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Activities at Thoracic Aortic Research Center, IRCCS Policlinico San Donato

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The Thoracic Aortic Research Center (TARC) of the IRCCS Policlinico San Donato (PSD) aims to promote research on thoracic aortic diseases, to disclose the scientific knowledge and clinical experience and to develop new scientific paths within the Hospital and the aortic community, in collaboration with other national and international centres. Thoracic Aortic Research Center collaborates with many centres in both Europe (e.g. University of Utrecht, the Netherlands) and the USA (e.g. University of Michigan). This has led to multiple highly regarded publications in respected cardiovascular journals and has led to several PhD programmes resulting in doctorate degrees. Within Italy, in association with the Bioengineering School of the University of Pavia, TARC has founded the "BETA-lab" (*B*iomechanics for *E*ndovascular *T*reatment of the *A*orta laboratory), where MDs, Bioengineers, and PhD fellows conduct experimental studies using *in vitro*/*ex vivo* models of the physiologic aorta and aortic diseases. Furthermore, a database (iCardiocloud) where the medical imaging of cardiovascular patients from the PSD is structured, for *in silico* analysis utilizing computational fluid dynamics, and *in vitro* studies using also 3D printed aortic models. With the role of principal investigator or co-investigator, TARC at PSD has been participating in other several projects, including the International Registry of Acute Aortic Dissection, the International Aortic Arch Surgery Study Group, the European Registry of Endovascular Aortic Repair Complications, the ADSORB and ASSIST trials, and the GREAT registry. International collaborations have included also studies on predictors of aortic growth after dissection with the Yale University and University of Virginia, and on aortic biomarkers with the University of Tokyo.

Introduction

Within the department of cardiovascular surgery at IRCCS Policlinico San Donato (PSD), affiliated with the University of Milan, Italy, over the years >70 000 of patients have been treated, as the hospital is the one with the highest number of cardiac surgery interventions in Italy since 1995 (>1500 per year, 1541 in 2013). In this setting, ~2000 patients affected by thoracic aortic aneurysm and dissection have been operated on, and for such reason, the Italian Ministry endorsed the hospital with the title of 'Scientific Institute for Research, Hospitalization and

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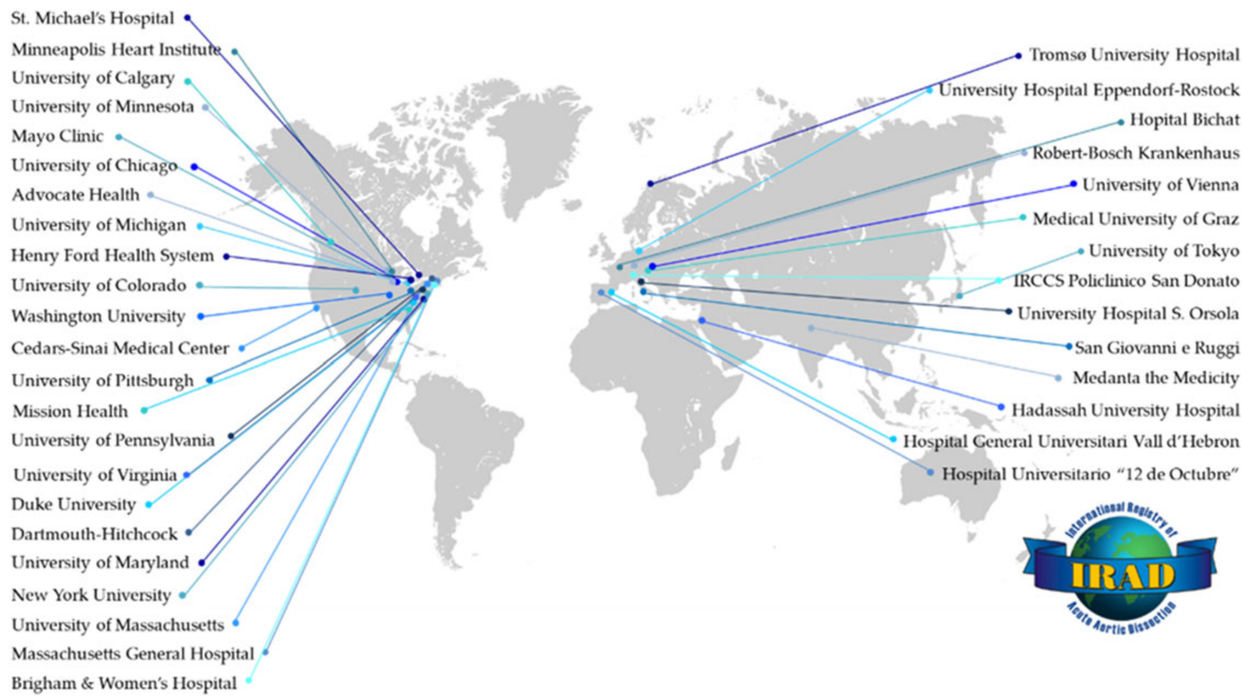

Figure 1 Overview of participating International Registry of Acute Aortic Dissection centres worldwide.

Health Care (IRCCS)', specifically for the Study and Care of Diseases of heart and blood vessels in adults and children. This acts as a trigger for a continuous cardiovascular research programmes, which has been conducted both as clinical single centre analysis and as Principal Investigators or Co-Investigators in many international registries and trials. In this time, many physicians from foreign countries have completed their surgical fellowship and/or PhD programme in San Donato. On these bases, in 2011, the Thoracic Aortic Research Center (TARC) was established, with the aim to promote research on thoracic aortic diseases, to disclose the scientific knowledge and clinical experience at the PSD, and to develop new scientific paths within the Hospital and the aortic community, in collaboration with other national and international centres.

Collaborations

The TARC conducts clinical, translational and basic science research within a wide range of collaborations in Italy and worldwide. A close relationship with the University of Michigan has headed to PSD participation in the International Registry of Acute Aortic Dissection (IRAD), which is the largest aortic dissection database worldwide. It includes patients observed at 30 centres in >30 countries globally (*Figure 1*). International Registry of Acute Aortic Dissection has led to a large number of publications (over 70) with considerable impact on the worldwide acute aortic dissection management.[1–4] The PSD has also the role of principal investigators in the IRAD Surgical/Endovascular programme. Some summaries of IRAD publications are described below.[5]

Figure 2 Three-dimensional-printed model of aortic dissection for research and education purposes.

Since 2008, TARC at PSD has facilitated a number of PhD programmes from the University of Utrecht (the Netherlands). This ongoing collaboration has been heading several doctoral degrees focusing on thoracic aortic diseases. TARC at PSD supervises the PhD programmes, during which the researchers spend time in the USA and Italy.

Centres that are connected to this network are the University of Michigan, Yale University, Harvard University, and the University of Virginia. This network has led to several regarded publications in respected cardiovascular journals.[6–12]

Within Italy, in association with the Bio-engineering School of the University of Pavia, TARC has founded a research laboratory named 'BETA-lab' (*B*iomechanics for *E*ndovascular *T*reatment of the *A*orta laboratory). In this laboratory, through a close collaboration between MDs, Bio-engineers, and PhD fellows in medicine and engineer, experimental studies using *in vitro* and *ex vivo* models of physiologic aorta and aortic diseases are performed. Furthermore, a database where the medical imaging of cardiovascular patients from the PSD is structured, for *in silico* studies utilizing Computational Fluid Dynamics (CFD).[13] This database, called 'iCardioCloud', is accessible by the engineers for CFD analyses, for instance blood flow patterns and wall shear stress in thoracic aortic diseases. Similarly, computed tomography and magnetic resonance imaging (MRI) of such patients have been also used to simulate interventions and, of consequence, to investigate whether such information may be useful in planning thoracic endovascular aortic repair (TEVAR) and, potentially, preventing failure or complications.[14] With the same purpose, the BETA-lab also includes a research programme to evaluate the usefulness of the 3D printed technology for better understanding and planning (*Figure 2*). In Italy, TARC at PSD has also an ongoing fruitful clinical aortic research programme with the University of Insubria.[15]

With the role of principal investigator or co-investigator, TARC at PSD has been participating in other several projects, including the International Aortic Arch Surgery Study Group (IAASSG),[16,17] ADSORB study,[18] ASSIST study, the European Registry of Endovascular Aortic Repair Complications (EuREC),[19] and the GREAT registry. International collaborations have also included studies on predictors of aortic growth after dissection with the Yale University.[20,21]

In the following paragraphs, we will report some of the TARC research activity over the last years.

International Registry of Acute Aortic Dissection

Importance of refractory pain and hypertension in acute type B aortic dissection

In patients with acute type B aortic dissection (ABAD), the presence of recurrent or refractory pain and/or refractory hypertension on medical therapy is sometimes used as an indication for invasive treatment. International Registry of Acute Aortic Dissection was used to investigate the risk profile in these patients (Group I) at 'intermediate risk' compared with those patients not presenting clinical complications at presentation (Group II). The in-hospital mortality was increased in Group I compared with Group II, 17.4 vs. 4.0%, $P = 0.0003$, and was even more significant after medical management (Group I 35.6% vs. Group II 1.5%, $P = 0.0003$). These observations suggest that more invasive treatment is indicated in this intermediate risk group.[2]

Importance of aortic diameter in type B dissection

The vast majority of patients with ABAD present with a descending aortic diameters <5.5 cm prior to dissection, and do not fall within the guidelines for elective descending thoracic aortic repair. Although it is not indicated to operate patients at lower threshold for preventing B dissection, aortic diameter measurements do not appear to be a useful parameter to prevent aortic dissection, and other methods are needed to identify patients at risk for ABAD.[22,23]

About one-fifth of patients with ABAD do not present any previous aortic dilatation. These are more frequently female and younger patients, when compared with patients with previous aortic dilatation. The analysed ABAD cohort did not present with higher incidence of Marfan syndrome or bicuspid aortic valve. Further research is needed to investigate risk factors for aortic dissection in the absence of aortic enlargement.[24]

Aortic expansion after acute type B aortic dissection

White race and a small initial aortic diameter were associated with increased aortic expansion during follow-up,

Figure 3 *Ex vivo* experiment using porcine aortas.

Figure 4 Custom-made stent-graft delivery system.

while decreased aortic expansion was observed among females, patients with intramural haematoma (IMH), and those on calcium channel blockers. These data raise the possibility that the use of calcium channel blockers following ABAD may reduce the rate of aortic expansion, and therefore, further investigation is warranted.[25]

Intramural haematoma type B

Intramural haematoma is an atypical form of aortic dissection, characterized by a crescentic thickening of the aorta in absence of an intimal flap or entry tear, resulting from a haemorrhage within the aortic wall. International Registry

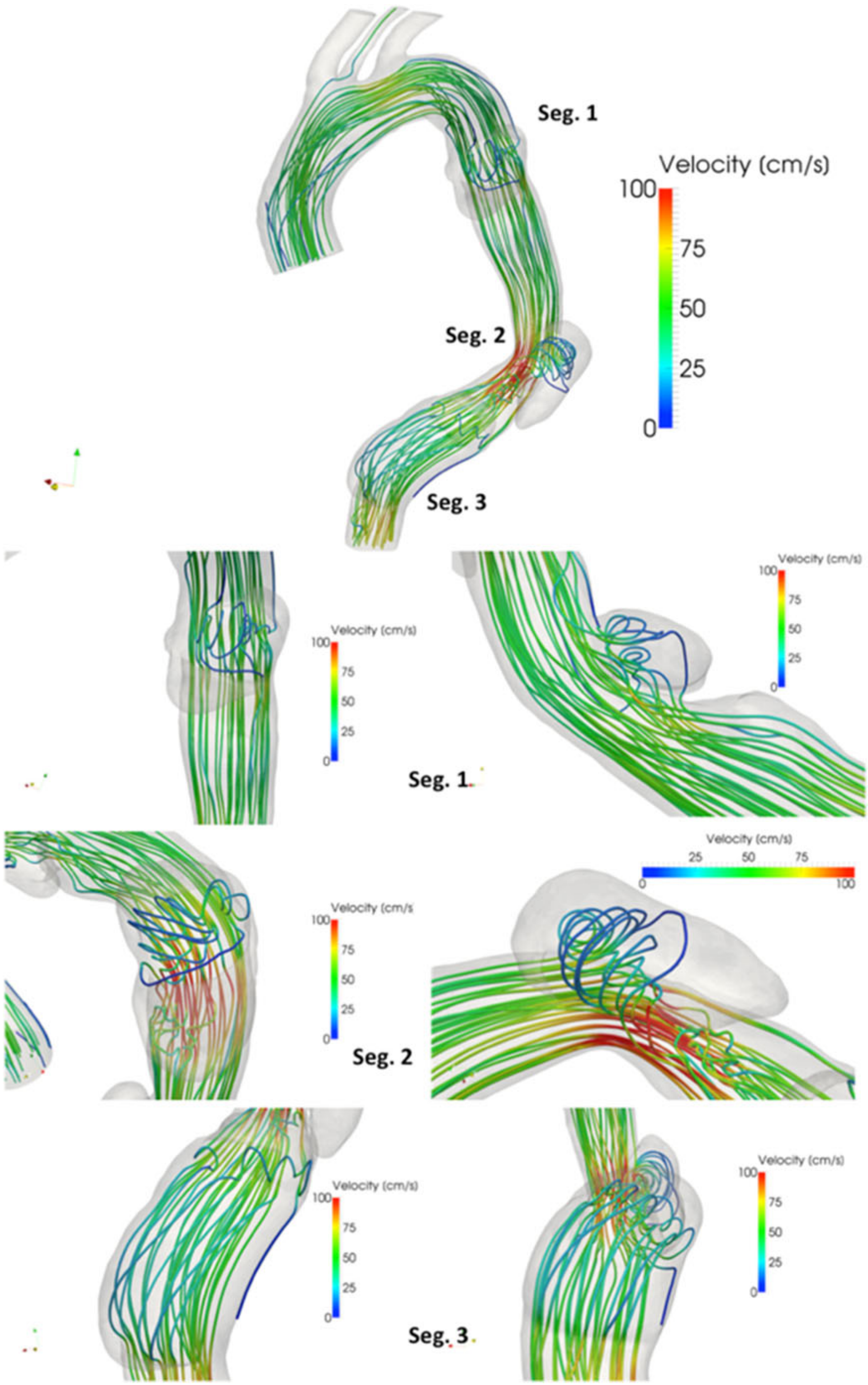

Figure 5 Computational fluid dynamics-generated velocity streamlines in a patient with three separate saccular aortic lesions.

of Acute Aortic Dissection data showed that the overall incidence of IMH is 6.3%, occurs in older patients compared with classic dissection (68.7 vs. 61.7 years), and more often is observed in the descending (58%) rather than in the ascending aorta (42%). Initially, it was believed that type B aortic intramural haematoma (IMHB) was relatively rare compared with classic ABAD, although presenting with similar symptoms, morbidity, and mortality rates. However, more recent studies suggest that the incidence of IMHB is much higher, and may account for >20% of all ABAD in some series. In IMHB, IRAD reports an overall mortality rate of 6%, 13% after surgery, and 5% after medical treatment. The outcome is slightly favourable compared with classic ABAD in the acute setting. Type B aortic intramural haematoma shows a relative unpredictable course, and in the absence of suitable predictors for high-risk patients, a complication-specific approach should be adopted. Medical treatment combined with close follow-up should be administered in all patients and intervention should be reserved for complicated patients.[26]

International Aortic Arch Surgery Study Group

The arch projects—design and rationale

The effectiveness of current arch studies in assessing optimal neuroprotection strategies is limited by several factors, including insufficient patient numbers, heterogenous definitions of clinical variables, multiple technical strategies, inadequate reporting of surgical outcomes, and a lack of collaborative effort. The IAASSG has been formed by 38 aortic centres from 10 countries to better evaluate patient outcomes after aortic arch surgery. The main objectives of the IAASSG are four-fold: (i) to determine the optimal neuroprotection strategies and operative parameters for patients undergoing hemi-arch and total arch surgery; (ii) to assess perioperative mortality, morbidities, and predictors for operative risk; (iii) to formulate a risk predictor model in arch surgery; and (iv) to evaluate long-term survival outcomes and quality of life after aortic arch surgery.[17]

Standardizing clinical endpoints in aortic arch surgery: a consensus statement from the International Aortic Arch Surgery Study Group

Stratifying the severity of relevant complications into grades allows more thorough analysis to assist benchmarking of existing procedures, identifying areas in need of improvement, guiding prospective research, and evaluating the effectiveness of interventions. International Aortic Arch Surgery Study Group proposes a system for grading adverse outcomes specific for aortic arch surgery. Clinical complications are stratified into five major grades, from those that are self-limiting or require simple therapeutic regimens (Grade I) to life-threatening complications or organ dysfunction (Grade IV). Mortality is classified as a Grade V complication according to the causal organ dysfunction. Fifteen clinical endpoints from six major systems were deemed pertinent for aortic arch surgery and therefore graded according to their clinical manifestations, time course and severity, and treatment provided. These six major systems include neurological, cardiovascular, respiratory, renal, gastrointestinal, and other systems. In the absence of standardized reporting of clinical endpoints, the IAASSG also conducted a consensus survey on the systematic reporting of adverse events after aortic arch surgery using the grading system described above. Such classification can be able to promote consistent reporting, uniform definitions, and a reliable systematic appraisal of arch surgery.[16]

Biomechanics for Endovascular Treatment of the Aorta laboratory

Influence of stent grafts on pulsatile environment

One of the ongoing experiments focusses on the impact of TEVAR on the pulsatile environment of the aorta. Thoracic endovascular aortic repair is now a widespread technique, but the exact impact of TEVAR on the cardiovascular system and the aorta is unknown. We connected porcine aortas to the continuous pump (*Figure 3*) and simulated different aortic blood pressures. By taking snapshots of the aorta at these different pressures (*Figure 4*), the longitudinal distensibility can be computed using custom software. The measures were taken before and after deployment of a stent graft, to see the impact of TEVAR on the aorta. Radial distensibility is another quantifiable outcome using this set-up. Preliminary results show that although radial distensibility is preserved, longitudinal distensibility decreases, especially in the stented segments. In other words, the aorta becomes stiffer after TEVAR. This might influence the occurrence of complications and outcome after TEVAR, and could influence stent-graft design in the future.

In vitro dissection model

Using a 3D printer, we created an *in vitro* aortic dissection model. It consists of a single tube-like main body, in which different lamella can be placed to mimic a dissection flap and subsequently a true and a false lumen. The lamella is made up of silicone material, and by printing different configurations, we can alternate the number of entry tears, position of the entry tear, and size/shape of the entry tear. The model is then connected to either the continuous or the pulsatile pump. Pressure sensors register the different pressures in the true and false lumen, and by placing the set-up under a MRI scan, flow within the model can be investigated.

Ex vivo dissection model

A combination of the above-mentioned projects has been used to develop an *ex vivo* dissection model. Using porcine aortas, entry tears of different shapes and sizes in an actual aorta have been created. Furthermore, it is possible to steer the direction of the aorta, to produce, for instance, spiral dissection. The exact technique of creating this dissection model will be published in the near future. This project is developing, but the early outcomes and testing have shown that it is a useful and reproducible way to test the biomechanical properties of different types of aortic dissection.

ICardioCloud, computational fluid dynamics

The main focus of the iCardioCloud project is CFD. Computational Fluid Dynamics is a computer-based simulation able to solve in an approximate manner the Navier–Stokes equations for incompressible fluid dynamics.[13] The computational domain (mesh) is the volume occupied by the arterial blood. The wall of the computational domain (i.e. the luminal surface of the aorta) is considered to be rigid in our analyses so far. Consequently, vessel displacement during the cardiac cycle due to pulsatile loading is neglected. Some parameters that can be subtracted from the CFD analyses are lesion dimensions, wall shear stress (WSS), time-averaged WSS, blood flow velocity and flow patterns (*Figure 5*), and Oscillatory Shear Index. With this project, we aim to investigate what the translational impact of CFD on clinical observations and outcomes is. By doing so, CFD might even prove to become a potential biomarker in the future of cardiovascular diagnostics.

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