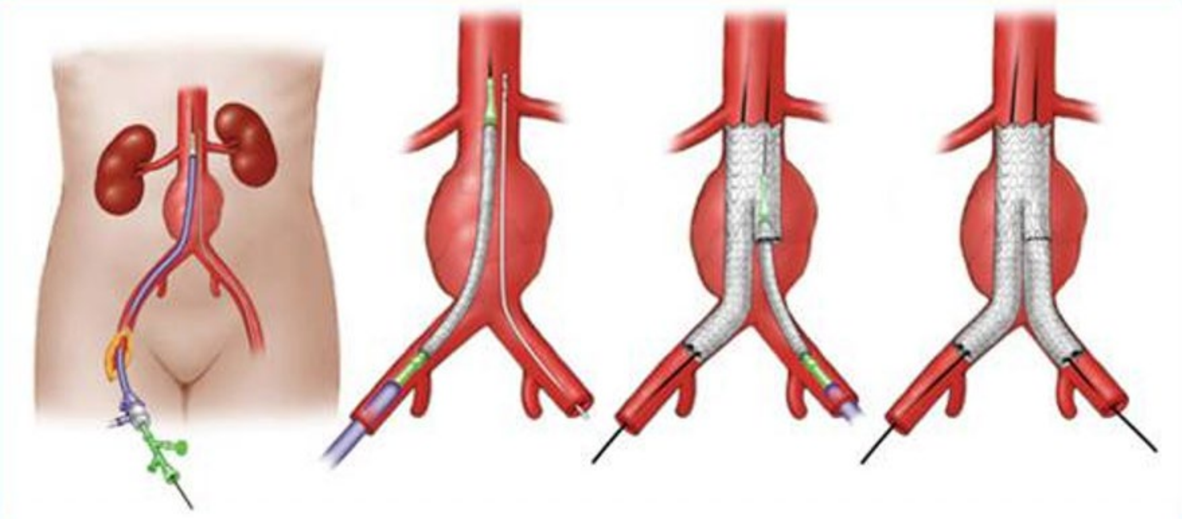
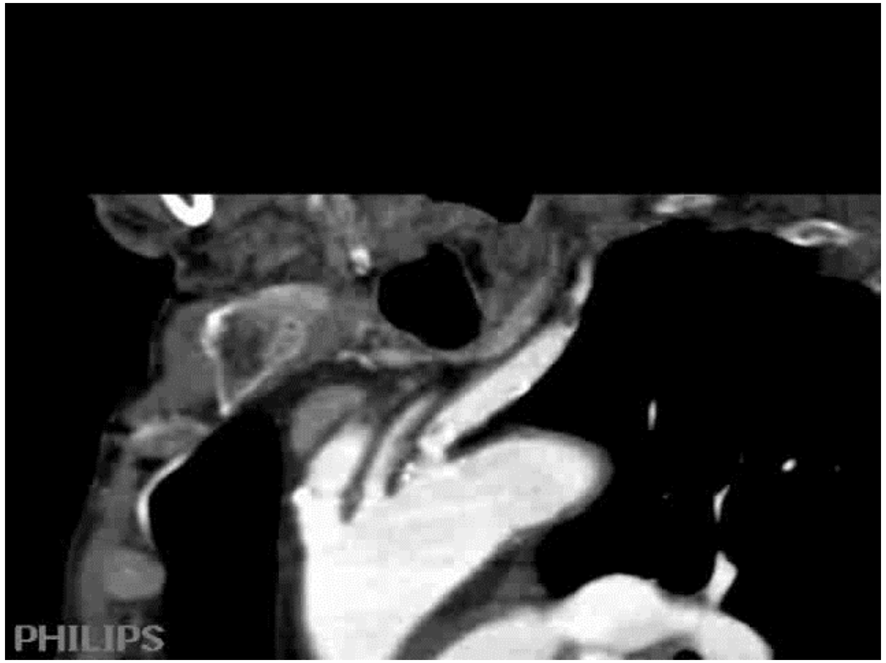




Aortic hemodynamic – change after stent graft deployment



Stent graft induced **aortic stiffening**

Modeling - Aortic stiffness

OBJECTIVES: Current endografts for thoracic endovascular aortic repair (TEVAR) are much stiffer than the aorta and have been shown to induce acute stiffening. In this study, we aimed to estimate the impact of TEVAR on left ventricular (LV) stroke work (SW) and mass using a non-invasive image-based workflow.

8 patients

CONCLUSIONS: TEVAR was associated with increased LV SW and mass during follow-up. Medical device manufacturers should develop more compliant devices to reduce the stiffness mismatch with the aorta. Additionally, intensive antihypertensive management is needed to control blood pressure post-TEVAR.

Key question

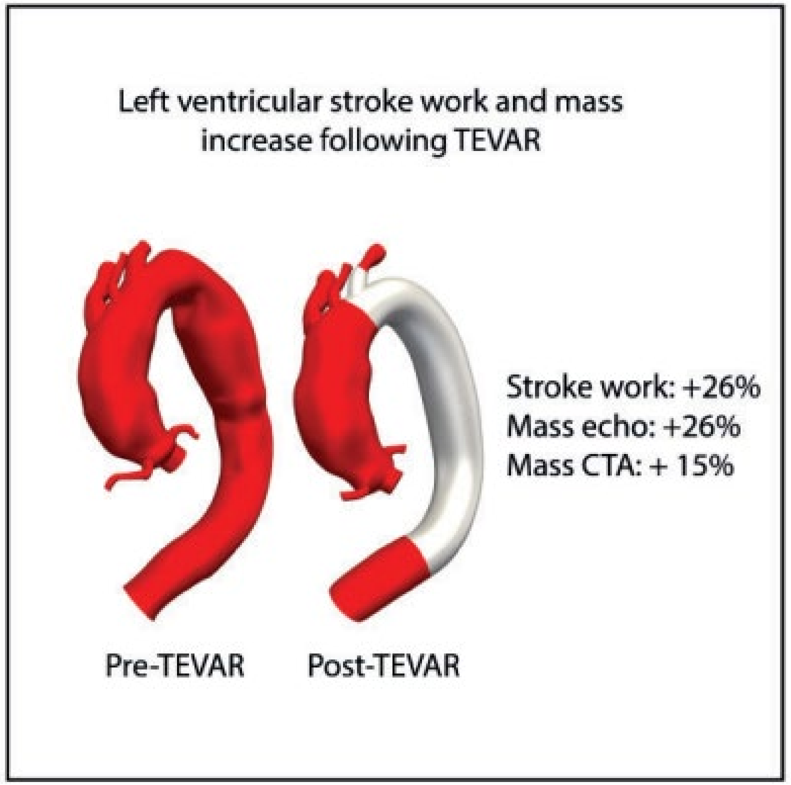
How does the stiffness mismatch between endograft and aorta affect the left ventricle (LV) following TEVAR?

Key findings

LV stroke work increased; LV mass increased.
LV mass increase correlated with stroke work and mean blood pressure.

Take-home message

TEVAR increases LV stroke work and mass during follow-up. Compliant endografts should be developed to prevent adverse LV remodelling.

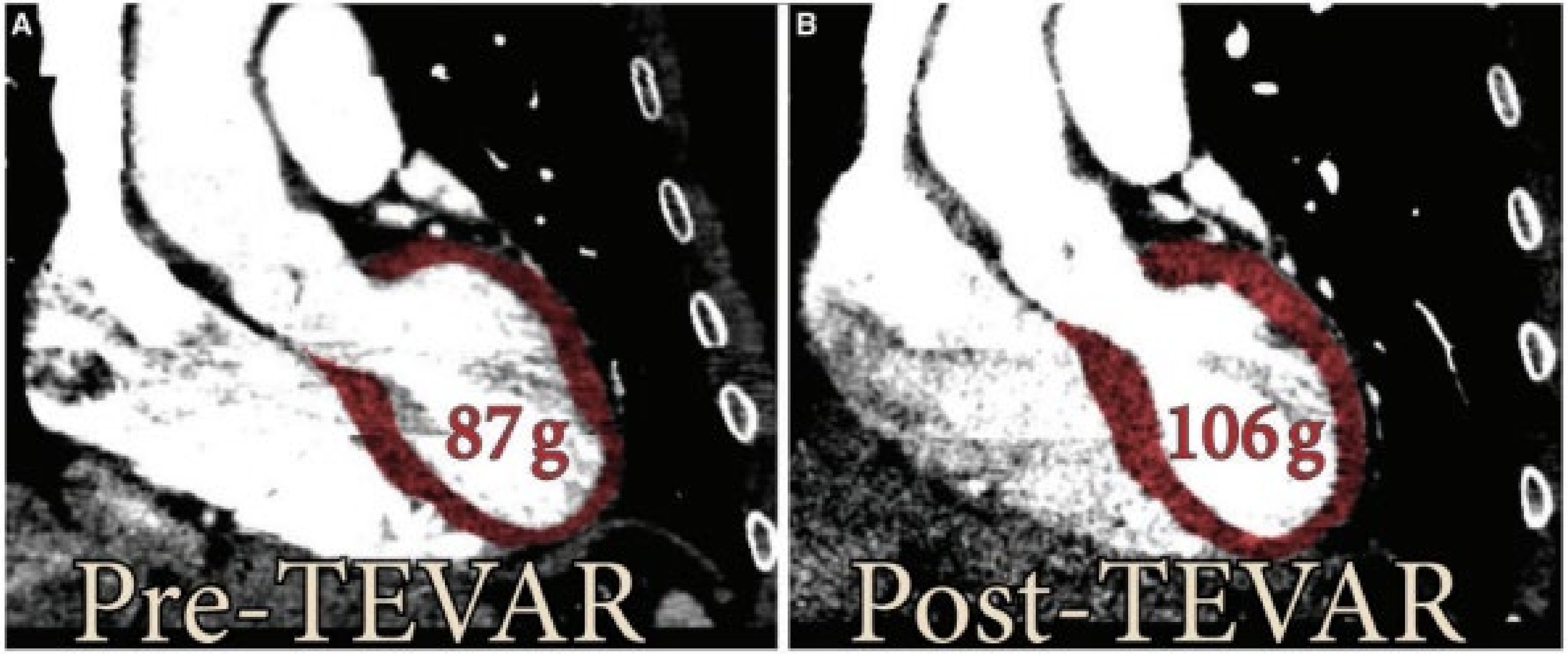


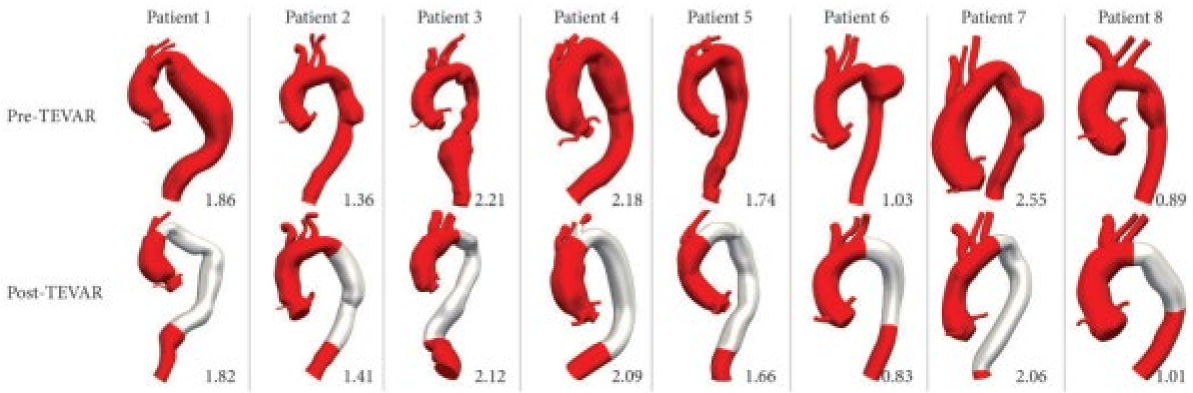
Cardiac remodelling following thoracic endovascular aortic repair for descending aortic aneurysms

Theodorus M.J. van Bakel[a,b,c,*], Christopher J. Arthurs[d], Foeke J.H. Nauta[a,b,c], Kim A. Eagle[e], Joost A. van Herwaarden[b], Frans L. Moll[b], Santi Trimarchi[c,f], Himanshu J. Patel[g] and C. Alberto Figueroa[a,h]

European Journal of Cardio-Thoracic Surgery 55 (2019) 1061–1070
doi:10.1093/ejcts/ezy399 Advance Access publication 6 December 2018

Modeling - Aortic stiffness





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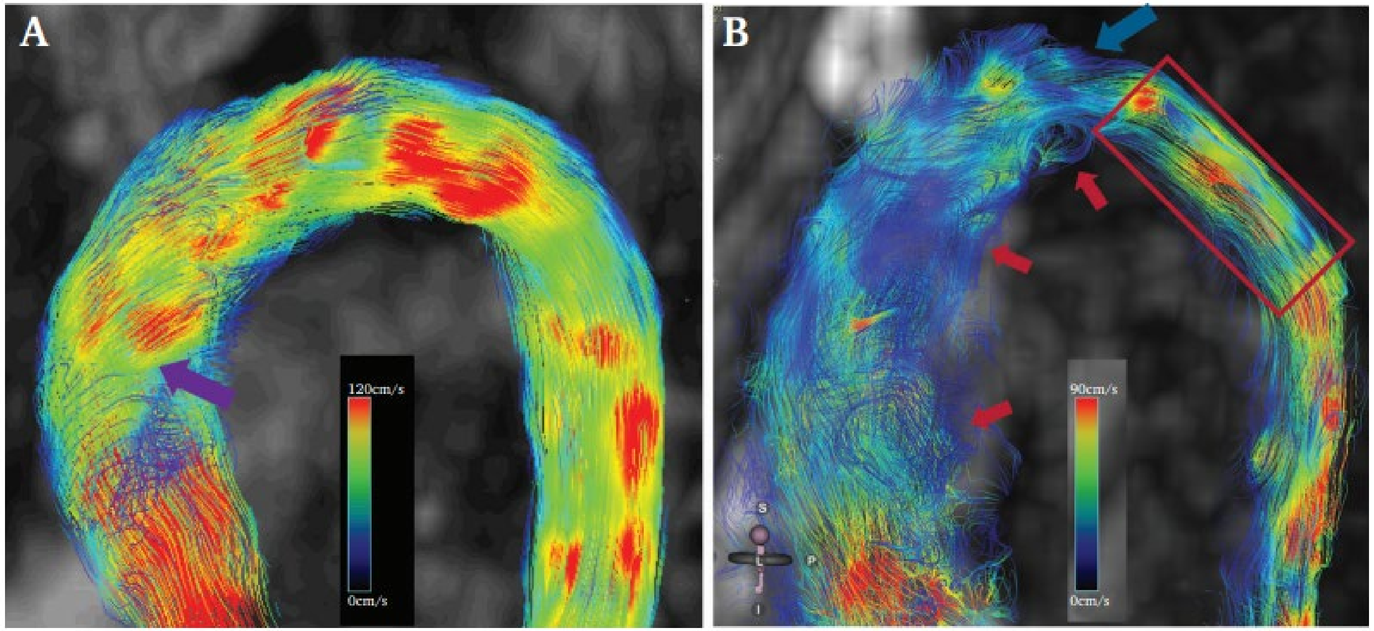


Figure 5. Visual comparison between (A) a healthy volunteer and (B) a patient with blunt thoracic aortic injury treated by thoracic endovascular aortic repair (TEVAR). Red rectangle highlights the location of the TEVAR. Streamline visualisation was obtained with CVI42 (Circle Cardiovascular Imaging Inc., Calgary, Canada). Violet arrow indicates normal helical flow, blue arrow indicates high bending proximal to the TEVAR, and red arrows recirculation zones.

Basic Research and Translational Medicine

Eur J Vasc Endovasc Surg (2021) 62, 797—807

Geometric, Biomechanic and Haemodynamic Aortic Abnormalities Assessed by 4D Flow Cardiovascular Magnetic Resonance in Patients Treated by TEVAR Following Blunt Traumatic Thoracic Aortic Injury

Daniel Gil-Sala [a,b,†], Andrea Guala [c,d,†], Marvin E. Garcia Reyes [a,*], Maria A. Azancot [e], Lydia Dux-Santoy [c], Nicolas Allegue Allegue [a], Gisela Teixido Turà [c,d,f], Gabriela Goncalves Martins [a,b], Aroa Ruiz Muñoz [c,d], Ivan Constenla García [a], Arturo Evangelista [b,c,d,f,g], Cristina Tello Díaz [a], Ignacio Ferreira González [f,h,i], Jose F. Rodríguez-Palomares [c,d,f,§], Sergi Bellmunt [a,b,§]

In-Vivo Stiffness

WHAT THIS PAPER ADDS

This systematic review describes aortic stiffness, blood pressure, cardiac mass, and aortic size increases after follow up of thoracic endovascular aortic repair for blunt thoracic aortic injury. These modifications could have potential adverse effects on both the cardiovascular system and target organs (e.g., kidneys and brain), which emphasise the need for continuous surveillance and patient specific, tailored medicine, particularly in young patients with a long life expectancy.

Table 4. Aortic stiffness and blood pressure outcomes for the five studies included in the systematic review that evaluated this after endovascular repair for blunt thoracic aortic injury

Author, year	Group	HT, baseline – %	HT, FU – %	SBP, FU – mmHg	PP, FU – mmHg	Antihypertensive drug treatment at FU (*n*)	Risk factors for postimplant HT	PWV – location	PWV, FU – m/sec	AIx – %
Kamenskiy, 2020[27]	Patient	5	50	—	—	—	—	—	—	—
	Control	24	29	—	—	—	—	—	—	—
	Males/ females	19/24	19/38							
Tzilalis, 2012[28]	Patient	—	—	134.1 ± 13.75; $p = .016$	60.45 ± 19.42; $p = .020$	Irbesartan–metoprolol (1), irbesartan (1), captopril–metoprolol (1)	—	RCCA to RFA	10.41 ± 0.85; $p = .006$	—
	Control	—	—	121.36 ± 7.1	44.1 ± 4.37	—	—	RCCA to RFA	7.45 ± 0.66	—
Vallerio, 2019[29]	Patient	0	55	<3 y: 120.1 ± 6.6; >3 y: 128.3 ± 14.3; $p < .01$	—	Treated (12; 55%)	—	—	<3 y: 6.3 ± 1.1; >3 y: 7.5 ± 1.9; NS	<3 y: 16.2 ± 7.4; >3 y: 19.1 ± 7.6; NS
Youssef, 2020[30]	Patient	0	36	—	—	Treated (5; 36%), 3–5 diastolic dysfunction grade I without AR	—	Right upper limb to both thighs	10.34 ± 2.07, $p < .001$	—
	Control	—	—	—	—	—	—	Right upper limb to both thighs	7.42 ± 1.22	—
Tigkiropoulis, 2018[37]	Patient	—	34.8 (previously no HT)	—	—	Beta blockers (8), calcium channel blocker (4), ACEi (2), clonidine (1)	Younger age, $p = .027$; LSA coverage, $p = .01$	—	—	—

Conclusion

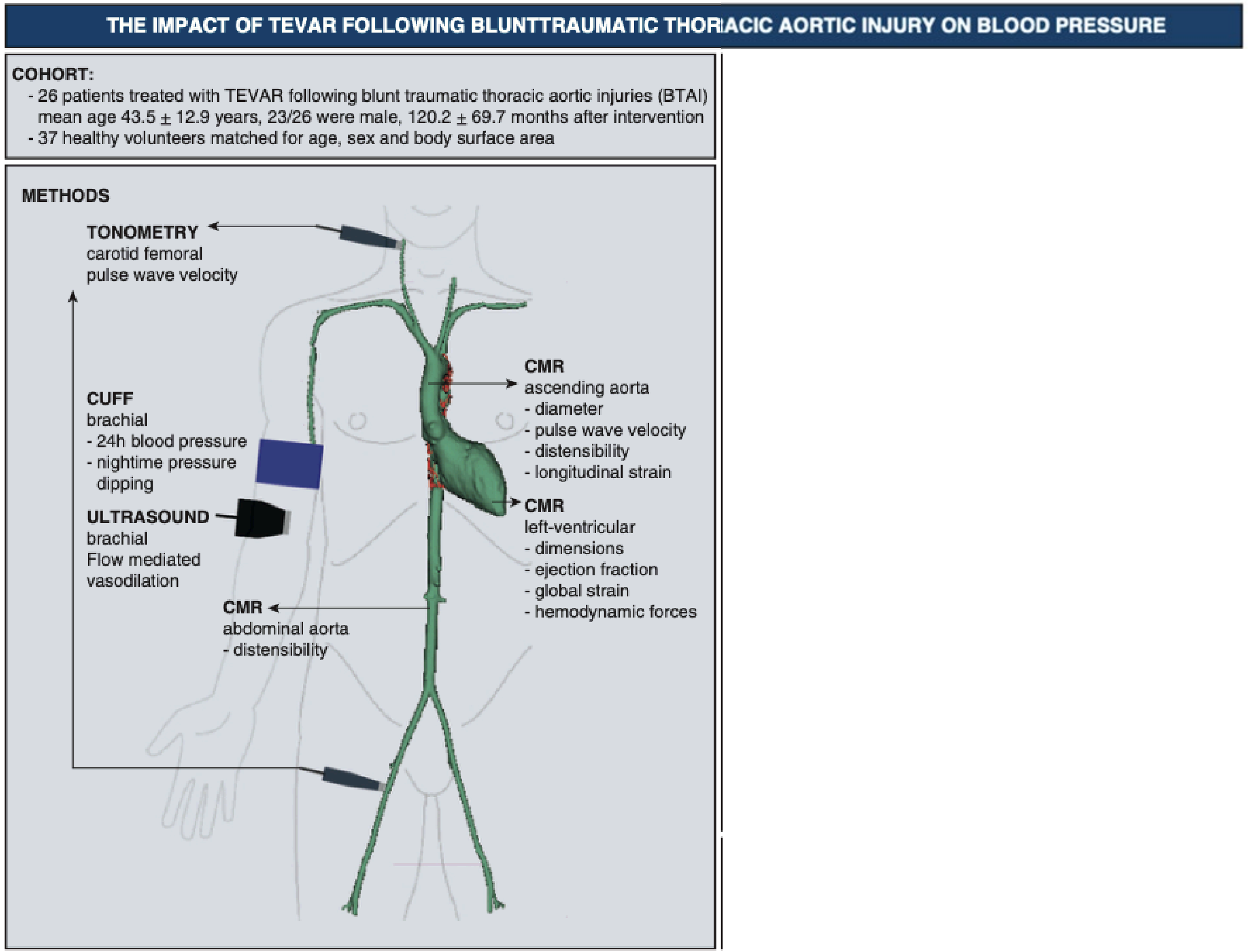
Expanding indications for endovascular aortic repair in a younger patient group raises several concerns regarding the possible adverse effects on the cardiovascular system and target organs. The main findings illustrate several significant modifications at the cardiac and aortic level but with great clinical heterogeneity. These might have detrimental effects in the long term, and lifelong surveillance with patient specific tailored medicine to prevent complications are warranted, focusing not only on technical results, but also on adverse cardiovascular changes. Endograft manufacturers should focus on the development of more compliant and possibly shorter endografts for the treatment of BTAI.

Cardiac and Aortic Modifications After Endovascular Repair for Blunt Thoracic Aortic Injury: A Systematic Review

Tim J. Mandigers [a,b,*], Daniele Bissacco [a], Maurizio Domanin [a,c], Ilenia D'Alessio [d], Valerio S. Tolva [d], Gabriele Piffaretti [e], Joost A. van Herwaarden [b], Santi Trimarchi [a,c]

Eur J Vasc Endovasc Surg (2022) 64, 176—187

In-Vivo Stiffness



Impact of thoracic endovascular aortic repair following blunt traumatic thoracic aortic injury on blood pressure

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Andrea Guala, PhD,[a,b] Daniel Gil-Sala, MD,[c,d] Marvin E. Garcia Reyes, MD,[e] Maria A. Azancot, PhD,[f] Lydia Dux-Santoy, PhD,[a] Nicolas Allegue Allegue, MD,[e] Gisela Teixido-Turà, PhD,[a,b,g] Gabriela Goncalves Martins, MD,[e] Laura Galian-Gay, PhD,[a,g] Juan Garrido-Oliver, BSc,[a] Ivan Constenla García, MD,[e] Arturo Evangelista, PhD,[a,b,g,h] Cristina Tello Díaz, MD,[e] Alejandro Carrasco-Poves, BSc,[a] Alberto Morales-Galán, BSc,[a] Ignacio Ferreira-González, PhD,[a,g,i,j] Jose Rodríguez-Palomares, PhD,[a,b,g,j] and Sergi Bellmunt Montoya, PhD[a,d,e]

The Journal of Thoracic and Cardiovascular Surgery • November 2024

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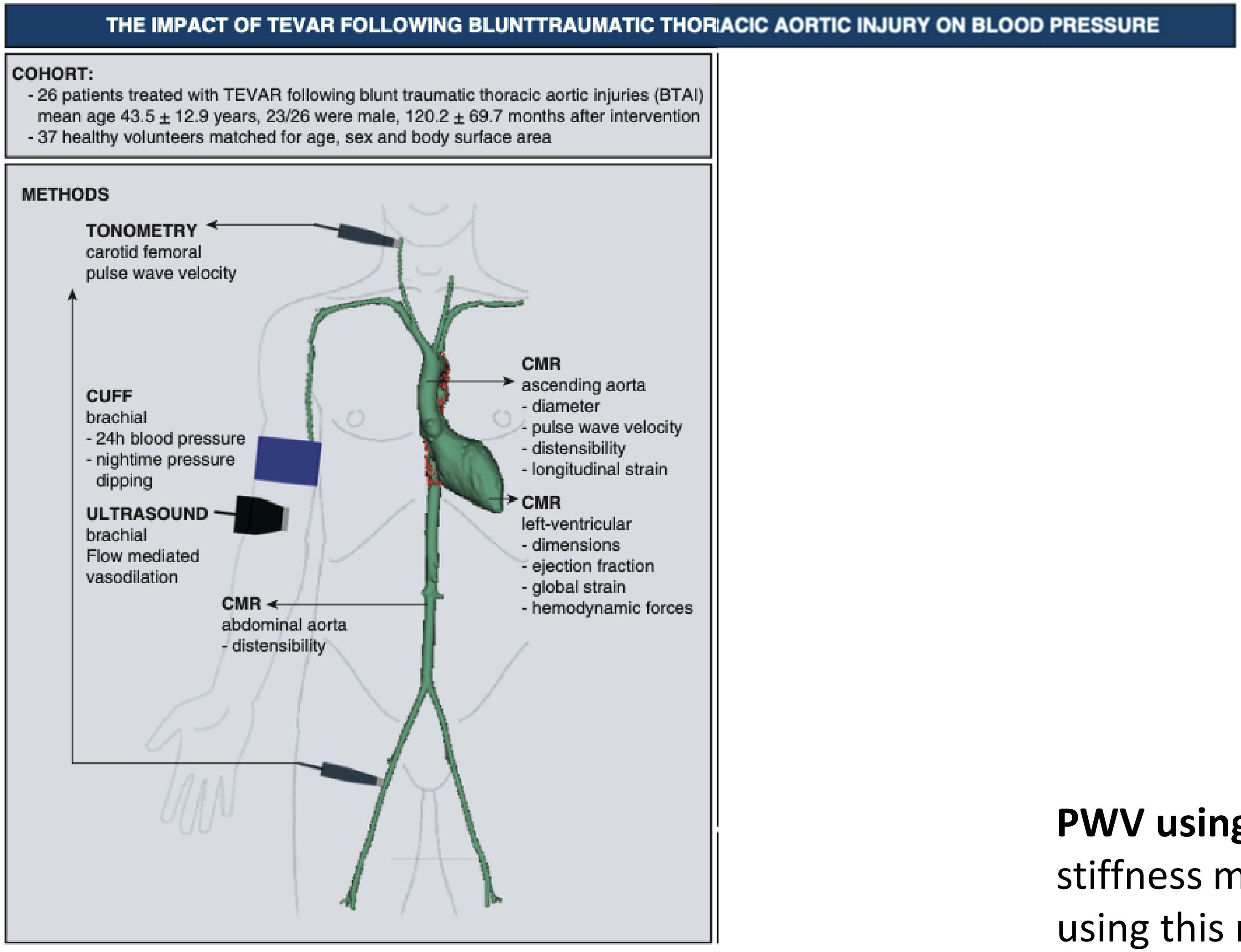
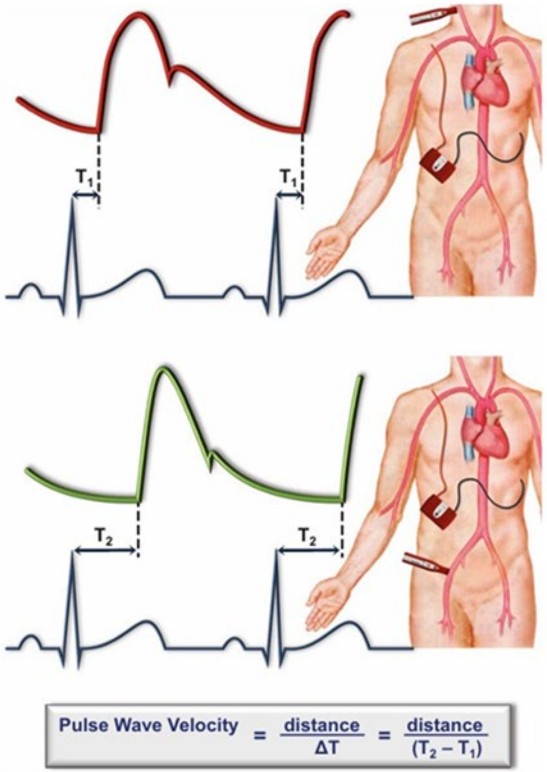
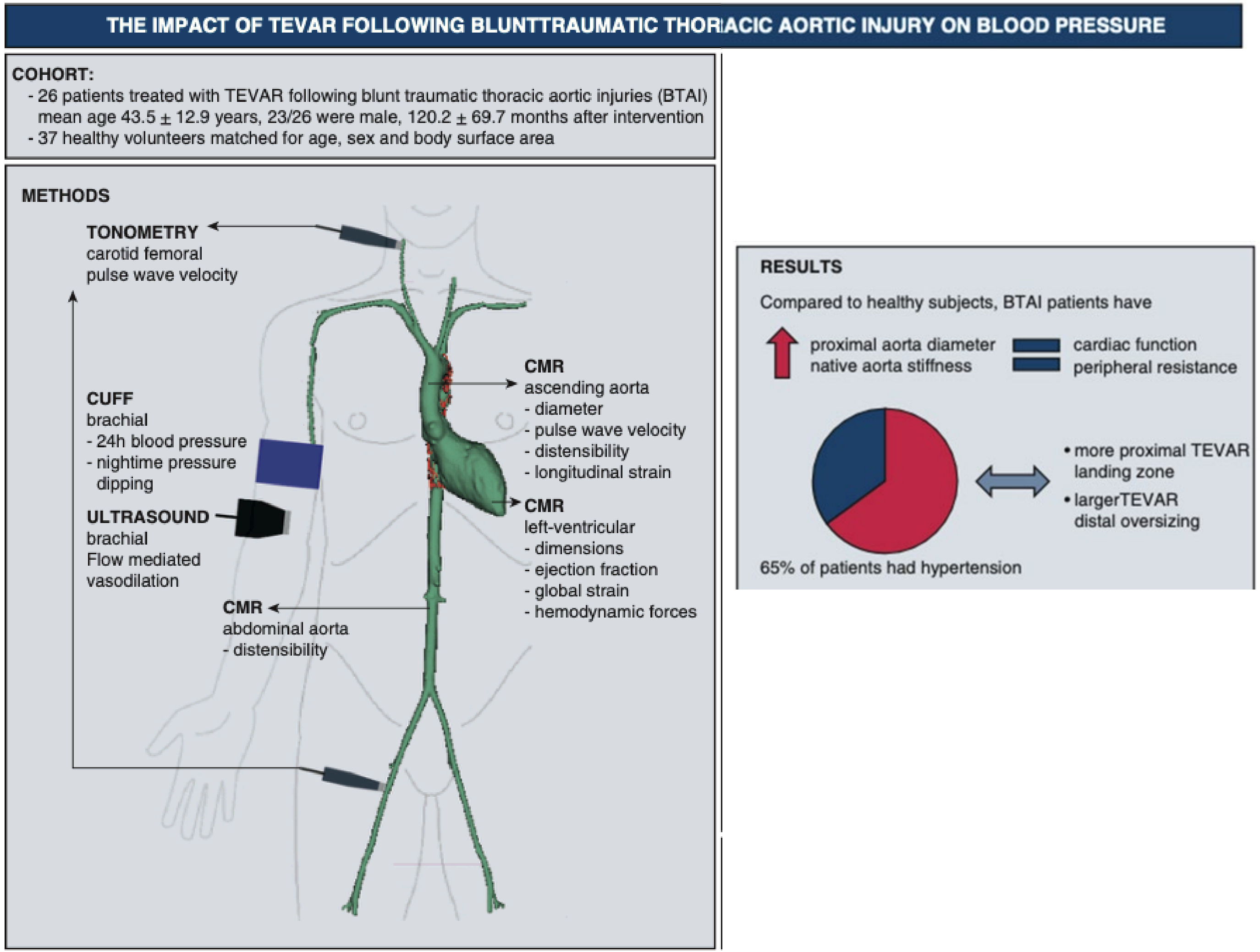




PWV using carotid-femoral "route" is the **'gold standard'** for arterial stiffness measurement, due to the amount of published evidence using this method and because it requires little technical expertise

In-Vivo Stiffness



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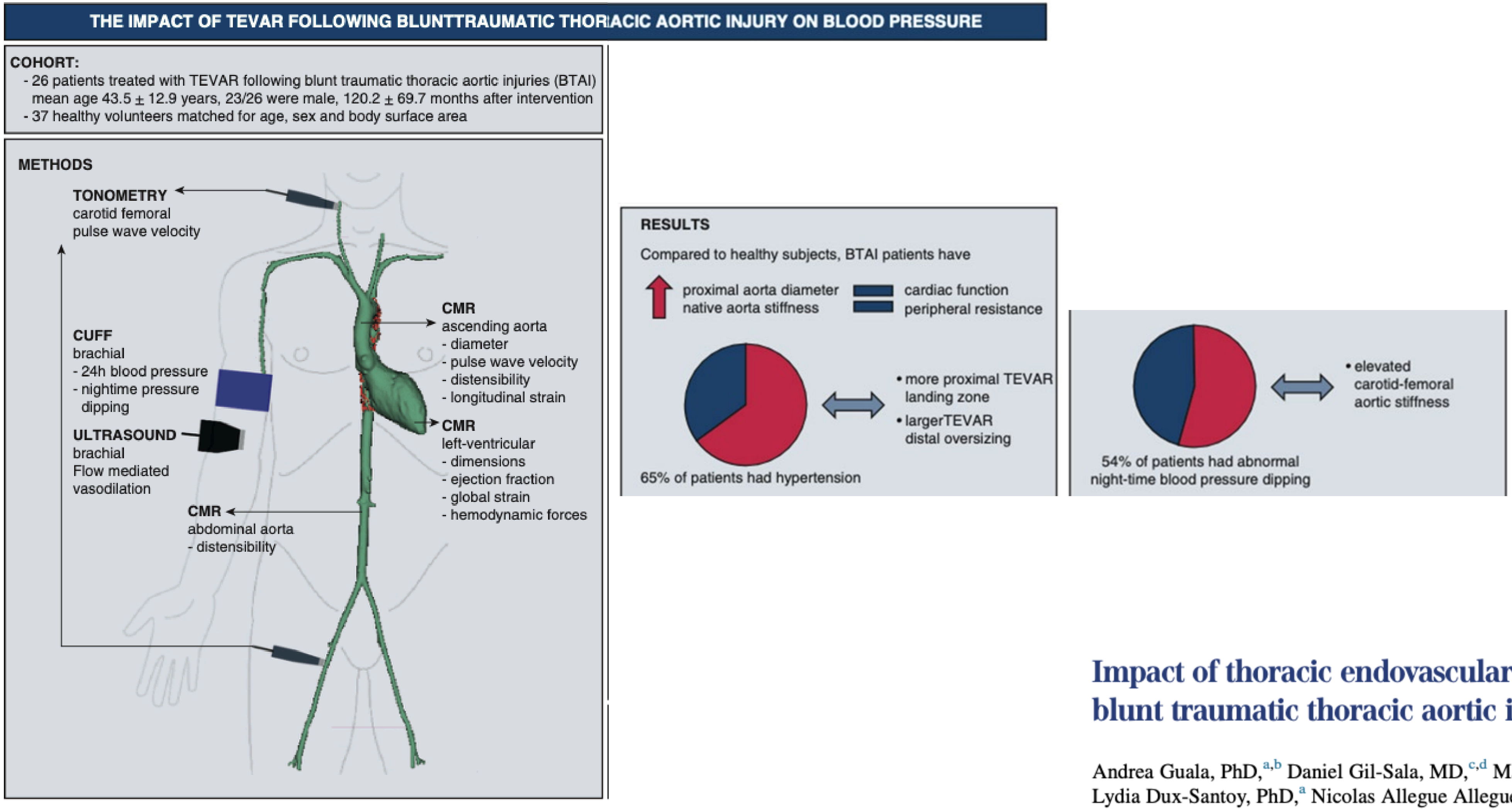

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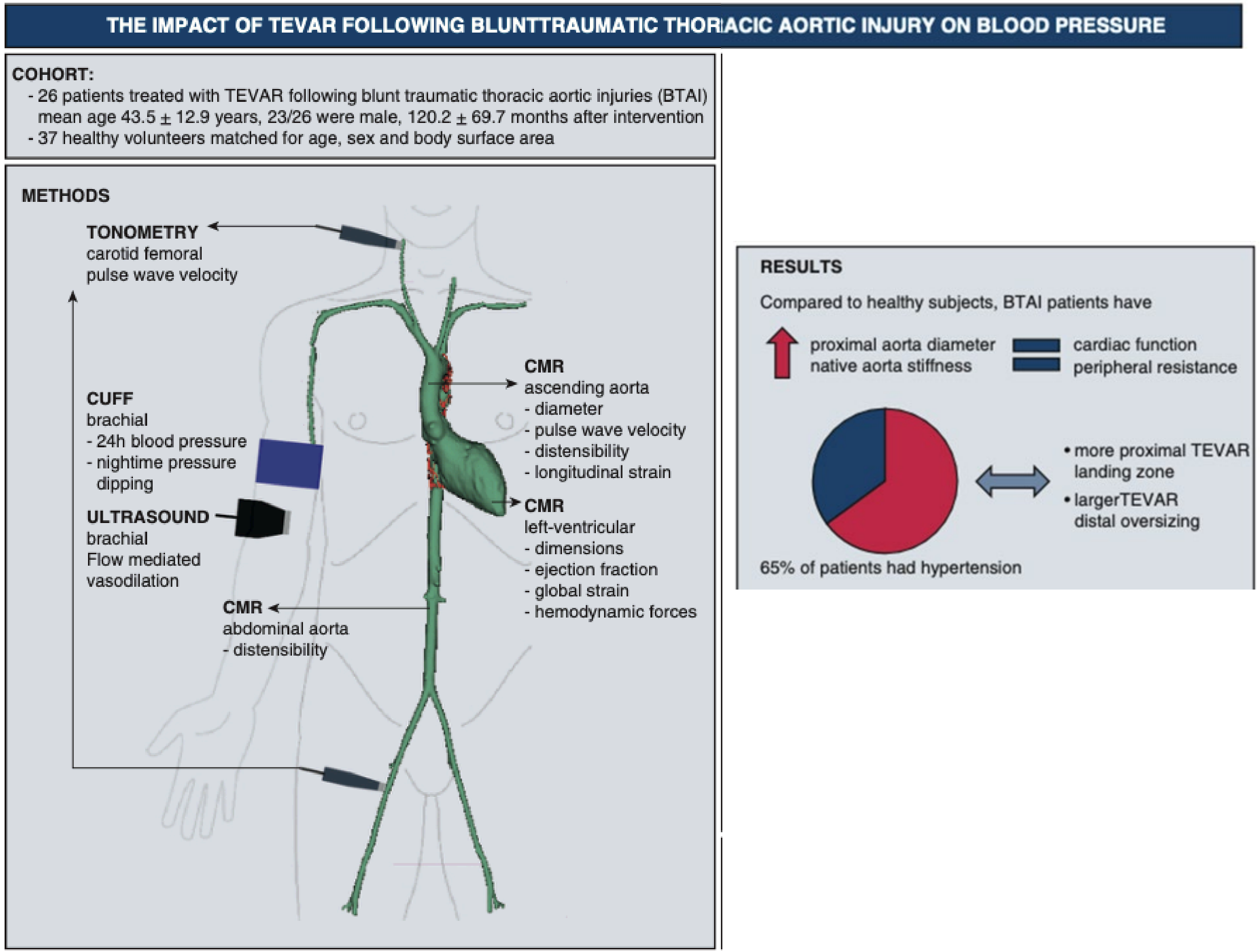

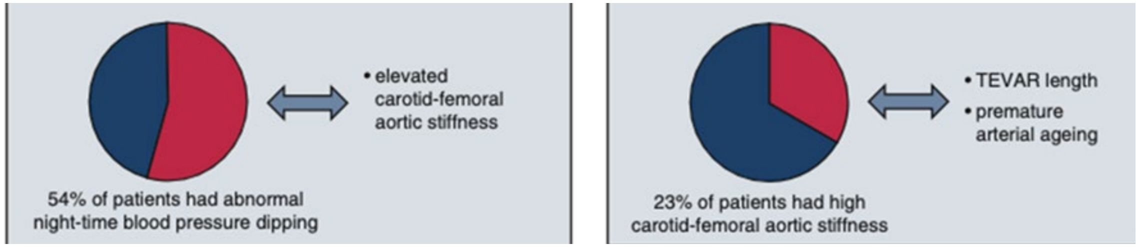

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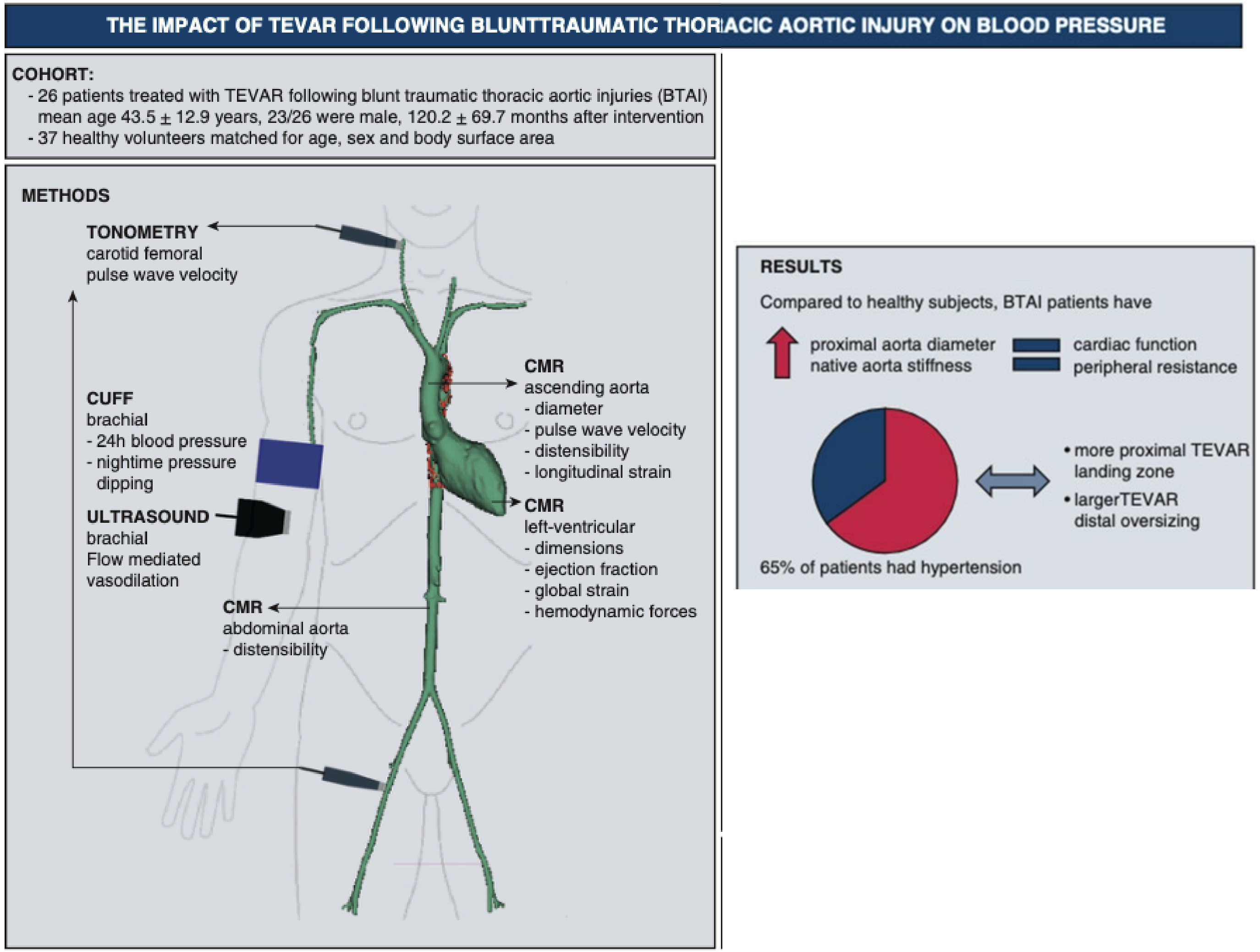

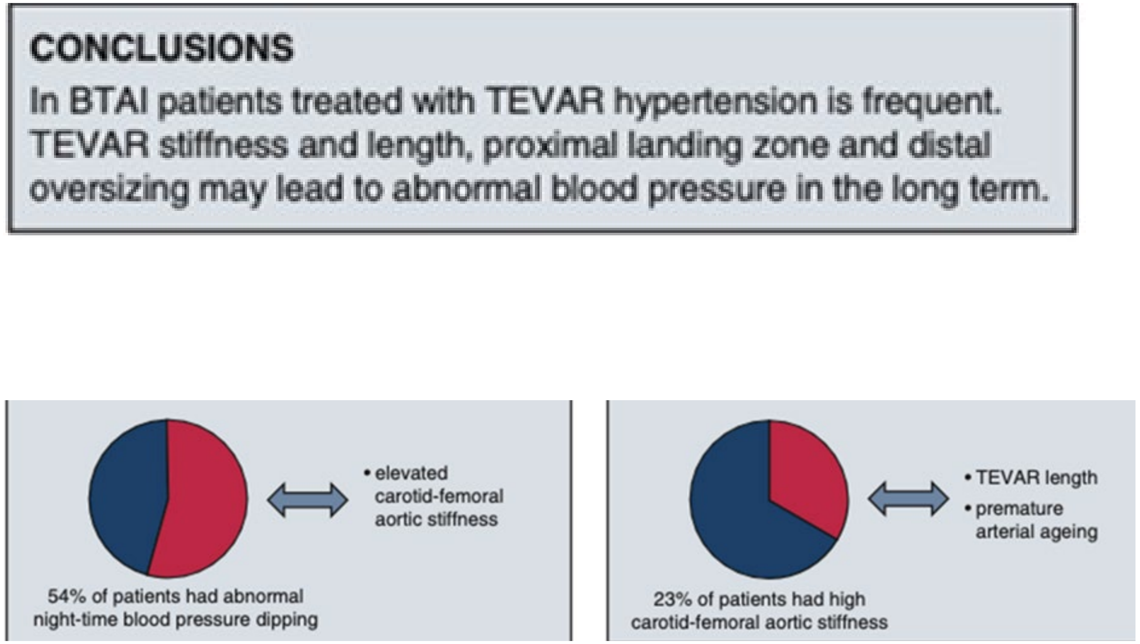

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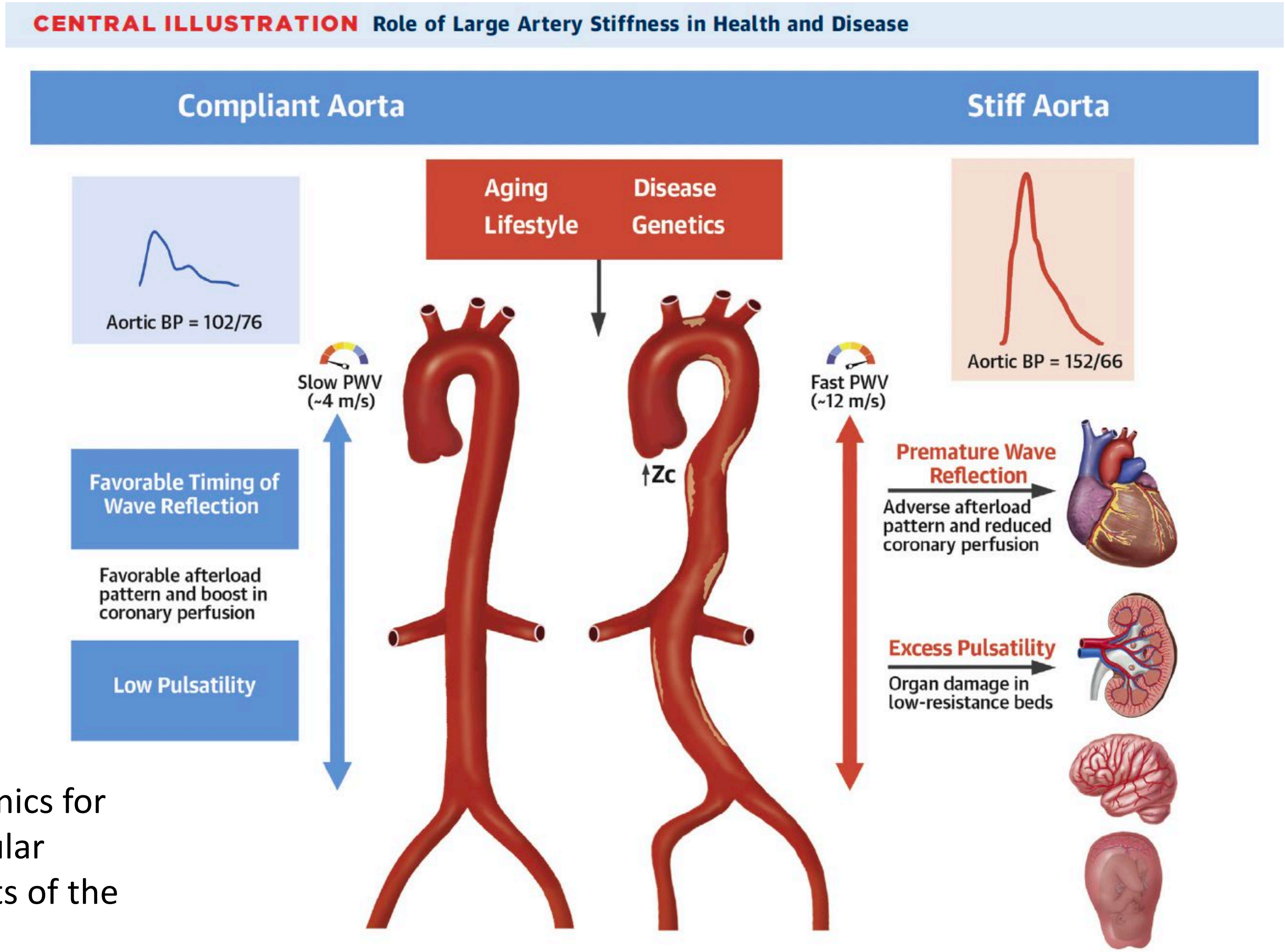
The Journal of Thoracic and Cardiovascular Surgery • November 2024

Aortic Stiffness

- Aging
- TEVAR
- Geometry?
  i.e., Angulation
- Open surgery?
  i.e., Dacron graft

Biomechanics for **E**ndovascular **T**reatments of the **A**orta



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Ex vivo "Mechanical coupling"

PhD Foeke — PhD Hector — PhD Diederik @ UMICH — PhD Tim — PhD Jasper — PhD Nesar

2011 — 2015 — 2017 — 2018 — 2019 — 2021 — 2022 — 2023 — 2024 — 2025

In silico modelling — *Ex vivo* modelling — *Ex vivo* modelling

1 2 3 4

Start

β-lab

Longitudinal strain:

An experimental investigation of the impact of thoracic endovascular aortic repair on longitudinal strain[†]

Foeke J.H. Nauta[a,b,*], Michele Conti[c], Stefania Marconi[c], Arnoud V. Kamman[a,b], Gianluca Alaimo[c], Simone Morganti[d], Anna Ferrara[c], Joost A. van Herwaarden[b], Frans L. Moll[b], Ferdinando Auricchio[d] and Santi Trimarchi[a]

European Journal of Cardio-Thoracic Surgery 50 (2016) 955–961

ELSEVIER CrossMark

Stent-Graft Deployment Increases Aortic Stiffness in an Ex Vivo Porcine Model

Hector W.L. de Beaufort,[1] Michele Conti,[2] Arnoud V. Kamman,[1] Foeke J.H. Nauta,[1] Ettore Lanzarone,[3] Frans L. Moll,[4] Joost A. van Herwaarden,[4] Ferdinando Auricchio,[2] and Santi Trimarchi,[1] Milan and Pavia, Italy, and Utrecht, The Netherlands

Ann Vasc Surg 2017; 43: 302–308

Radial strain:

Impact of thoracic endovascular aortic repair on radial strain in an *ex vivo* porcine model

Foeke J.H. Nauta[a,b,*], Hector W.L. de Beaufort[a,b], Michele Conti[c], Stefania Marconi[c], Arnoud V. Kamman[a,b], Anna Ferrara[c], Joost A. van Herwaarden[b], Frans L. Moll[b], Ferdinando Auricchio[c] and Santi Trimarchi[a]

European Journal of Cardio-Thoracic Surgery 51 (2017) 783–789

RESEARCH ARTICLE

Changes in aortic pulse wave velocity of four thoracic aortic stent grafts in an *ex vivo* porcine model

Hector W. L. de Beaufort[1], Margherita Coda[2], Michele Conti[2], Theodorus M. J. van Bakel[1], Foeke J. H. Nauta[1], Ettore Lanzarone[3], Frans L. Moll[4], Joost A. van Herwaarden[4], Ferdinando Auricchio[2], Santi Trimarchi[1]*

2018 PLoS ONE 12(10): e0186080.

Aortic stiffness:

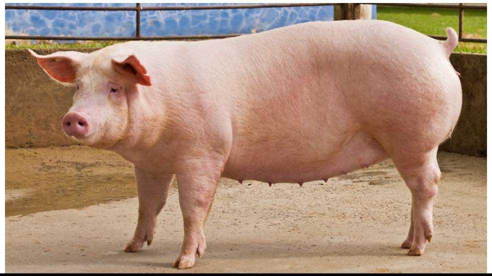
1. **TEVAR generations and stiffness**
2. Improvements set-up
3. **Angulation and stiffness**
4. **Open surgical repair and stiffness**

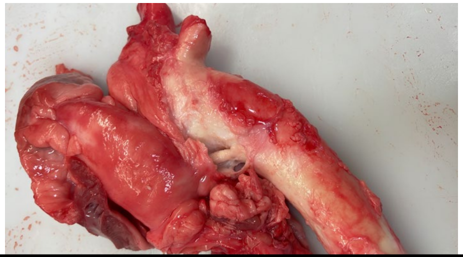
UNIVERSITÀ DI PAVIA — Utrecht University — Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico — UNIVERSITÀ DEGLI STUDI DI MILANO

Aortic Stiffness

Aortic samples for all projects

- Thoracic porcine aortic samples (young healthy pigs, 10 – 12 months, 160 – 180 kg)
  → solely raised for commercial purposes
- Pigs evaluated by a veterinary physician
- Local slaughterhouse – Transportation – Beta-lab
- Surgical preparation: ligating side-branches and removing excess tissue

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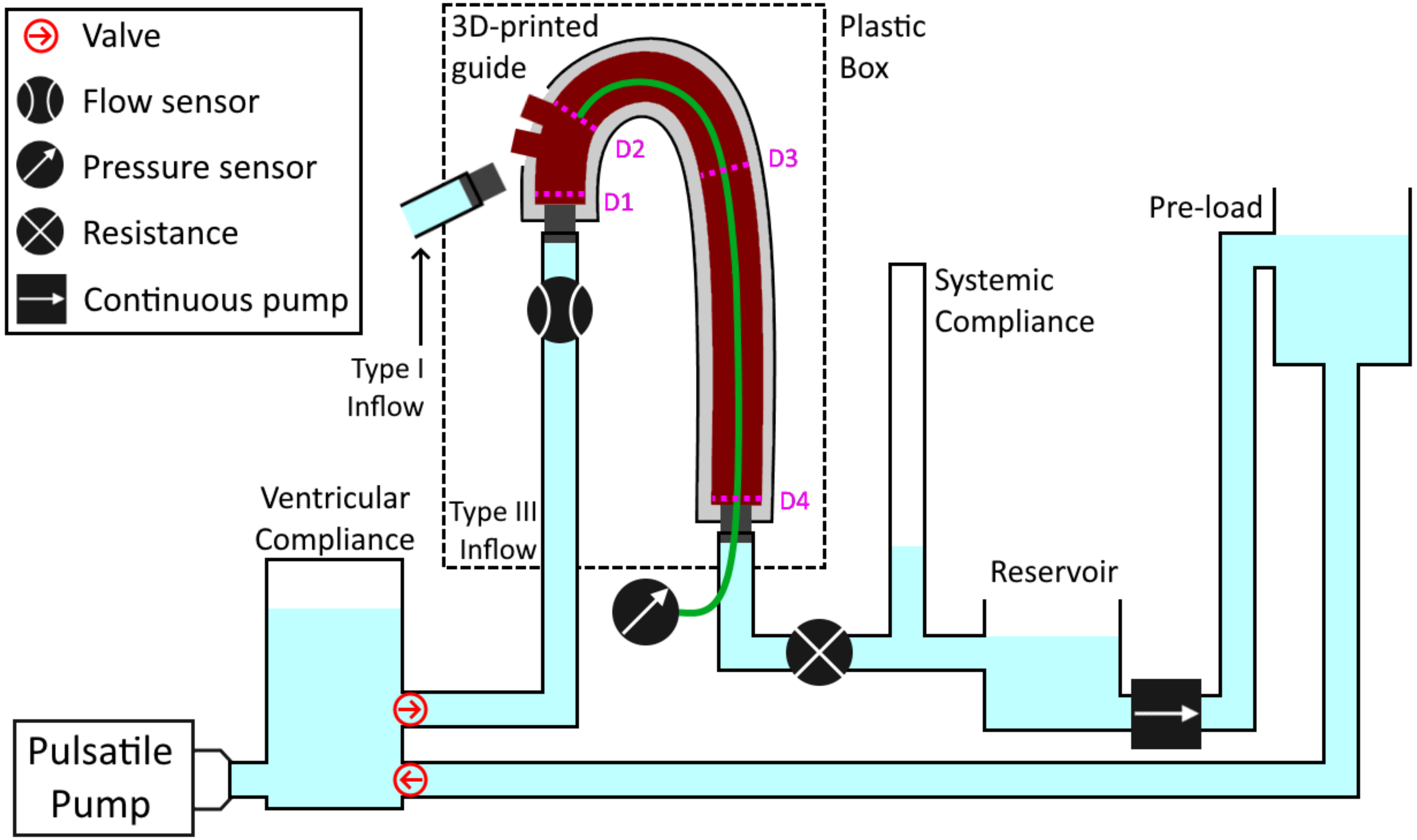
UNIVERSITÀ DEGLI STUDI DI MILANO

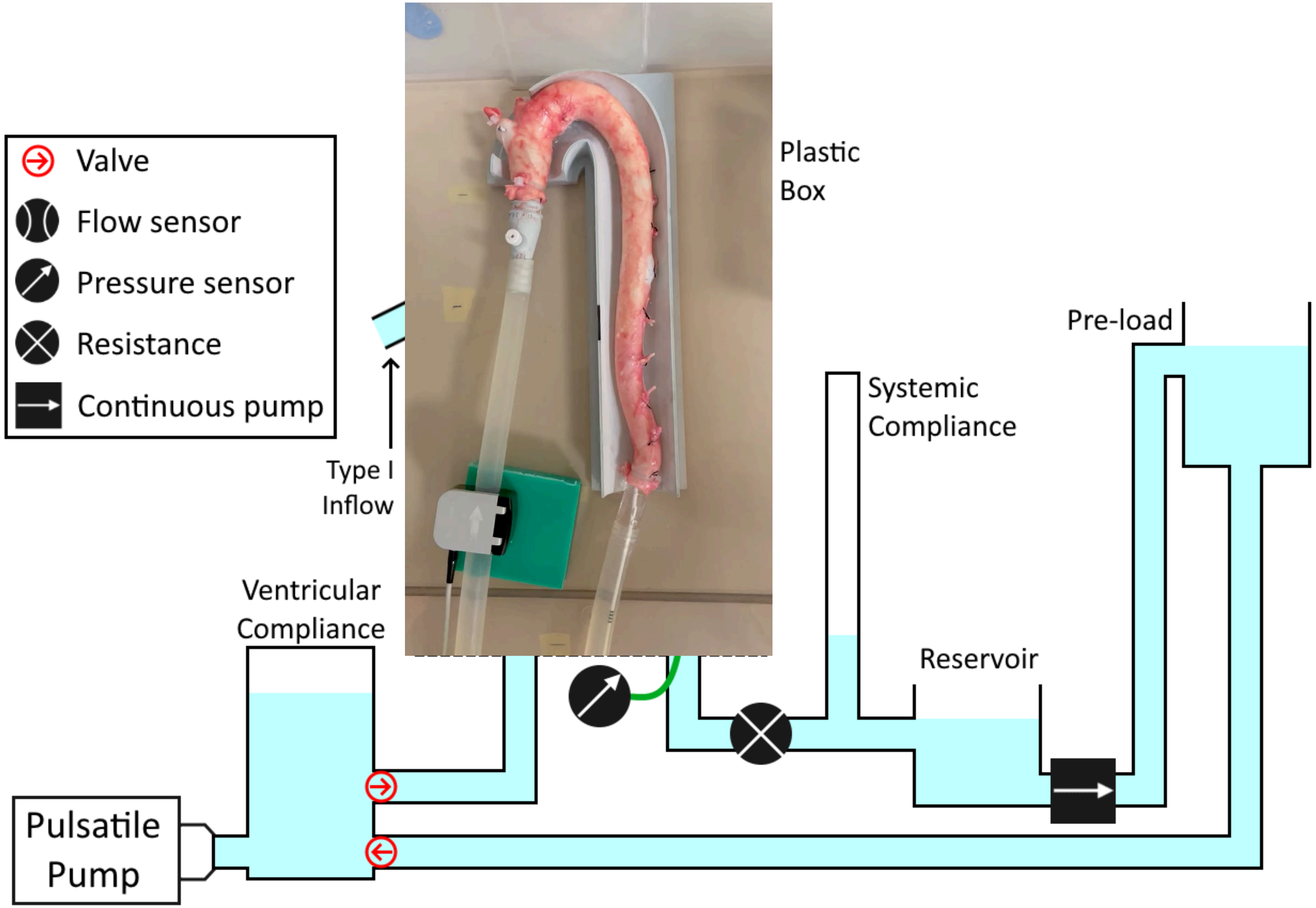
Aortic Stiffness

Experimental set-up



Aortic Stiffness

Experimental set-up



Ex vivo model: longitudinal and radial strain

Mechanical coupling TEVAR - Aorta

Workflow

Stent graft
insertion

Pressure 100-180 mmHg
HD camera
Diameter measurement

= strain post-TEVAR

An experimental investigation of the impact of thoracic endovascular aortic repair on longitudinal strain[†]

Foeke J.H. Nauta[a,b,*], Michele Conti[c], Stefania Marconi[c], Arnoud V. Kamman[a,b], Gianluca Alaimo[c], Simone Morganti[d], Anna Ferrara[c], Joost A. van Herwaarden[b], Frans L. Moll[b], Ferdinando Auricchio[d] and Santi Trimarchi[a]

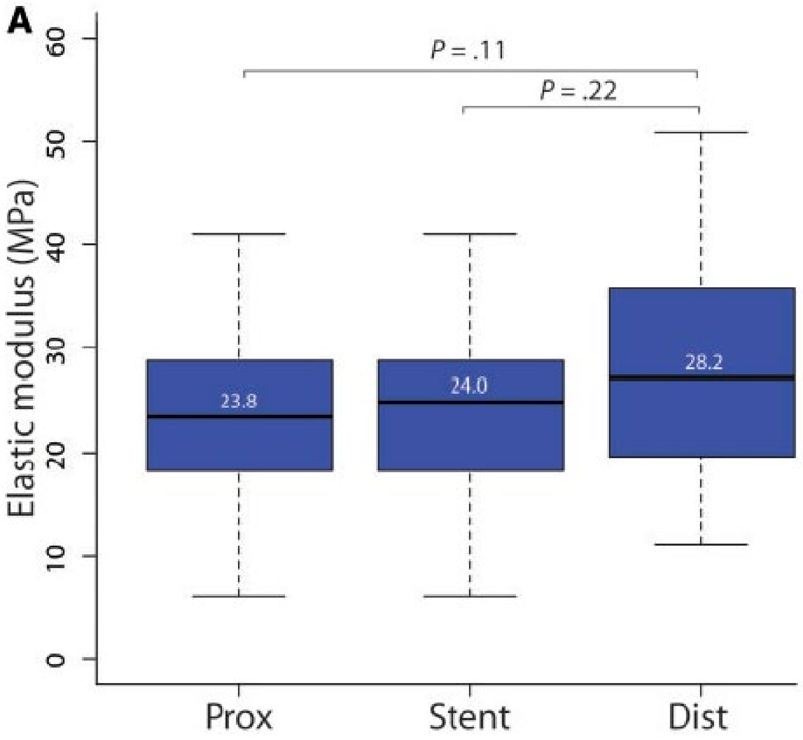
European Journal of Cardio-Thoracic Surgery 50 (2016) 955–961

Impact of thoracic endovascular aortic repair on radial strain in an *ex vivo* porcine model

Foeke J.H. Nauta[a,b,*], Hector W.L. de Beaufort[a,b], Michele Conti[c], Stefania Marconi[c], Arnoud V. Kamman[a,b], Anna Ferrara[c], Joost A. van Herwaarden[b], Frans L. Moll[b], Ferdinando Auricchio[c] and Santi Trimarchi[a,d]

European Journal of Cardio-Thoracic Surgery 51 (2017) 783–789

Ex vivo model: longitudinal and radial strain



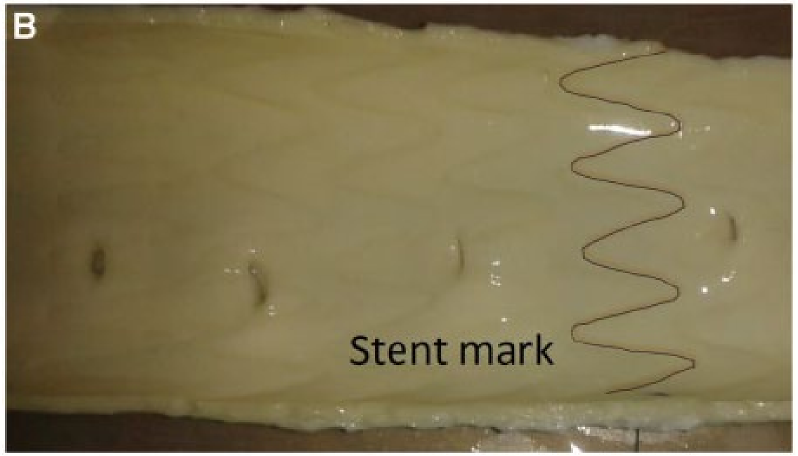


Figure 6: Uniaxial tensile testing (*n* = 20). (**A**) Mean maximum elastic moduli per zone. (**B**) Stent marks along the intima of the thoracic porcine aorta. Dist, distal; Prox, proximal; Stent, stented.

Impact of thoracic endovascular aortic repair on radial strain in an *ex vivo* porcine model

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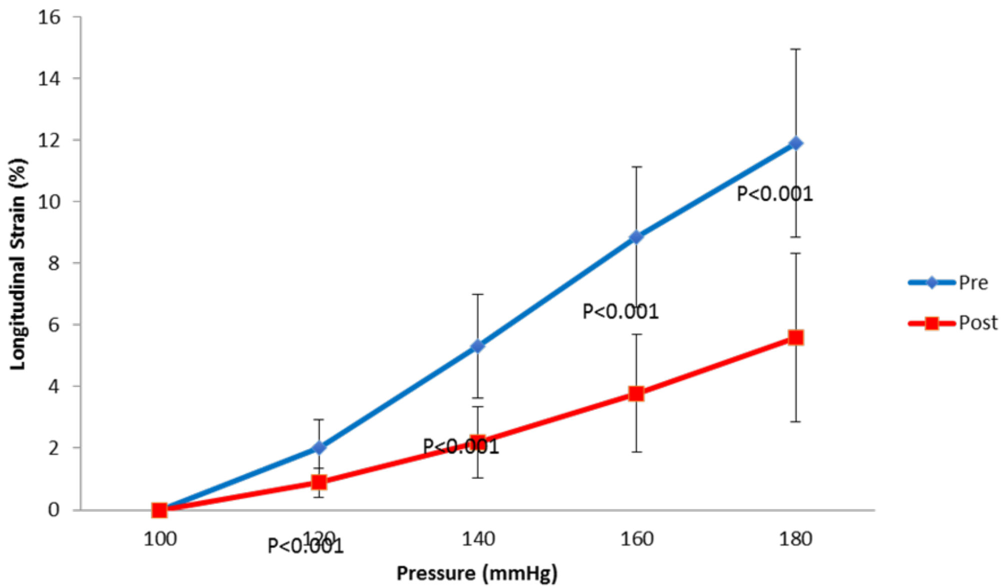
European Journal of Cardio-Thoracic Surgery 51 (2017) 783–789

Ex vivo model: longitudinal and radial strain

- Longitudinal strain reduced by up to 53% (p<0.001)

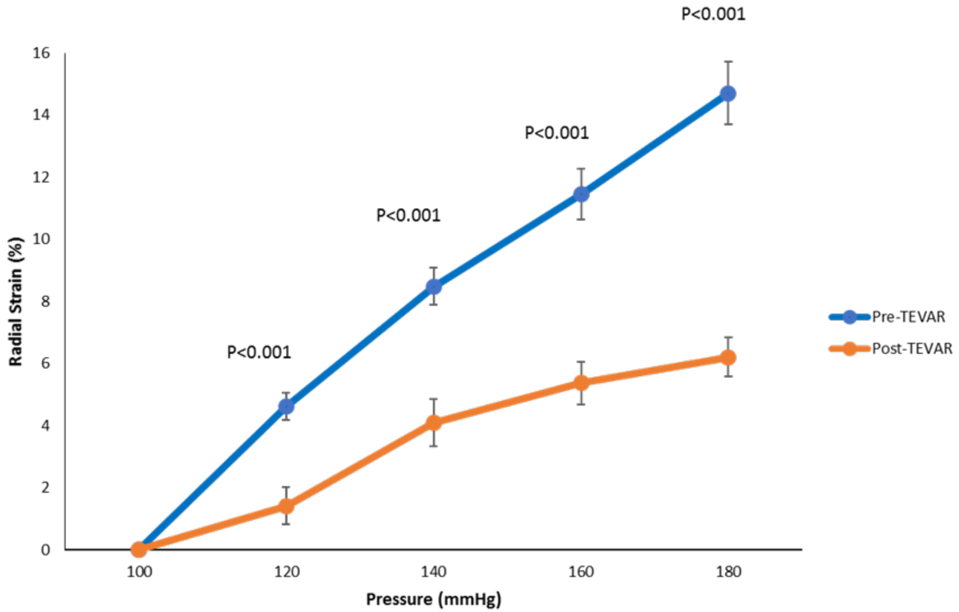


An experimental investigation of the impact of thoracic endovascular aortic repair on longitudinal strain†

Foeke J.H. Nauta[a,b,*], Michele Conti[c], Stefania Marconi[c], Arnoud V. Kamman[a,b], Gianluca Alaimo[c], Simone Morganti[d], Anna Ferrara[c], Joost A. van Herwaarden[b], Frans L. Moll[b], Ferdinando Auricchio[d] and Santi Trimarchi[a]

European Journal of Cardio-Thoracic Surgery 50 (2016) 955–961

- Radial strain reduced by up to 49% (p<0.001)

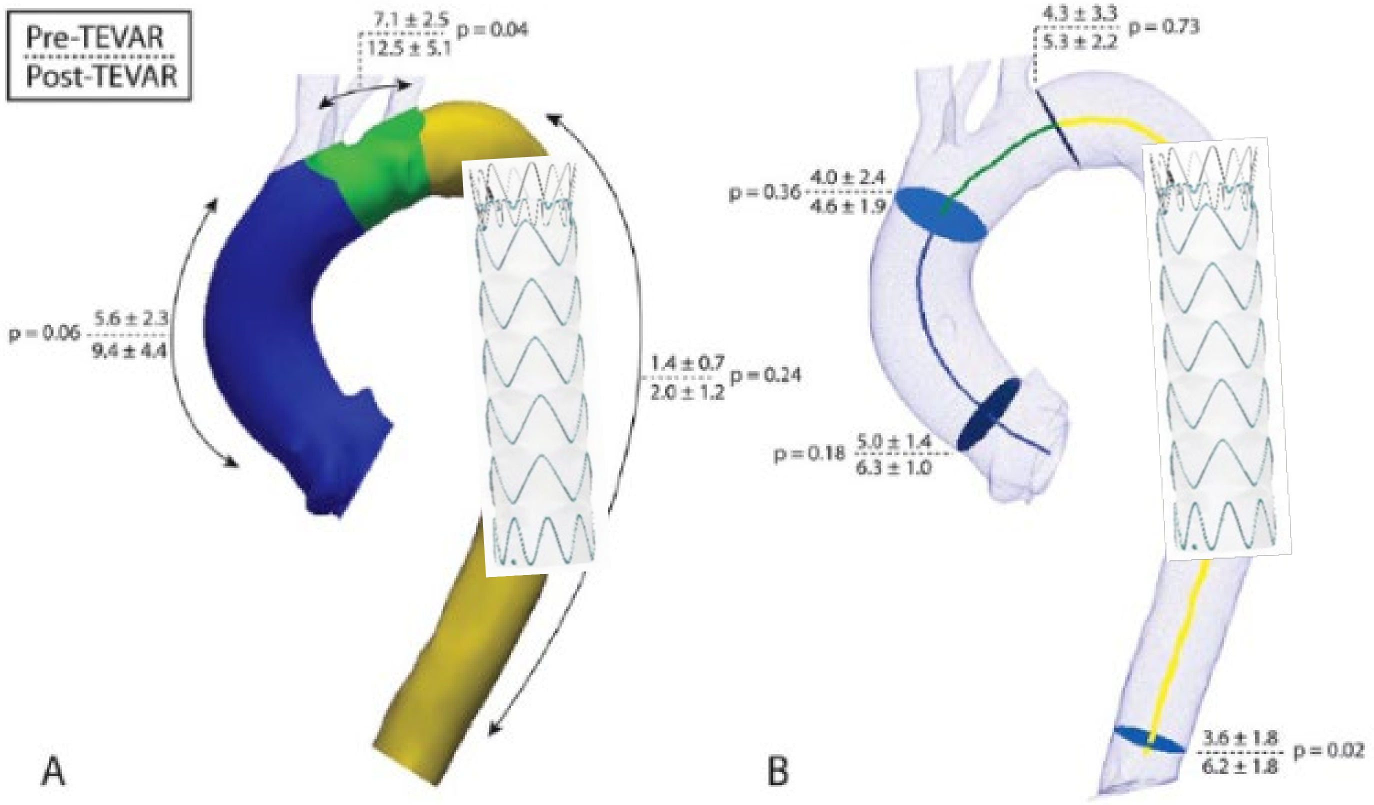


Impact of thoracic endovascular aortic repair on radial strain in an *ex vivo* porcine model

Foeke J.H. Nauta[a,b,*], Hector W.L. de Beaufort[a,b], Michele Conti[c], Stefania Marconi[c], Arnoud V. Kamman[a,b], Anna Ferrara[c], Joost A. van Herwaarden[b], Frans L. Moll[b], Ferdinando Auricchio[c] and Santi Trimarchi[a,d]

European Journal of Cardio-Thoracic Surgery 51 (2017) 783–789

Modeling - Aortic stiffness



Ascending and arch length

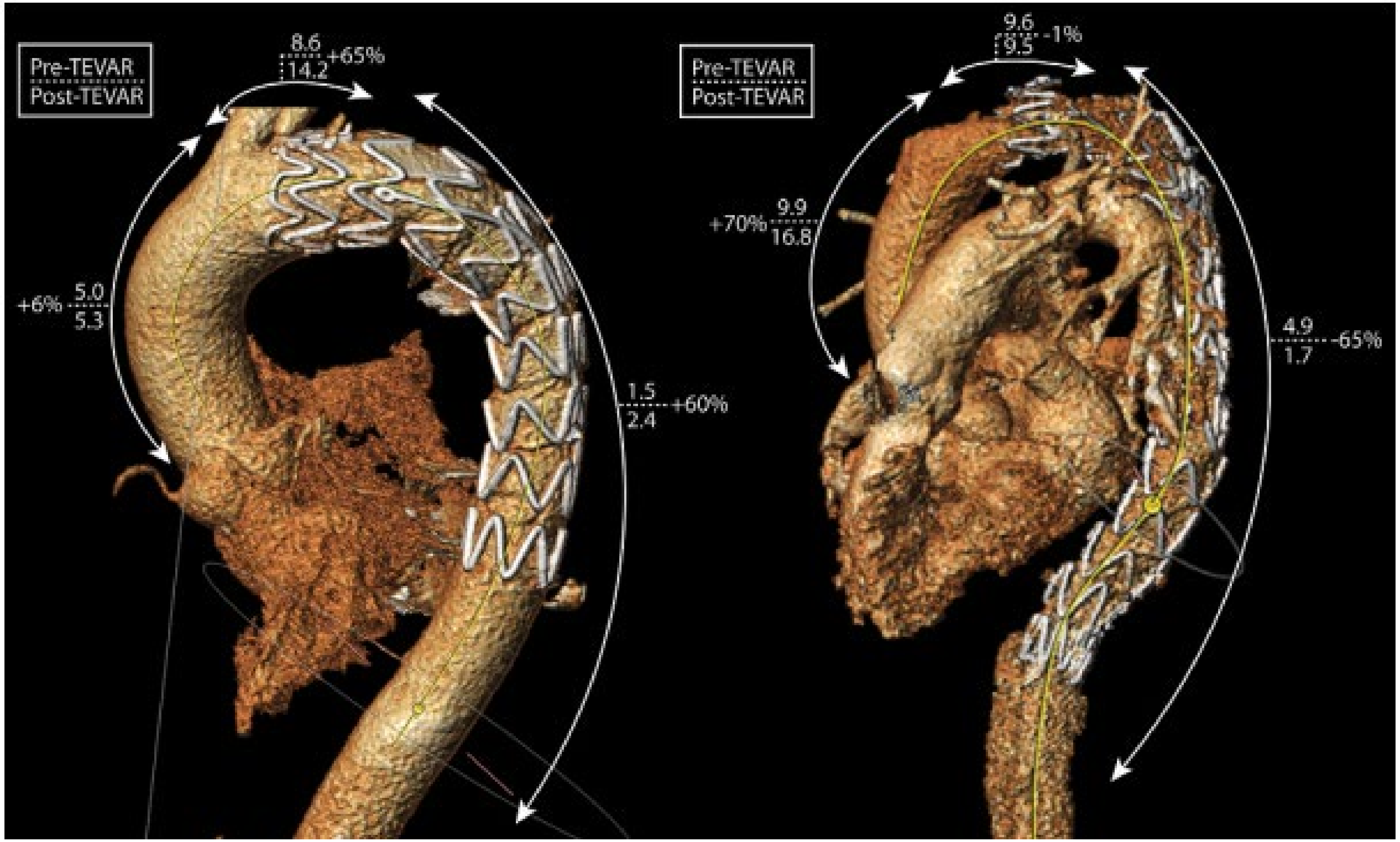
Circumference

Impact of Thoracic Endovascular Aortic Repair on Pulsatile Circumferential and Longitudinal Strain in Patients With Aneurysm

Journal of Endovascular Therapy
Volume 24, Issue 2, April 2017, Pages 281-289

Foeke J. H. Nauta, MD, PhD[1,2], Guido H. W. van Bogerijen, MD, PhD[1,2], Chiara Trentin, PhD[3], Michele Conti, PhD[4], Ferdinando Auricchio, PhD[3,4], Frans L. Moll, MD, PhD[2], Joost A. van Herwaarden, MD, PhD[2], and Santi Trimarchi, MD, PhD[1]

Modeling - Aortic stiffness



↑ Ascending and arch length

Impact of Thoracic Endovascular Repair on Pulsatile Aortic Strain in Acute Type B Aortic Dissection

Preliminary Results

AORTA, April 2017, Volume 5, Issue 2:42-52

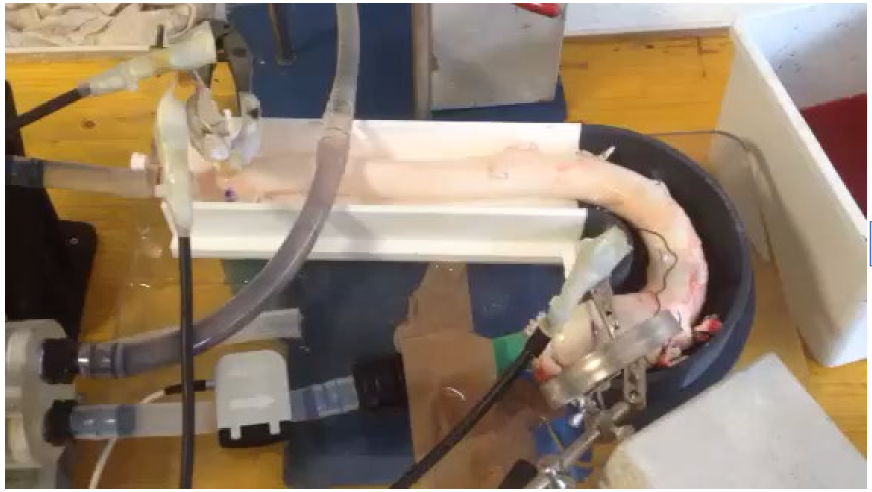
Foeke J.H. Nauta, MD, PhD[1,2*], Guido H.W. van Bogerijen, MD, PhD[1,2], Michele Conti, PhD[3], Chiara Trentin, PhD[4], Frans L. Moll, MD, PhD[2], Joost A. Van Herwaarden, MD, PhD[2], Ferdinando Auricchio, PhD[3,4], Santi Trimarchi, MD, PhD[1]

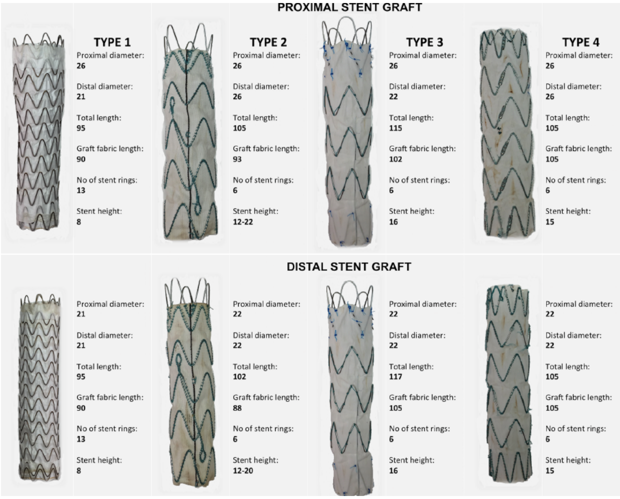
Ex-vivo model: aortic stiffness

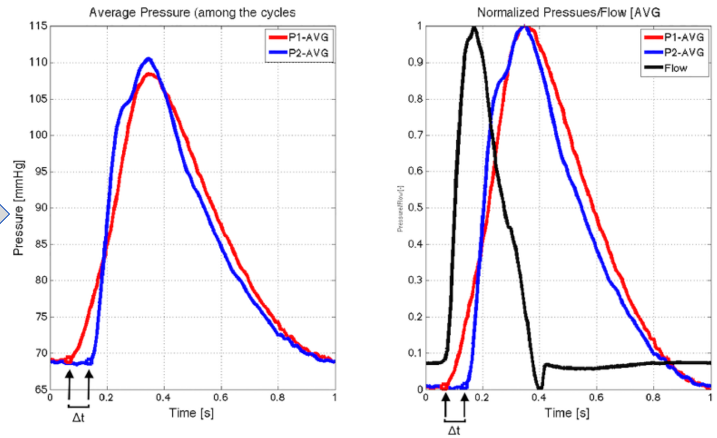
Objective: understanding the impact of TEVAR on aortic stiffness

Methods: Porcine aorta –Pulse Wave Velocity

Facilities: pulsatile hydraulic circuit and flow/pressure sensors @ B-Lab







2017

PLOS | ONE

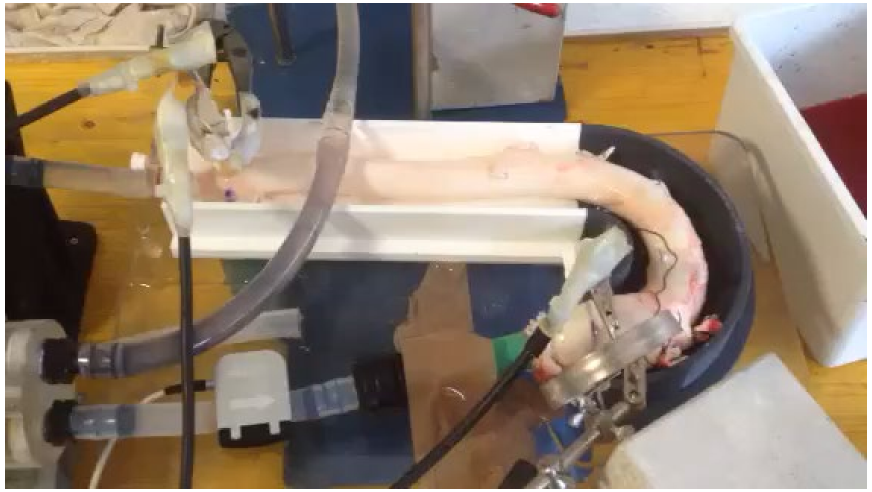
Changes in aortic pulse wave velocity of four thoracic aortic stent grafts in an *ex vivo* porcine model

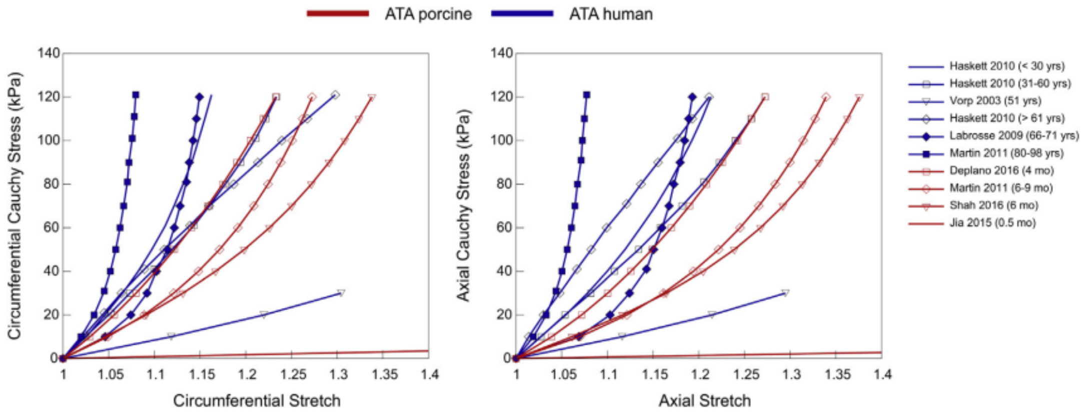
Hector W. L. de Beaufort[1], Margherita Coda[2], Michele Conti[2], Theodorus M. J. van Bakel[1], Foeke J. H. Nauta[1], Ettore Lanzarone[3], Frans L. Moll[4], Joost A. van Herwaarden[4], Ferdinando Auricchio[2], Santi Trimarchi[1] *

Ex-vivo model: aortic stiffness

WHAT THIS PAPER ADDS

This study uses a method to compare published data on porcine and human thoracic aortic stiffness from different studies consistently. The results of this analysis show that the stiffness of young porcine aortas is similar to that of human tissue aged under 60 years and less stiff than human tissue aged 60 years or more. This has implications for using the porcine aorta as a model for human aorta in research.





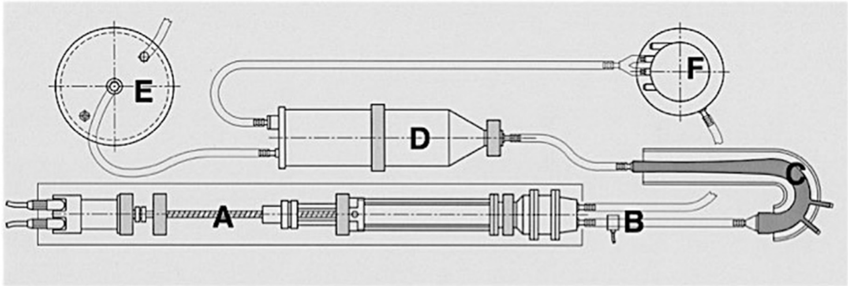
Comparative Analysis of Porcine and Human Thoracic Aortic Stiffness

Hector W.L. de Beaufort [a], Anna Ferrara [d], Michele Conti [d], Frans L. Moll [c], Joost A. van Herwaarden [c], C. Alberto Figueroa [e], Jean Bismuth [f], Ferdinando Auricchio [d], Santi Trimarchi [b,*]

Eur J Vasc Endovasc Surg (2018) 55, 560—566

Ex-vivo model: aortic stiffness

Mock loop



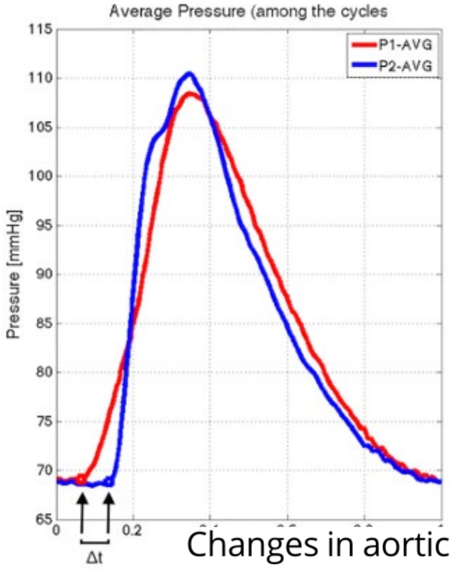
Stent-Graft Deployment Increases Aortic Stiffness in an ExVivo Porcine Model

Hector W.L. de Beaufort [1], Michele Conti [2], Arnoud V. Kamman [1], Foeke J.H. Nauta [1], Ettore Lanzarone [3], Frans L. Moll [4], Joost A. van Herwaarden [4], Ferdinando Auricchio [2], Santi Trimarchi [1]

Annals of Vascular Surgery
Volume 43, August 2017, Pages 302-308

Initial version

- Circuit
  - No ventricular compliance
  - No preload
  - Manual afterload
- PWV computation
  - Manual Δt, single point method
  - Manual length (using wire)
- No supra-aortic branches



Changes in aortic pulse wave velocity of four thoracic aortic stent grafts in an *ex vivo* porcine model

PLOS ONE | https://doi.org/10.1371/journal.pone.0186080 October 5, 2017

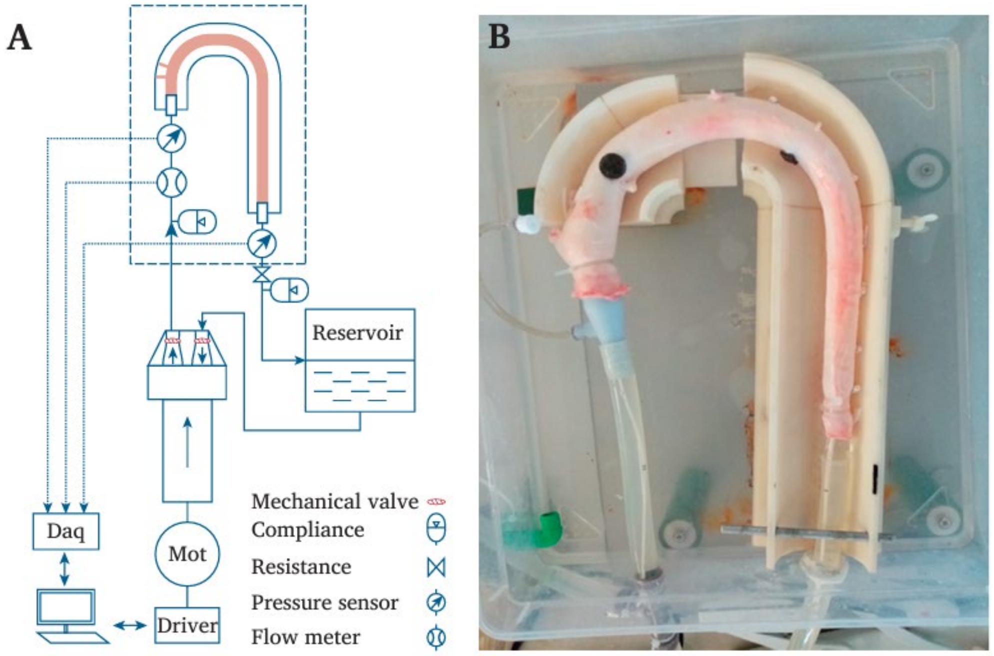
Hector W. L. de Beaufort [1], Margherita Coda [2], Michele Conti [2], Theodorus M. J. van Bakel [1], Foeke J. H. Nauta [1], Ettore Lanzarone [3], Frans L. Moll [4], Joost A. van Herwaarden [4], Ferdinando Auricchio [2], Santi Trimarchi [1] *

Ex-vivo model: aortic stiffness

Mock loop

Intermediate version

- Circuit
  - Fixed ventricular compliance
  - Manual preload
  - Manual afterload
- PWV computation
  - Manual Δt, single point method
  - Manual length (using picture)
- No supra-aortic branches



Comparison of Two Generations of Thoracic Aortic Stent Grafts and Their Impact on Aortic Stiffness in an *Ex Vivo* Porcine Model

EJVES Vascular Forum (2023) 59, 8–14

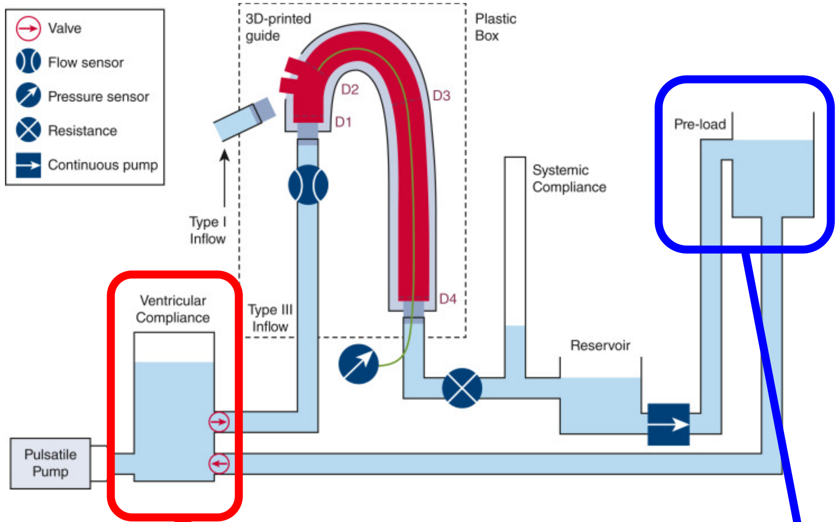
Tim J. Mandigers [a,b,*], Michele Conti [c], Sara Allievi [a], Francesca Dedola [c], Daniele Bissacco [a], Daniele Bianchi [c], Stefania Marconi [c], Maurizio Domanin [a,d], Joost A. Van Herwaarden [b], Ferdinando Auricchio [c], Santi Trimarchi [a,d]

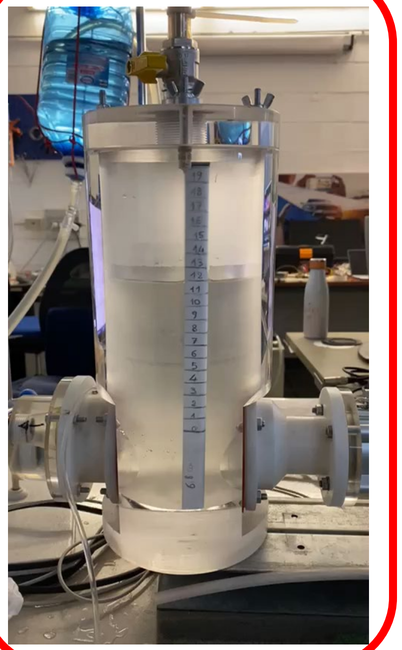
Ex-vivo model: aortic stiffness

Mock loop

<u>Current version</u>

- Circuit
  - Adjustable ventricular compliance
  - Automatic preload
  - Manual afterload
- PWV computation
  - Automatic Δt, upslope method
  - Manual length (using picture)
- Inclusion of supra-aortic branches





Type III aortic arch angulation increases aortic stiffness: Analysis from an ex vivo porcine model

Check for updates

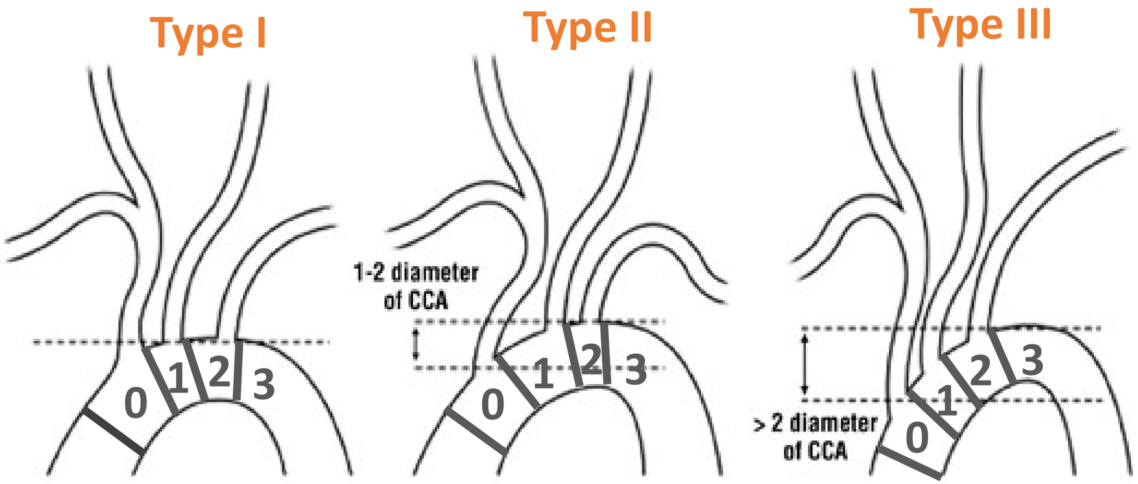
JTCVS Open • February 2024

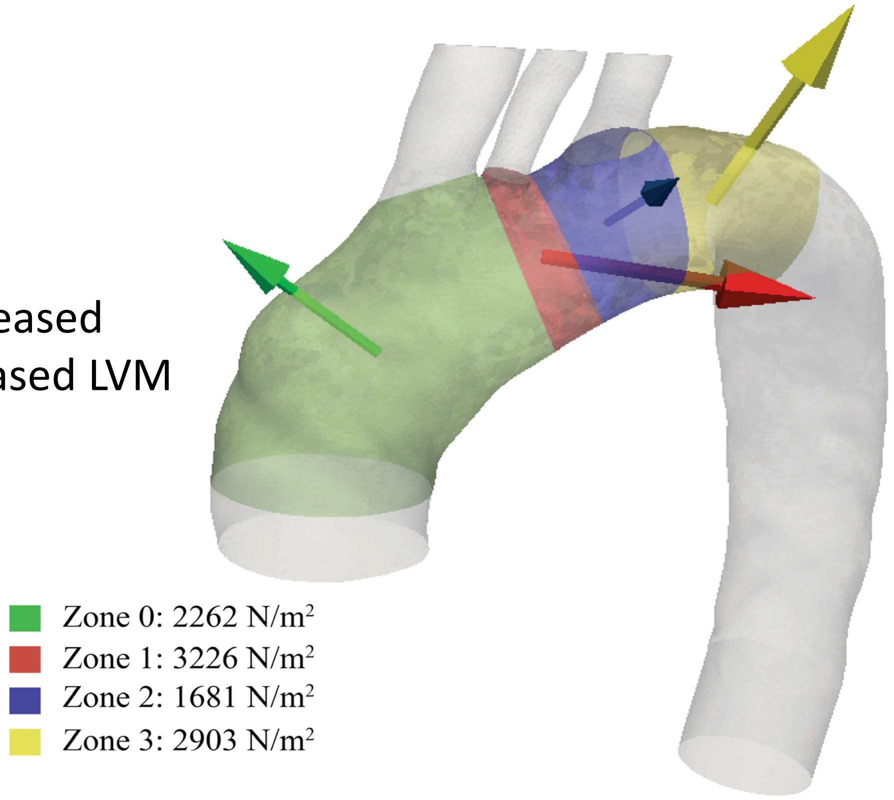
Tim J. Mandigers, MD,[a,b] Ariel F. Pascaner, PhD,[c] Michele Conti, PhD,[c] Martina Schembri, MS,[c] Sonja Jelic, BS,[c] Alessandra Favilli, DVM,[d] Daniele Bissacco, MD,[a] Maurizio Domanin, MD,[a,e] Joost A. van Herwaarden, MD, PhD,[b] Ferdinando Auricchio, PhD,[c] and Santi Trimarchi, MD, PhD[a,e]

Ex-vivo model: aortic stiffness

Aortic arch angulation

- Successful TEVAR dependent on favourable anatomy
- Arch classification
- Type III associated with birdbeak, hostile drag forces
- Open coarctation repair in Type III found hypertension, increased aortic stiffness, increased systolic wave reflection and increased LVM





The Modified Arch Landing Areas Nomenclature (MALAN) Improves Prediction of Stent Graft Displacement Forces: Proof of Concept by Computational Fluid Dynamics Modelling☆

Massimiliano M. Marrocco-Trischitta [a,b,*], Theodorus M. van Bakel [b], Rodrigo M. Romarowski [c], Hector W. de Beaufort [b], Michele Conti [d], Joost A. van Herwaarden [e], Frans L. Moll [e], Ferdinando Auricchio [d], Santi Trimarchi [a,b,f]

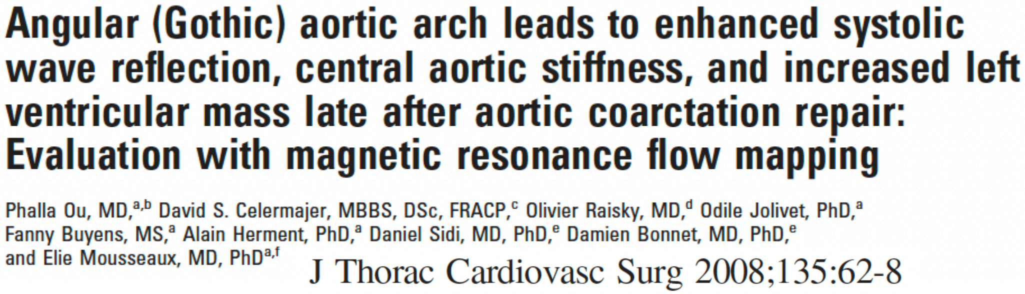
Aortic arch angulation

- But the effect of arch angulation on aortic flow dynamics is largely unknown

- Previous studies after successful open coarctation repair found:

Gothic *Crenel* *Normal*

* hypertension
* increased systolic wave reflections
* central aortic stiffness

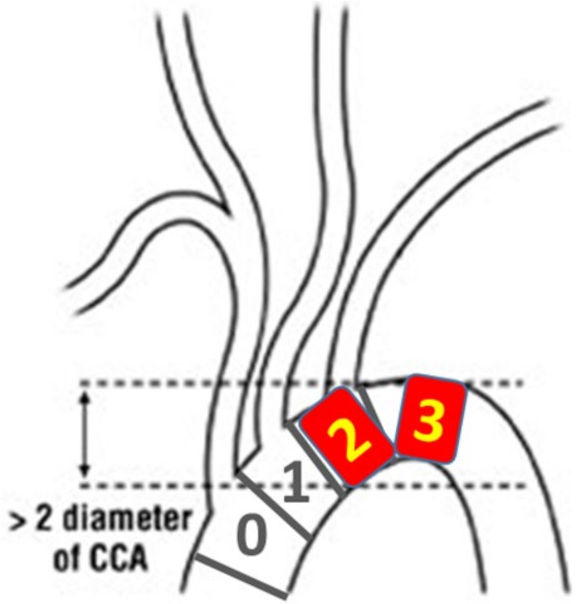

Angular (Gothic) aortic arch leads to enhanced systolic wave reflection, central aortic stiffness, and increased left ventricular mass late after aortic coarctation repair: Evaluation with magnetic resonance flow mapping

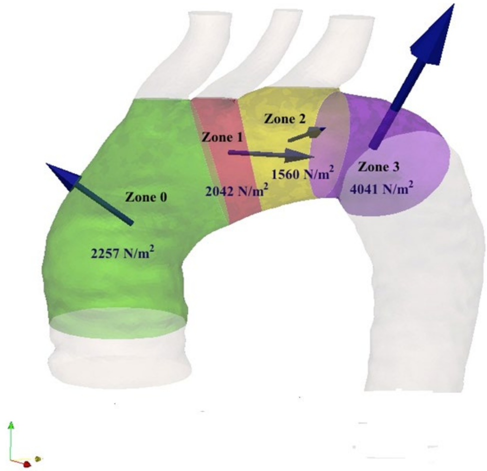
Phalla Ou, MD,[a,b] David S. Celermajer, MBBS, DSc, FRACP,[c] Olivier Raisky, MD,[d] Odile Jolivet, PhD,[a] Fanny Buyens, MS,[a] Alain Herment, PhD,[a] Daniel Sidi, MD, PhD,[e] Damien Bonnet, MD, PhD,[e] and Elie Mousseaux, MD, PhD[a,f]

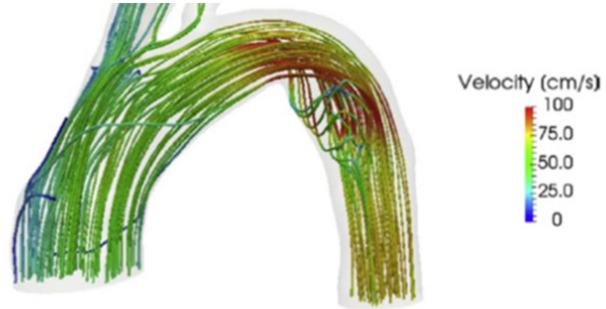
J Thorac Cardiovasc Surg 2008;135:62-8

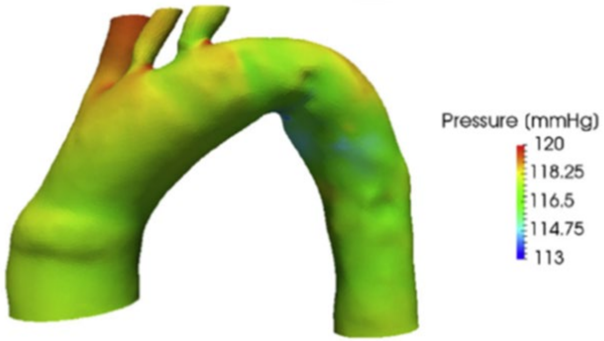
Aorta & TEVAR: PROXIMAL angulation & drag forces

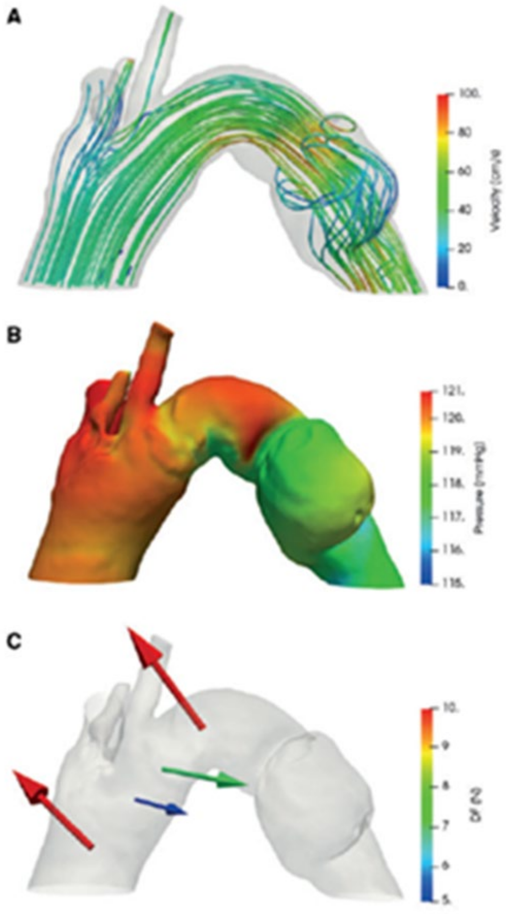
Type III







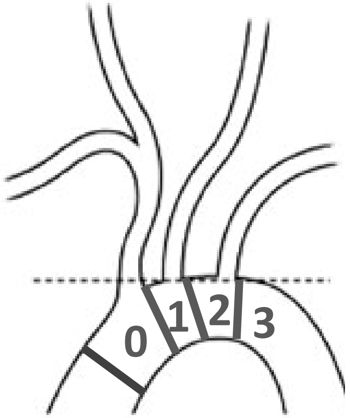




Aortic arch angulation

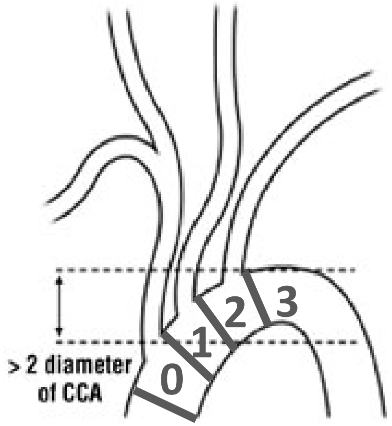
- Hypothesis: "Type III aortic arch configuration increases aortic pulse wave velocity, as compared to a (baseline) Type I aortic arch configuration"
- Additionally, we investigated if the TEVAR induced stiffening is exacerbated by an increased arch angulation

Type I



Versus

Type III



→ ***ΔPWV?***

Ex-vivo model: aortic stiffness

Arch guides + aortic sample connected (pulsatile)

Type I Arch

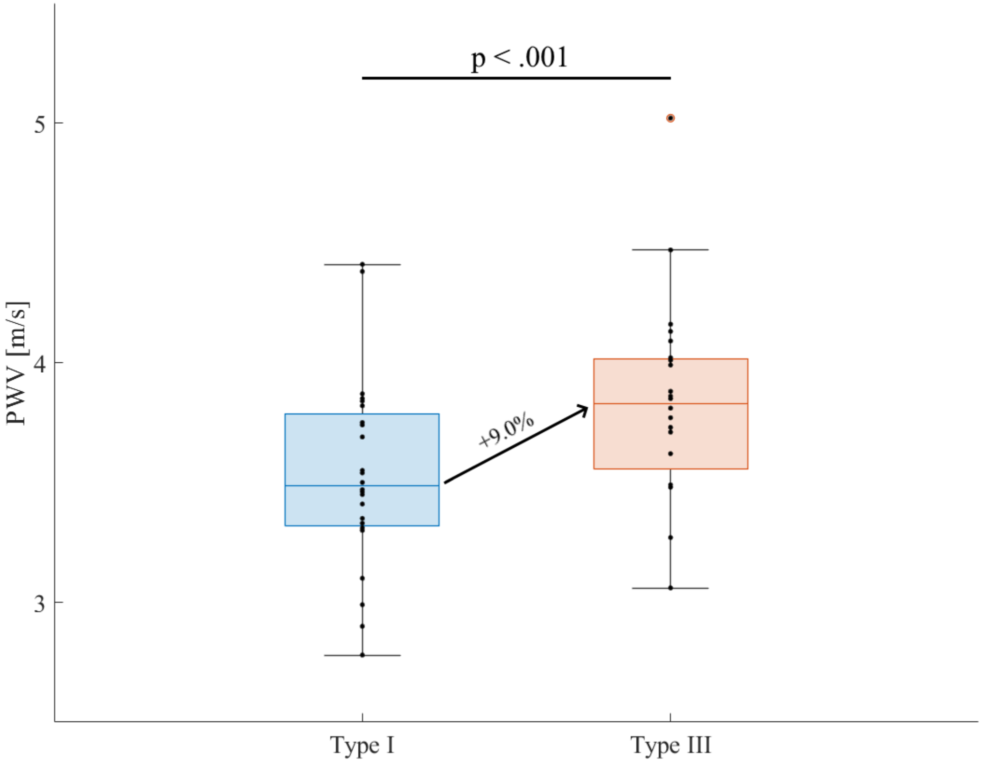
Type III Arch

Intra-luminal view of the stent graft

Ex-vivo model: aortic stiffness

Results

- Aortic Pulse Wave Velocity increased with a change to a Type III Arch (n= 24)



Type III aortic arch angulation increases aortic stiffness: Analysis from an ex vivo porcine model

Check for updates

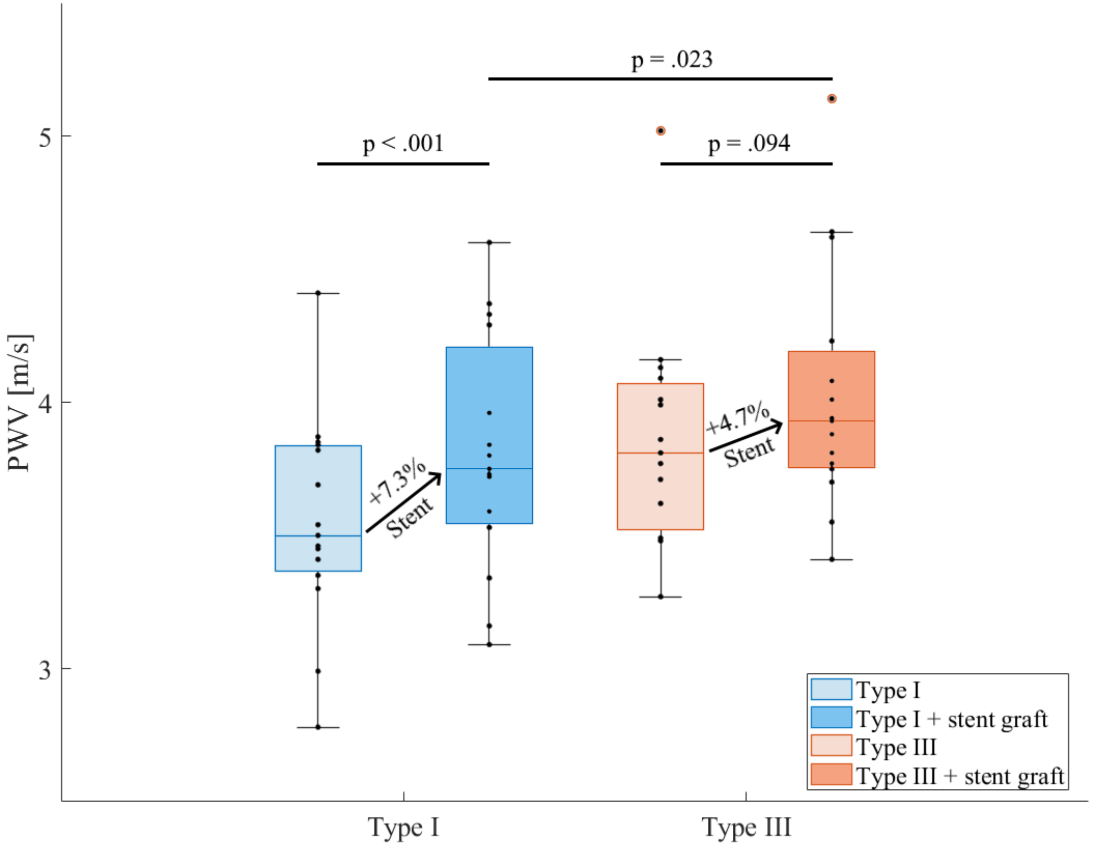
JTCVS Open • February 2024

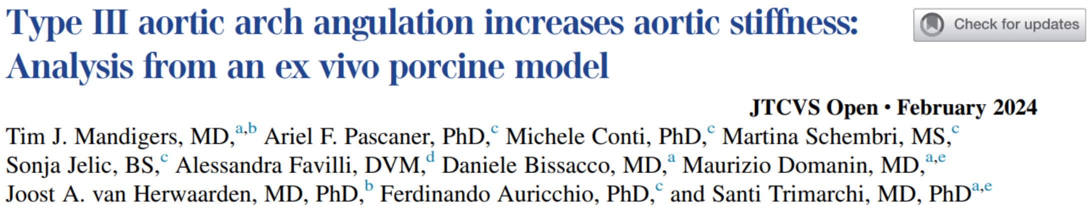
Tim J. Mandigers, MD,[a,b] Ariel F. Pascaner, PhD,[c] Michele Conti, PhD,[c] Martina Schembri, MS,[c] Sonja Jelic, BS,[c] Alessandra Favilli, DVM,[d] Daniele Bissacco, MD,[a] Maurizio Domanin, MD,[a,e] Joost A. van Herwaarden, MD, PhD,[b] Ferdinando Auricchio, PhD,[c] and Santi Trimarchi, MD, PhD[a,e]

Ex-vivo model: aortic stiffness

Results

- Stent graft deployment (Captivia) in case of correct oversizing to reach 10 – 20% oversizing (n = 15)

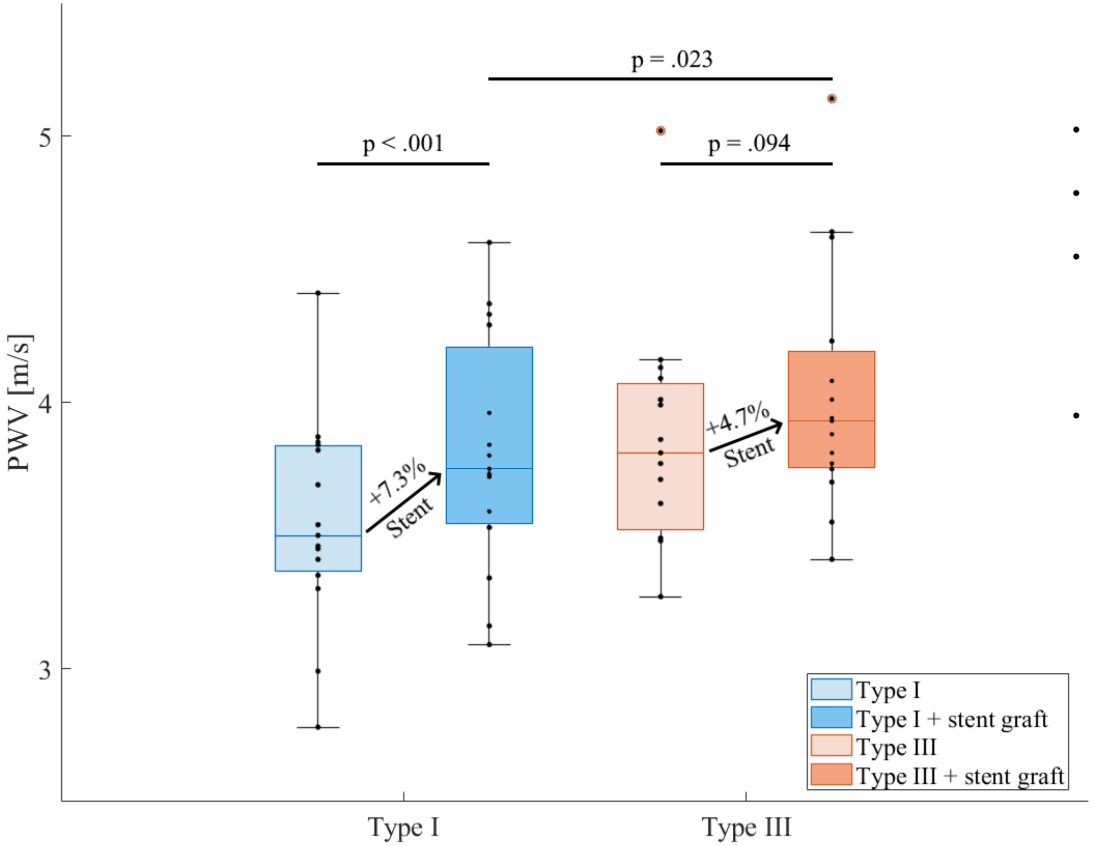




Ex-vivo model: aortic stiffness

Results

- Stent graft deployment (Captivia) in case of correct oversizing to reach 10 – 20% oversizing (n = 15)



- Increases in aortic arch angulation affect blood pressure responses and aortic pulse wave velocity
- This might be related to an increased systemic vascular resistance (afterload) in a type III arch
- A more angulated **type III arch is associated with higher blood pressures and aortic pulse wave velocity**, compared to the less angulated type I arch, especially after TEVAR

"ANGULATION MATTERS !"

- These aspects negatively impact a patient's cardiovascular health, both before and after TEVAR

Type III aortic arch angulation increases aortic stiffness: Analysis from an ex vivo porcine model

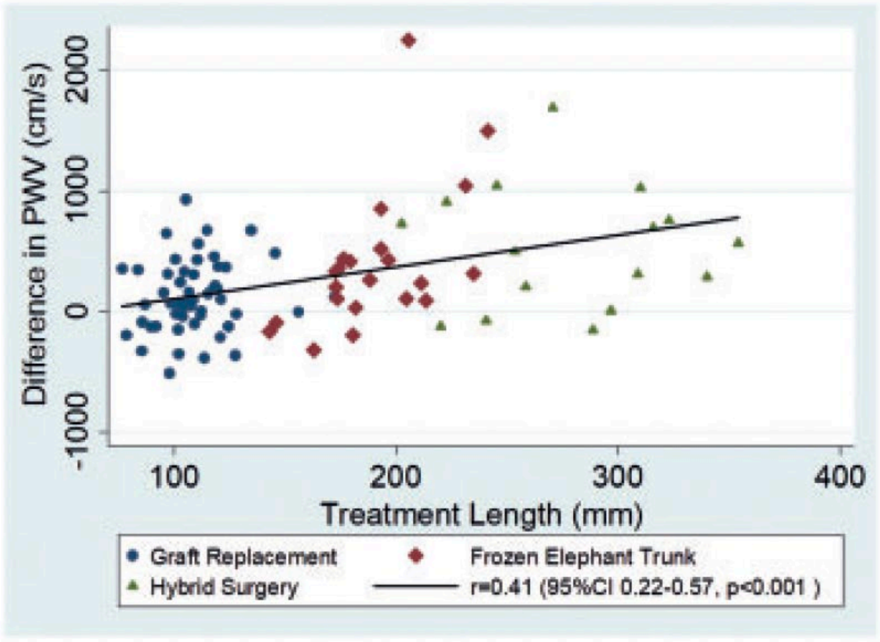
Check for updates

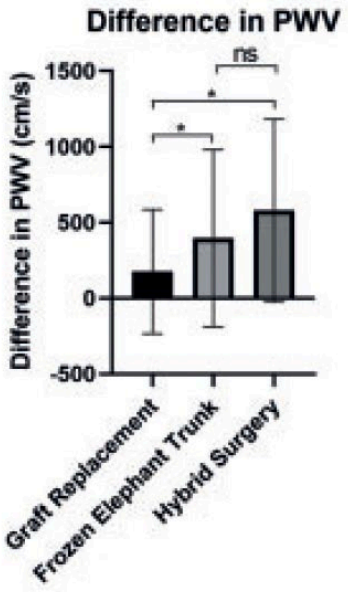
JTCVS Open • February 2024

Tim J. Mandigers, MD,[a,b] Ariel F. Pascaner, PhD,[c] Michele Conti, PhD,[c] Martina Schembri, MS,[c] Sonja Jelic, BS,[c] Alessandra Favilli, DVM,[d] Daniele Bissacco, MD,[a] Maurizio Domanin, MD,[a,e] Joost A. van Herwaarden, MD, PhD,[b] Ferdinando Auricchio, PhD,[c] and Santi Trimarchi, MD, PhD[a,e]

Stiffness after Open Surgical Graft

- No uniform answer in literature if open surgical repair with Dacron ‘stiffens’ the aorta
- One recent study on stiffness after Dacron repair/FET/Hybrid for arch aneurysms





Interactive CardioVascular and Thoracic Surgery 34 (2022) 652–659
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ORIGINAL ARTICLE

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The effect of aortic arch replacement on pulse wave velocity after surgery

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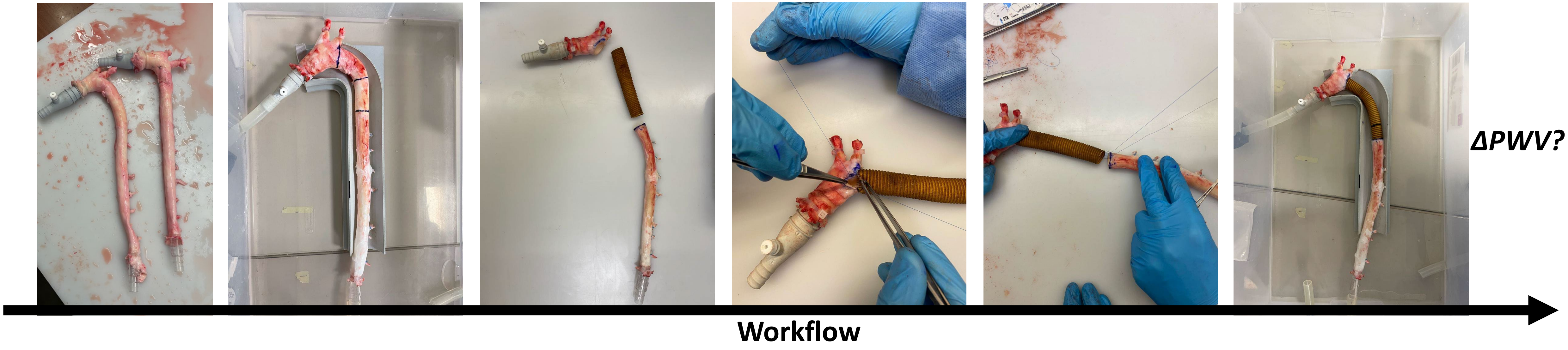
Ex-vivo model: aortic stiffness

Methods

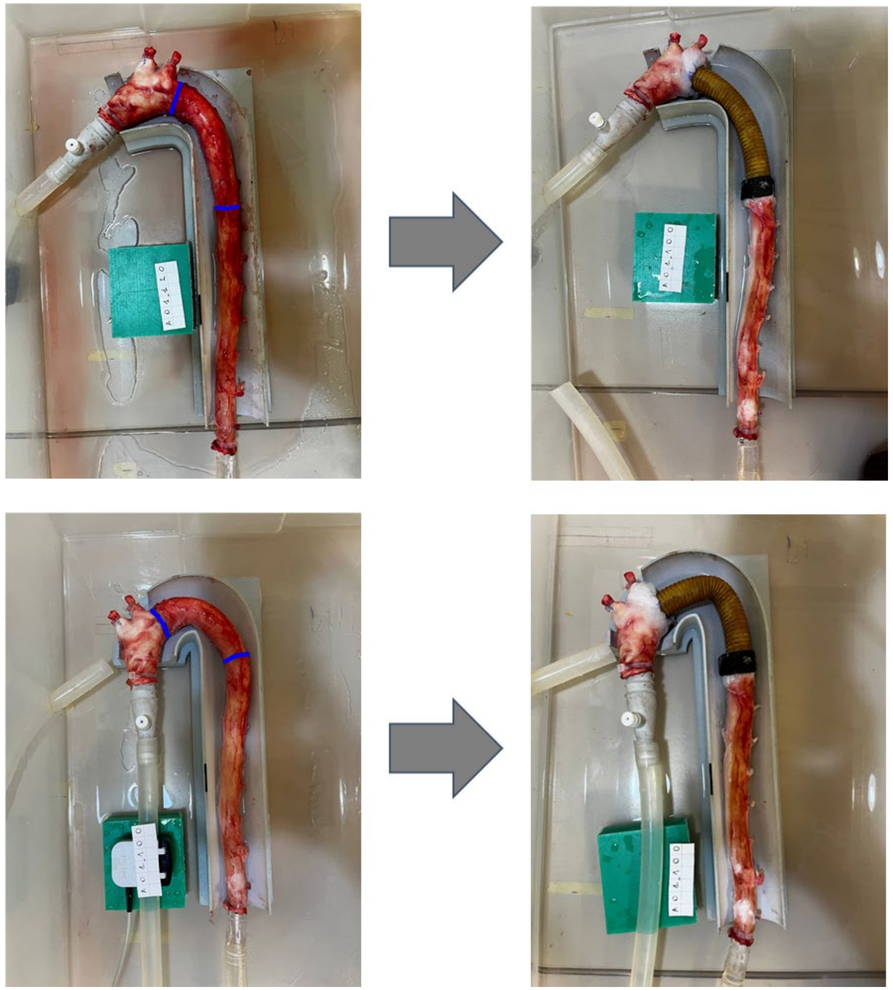
- Type I and III arch configuration
- Aortic PWV calculation using flow curves (cross-correlation method)

- Hypothesis 1: “Open surgical repair increases aortic pulse wave velocity”
- Hypothesis 2: “Open surgical repair increases aortic pulse wave velocity less compared to TEVAR”
- 10 cm surgical graft (Silver-coated)



Methods

- Type I and Type III Arch



Ex-vivo model: aortic stiffness

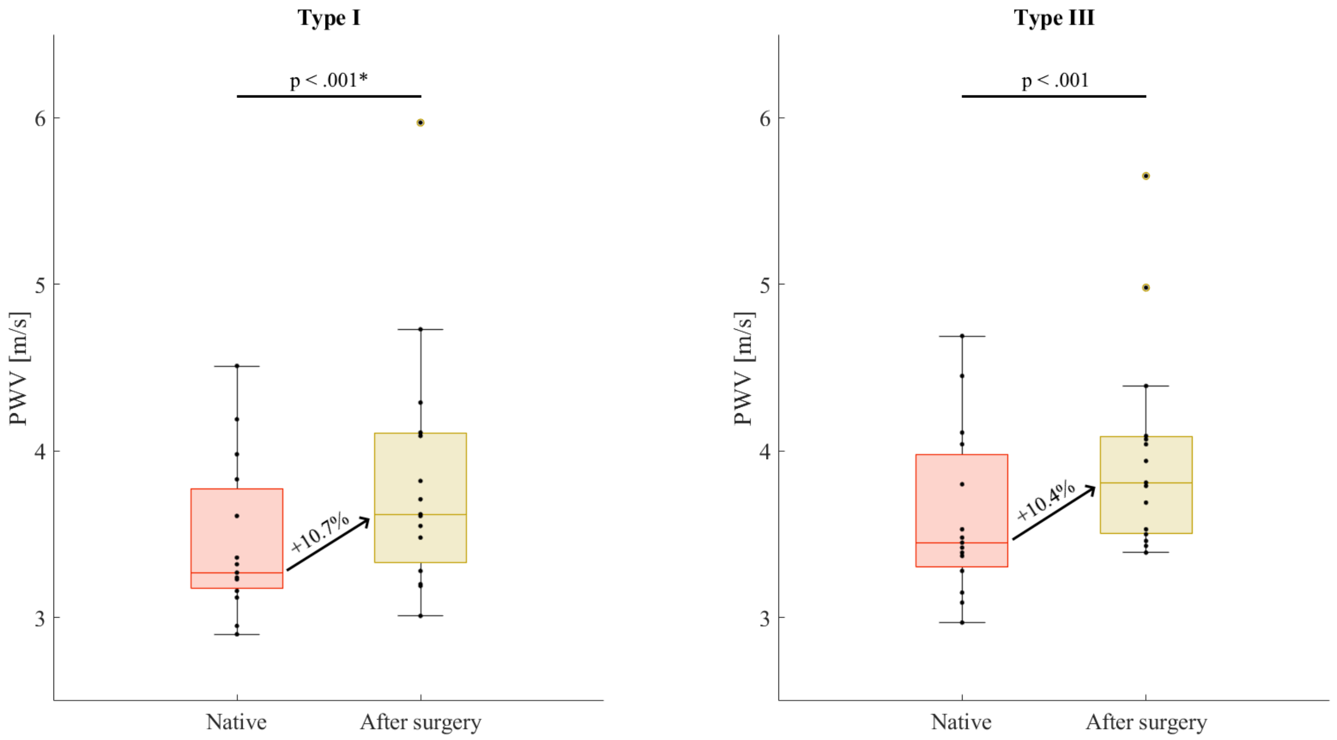
Methods

Intra-luminal view of the descending aorta after surgical graft

Ex-vivo model: aortic stiffness

Results

- In both Type I and Type III Arch there is a significant increase in PWV after Dacron interposition (n = 15)



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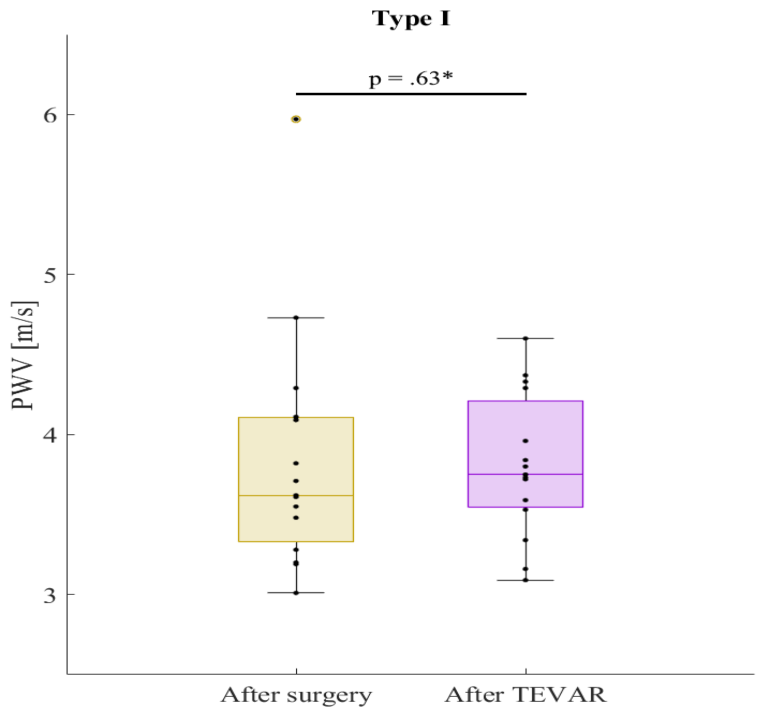
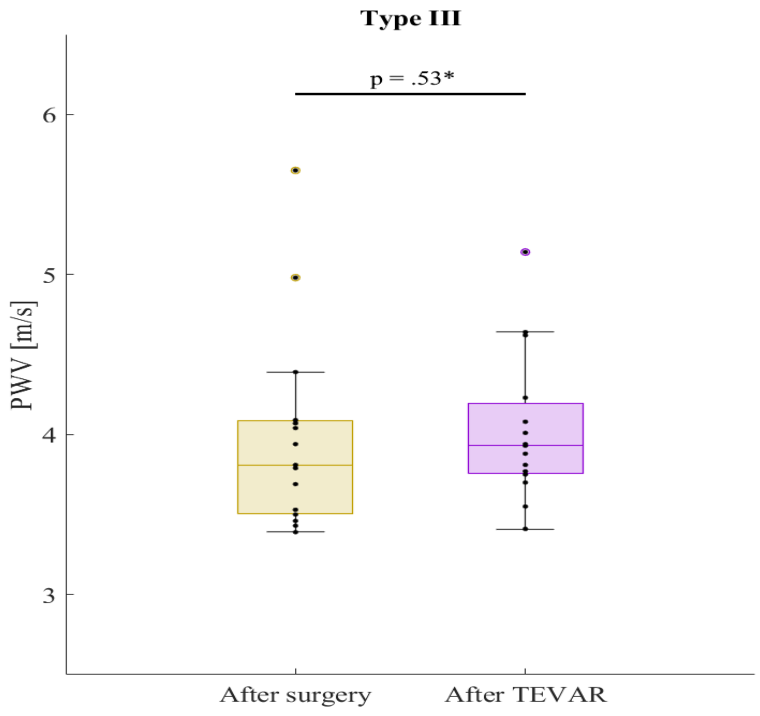
Ex-vivo model: aortic stiffness

Results

- Increase in PWV between Open Surgical Repair and Stent-grafting of descending thoracic aorta non-significantly different





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Ex-vivo model: aortic stiffness

Results

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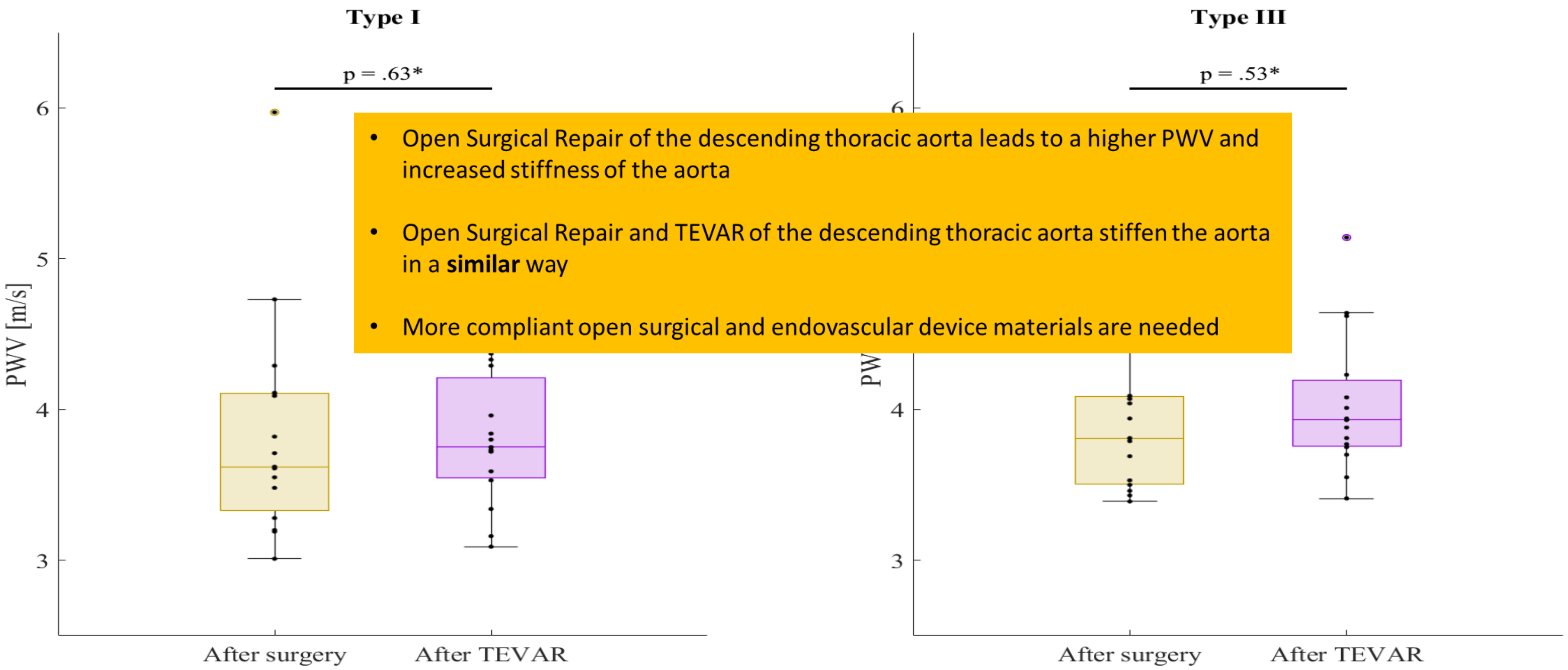

- Open Surgical Repair of the descending thoracic aorta leads to a higher PWV and increased stiffness of the aorta
- Open Surgical Repair and TEVAR of the descending thoracic aorta stiffen the aorta in a **similar** way
- More compliant open surgical and endovascular device materials are needed

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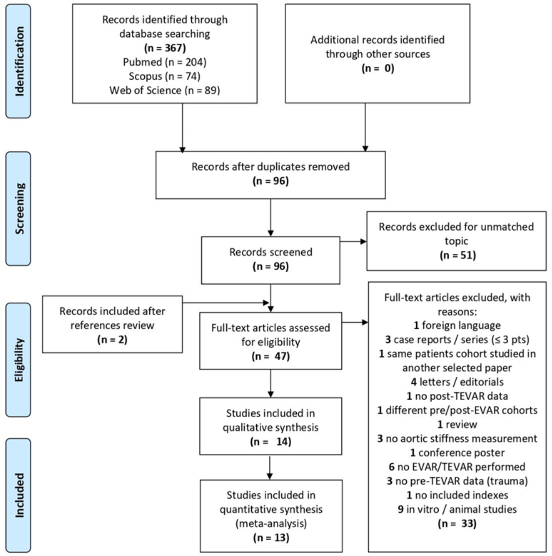
Clinical research – Aim

To evaluate the **impact of** endovascular or non-endovascular aortic repair on **aortic stiffness** (**TEVAR, EVAR** and open surgical repair [**OSR**])

- PROSPERO, registration number 212257
- PRISMA statement
- PubMed, Scopus and Web of Science, using as time range "January 1, 2000 - October 31, 2020"
- Keywords "vascular stiffness", "arterial stiffness", "aortic stiffness", "pulse wave velocity", "PWV", "elastic modulus", "pulsatility index" and "aortic compliance" were combined with "endovascular aortic repair", "EVAR" and "TEVAR"
- Newcastle-Ottawa Scale was used for selected studies quality assessment



- **10 studies on EVAR**
- **3 studies on TEVAR**
- **1 mixed cohort**

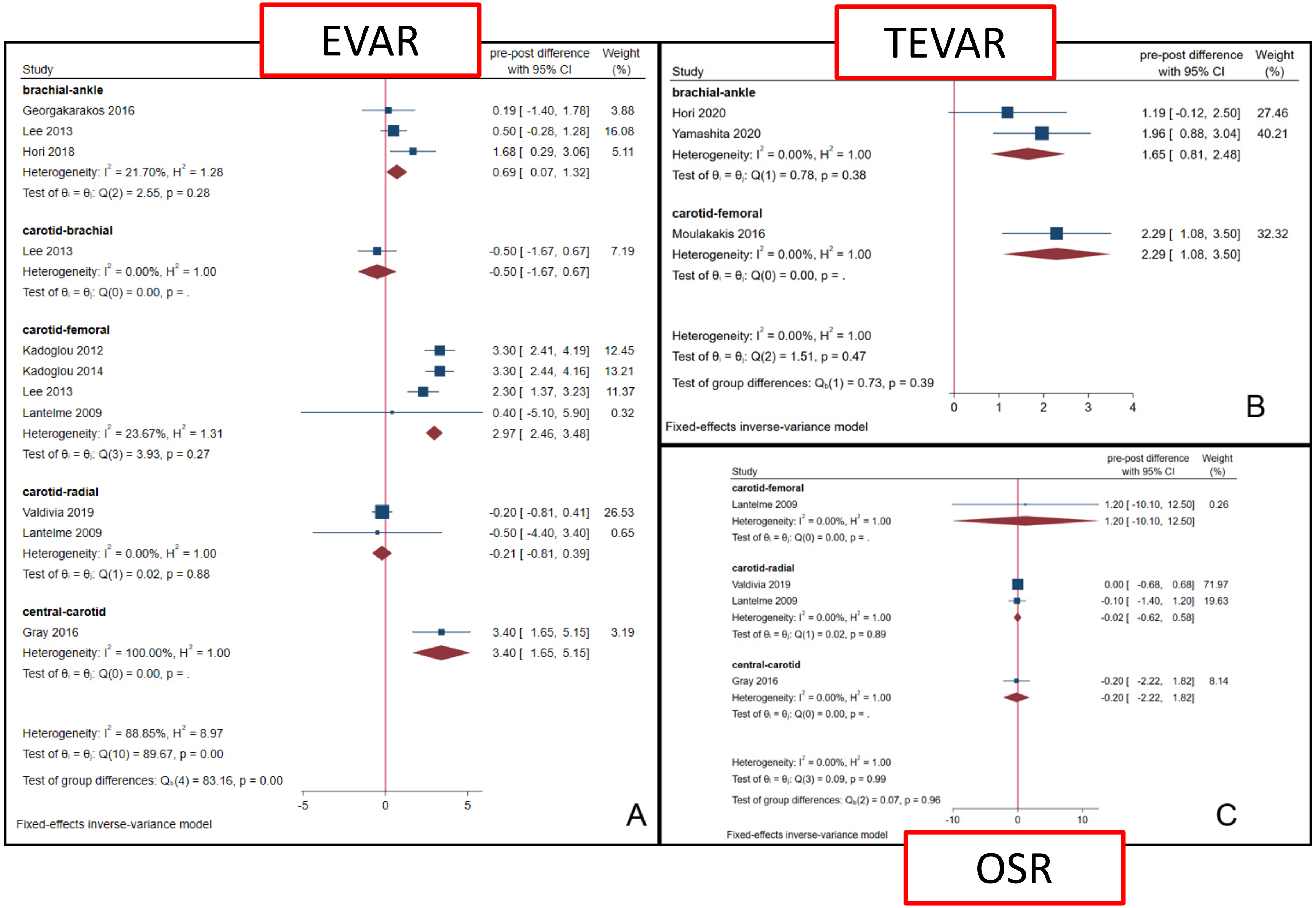
- 9 case-control studies
- 13 selected articles for meta-analysis

Modifications in Aortic Stiffness After Endovascular or Open Aortic Repair: A Systematic Review and Meta-Analysis

Daniele Bissacco [a], Michele Conti [b], Maurizio Domanin [a,c], Daniele Bianchi [b], Luigia Scudeller [d], Tim J. Mandigers [a], Sara Allievi [a], Ferdinando Auricchio [b], Santi Trimarchi [a,c,*]

Eur J Vasc Endovasc Surg (2022) 63, 567—577

Results


EVAR
Study
pre-post difference with 95% CI
Weight (%)
brachial-ankle
Georgakarakos 2016 0.19 [-1.40, 1.78] 3.88
Lee 2013 0.50 [-0.28, 1.28] 16.08
Hori 2018 1.68 [0.29, 3.06] 5.11
Heterogeneity: I² = 21.70%, H² = 1.28 0.69 [0.07, 1.32]
Test of θi = θj: Q(2) = 2.55, p = 0.28
carotid-brachial
Lee 2013 -0.50 [-1.67, 0.67] 7.19
Heterogeneity: I² = 0.00%, H² = 1.00 -0.50 [-1.67, 0.67]
Test of θi = θj: Q(0) = 0.00, p = .
carotid-femoral
Kadoglou 2012 3.30 [2.41, 4.19] 12.45
Kadoglou 2014 3.30 [2.44, 4.16] 13.21
Lee 2013 2.30 [1.37, 3.23] 11.37
Lantelme 2009 0.40 [-5.10, 5.90] 0.32
Heterogeneity: I² = 23.67%, H² = 1.31 2.97 [2.46, 3.48]
Test of θi = θj: Q(3) = 3.93, p = 0.27
carotid-radial
Valdivia 2019 -0.20 [-0.81, 0.41] 26.53
Lantelme 2009 -0.50 [-4.40, 3.40] 0.65
Heterogeneity: I² = 0.00%, H² = 1.00 -0.21 [-0.81, 0.39]
Test of θi = θj: Q(1) = 0.02, p = 0.88
central-carotid
Gray 2016 3.40 [1.65, 5.15] 3.19
Heterogeneity: I² = 100.00%, H² = 1.00 3.40 [1.65, 5.15]
Test of θi = θj: Q(0) = 0.00, p = .
Heterogeneity: I² = 88.85%, H² = 8.97
Test of θi = θj: Q(10) = 89.67, p = 0.00
Test of group differences: Qb(4) = 83.16, p = 0.00
-5
0
5
A
Fixed-effects inverse-variance model
TEVAR
Study
pre-post difference with 95% CI
Weight (%)
brachial-ankle
Hori 2020 1.19 [-0.12, 2.50] 27.46
Yamashita 2020 1.96 [0.88, 3.04] 40.21
Heterogeneity: I² = 0.00%, H² = 1.00 1.65 [0.81, 2.48]
Test of θi = θj: Q(1) = 0.78, p = 0.38
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Heterogeneity: I² = 0.00%, H² = 1.00 2.29 [1.08, 3.50]
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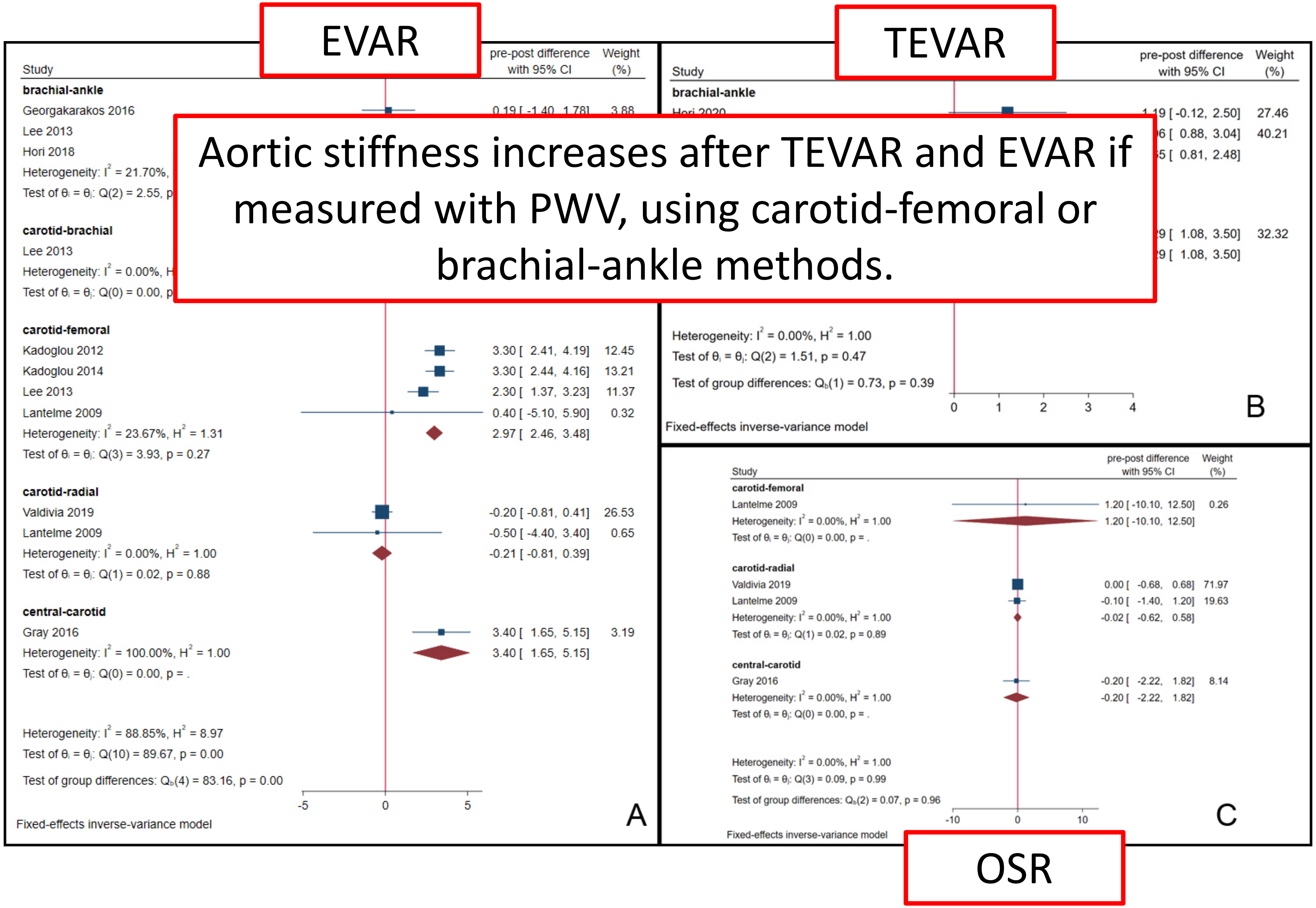
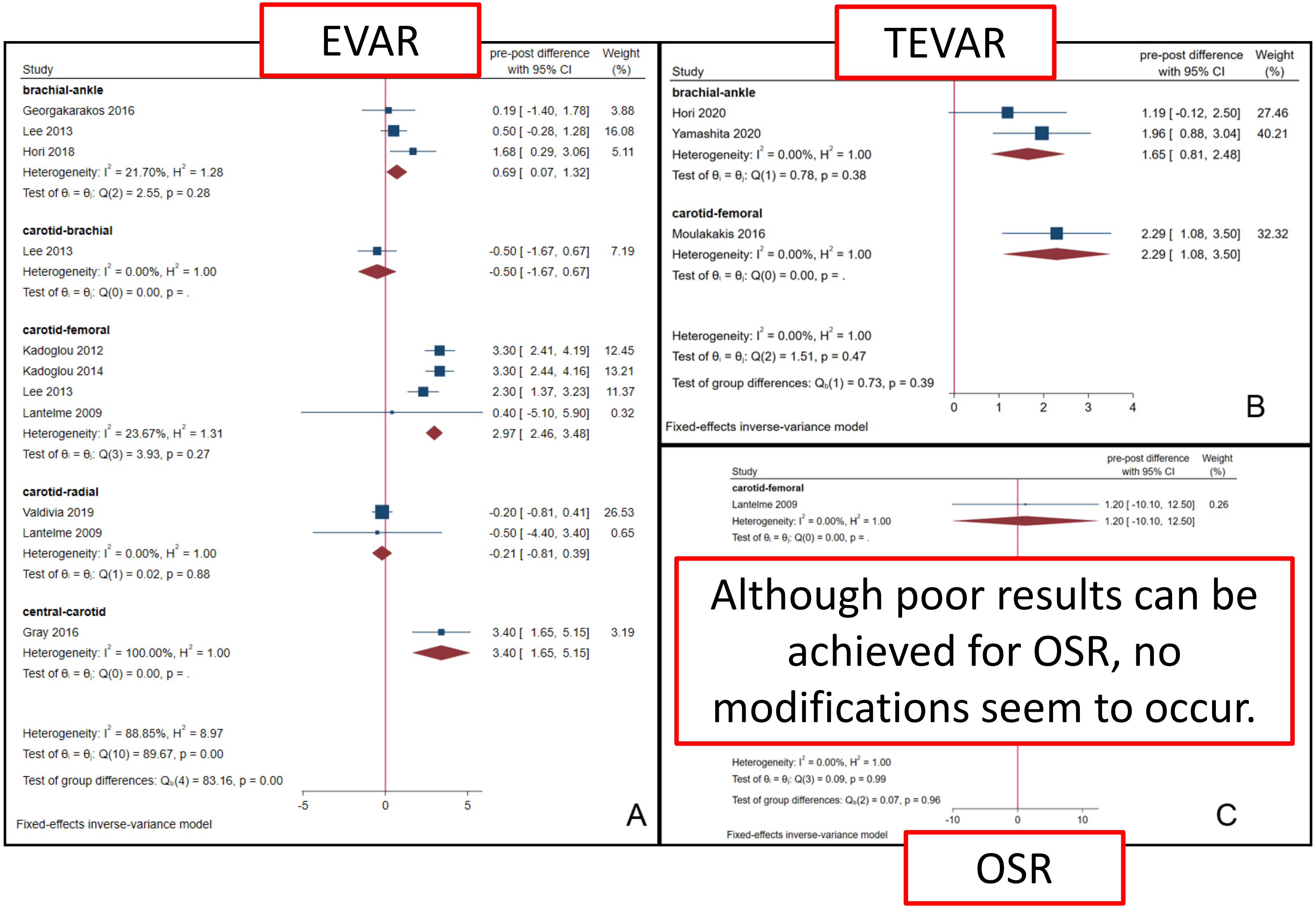
Heterogeneity: I² = 0.00%, H² = 1.00
Test of θi = θj: Q(2) = 1.51, p = 0.47
Test of group differences: Qb(1) = 0.73, p = 0.39
0
1
2
3
4
B
Fixed-effects inverse-variance model
Study
pre-post difference with 95% CI
Weight (%)
carotid-femoral
Lantelme 2009 1.20 [-10.10, 12.50] 0.26
Heterogeneity: I² = 0.00%, H² = 1.00 1.20 [-10.10, 12.50]
Test of θi = θj: Q(0) = 0.00, p = .
carotid-radial
Valdivia 2019 0.00 [-0.68, 0.68] 71.97
Lantelme 2009 -0.10 [-1.40, 1.20] 19.63
Heterogeneity: I² = 0.00%, H² = 1.00 -0.02 [-0.62, 0.58]
Test of θi = θj: Q(1) = 0.02, p = 0.89
central-carotid
Gray 2016 -0.20 [-2.22, 1.82] 8.14
Heterogeneity: I² = 0.00%, H² = 1.00 -0.20 [-2.22, 1.82]
Test of θi = θj: Q(0) = 0.00, p = .
Heterogeneity: I² = 0.00%, H² = 1.00
Test of θi = θj: Q(3) = 0.09, p = 0.99
Test of group differences: Qb(2) = 0.07, p = 0.96
-10
0
10
C
Fixed-effects inverse-variance model
OSR

Results



Aortic stiffness increases after TEVAR and EVAR if measured with PWV, using carotid-femoral or brachial-ankle methods.

Results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-5 0 5
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B
Fixed-effects inverse-variance model
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pre-post difference with 95% CI
Weight (%)
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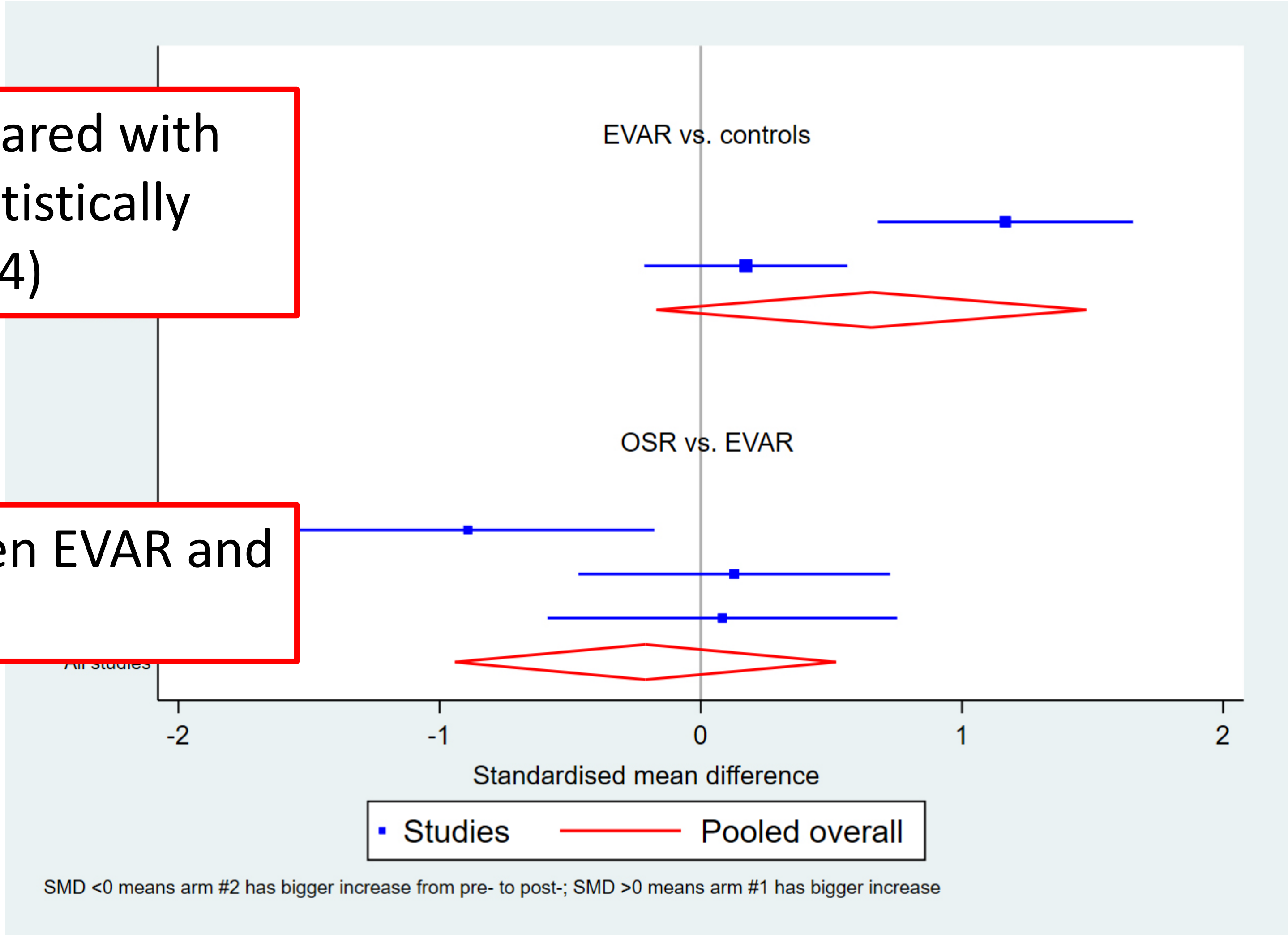
Heterogeneity: I² = 0.00%, H² = 1.00 1.20 [-10.10, 12.50]
Test of θi = θj: Q(0) = 0.00, p = .
Although poor results can be achieved for OSR, no modifications seem to occur.
Heterogeneity: I² = 0.00%, H² = 1.00
Test of θi = θj: Q(3) = 0.09, p = 0.99
Test of group differences: Qb(2) = 0.07, p = 0.96
-10 0 10
C
Fixed-effects inverse-variance model
OSR

Results

PWV after EVAR was higher if compared with controls, although this was not statistically significant (IC95% –0.05-0.94)

No differences were observed between EVAR and OSR



Results

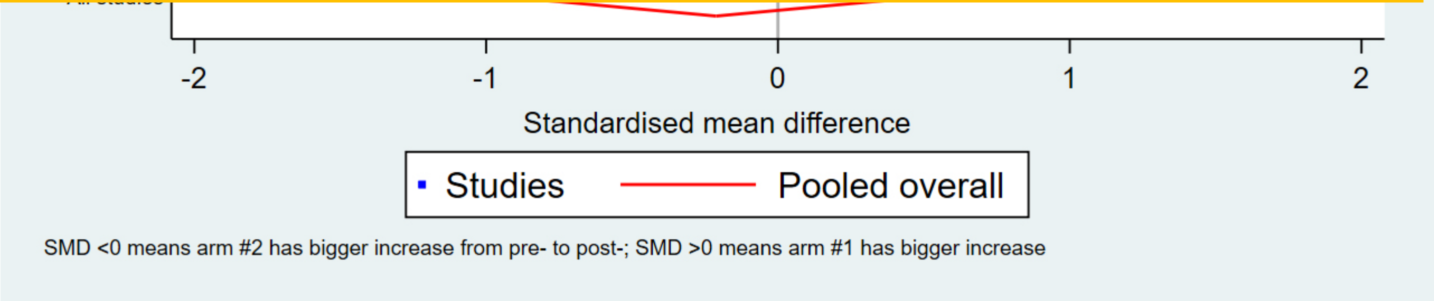
- **Both EVAR and TEVAR increase AoS**, while OSR does not modify the AoS

- However, no definitive conclusions can be made due to the wide range of AoS measurement modalities

- Further rigorous studies are needed to describe a valid protocol for level and unit of measure used to calculate AoS, analyzing long-term cardiovascular remodeling and complications, particularly in young patients

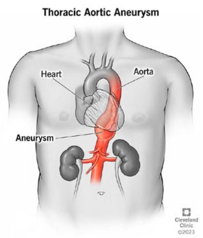
- In patients treated with endovascular aortic repair, careful lifelong follow-up evaluation should be recommended, not only to improve aortic-related but also cardiac-related outcomes.

- Device manufacturers should be encouraged to improve graft characteristics that mimic the native aorta, in terms of mechanical and fluid dynamic properties



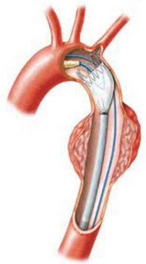
Aortic Stiffness in vivo - Studio Clinico in corso

Inizio



Arruolamento dei pazienti

Misurazione pre operatoria



Riparazione aortica endovascolare

Misurazione post-operatoria

Analisi dei dati

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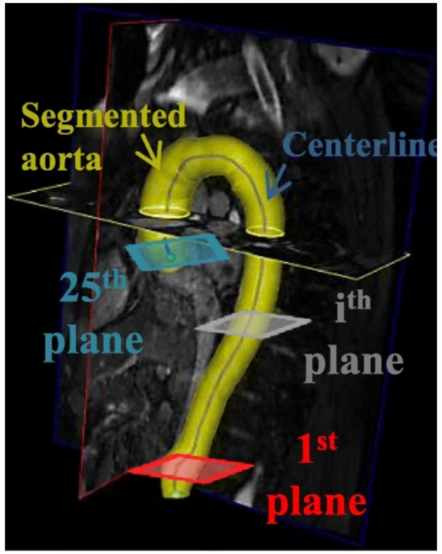
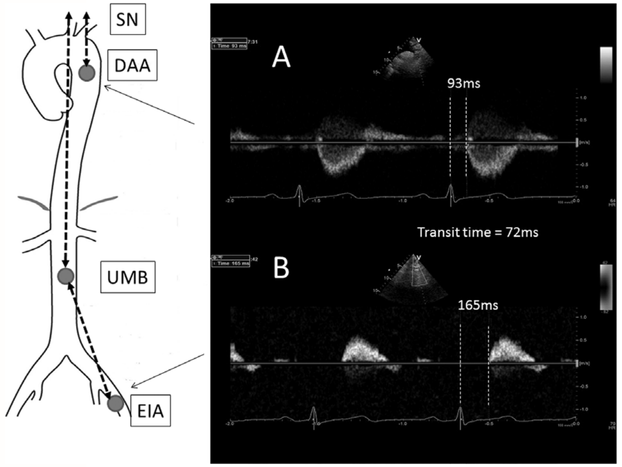
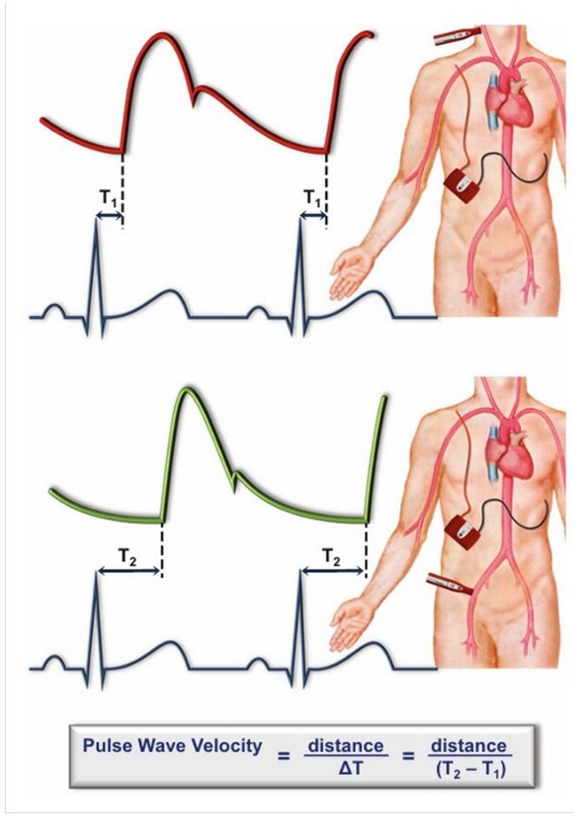
Misurazione della PWV come surrogato della Stiffness Aortica prima e dopo trattamento aortico endovascolare



2D MRI – 4D-flow MRI



Ultrasonografia Doppler



PulsePen

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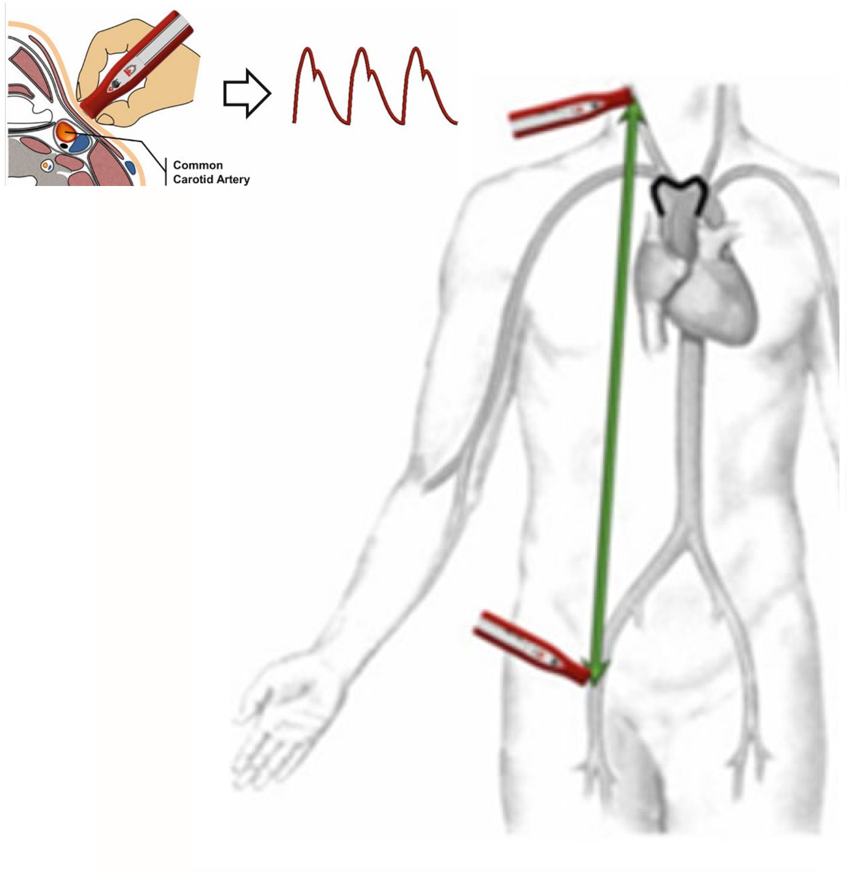
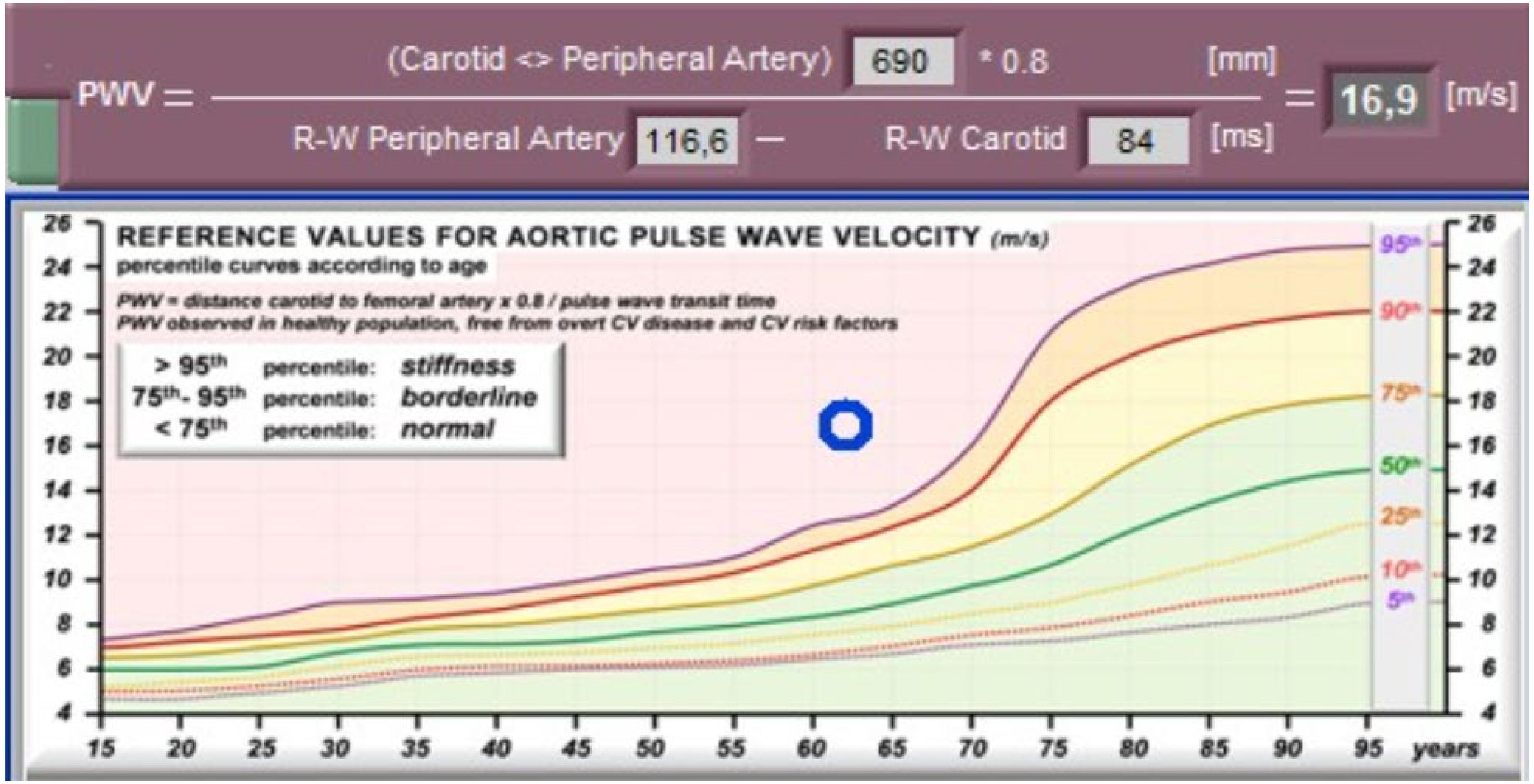
C - F PWV = distanza carotido femorale / DT





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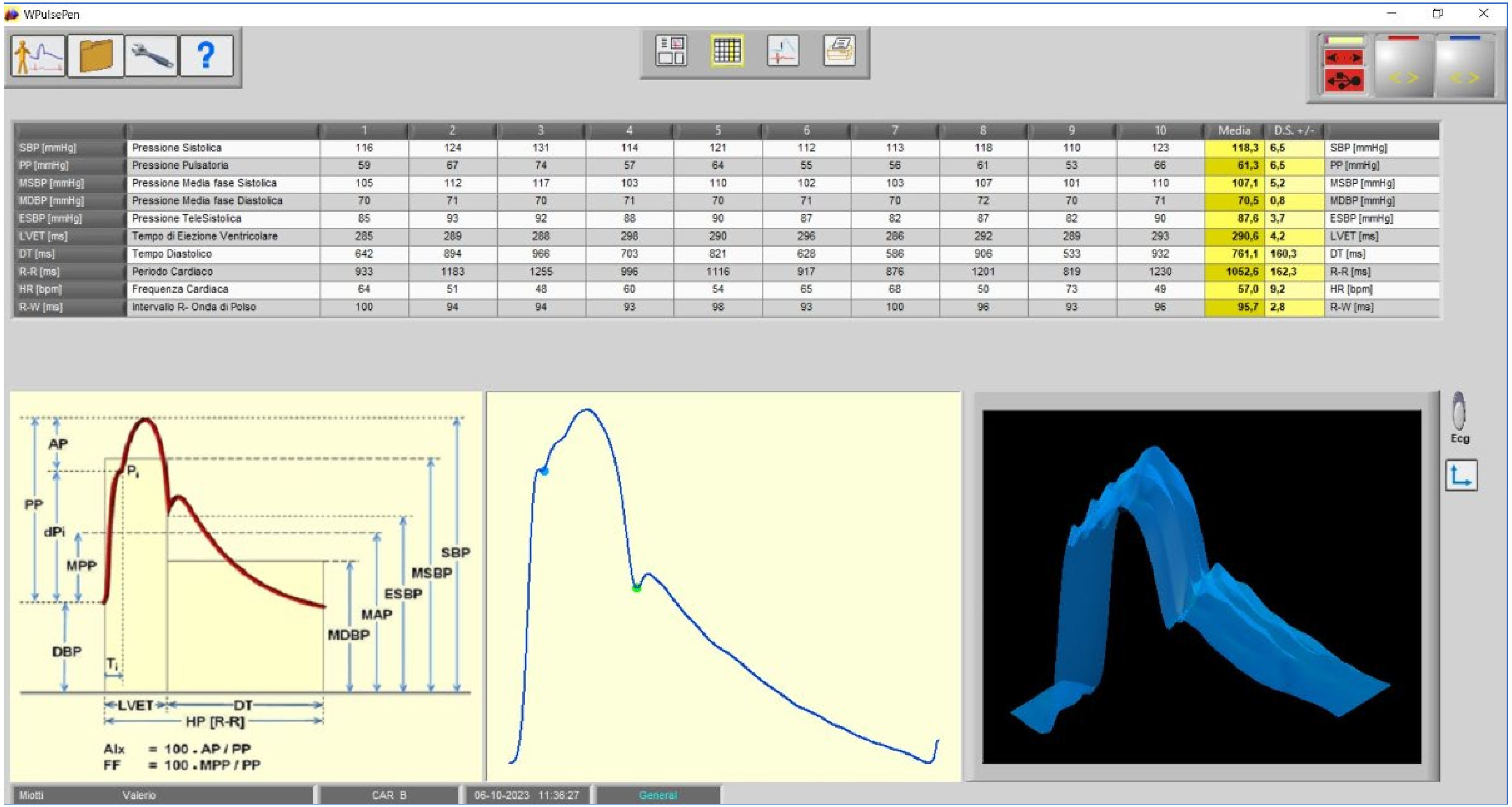
Selezione delle onde sfigmiche

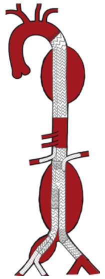


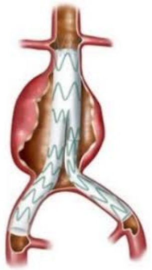
		1	2	3	4	5	6	7	8	9	10	Media	D.S. +/-	
SBP [mmHg]	Pressione Sistolica	116	124	131	114	121	112	113	118	110	123	118,3	6,5	SBP [mmHg]
PP [mmHg]	Pressione Pulsatoria	59	67	74	57	64	55	56	61	53	66	61,3	6,5	PP [mmHg]
MSBP [mmHg]	Pressione Media fase Sistolica	105	112	117	103	110	102	103	107	101	110	107,1	5,2	MSBP [mmHg]
MDBP [mmHg]	Pressione Media fase Diastolica	70	71	70	71	70	71	70	72	70	71	70,5	0,8	MDBP [mmHg]
ESBP [mmHg]	Pressione TeleSistolica	85	93	92	88	90	87	82	87	82	90	87,6	3,7	ESBP [mmHg]
LVET [ms]	Tempo di Eiezione Ventricolare	285	289	288	298	290	296	286	292	289	293	290,6	4,2	LVET [ms]
DT [ms]	Tempo Diastolico	642	894	966	703	821	628	586	906	533	932	761,1	160,3	DT [ms]
R-R [ms]	Periodo Cardiaco	933	1183	1255	996	1116	917	876	1201	819	1230	1052,6	162,3	R-R [ms]
HR [bpm]	Frequenza Cardiaca	64	51	48	60	54	65	68	50	73	49	57,0	9,2	HR [bpm]
R-W [ms]	Intervallo R- Onda di Polso	100	94	94	93	98	93	100	96	93	96	95,7	2,8	R-W [ms]

Aortic Stiffness in vivo - Studio Clinico in corso

Risultati preliminary su 28 pz

Attualmente arruolati 60 pt



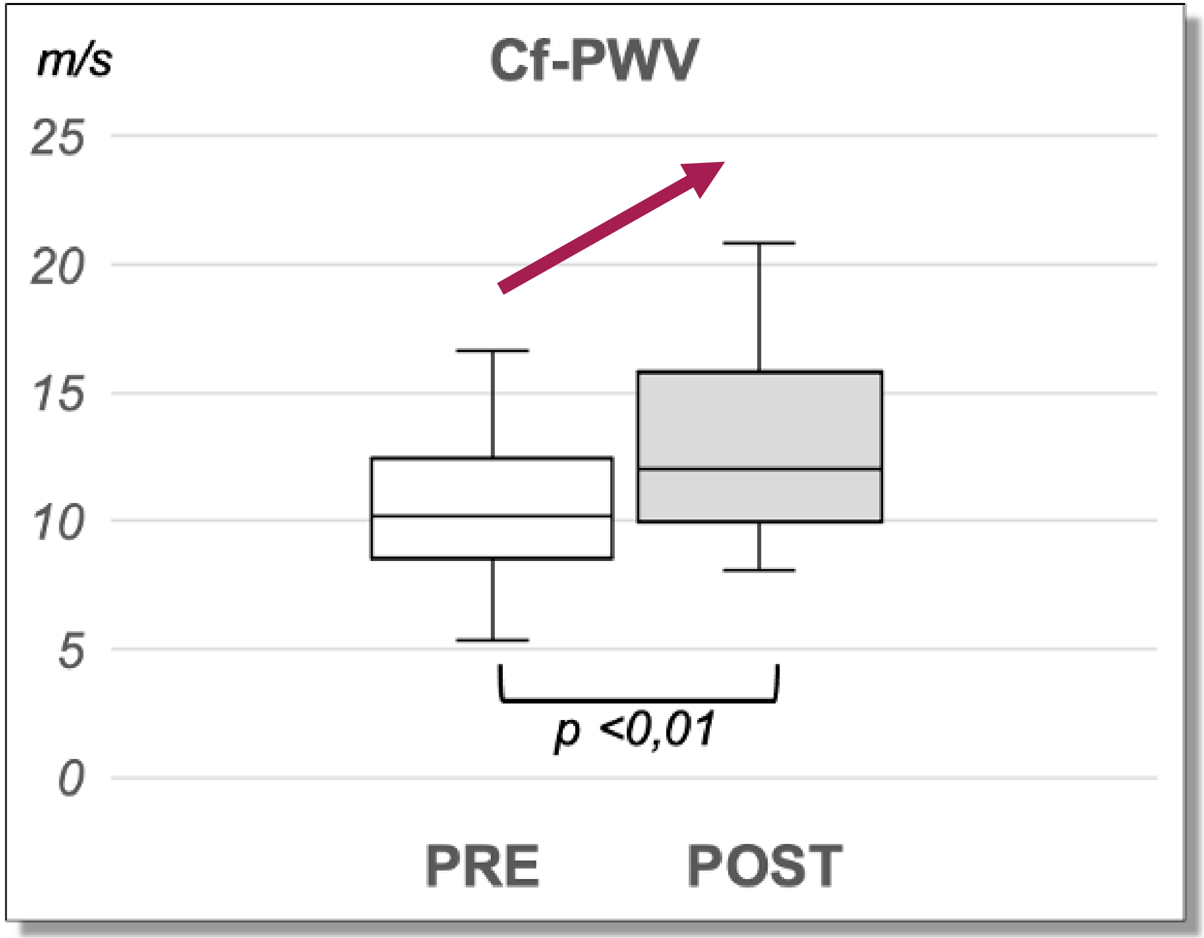


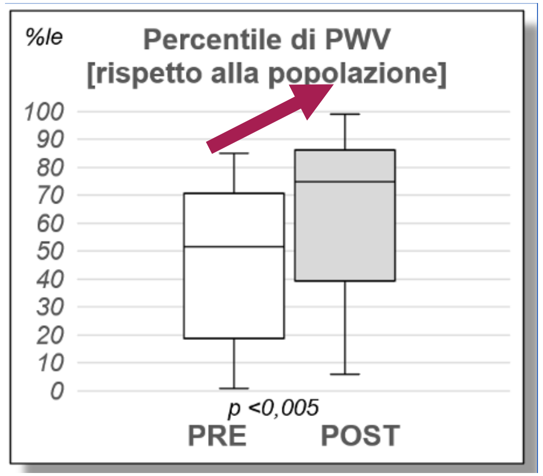
Parametri	Tutti	TEVAR	EVAR
n	28	10	18
M	22	7	15
F	6	3	3
≥ 65 aa	22	6	15
< 65 aa	6	4	3

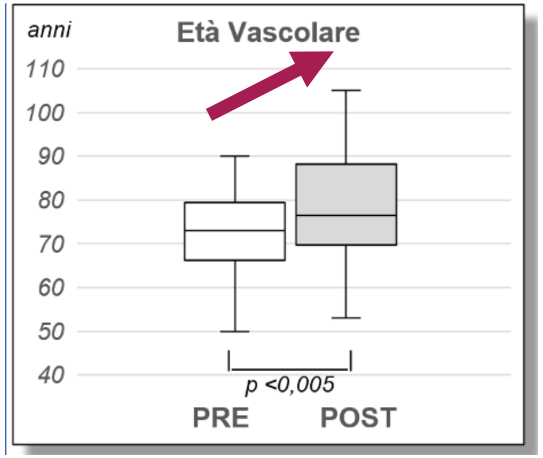
Aortic Stiffness in vivo - Studio Clinico in corso

Risultati

Pulse Wave Velocity Carotido-Femorale (Cf-PWV)



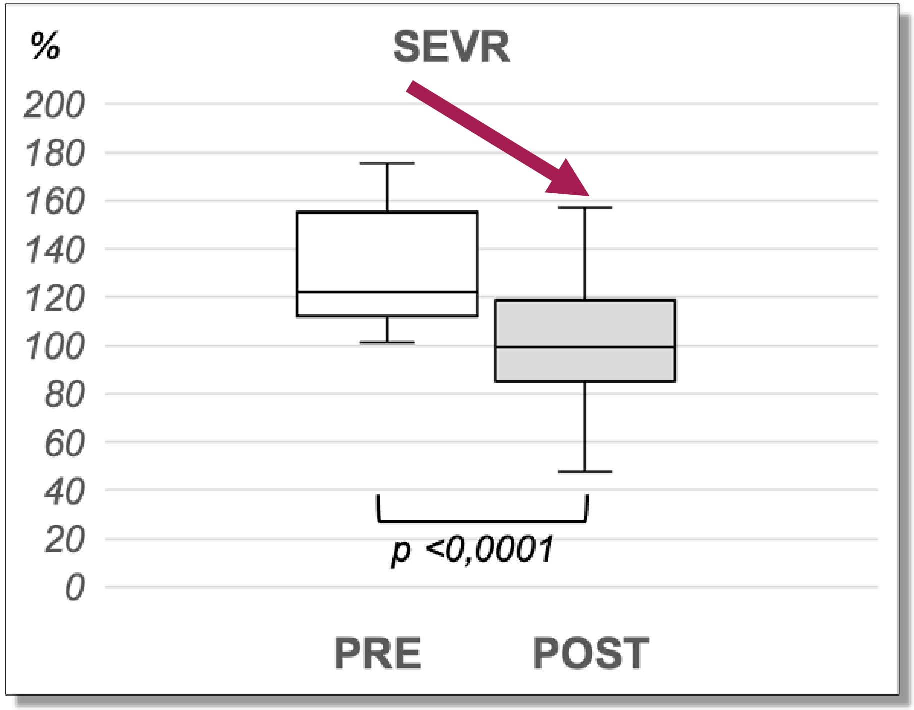


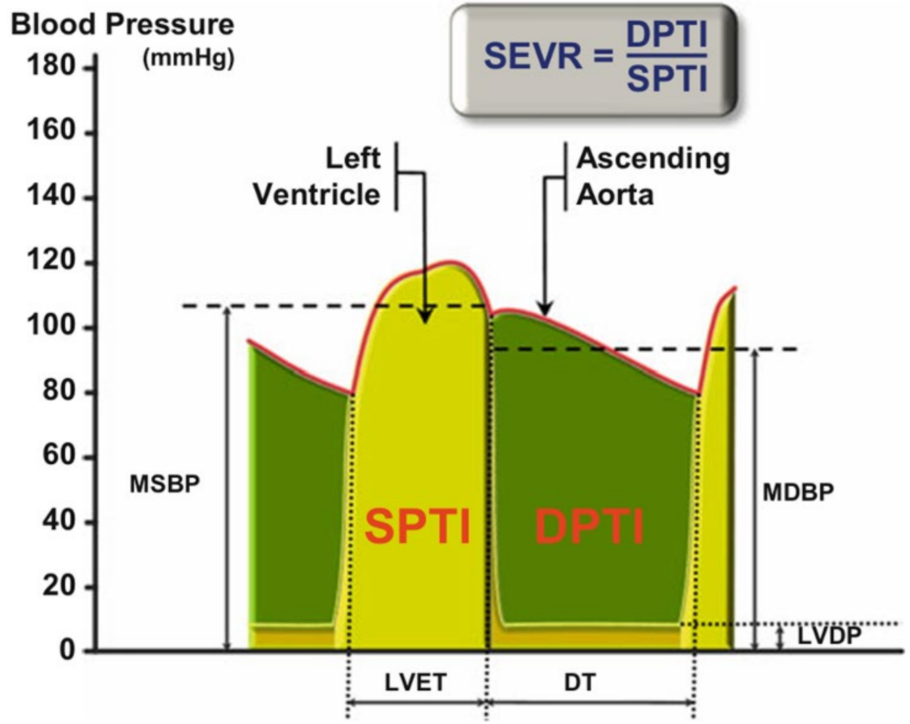


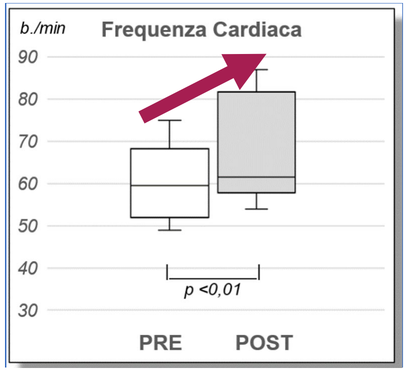
Aortic Stiffness in vivo - Studio Clinico in corso

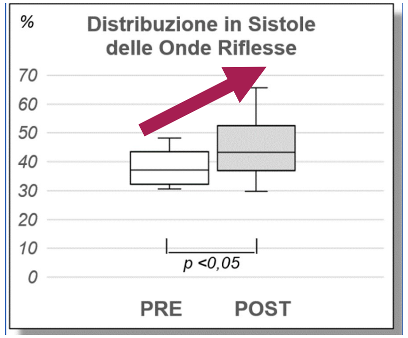
Risultati

Subendocardial Viability Ratio SEVR – Indice di Buckberg







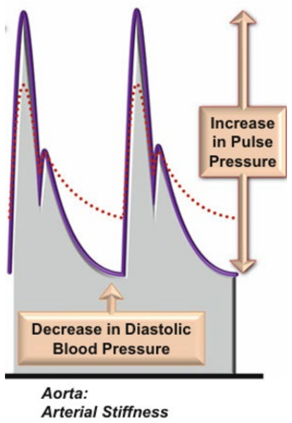


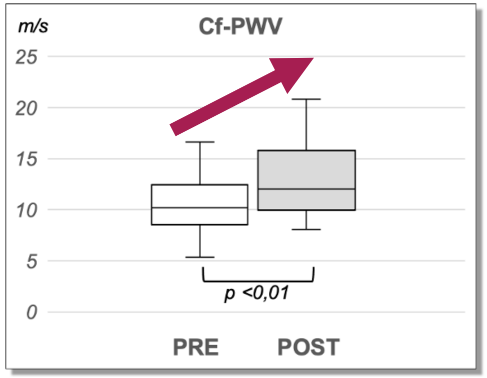
Aortic Stiffness in vivo - Studio Clinico in corso

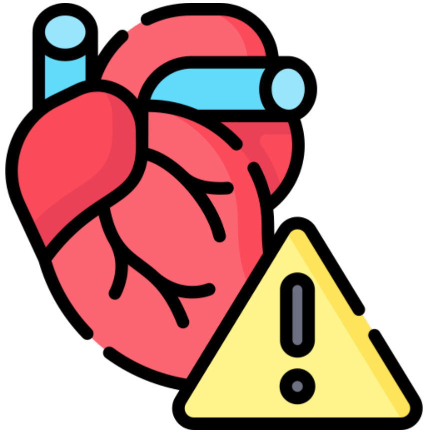
Risultati

Parametro	PREoperatorio	POSToperatorio	P value
FC (bpm)	61,3 ± 8,5	69,3 ± 12,2	< 0,001 ***
DT (ms)	691,7 ± 125	596,9 ± 142	< 0,001 ***
R-R (ms)	998 ± 144	894 ± 163	< 0,001 ***
Peak T (ms)	209,4 ± 30	173 ± 41	< 0,0001 ****
Ti	107,9 ± 24,7	92,8 ± 28	< 0,05 *
bT	258,7 ± 21,4	239,6 ± 23,3	< 0,001 ***
fWS/fW (%)	66,2 ± 6,3	70,6 ± 6,9	<0,01 **
fWD/fW (%)	33,8 ± 5,2	29,4 ± 3,7	<0,01 **
bWS/bW (%)	38,9 ± 3,1	43,2 ± 4,9	< 0,05 *
bWD/bW (%)	61,1 ± 6,1	56 ± 8,2	< 0,05 *
SySlope (mmHg/ms)	0,7 ± 0,3	0,9 ± 0,3	< 0,05 *
LVDP (mmHg)	14,8 ± 3,8	13,8 ± 6,4	< 0,001 ***

Aortic Stiffness in vivo - Studio Clinico in corso







↑ Aortic Stiffness

↑ PWV ↓ SEVR

↑ Rischio CV

Future directions

Hypertension effects before and after TEVAR implantation are clear, therefore a strict systolic blood pressure control is necessary for all patients. New follow up protocols should be performed for:

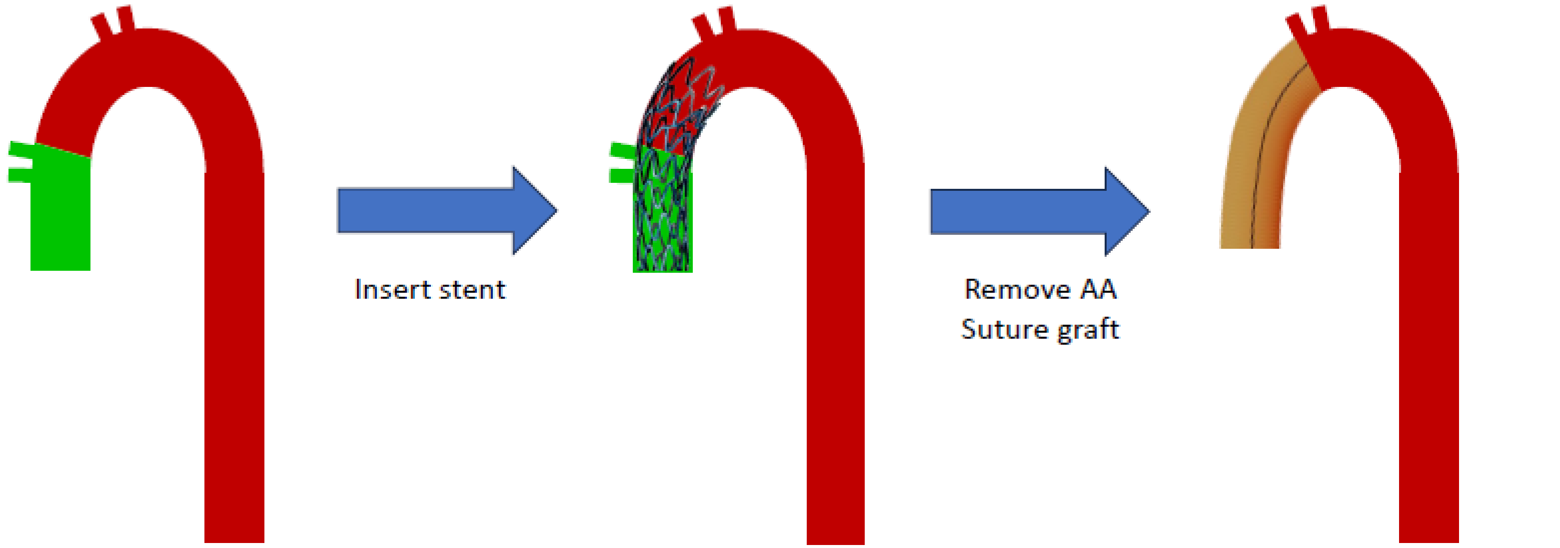
TEVAR reduces mortality, pressure control reduces long term morbidity

Ex-vivo model: aortic stiffness

How will treatment of the ascending aorta impact the aortic stiffness?

aTEVAR vs Open Surgical replacement with Dacron

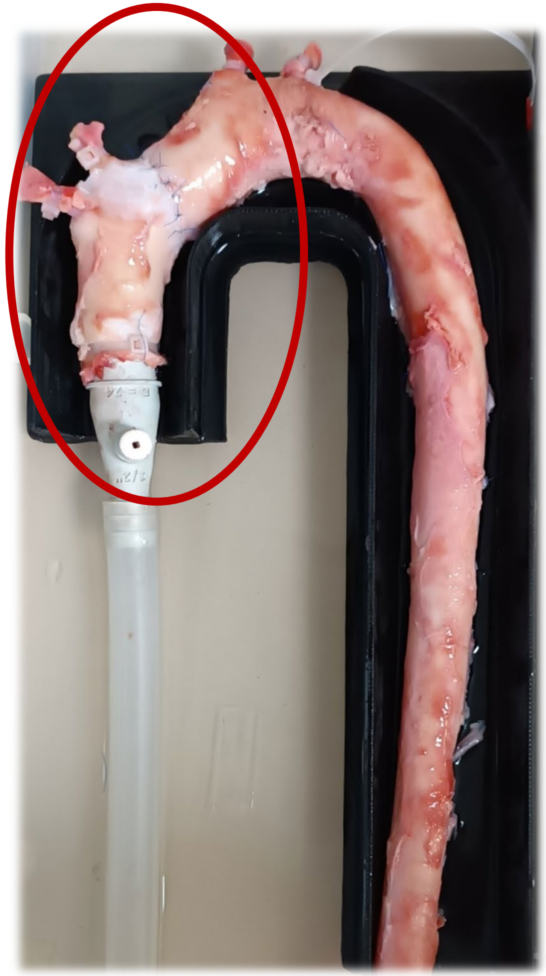
Experimental protocol overview



Set flow at 4-5 L/min (baseline)
Set pressure at 120/80 mmHg
→ Measure PWV

Set same flow as baseline
→ Measure pressure
→ Measure PWV

Set same flow as baseline
→ Measure pressure
→ Measure PWV



Ex-vivo model: aortic stiffness

Main issue:

- Porcine aorta is very short

Solution #1

Solution #2

Ex-vivo model: aortic stiffness

Validation of Ascending Aorta model:

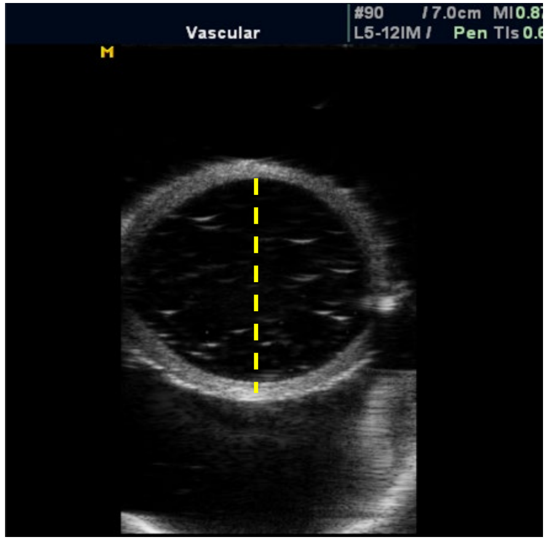
- Measure diameter with static echo along the centerline at landmarks
- Measure total model length with photo

Ex-vivo model: aortic stiffness

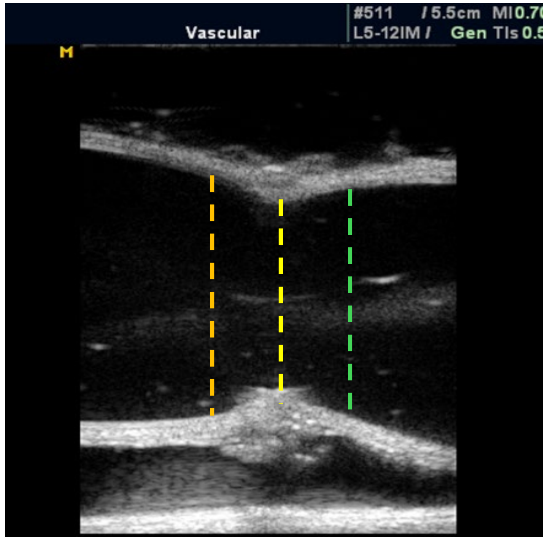
Validation of Ascending Aorta model:

- Measure diameter with static echo along the centerline at landmarks
- Measure total model length with photo

Axial image



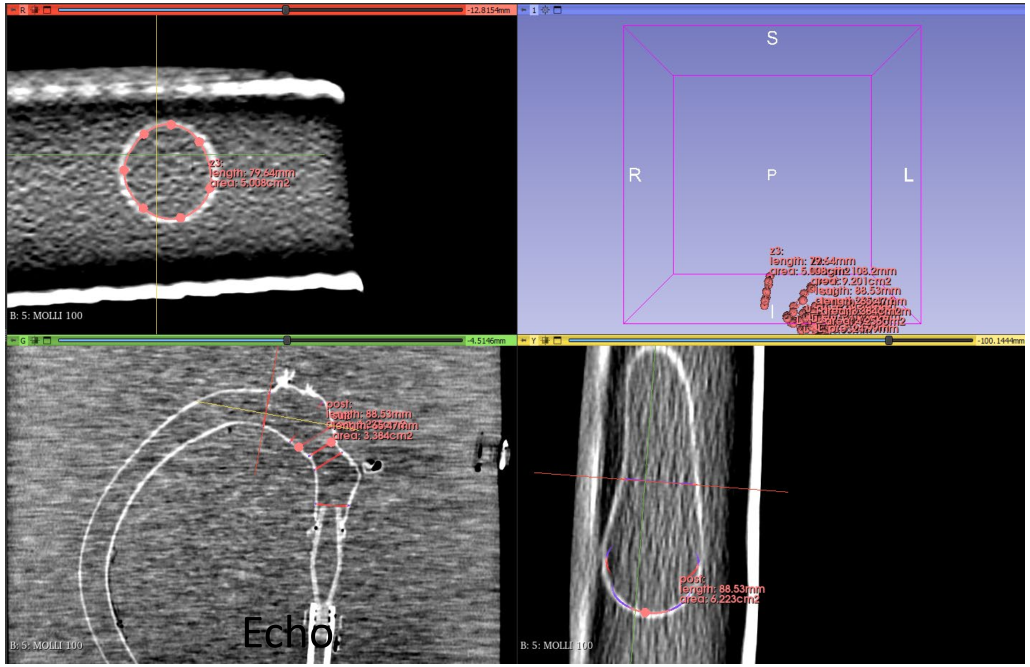
Longitudinal image

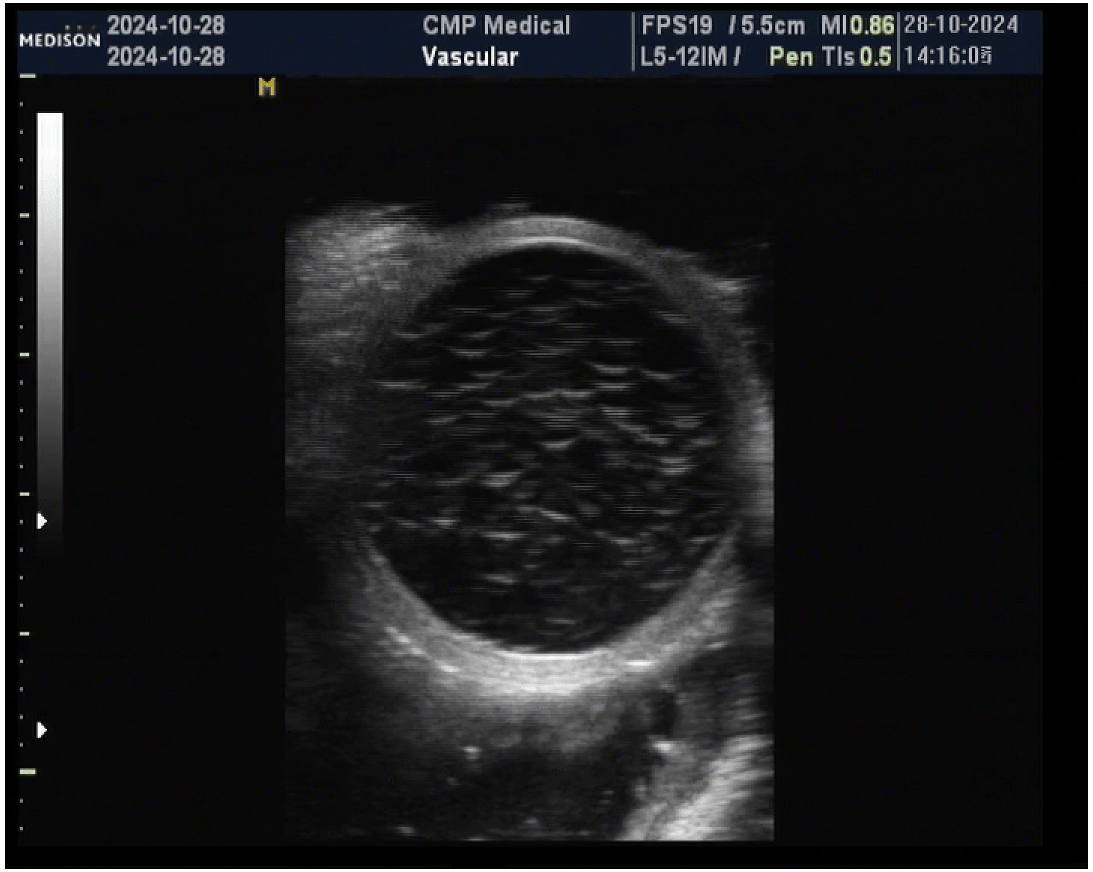


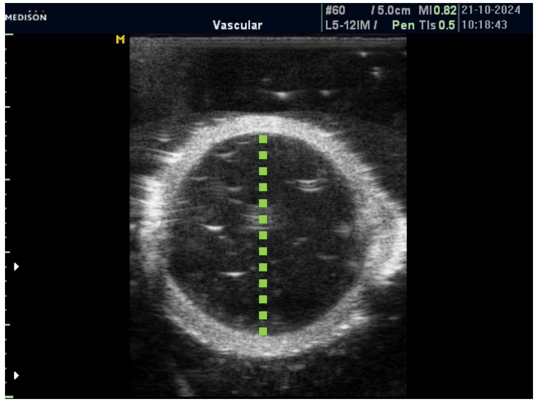
Ex-vivo model: aortic stiffness

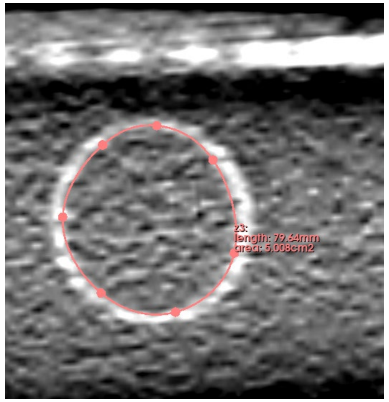
Validation of Ascending Aorta Model:

- For 1 model, we did Echo and CT at 80, 100, 120 mmHg (continuous flow)
- Mean error between echo and CT: 0.82 ± 0.71 mm (3.18 ± 2.54 %)









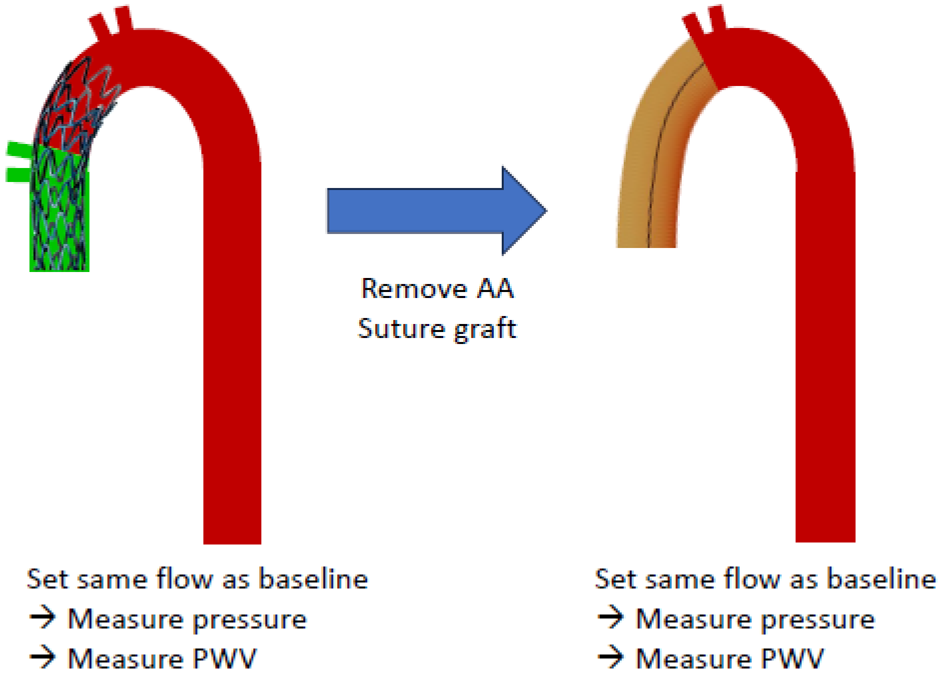
Ex-vivo model: aortic stiffness

Future work:

- Do baseline measures with a pulsatile flow

- Deploy stent-graft in ascending aorta
- Repeat measurements

- Remove ascending aorta + stent-graft
- Suture Dacron graft place
- Repeat measurements



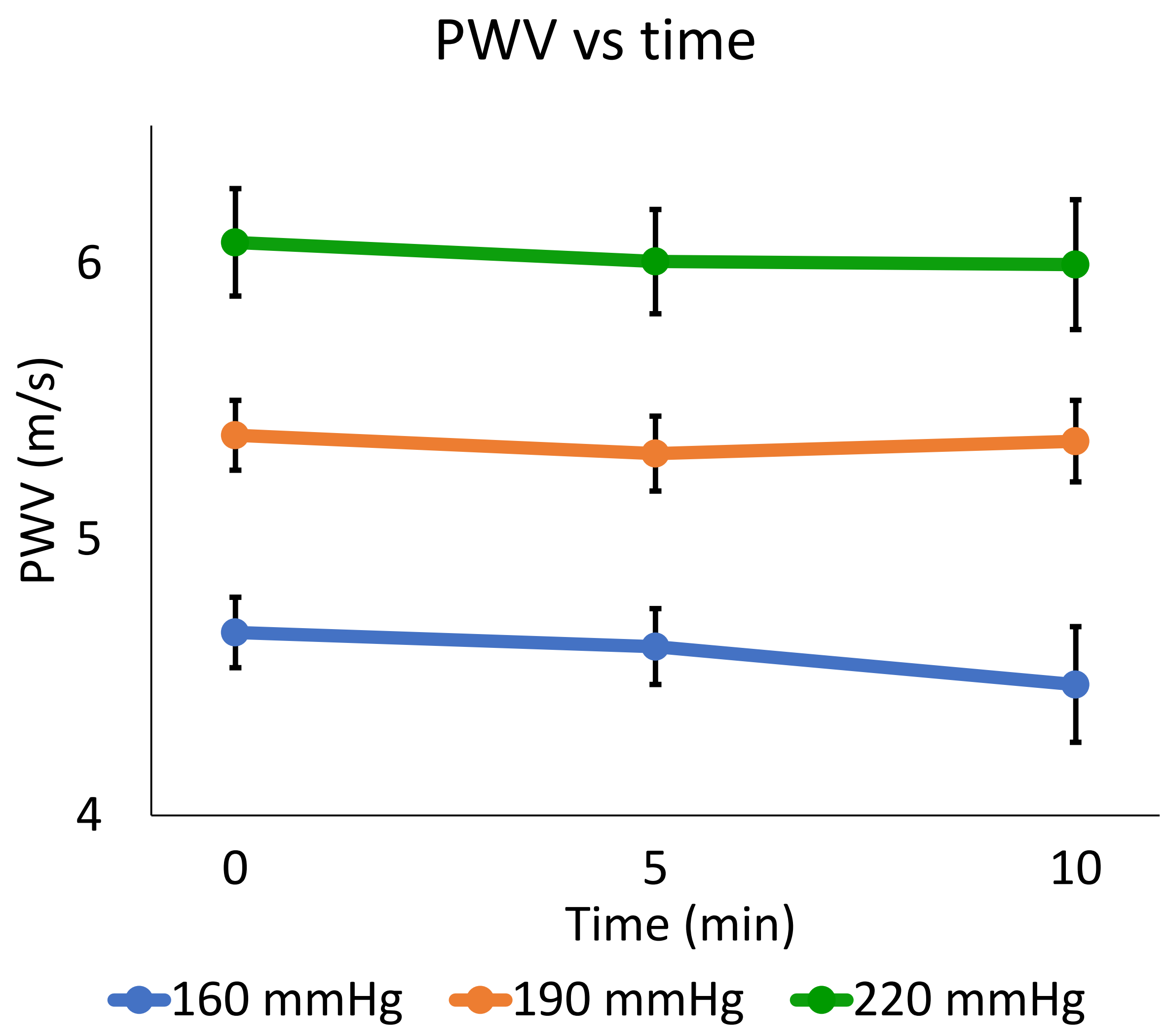
Ex-vivo model: aortic stiffness

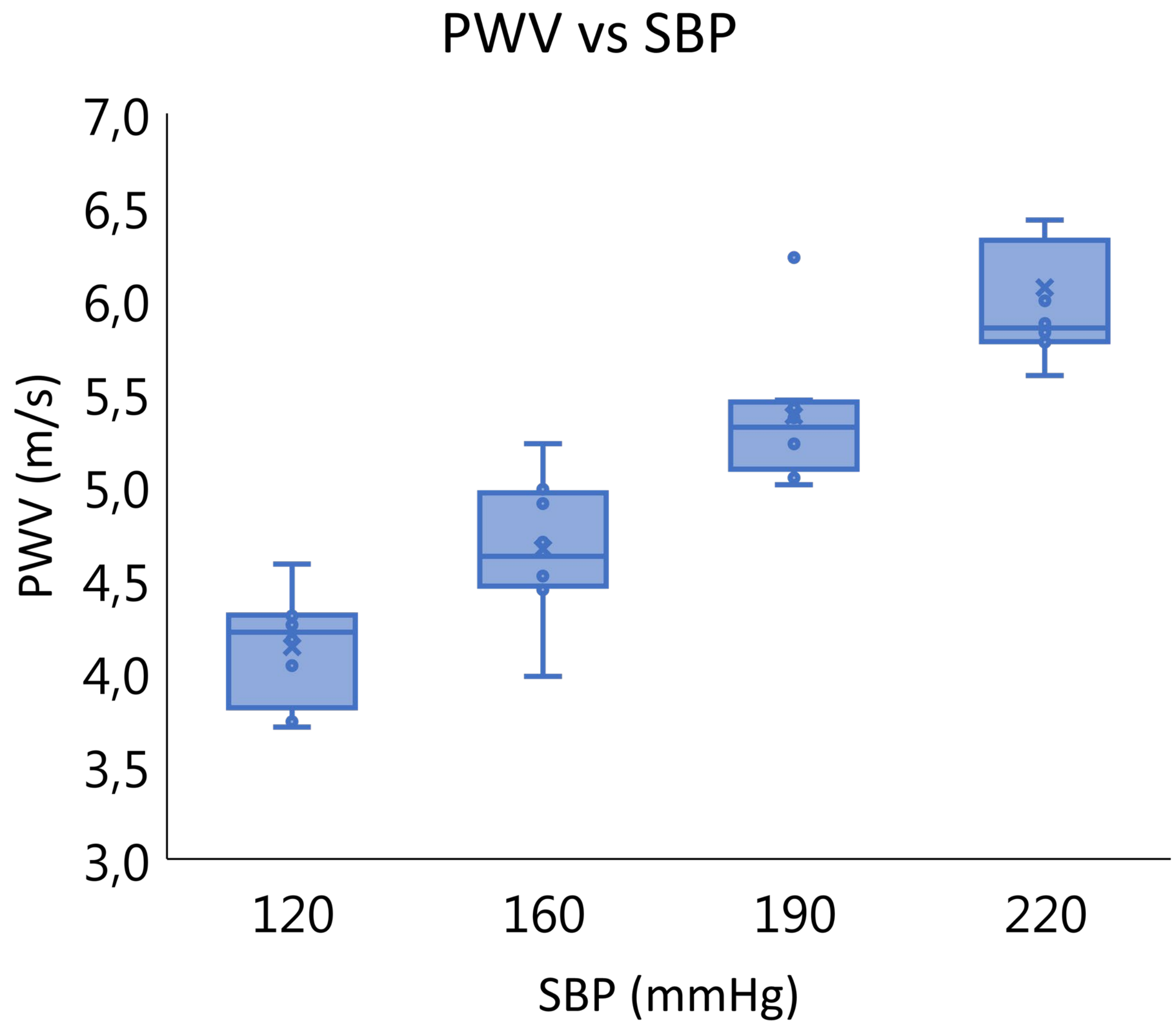
Hypertension and stiffness

- Goal: To study the relationship between hypertensive peaks and stiffness ex-vivo
- Experimental protocol:
  - N = 8 pig aortas
  - Acquisition of baseline at 5 L/min, 120/80 mmHg
  - Acquisition of 3 hypertensive levels:
    - SBP: 160 mmHg, 190 mmHg, 220 mmHg
  - Each SBP level was kept for 10 minutes
    - Acquisition at: 0 min, 5 min, 10 min

Ex-vivo model: aortic stiffness

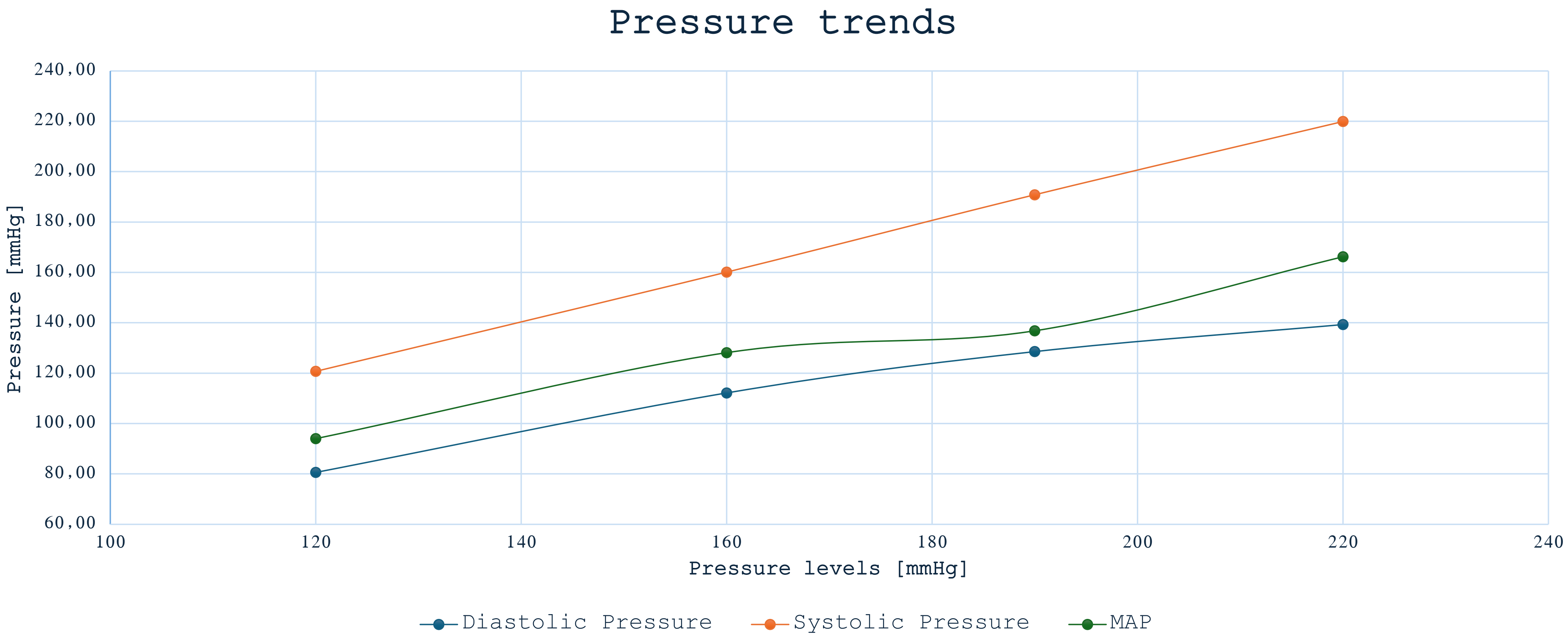
Results





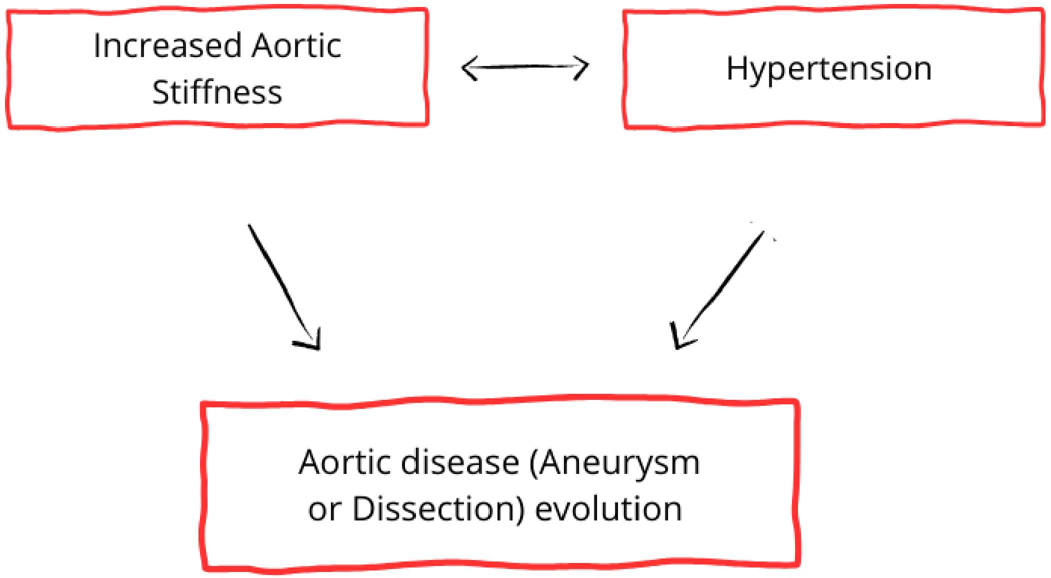
Ex-vivo model: aortic stiffness

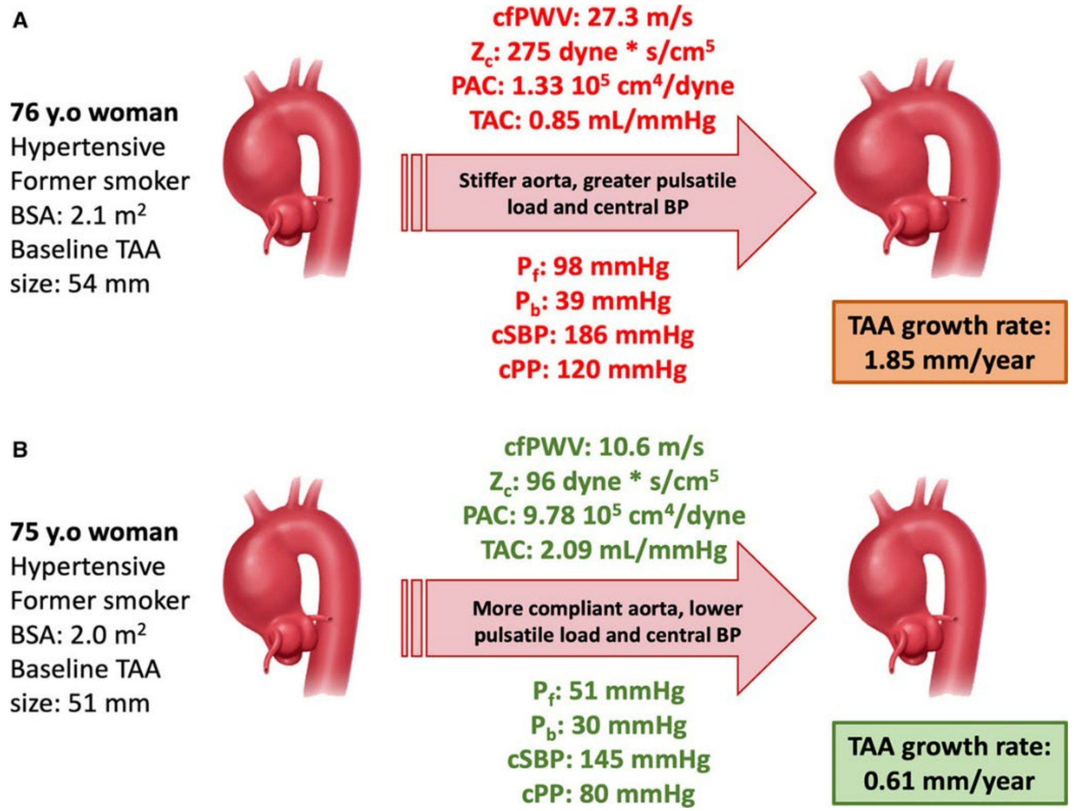
Results



Ex-vivo model: aortic stiffness

Hypertension increases stiffness and stiffness increases aortic disease evolution



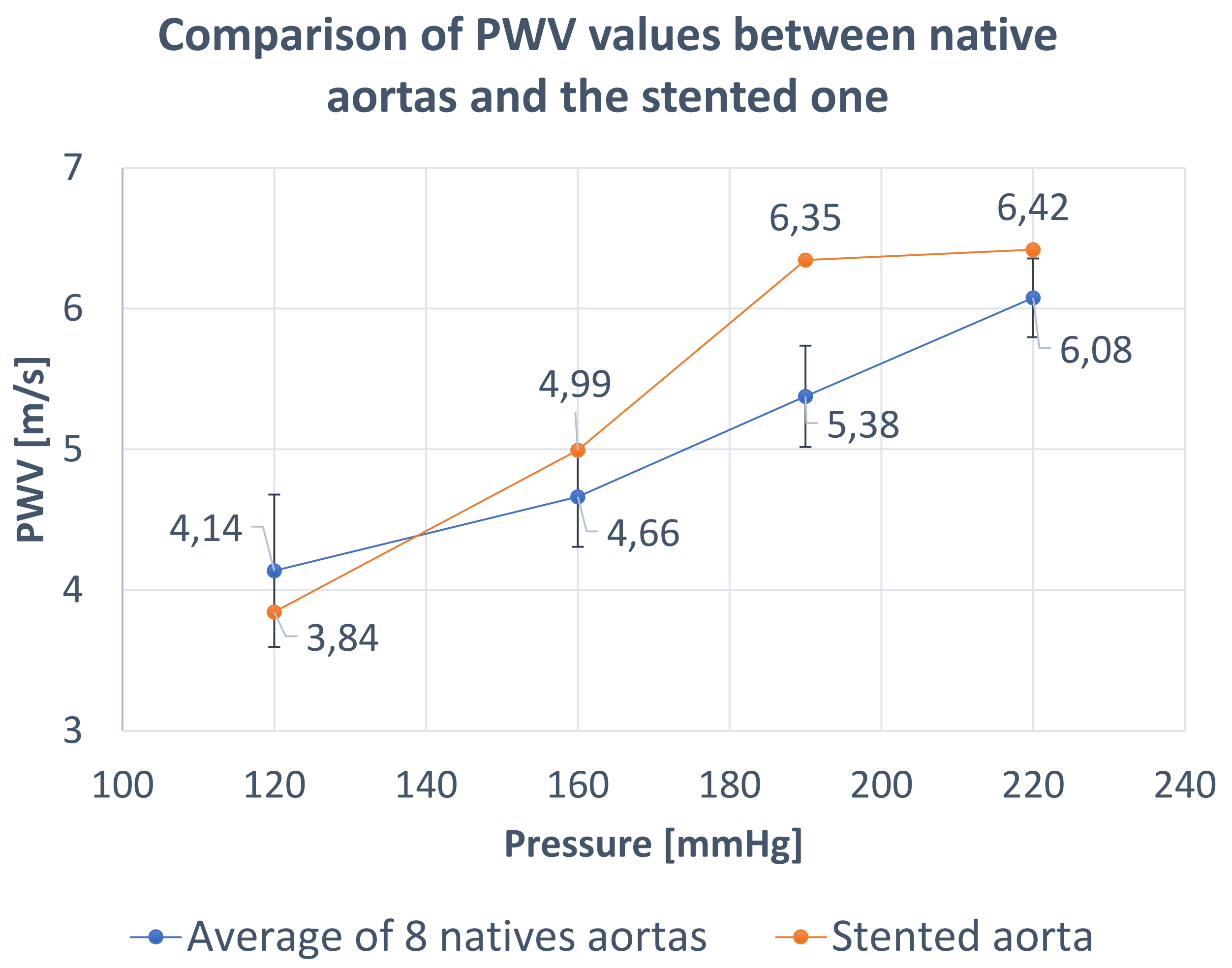


(Boczar et al., 2021)

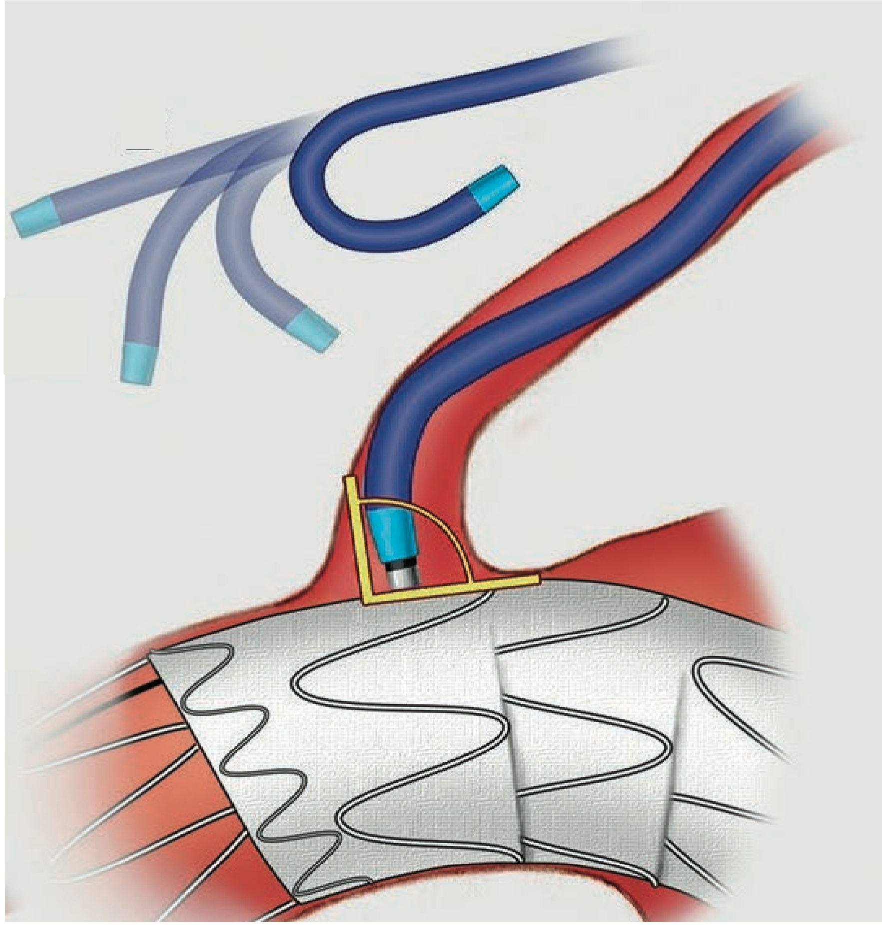
Ex-vivo model: aortic stiffness

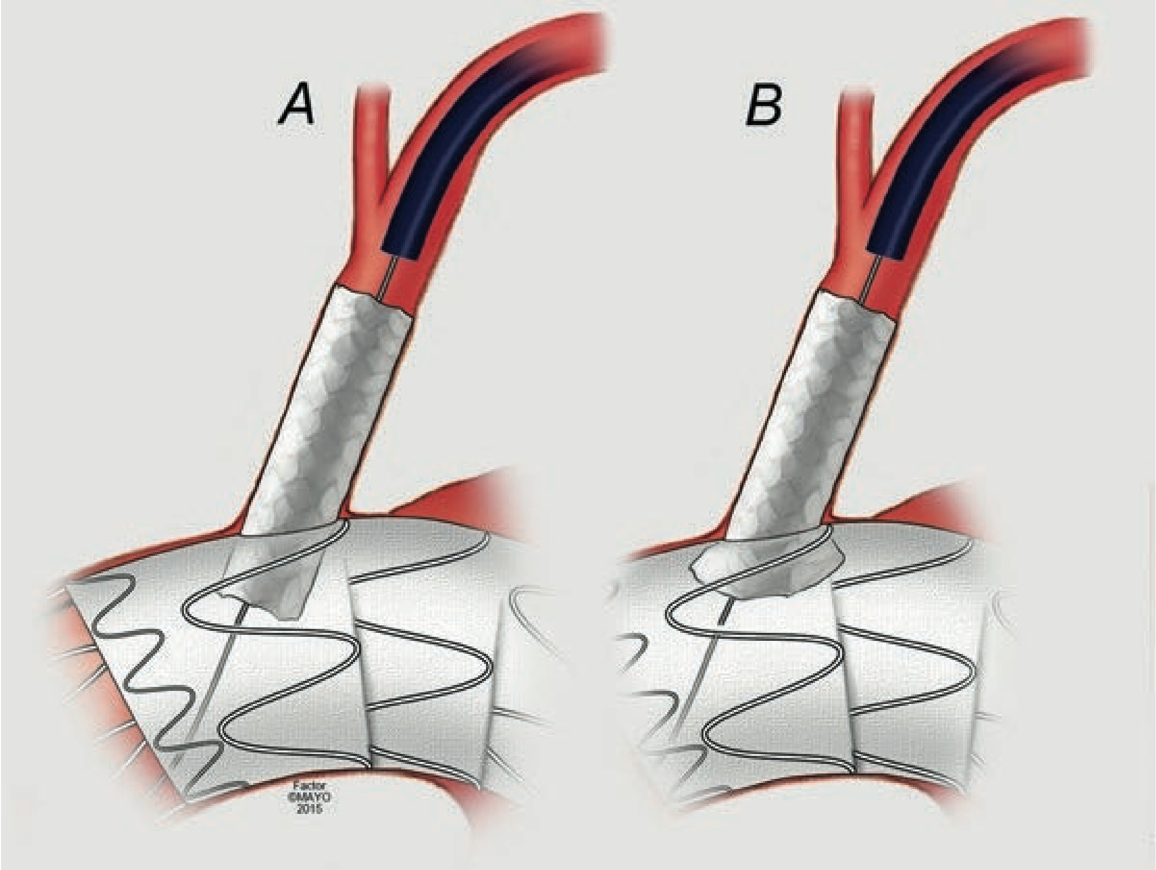
Relationship between Hypertension and TEVAR

- Uncontrolled hypertension after TEVAR is associated with increased risk of adverse events, as endoleaks. (Li et al. 2023).



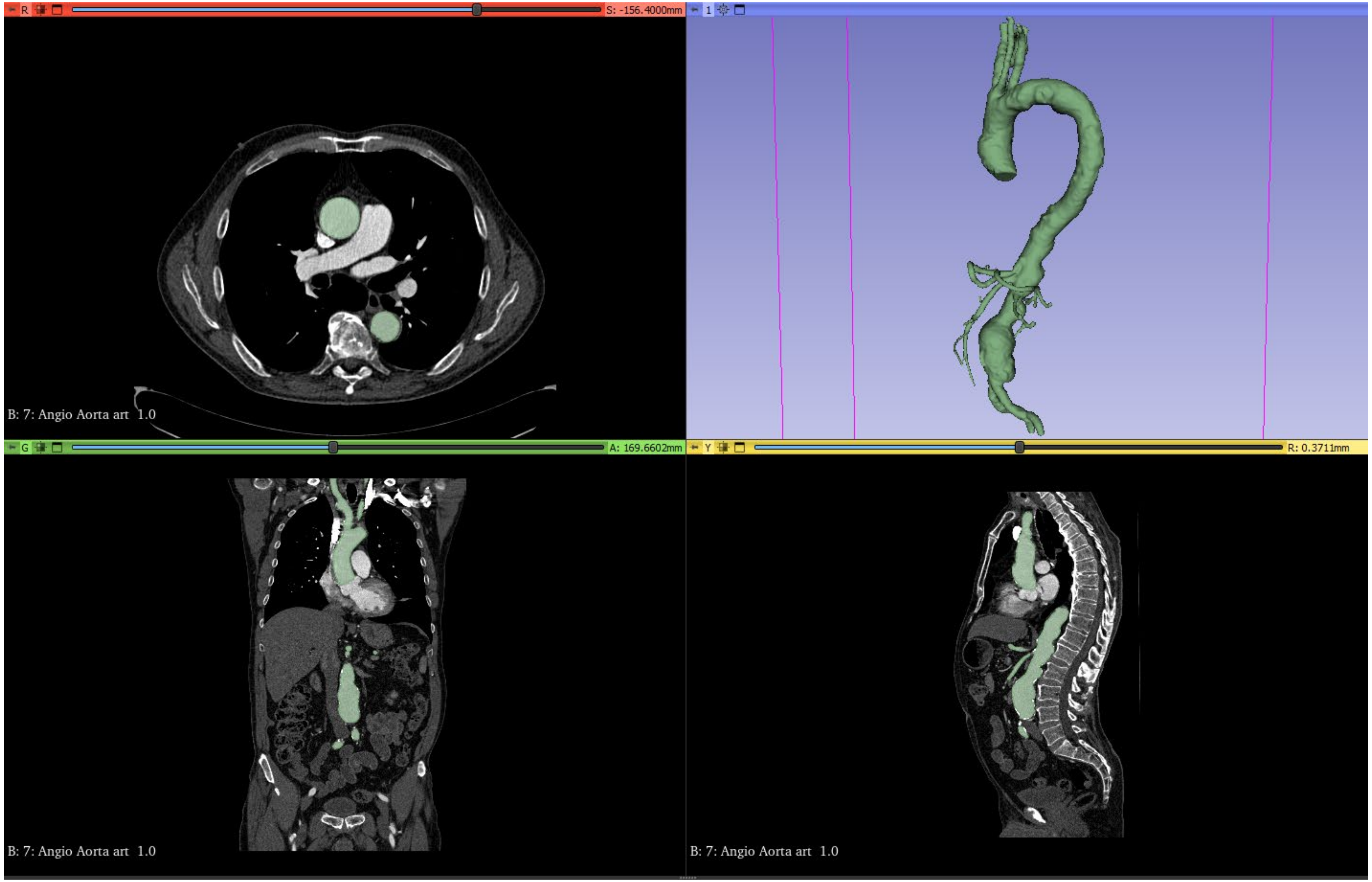
Ankura prosthesis





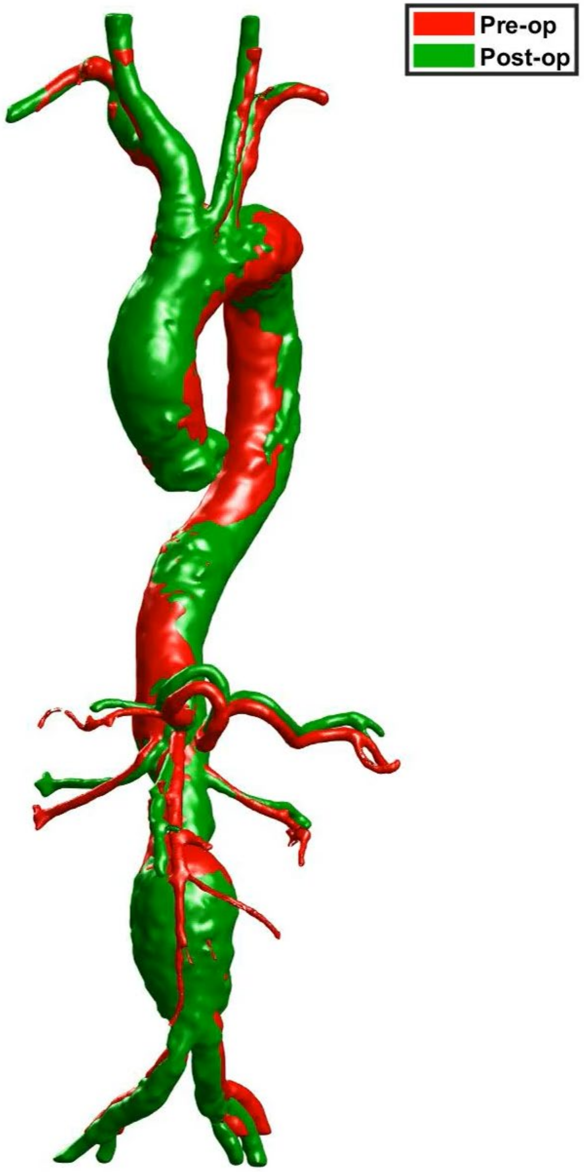
Images courtesy of:

Example patient

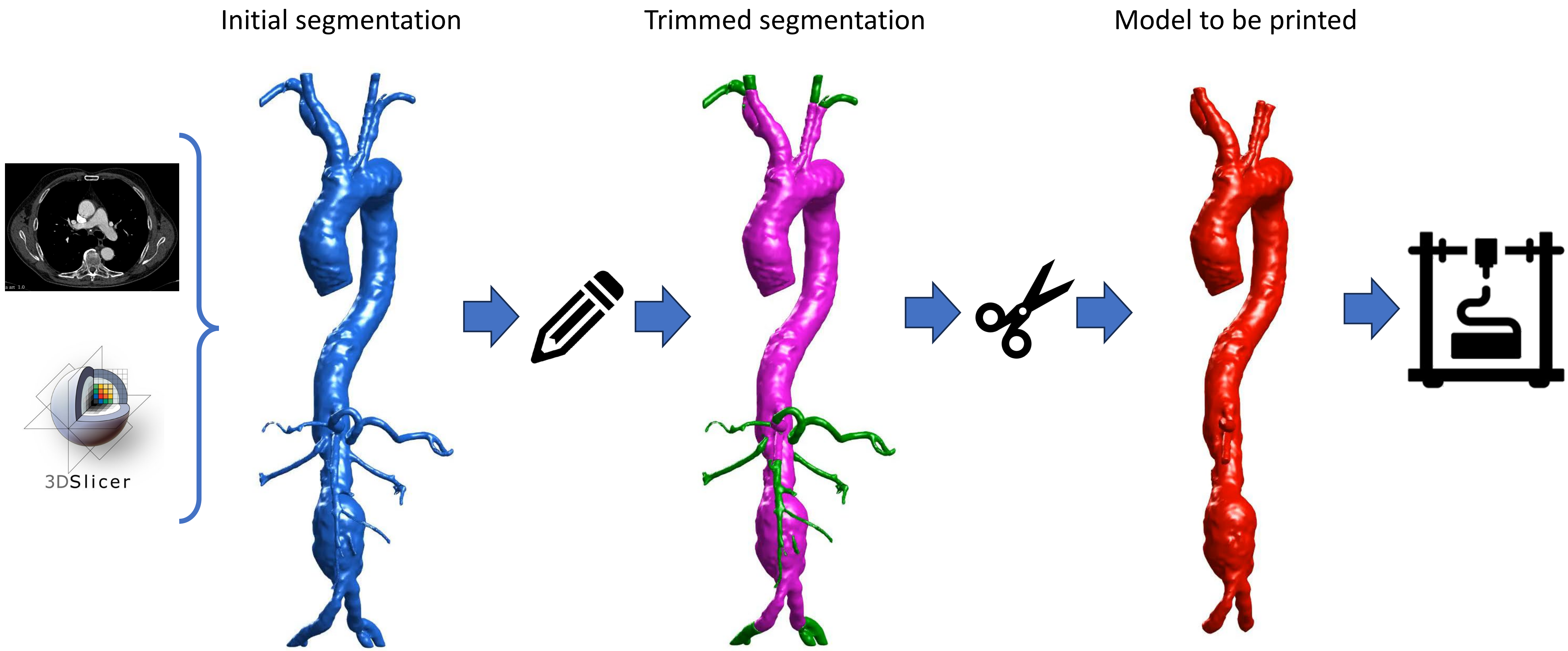


Pre and post procedure

- Slight increase of arch radius of curvature
- No significant geometrical changes



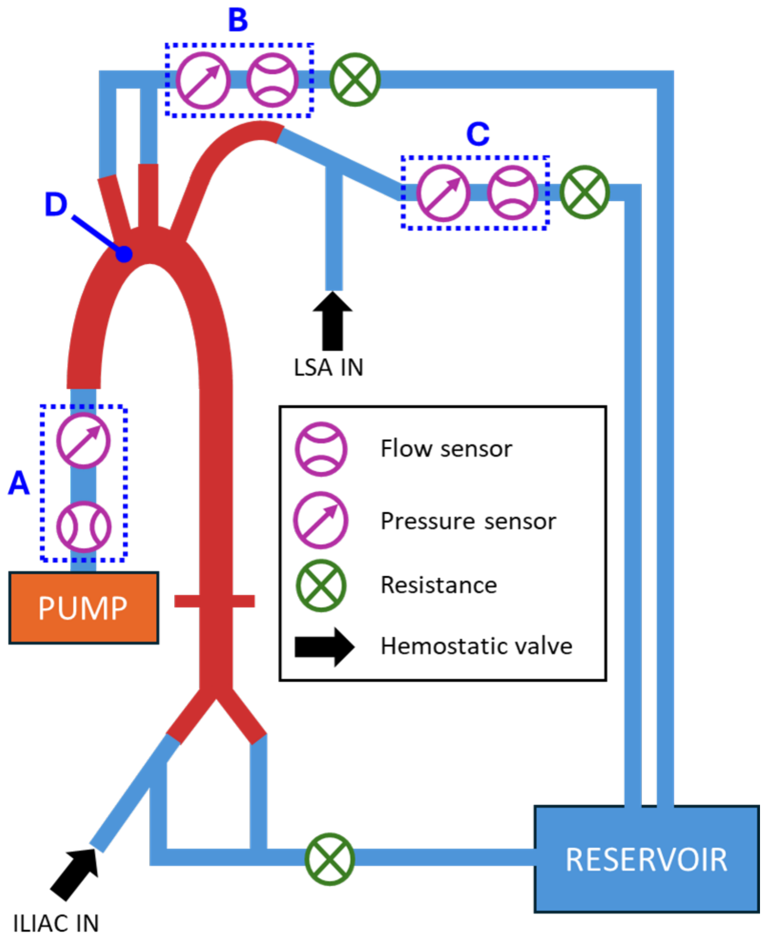
Model post-processing

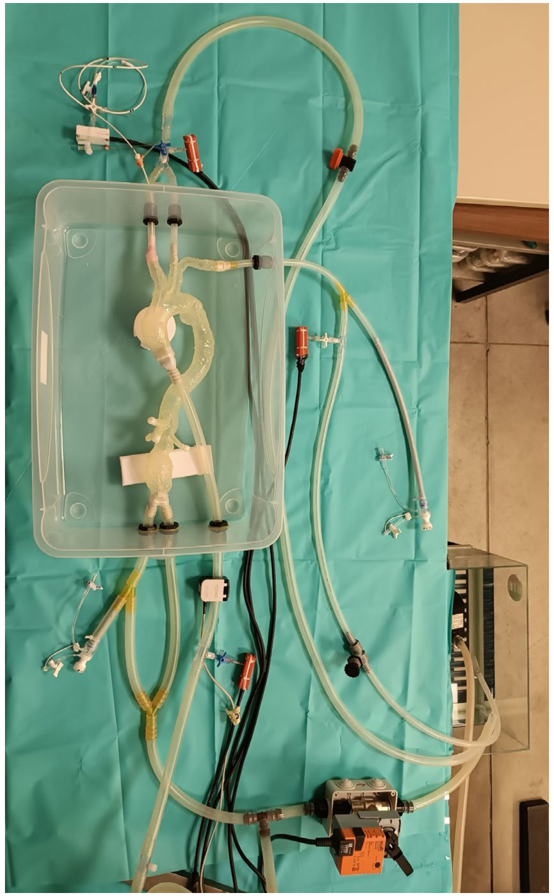


Ankura Overview

Protocol review
- Pulsatile regime, cardiac output: ~5 L/min
- Pulse pressure: ~40 mmHg *
- Flow split: 20% to supra-aortic branches

Clinical outcomes
- Does LSA perfusion change?
- Does the flow split change?
- Does cardiac output change?
- Does aortic pressure change?
- Does the geometry change?

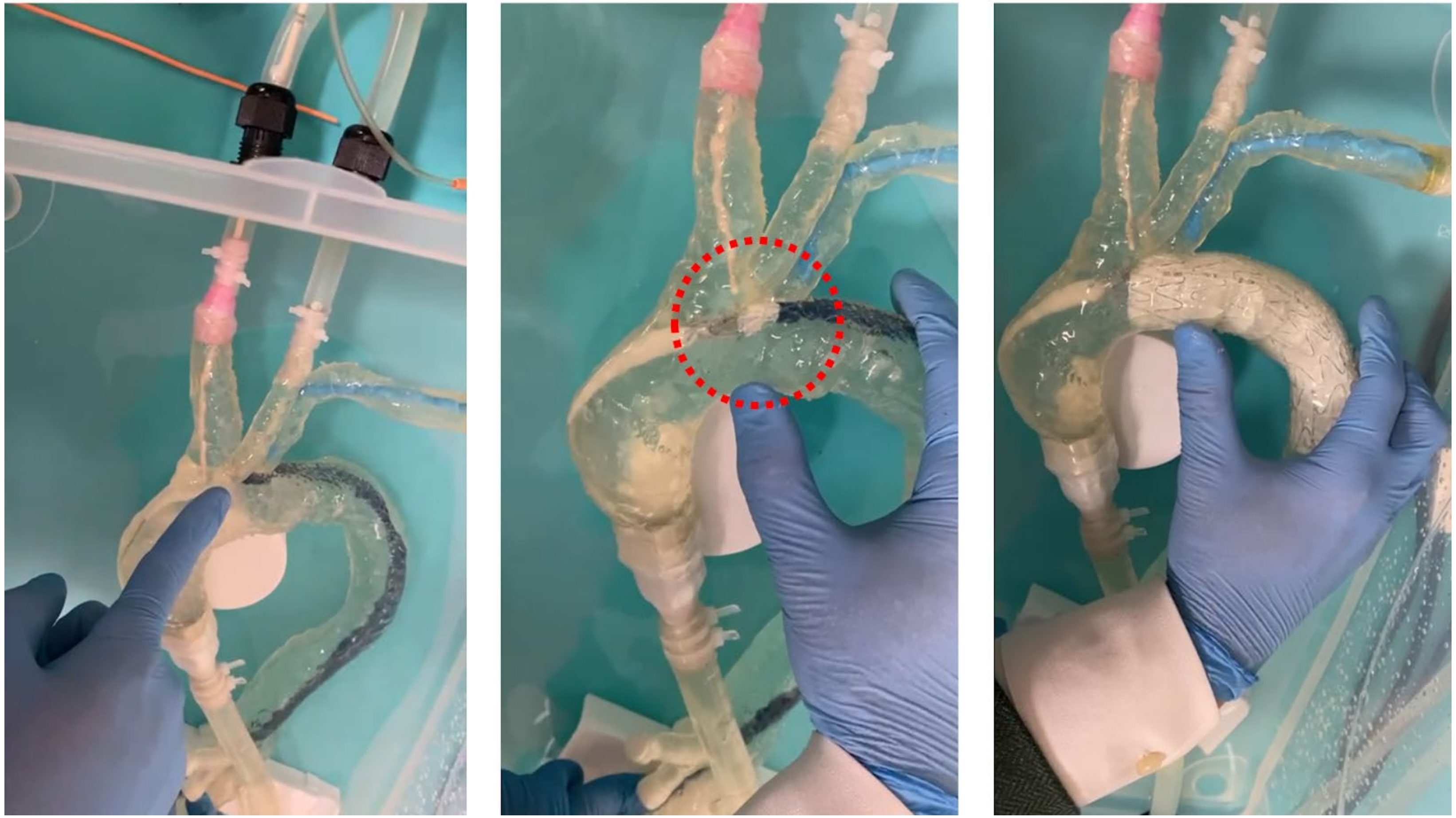




Aortic Stent Release

Aortic Stent Release

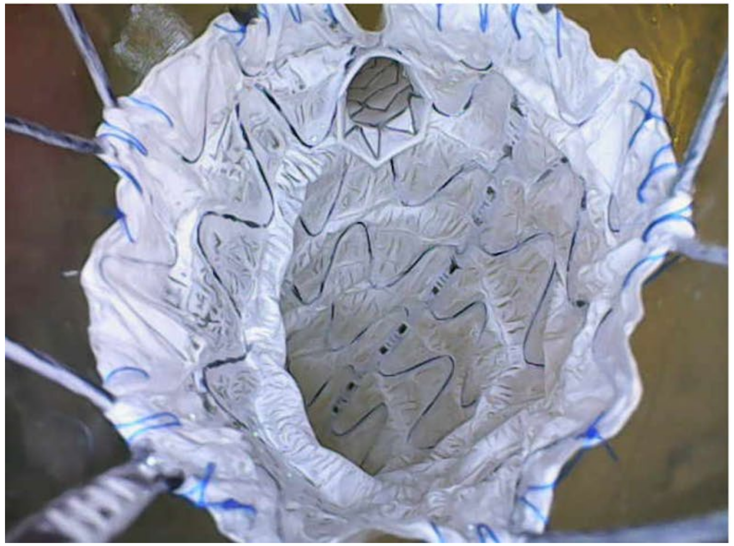
Tip positioning | Alignment check | Stent release



LSA stent release

Prosthesis Explantation

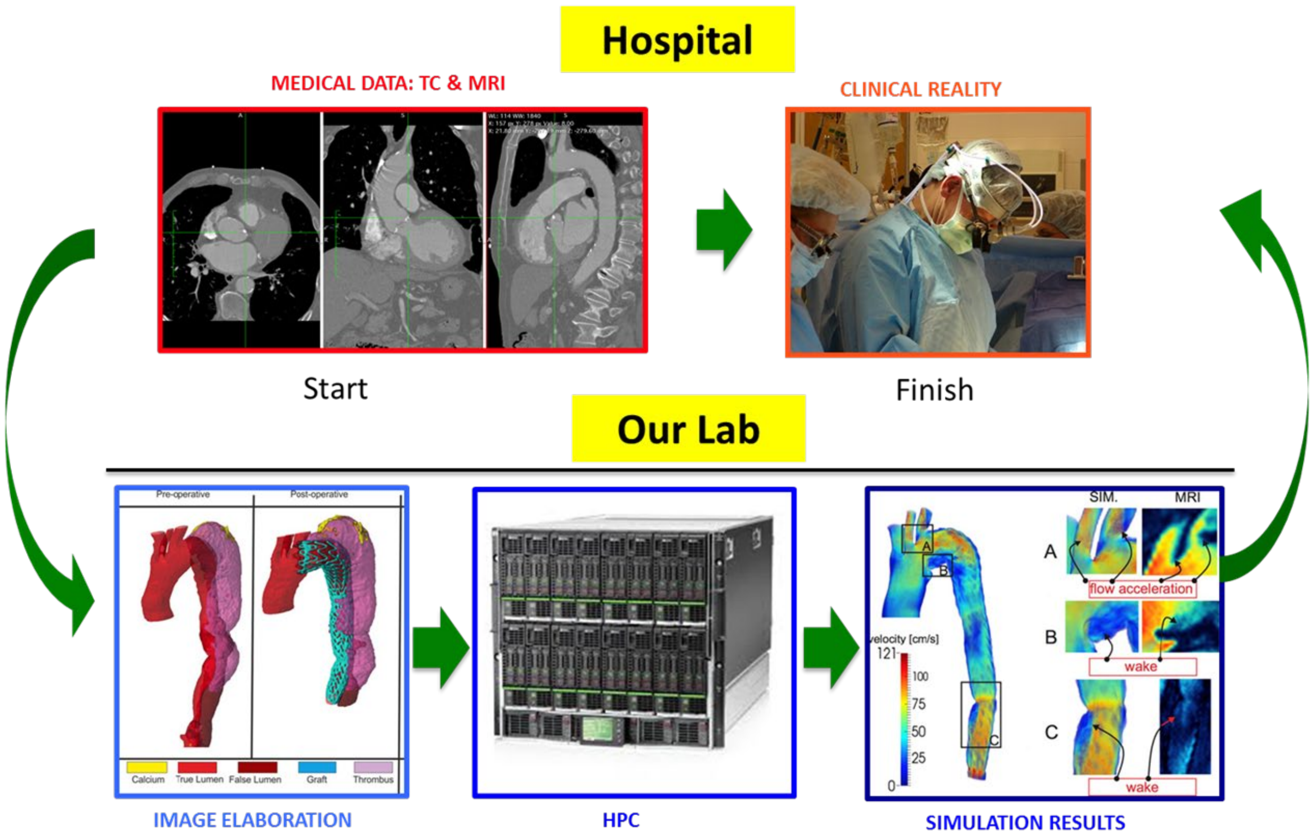
From AA



From DA

What is a simulation?

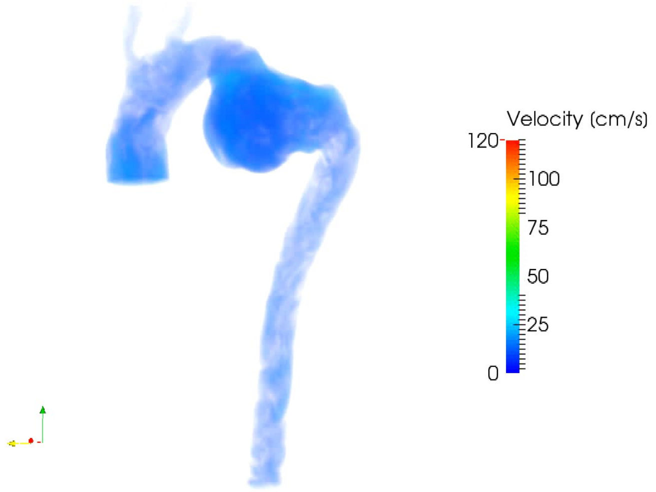
Over recent years, there has been a rise in the development and application of *in silico* computational tools to evaluate haemodynamic parameters and to help pre-procedural planning by simulating the TEVAR procedure and predicting technical and clinical results.[7–10]

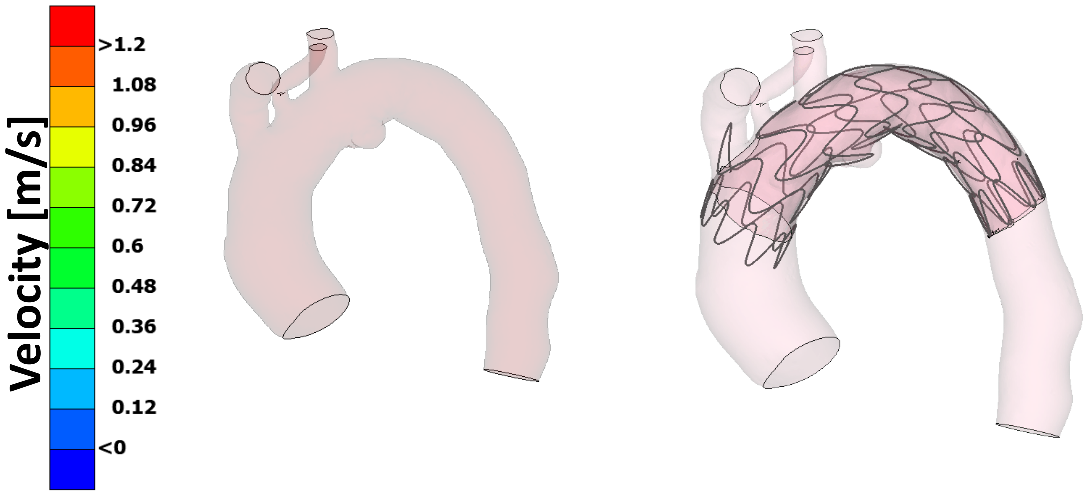


What is a simulation?

Computational Fluid Dynamics (CFD)

CFD simulating aortic haemodynamics in a rigid aorta

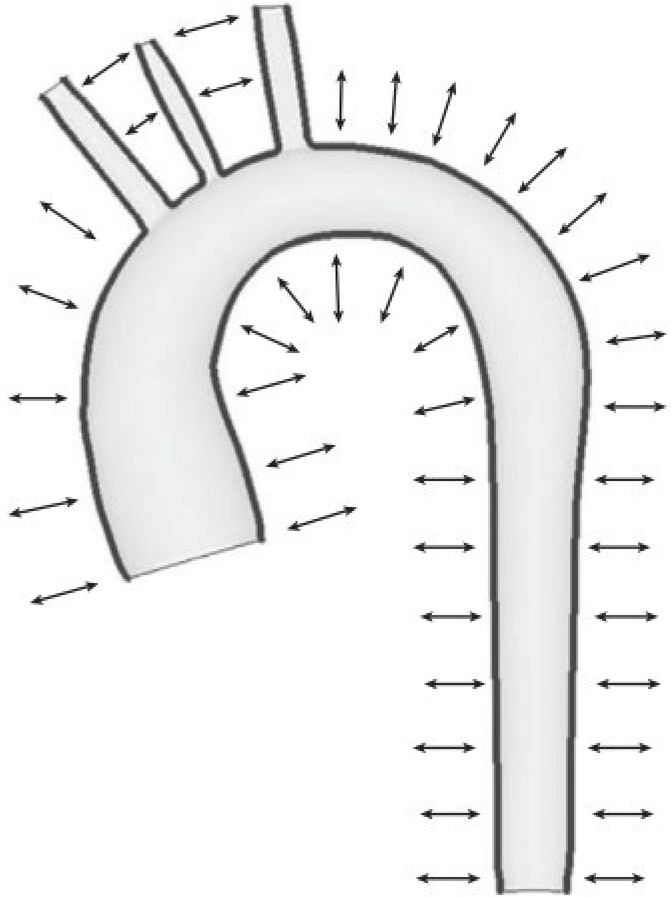


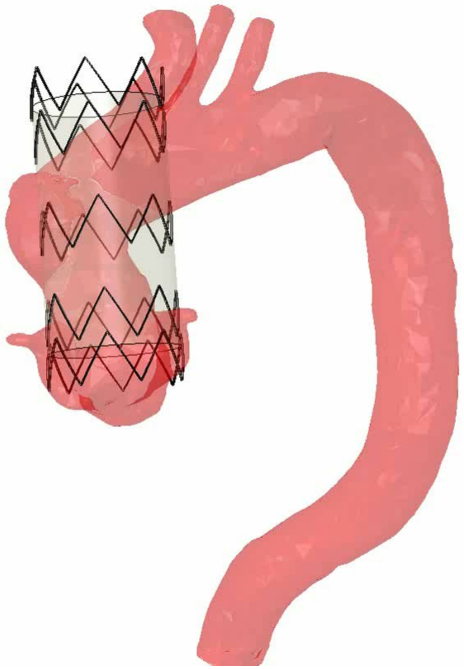


What is a simulation?

Finite Element Analysis (FEA)

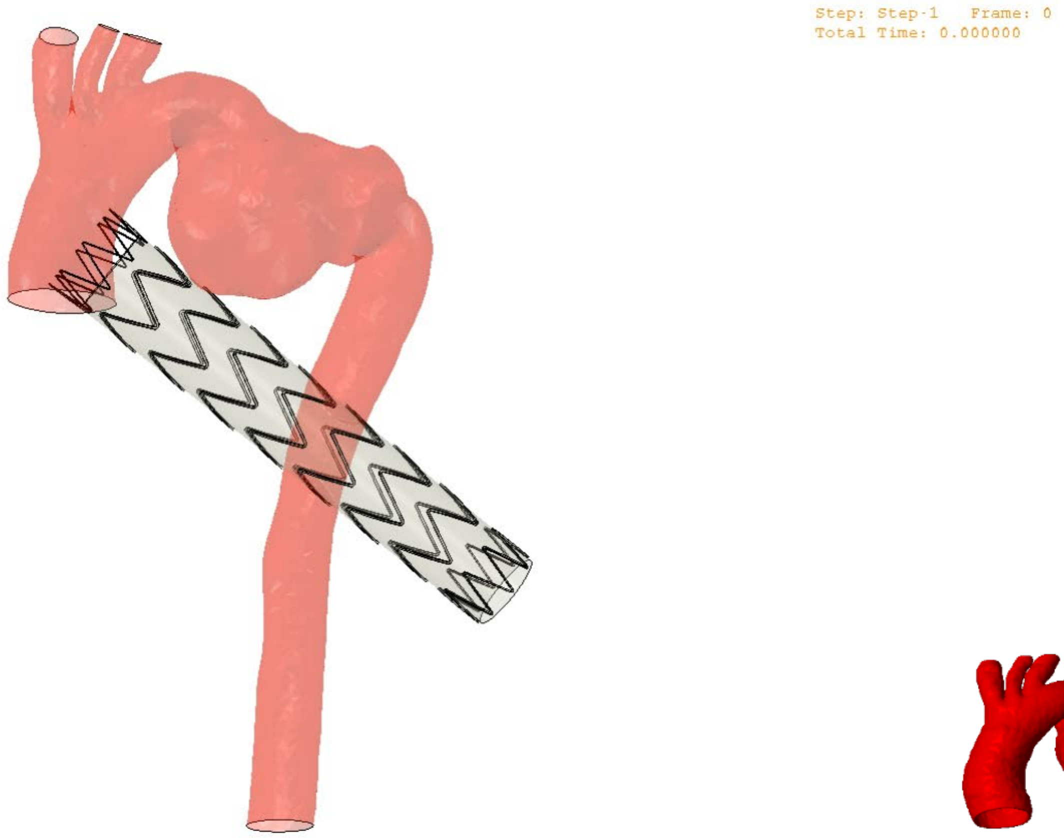
FEA simulates structural mechanics of the aortic wall

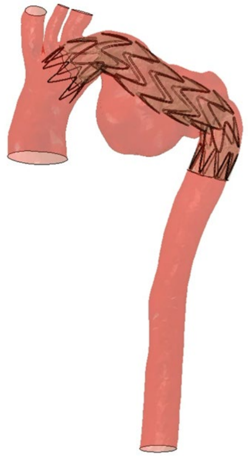




What is a simulation?

Finite Element Analysis (FEA)

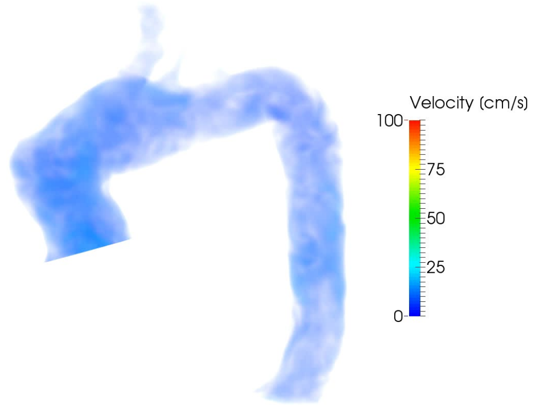


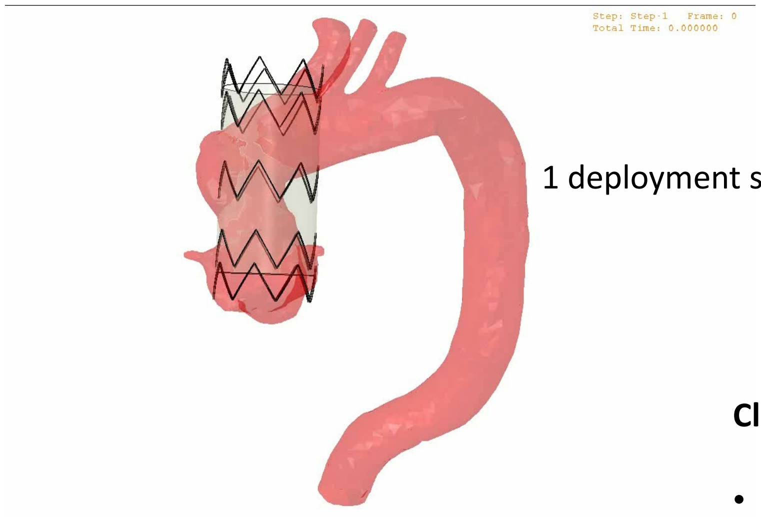


Clinical decision

- LCCA – LSA bypass + TEVAR
- Complete exclusion of the aneurysm @ 6 yrs FU

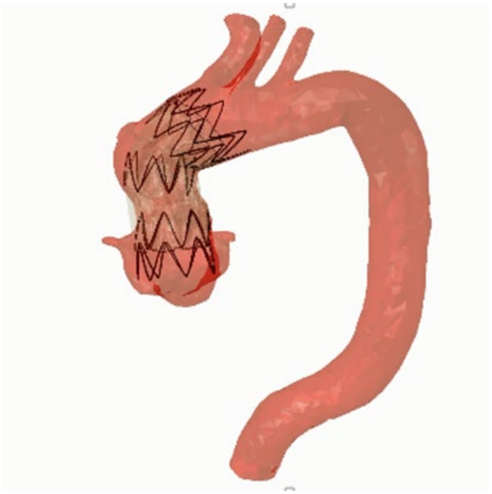
Finite Element Analysis - Simulation





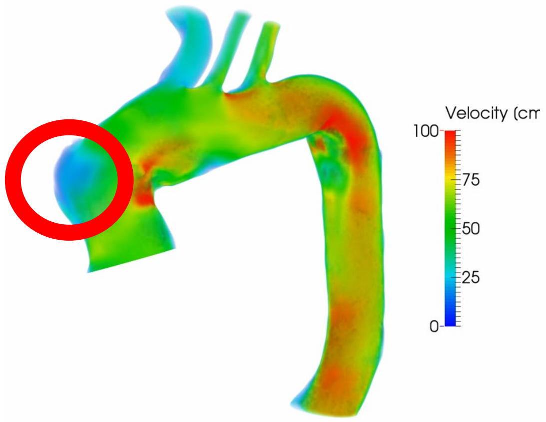
1 deployment step

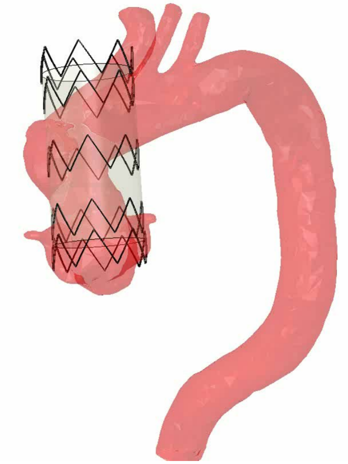
available



Clinical decision

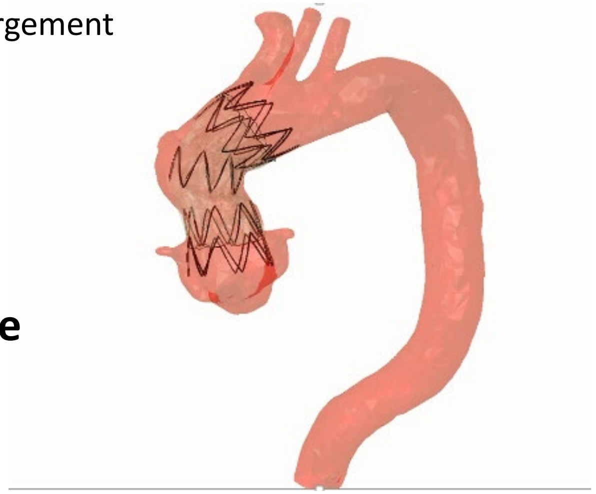
- Endograft not provided by the company
- Conservative treatment
- Patient deceased 2 yr later for cancer
- No pseudoaneurysm enlargement





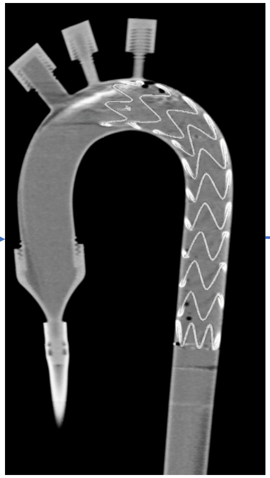
6 deployment steps

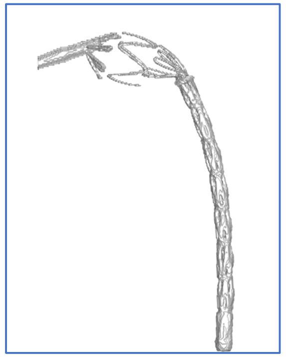
NOT available



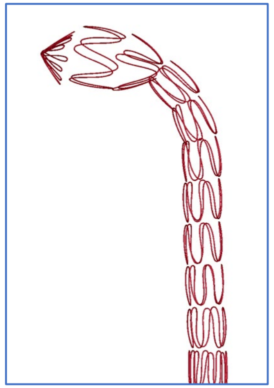
High-Fidelity TEVAR simulations

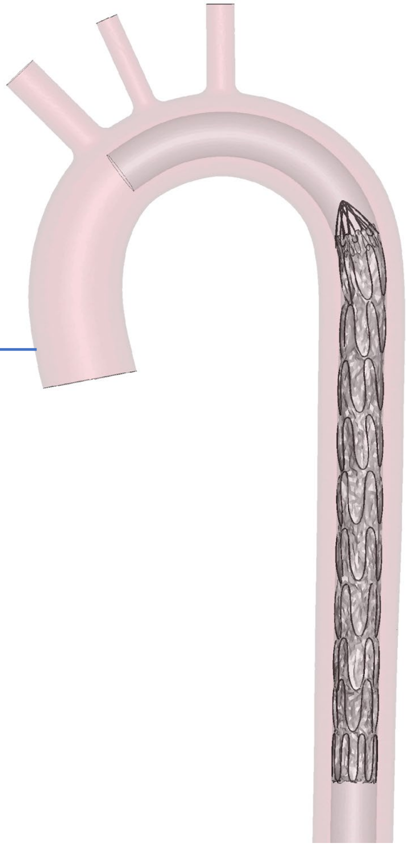
CT SCAN



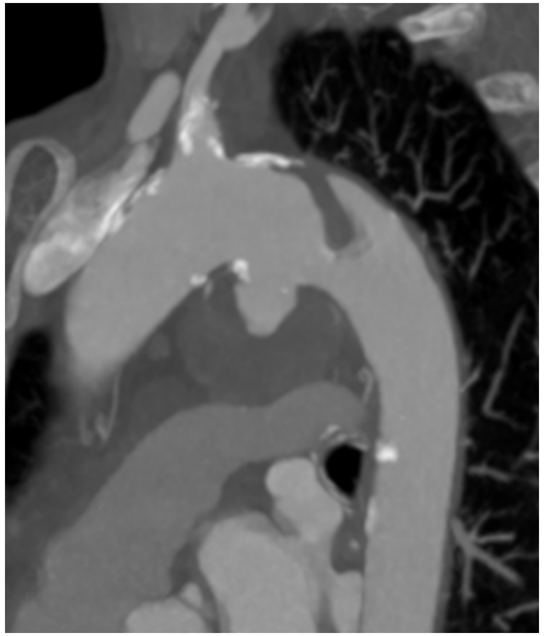


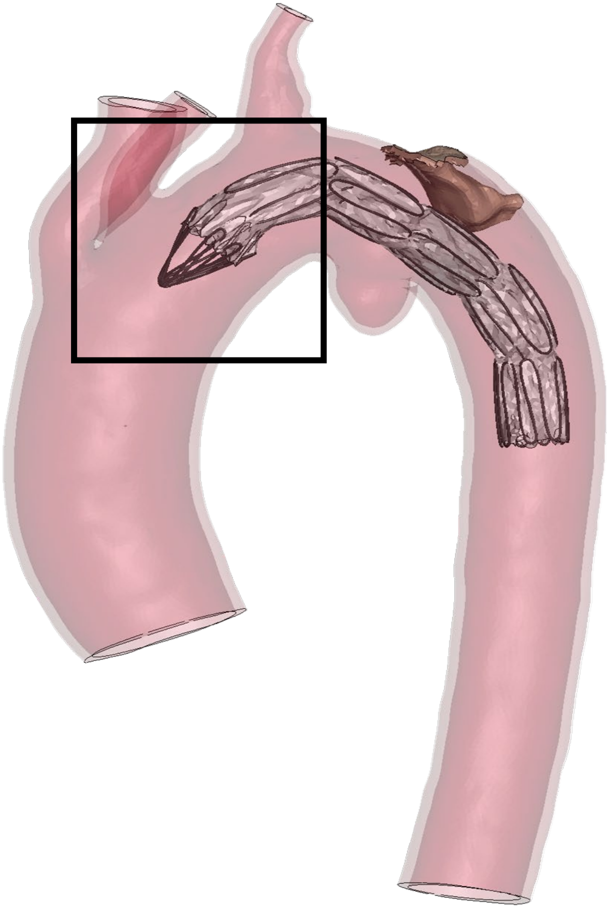
FEA ANALYSIS

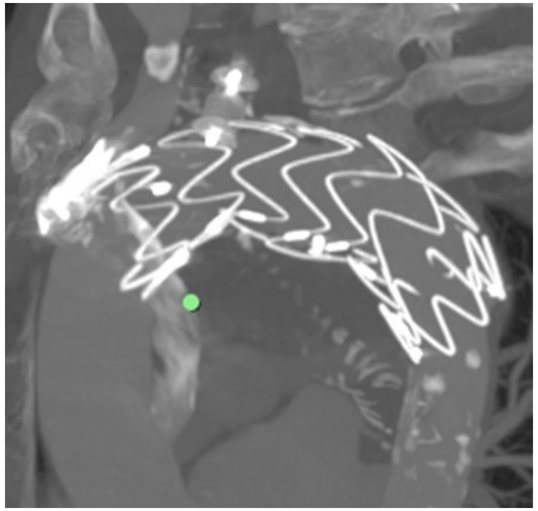




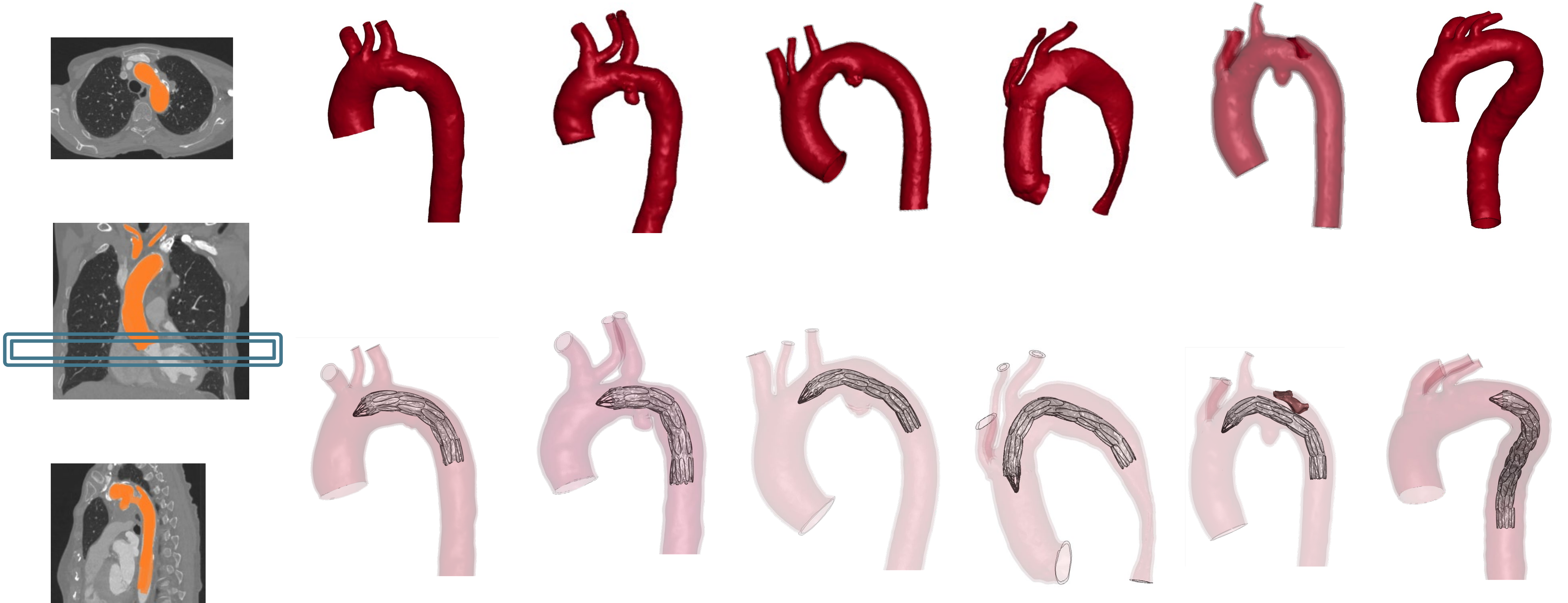
Computational Simulation





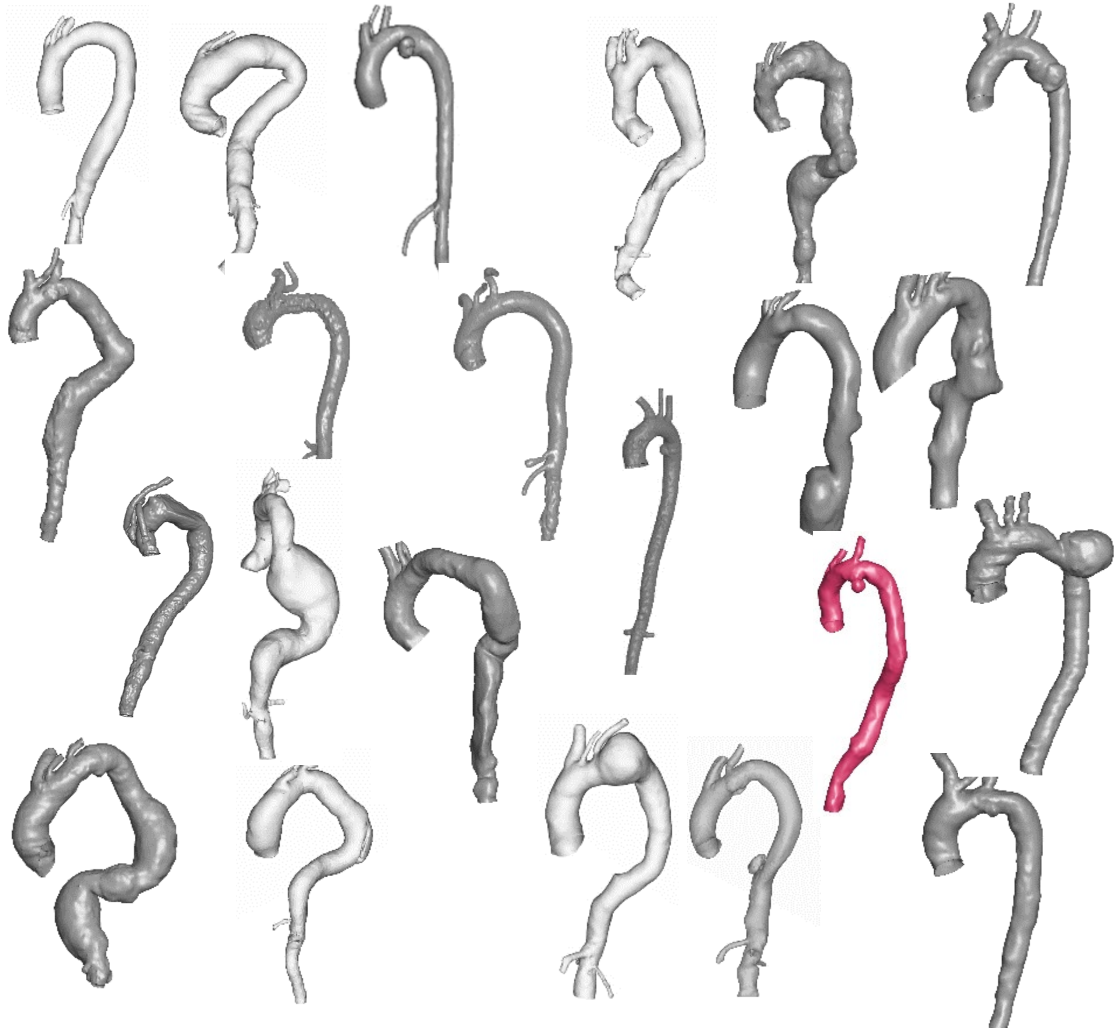


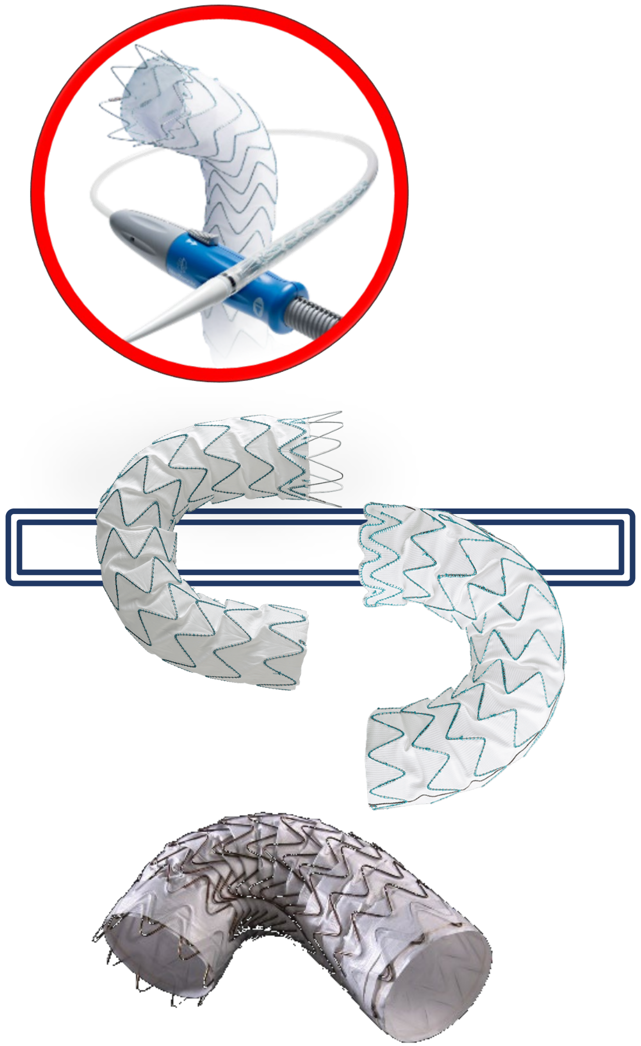
Computational Simulation



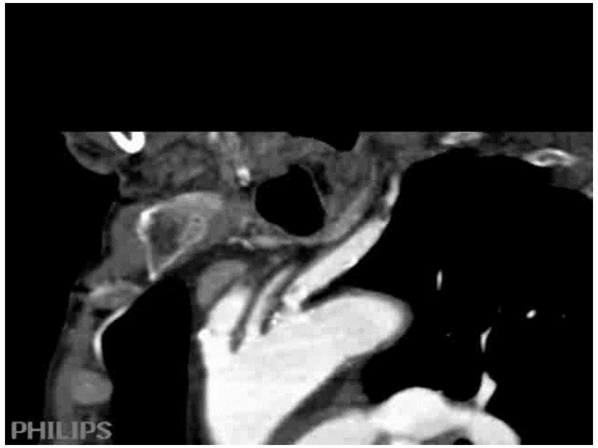
9.8% 11.9% In progress... 10.8% 11.1%

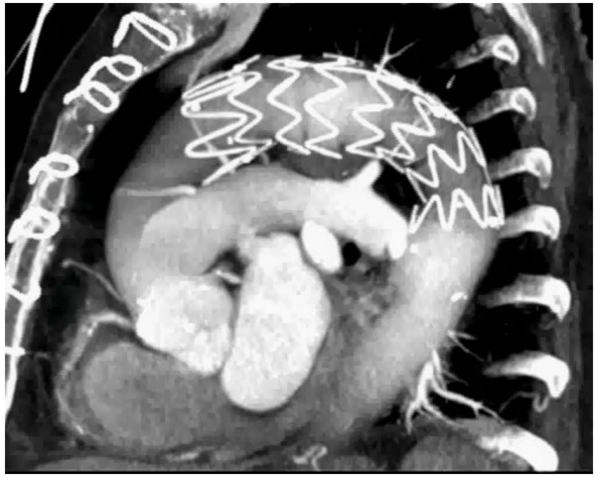
High-Fidelity TEVAR simulations

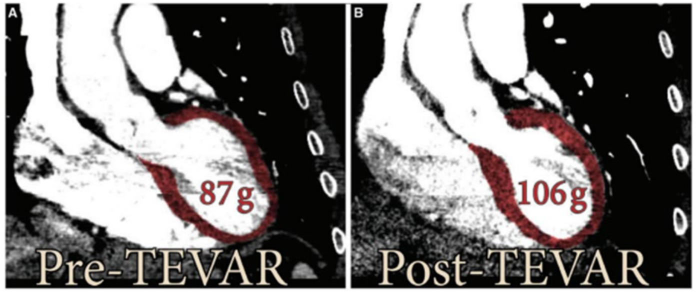


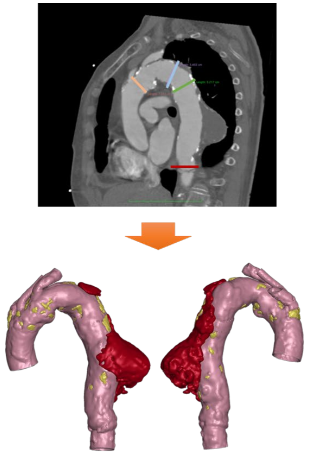


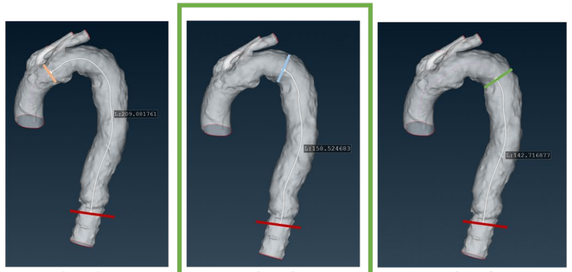
CONCLUSIONS: Aortic Stiffness and Computational Simulation











Caso 1:
Diametro LZ = 23.5 mm
Diametro distale = 26 mm
Length = 209 mm

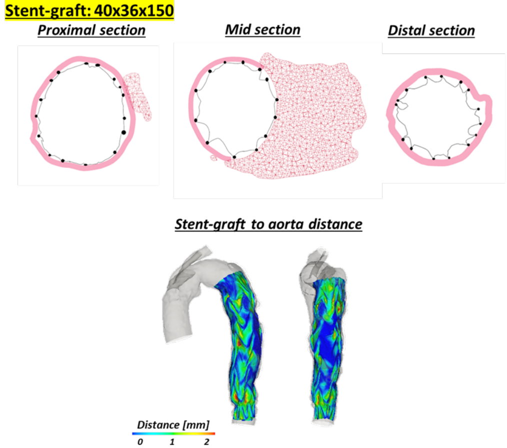
Stent-graft: 32x32x200

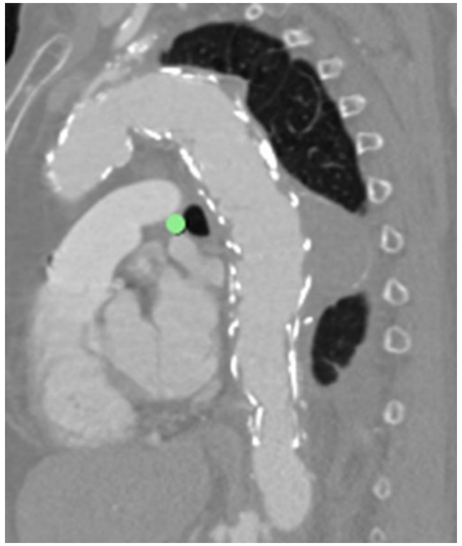
Caso 2:
Diametro LZ = 29.7 mm
Diametro distale = 26 mm
Length = 158 mm

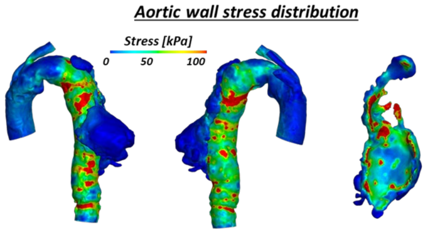
Stent-graft: 36x32x150
MDT=40X36X150

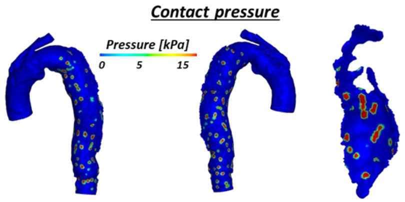
Caso 3:
Diametro LZ = 31.2 mm
Diametro distale = 26 mm
Length = 142 mm

Stent-graft: 36x36x100

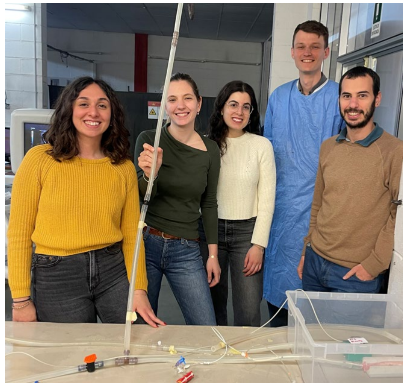




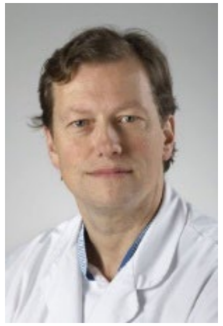




Collaborative Research group













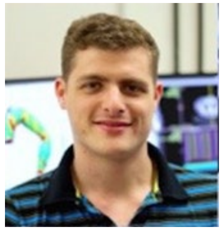












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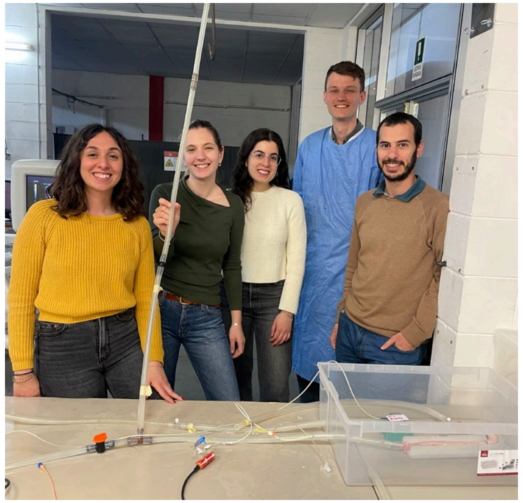

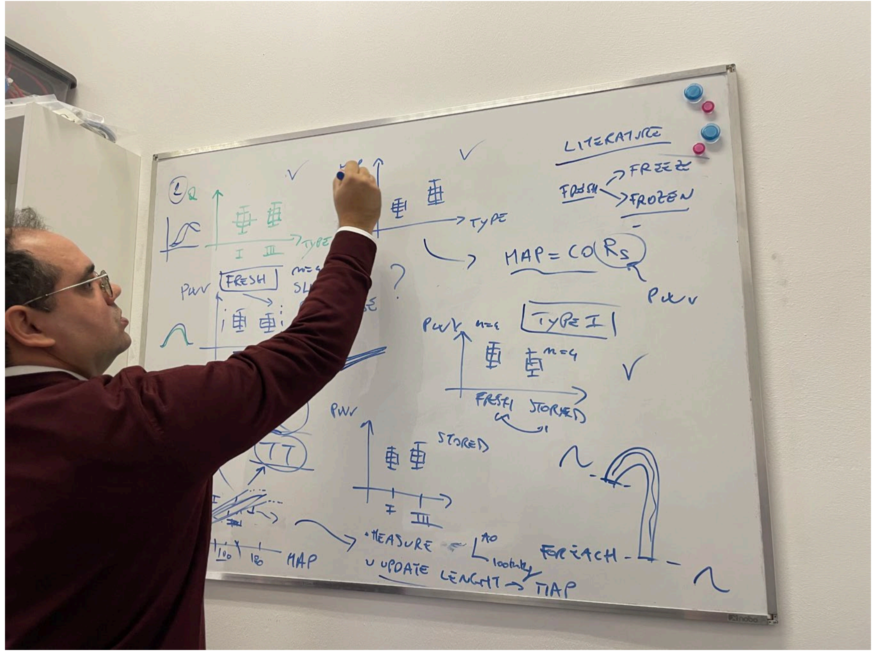

Thank you

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