

**New techniques and principles in acute aortic pathologies requiring emergency surgical interventions**

**PhD Thesis**

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## ***Introduction***

Aortic surgery, especially for pathologies requiring urgent surgical intervention has undergone significant changes in the past two decades leading to major improvement in short- and long-term outcomes. Better understanding of underlying diseases, improved guidelines and classifications have also contributed to more effective, prompt diagnosis and treatment of this high-risk segment of patient population. New imaging modalities, evolvement of perfusion methods, intra- and postoperative monitoring, improved intensive care are also of importance for achieving favourable outcomes. Nevertheless, continuous development of cardiac surgery itself is perhaps the most important component of this evolutionary process. As an example, the entry of catheter-based techniques including thoracic endovascular aortic repair and a combination of this method with conventional operative procedures resulted in novel devices, such as the “frozen elephant trunk”, which led to reduced operative burden, lower mortality/morbidity and favourable long-term results.

The aim of this thesis is to provide a comprehensive, up-to-date overview on clinical characteristics of acute aortic syndrome, with special emphasis on current operative treatment possibilities, including well-established and novel, innovative surgical approaches. Within this scheme further specific goals were to analyze different cannulation and perfusion options, the role of core temperature management during hypothermic circulatory arrest and impact of age-related differences in surgical approach of AAS.

## ***Aims***

Based on this background, we designed four clinical studies (Study I – IV) in the last decade aiming to improve diagnostics and treatment of aortic emergencies. The final goal of these protocols was to improve safety of this major surgical procedure.

The aim of Study I. was to develop a reliable central cannulation method in type A aortic dissection repairs. In Study II., the reliability of different body temperature measurement sites was investigated during aortic surgery; in Study III., management options for aortooesophageal fistulas; while in Study IV., age-related considerations of acute type A aortic dissection were analyzed.

***Study I - Central cannulation by Seldinger technique in type A aortic dissection repairs***

Extensive aortic disease, such as giant aneurysms combined with atherosclerosis or dissections that involve the ascending aorta, can complicate the choice of a cannulation site for cardiopulmonary bypass. Ideal perfusion during ascending aorta/arch surgery should allow easy implementation of antegrade cerebral perfusion while avoiding atheroembolization or false lumen perfusion in dissections. Alternative cannulation sites such as AxS or innominate artery have been recently preferred to the femoral artery to improve postoperative outcome in patients undergoing surgery of the thoracic aorta. Prompt establishment of antegrade perfusion may lead to favourable outcome in type A dissections, especially in case of hemodynamic instability. We started to employ direct cannulation of the true lumen targeting the concavity of aortic arch by Seldinger technique in aortic dissections, later this method was applied in ascending/arch aneurysm resections too. We have evaluated the efficacy of this access technique as an alternative arterial inflow target in aortic surgery.

***Study II - Body temperature measurement sites in aortic surgery***

We performed a retrospective, comparative analysis of different, but widely used temperature measurement sites during surgical repair of thoracic aorta in HCA to determine reliability of methods for intraoperative core temperature monitoring. Preservation of neurological function is one of the main goals in such patients. Safety of this type of procedure relies on adequate systemic cooling under strict control. If this control is incomplete or fails neurological injury may occur during HCA.

***Study III - Management options for aortooesophageal fistula***

Aortooesophageal fistula is a very rare clinical entity often leading to a life-threatening gastrointestinal bleeding. Thoracic aortic aneurysms are the most common cause of aortooesophageal fistula, further causes involve foreign body ingestion, trauma, which is in most of the cases iatrogenic, carcinoma, or very rarely aortitis tuberculotica. Conservative treatment of AOF results in a high in-hospital mortality rate, and conventional surgical procedure has a reported in-hospital mortality rate of nearly 40%. TEVAR as a stand-alone procedure has recently gained recognition as a possible technique for emergent treatment of AOF, despite a considerable risk of infection; in contrast to conventional solution of open thoracic surgery with higher mortality and morbidity. However, relatively little is known about long-term results of TEVAR for AOF due to its rarity and lack of large clinical experience.

#### ***Study IV - Age-related considerations in acute type A aortic dissection***

Our aim was to investigate on clinical and anatomic presentation of TAAD according to patients' age. Only a limited number of reports in literature are focused on preoperative features and their correlation with age of patients presenting with TAAD. On this basis, we have studied clinical and anatomic presentation of TAAD, characterized their relationship with patients' age and evaluated possible implications in terms of pathologic background and surgical management.

### ***Patients and Methods***

#### ***Study I - Central cannulation by Seldinger technique in type A aortic dissection repairs***

Twenty-four consecutive patients (mean age:  $59 \pm 14$  years) underwent type A aortic dissection repair using selective antegrade cerebral perfusion. Direct aortic cannulation was applied in 14 cases, subclavian access in 6 patients, and femoral entry in 4 patients. Perioperative factors were evaluated to identify reliability and eventual benefits of direct cannulation method at the aortic arch.

#### ***Study II - Body temperature measurement sites in aortic surgery***

22 patients (mean age:  $63 \pm 12$  years) underwent operations on the thoracic aorta with ultrasound guided Seldinger cannulation of the aortic arch concavity and selective antegrade cerebral perfusion during deep hypothermic circulatory arrest. Indications for surgical intervention were acute type A dissection in 14 (64%) patients, degenerative aneurysm in 6 (27%), aortic infiltration of thymic carcinoma in 1 (4.5%) and intra-aortic stent refixation in 1 (4.5%). Rectal, tympanic and bladder temperatures were evaluated to identify the best reference to arterial blood temperature during HCA and ACP.

#### ***Study III - Management options for aortooesophageal fistula***

Due to its rarity, there are no large scale multicentre studies present to evaluate the efficacy of different therapeutic management options of AOF. Since it is associated with significant morbidity and mortality, we have analysed various treatment approaches performed in our clinical practice.

#### ***Study IV - Age-related considerations in acute type A aortic dissection***

We retrospectively reviewed 235 consecutive patients, who underwent acute type A dissection repair between January 2000 and December 2014. The influence of age on anatomical presentation in the entire cohort and after exclusion of patients with known connective tissue disorders was assessed using logistic regression.

### ***Results***

#### ***Study I - Central cannulation by Seldinger technique in type A aortic dissection repairs***

There were no operative deaths and cumulative 30-day mortality rate was 25%. Permanent neurological deficits were not observed; in 1 patient transient changes occurred (4%). Time to reach circulatory arrest was the shortest in the direct access group, with mean  $27 \pm 11$  (CI: 20.6–33.3) min vs.  $43 \pm 22$  (28.0–78.0) min ( $p=0.058$ ) and  $32 \pm 8$  (23.6–40.4) min ( $p=0.34$ ) by femoral cannulation and subclavian entry, respectively. Direct arch cannulation resulted in the best renal function in the first 72 h after surgery and similar characteristics were observed in lactic acid levels.

#### ***Study II - Body temperature measurement sites in aortic surgery***

There were no operative deaths and 30-day mortality rate measured 13%. Permanent neurological deficits were not observed and transient changes occurred in two patients (9%). During re-warming, there was strong correlation between tympanic and arterial blood temperatures ( $r= 0.9541$ ,  $p<0.001$ ), in contrast to the rectal and bladder temperature ( $r=0.7654$ ,  $p= n.s$ ;  $r=0.7939$ ,  $p= n.s.$ , respectively).

#### ***Study III - Management options for aortooesophageal fistula***

The most straightforward therapeutic option may be an endovascular aortic repair and subtotal oesophageal resection followed by gastro-oesophageal reconstruction, but other alternative treatment possibilities are also present, although with probable higher morbidity.

#### ***Study IV - Age-related considerations in acute type A aortic dissection***

Males presented with type A acute aortic dissection at a younger age than females. Acute onset with signs of myocardial ischemia, connective tissue disorders, or bicuspid aortic valve characterized the younger population. Extension to coronary sinus(es) ( $p=0.0003$ ), descending thoracic aorta ( $p=0.016$ ), abdominal aorta ( $p=0.029$ ), and an intimal tear at the

level of aortic root ( $p=0.0017$ ) correlated inversely with patient age. Similar findings were obtained after exclusion of patients with connective tissue disorders or a bicuspid aortic valve. Younger patients require radical surgical approach due to the more extensive pathology.

## ***Discussion***

### ***Study I - Central cannulation by Seldinger technique in type A aortic dissection repairs***

This study demonstrates that direct cannulation on concavity of the aortic arch instead of femoral or right subclavian artery may improve outcomes of ascending aorta and aortic arch replacement, especially in case of haemodynamic instability, although it is an observational study because the three groups are not balanced.

Ascending aorta or arch cannulation may have the great advantage of technical simplicity, especially when there is haemodynamic instability or at dissected limb arteries. An access point at level of Botallo's ligament utilizing the Seldinger technique could provide a useful alternative to establish rapid arterial entry. At this section of aorta the pulmonary bifurcation is firmly connected by a massive connective tissue, which usually prevents a complete dissection in this area. With the aid of this rapid and atraumatic cannulation method CPB can be established, thereby reducing likelihood of perioperative shock, which would lead to an increased mortality. Although time demand to reach circulatory arrest was remarkably lower applying the direct cannulation technique compared to the other two accession methods, level of significance was not reached because of a relatively low number of patients in the other two groups, and greater standard deviation values.

Rapid establishment of arterial access facilitates quicker initiation of antegrade systemic perfusion and core cooling, which also contributes to effective reduction of surgical procedural duration. This may result in lower morbidity through enhanced organ perfusion and reduction of coagulation disorder probability. Our method of aortic cannulation has additional advantages. One additional benefit of this type of arch cannulation is having the tip of the cannula located in the proximal descending aorta. Consequently, turbulence at the tip of cannula occurs in the proximal descending aorta, thereby reducing the risk of embolization of debris into the carotid arteries. Further advantage of proximal descending aortic perfusion is a reduction of fluid jet stream – Coanda's - effect that can be associated with relative carotid hypoperfusion in patients undergoing perfusion with a short cannula from the

ascending aorta. Most patients suffering from TAAO undergo at least a “hemiarch replacement” in our practice, so the cannulation site is removed with the affected aortic wall segment and the repositioned cannula fits perfectly into the side-branched prosthesis.

In addition, transoesophageal or epiaortic ultrasonographic guidance may also be indispensable for reliable real lumen cannulation, which examinations are simple methods to obtain imaging information of ascending aorta and proximal arch. Although preoperative computed tomographic scan is mandatory to obtain correct operative planning, the ultrasonographic control provides real-time information on location of intimal tear, intimal flap, true and false lumen; as this intraluminal situation can change progressively following the tomographic scan. Moreover, the guide wire and correct position of the cannula can be checked continuously, so false lumen perfusion is surely avoided, which is not always the case at peripheral approaches. Simultaneous application of ultrasonographic control and cerebral monitoring by NIRS reduces the likelihood of malperfusion, thromboembolism and subsequent extension of false lumen. We have observed no local complications with Seldinger technique, but were always prepared to perform an apical cannulation described by Wada *et al.* as a bail-out procedure.

The challenge of neurological injury resulting from embolic events and cerebral malperfusion in aortic dissections should be discussed with having a regard to that there are a number of different cannulation approaches. Femoral cannulation is well known associated with a higher risk of retrograde embolization and potential perfusion of false lumen via a distal re-entry point, although in our cohort there were no perfusion complications in this group. In this view, techniques providing antegrade flow may offer a better option, especially in patients with Stanford A dissections.

As with other surgical approaches, there are some disadvantages, which need to be recognised. This includes cannulation of the false lumen with potential malperfusion or even complete rupture of the cannulated aorta. For those emergency situations, alternative strategies have to be available. In the above mentioned cases there are basically three major goals to be achieved; cerebral protection, myocardium conservation and finally a proper perfusion of the lower body. This stepwise approach necessitates an efficient cooperation of anaesthesiologist, perfusionist and surgeon to obtain optimal results.

Transapical cannulation is another elegant method for achieving reliable antegrade access, as described by Wada *et al.* In large cohort of 138 patients, the cannula was inserted through a

1 cm apical incision direct into the true lumen via the aortic valve under TOE guidance. The impact of causing an acute aortic insufficiency in this context is not discussed in detail. Wada's technique has disadvantages of resulting in prolonged cardiopulmonary bypass times, since no additional procedures can be performed during cooling, such as inspection and preparation of the aortic root.

AxS cannulation is also a widely applied method for arterial access during aortic arch surgery. However, it is presumably more time consuming, and carries the possibility of failure rates up to 4.2%-11%. Nevertheless, it provides an opportunity of continuous unilateral cerebral blood flow without interruption. Applying the standard technique, however, only the right hemisphere is continuously perfused, which can result in malperfusion of contralateral hemisphere, as Merkkola *et al.* demonstrated that up to 17% of patients have an incomplete circle of Willis. Even in presence of a complete circle of Willis, it is still an open question, if the exclusively right sided perfusion can sufficiently supply the left hemisphere. Our results with SACP demonstrate too, that the lowest perfusion volume is necessary to maintain a proper bilateral cerebral oxygenation in the direct cannulated group. Since the brachiocephalic trunk divides anatomically into two nearly equivalent branches, namely the right carotid and subclavian artery, the provided flow through the latter vessel on CPB can lead to a relative hyperperfusion of the right carotid parallel to a relative hypoperfusion of the aorta. This could explain our findings regarding SACP flow values and peripheral organ perfusion monitored by renal function and lactate level. The Seldinger technique delivers rapid arterial access, which results in a shorter ischemic period both cerebral and peripheral. AxS perfusion provides sufficient oxygenation for the right hemisphere, but may not for the contralateral side, so the required initial right SACP flow is similar to the direct group, but the left shows such values as in the femoral group. Additionally, a constant relative hyperperfusion of right hemisphere most probably leads to intracerebral oedema, which elevates SACP flow requirements to maintain a proper cerebral saturation at the end of HCA. Relative hypoperfusion of the body is characterized by diminished renal function at subclavian cannulation. It has to be considered as well, that at AxS approach usually smaller size cannulas can be applied due to the anatomical situation.

Femoral access is more time consuming to be established resulting in relative cerebral hypoperfusion/longer ischemic period demonstrated by higher initial SACP flow requirements in this group. Femoral perfusion, in case of no malperfusion, provides a proper renal blood supply, thus the renal function is better preserved than at subclavian access, but

the initial hypoxia due to delayed establishment of perfusion is visible comparing the creatinine levels in this group to the direct cohort. Peripheral arterial access is not only challenging in dissected vessels, but also at high body mass index, or on the other side of the spectrum, in patients with a delicate stature, e.g. in East-Asia.

Recent meta-analyses have also revealed advantages of central cannulation methods in complex aortic aneurysms and AAS surgery; proximal arterial cannulation adds-on a useful armamentarium for management of complex aortic disease in various aortic pathologies. Both Ma *et al.* (2018) and Shimura *et al.* (2019) have emphasized safety and advantages of ultrasound guided central aortic cannulation in TAAD regarding 33 and 208 patients in their series, respectively.

Seldinger technique delivers rapid arterial access, which results in shorter ischemic periods both cerebral and peripheral. Potential drawbacks of the technique require a smoothly operating team, which emphasises the importance of specialised aortic teams; technical ability to perform transapical cannulation as a bail-out; local dissection in cannulation area is extremely rare.

As eventual drawbacks do not impose significant challenges in moderate size cardiac centres and real-time ultrasonographic monitoring provides a safe procedure; the Seldinger cannulation on the lesser curvature is a good-to-know central arterial access in case of failing peripheral methods.

### ***Study II - Body temperature measurement sites in aortic surgery***

Our study on intraoperative core temperature monitoring demonstrates that tympanic measurements provide reliable temperature estimation during aortic surgery performed under HCA. This may aid in improved postoperative outcomes due to a reduced cooling phase and adequate rewarming. Although application of hypothermia has been an important contribution to patient management as a neuroprotective method from the dawn of cardiac surgery, proper body temperature management relies on accurate measurement of temperature, to enable adequate monitoring of changes during CPB and HCA. Oxygen consumption drops with lower body temperature so that ischaemic tolerance is increased by cooling. Cerebral oxygen requirement decreases to approximately one-fifth of normothermic needs at 20°C allowing a safe period of 45-50 minutes for HCA. In addition, hypothermia may contribute to neuroprotection by a variety of complex mechanisms including decreased vascular permeability, reduced ion influx and decreased excitatory transmitter release. During

the rewarming phase of CPB, conventional temperature monitoring sites may not reflect true brain temperature so that cerebral hyperthermia may not be detected, if conventional temperature monitoring underestimates brain temperature or there is a delay with arterial heat exchange. Monitoring rectal or urinary bladder temperature to control intraoperative core temperature is standard in many institutions all over the world. Rewarming, which aims to normalise temperature after HCA, relies on measured data from the above sites. We have shown that temperature measurement at these sites could be misleading, possibly due to latency in the heat exchange process at these points. Clinicians are often concerned about risks of postoperative hypothermia, such as shivering leading to increased myocardial oxygen consumption, arrhythmias, coagulopathy, higher risk of wound infections and elongated hospital stay, but possible side effects of cerebral hyperthermia are rarely taken into account. Thus, the rewarming phase must be carefully monitored and managed to avoid cerebral hyperthermia, since it elevates the risk of post-ischaemic tissue injury, and intraoperative hyperthermia is well known to be associated with post-operative neurological impairment.

Arterial blood temperature is considered to be the most accurate indicator of cerebral temperature. It is not surprising as this is the medium for heat exchange for the brain during HCA and SACP. According to our results, tympanic temperatures correlate well with arterial blood temperatures and hence with cerebral temperatures, not only during HCA but also during the rewarming phase of the surgical procedure. Urinary bladder and rectal temperatures lag behind arterial blood temperatures, therefore, these measurement sites cannot be relied upon to provide accurate estimation of temperature change. This affects management of these patients at various phases of cooling and re-warming. The tympanic membrane is situated in the immediate vicinity of internal carotid artery and is supplied by its branches. Thus, the tympanic temperature is well-placed to closely represent cerebral thermal state. Although some authors consider tympanic temperature as a good standard for cerebral temperature monitoring reflecting the hypothalamic status, others have suggested that tympanic temperature can be influenced by changes in ambient temperature. If prior to insertion of a tympanic probe, a debris-free status of the auditory channel is confirmed via otoscopic examination along with careful insulation by cotton swabs and the probe is securely fixed by tape and gauze bandage over the external ear, so the ambient temperature influence on tympanic measurement can be effectively diminished. Variations in urinary flow, which is a usual phenomenon during CPB and especially with HCA may affect the bladder temperature sensors. On the other hand, rectal probes can become lodged in faecal matter,

which insulates them from the surrounding tissues. The above factors can contribute to a weak correlation of these temperature measurements with those of arterial blood.

In our institute we do not use nasopharyngeal/oesophageal temperature monitoring in HCA as standard measurement site, as it has been shown in several studies to modestly, but significantly over- and underestimating brain temperatures during the cooling and rewarming phase, respectively. Probably this is a result of the suboptimal heat exchange environment as these probes are situated in larger air containing cavities. Although oesophageal probes are placed relatively close to the descending aorta, the open chest or eventually applied topical cooling in the pericardium could also influence measurement accuracy.

### ***Study III - Management options for aortooesophageal fistula***

Aortooesophageal fistula is a rare cause of gastrointestinal bleeding, characterized by significant morbidity and mortality, even with early diagnosis and intervention. Several therapeutical management options have been reported in literature, although all rely on the same principle; urgent management of the aortic tear with immediate or delayed repair of the oesophageal lesion. There are many approaches to treat AOF, but the treatment has to be adapted to the patient's wishes in some cases. In our experience the most straight-forward therapeutic option is emergency TEVAR followed by an urgent subtotal oesophageal resection; the therapeutic circle is completed by a second stage gastrooesophageal reconstruction. Securing the bleeding source as emergency, removing the oesophagus urgently to prevent sepsis, and subsequent elective reconstruction of gastrointestinal continuity appears to be a justified surgical approach, as the current available literature also states, although there are no large studies available. TEVAR is a new, lower risk emergency alternative, although stand-alone TEVAR leaves the oesophageal defect untreated, contributing to a higher risk of mediastinitis and increased mortality and morbidity. A similar conclusion resulted from the Regensburg experience; TEVAR is an effective emergency alternative to prevent early fatal exsanguinations, however, can rarely be utilized as a stand-alone procedure. A nationwide, multicentric Italian study provided information on 25 aortooesophageal and aortobronchial fistulas that were treated with TEVAR. The results demonstrated that patients, who underwent combined TEVAR and tracheobronchial/oesophageal intervention, had lower graft infection rates and better survival than patients receiving TEVAR treatment exclusively. Most probably, the long-term prognosis is affected by a concomitant mediastinal infection and graft contamination.

Surgical approach of the oesophageal lesion is controversial in the literature. Snyder *et al.* reported a primary suture of the oesophageal defect with minimal mediastinal contamination, although it was associated with a higher risk of dehiscence and fistula recurrence, probably due to local ischaemia. Instant oesophago-gastric anastomosis after subtotal oesophagectomy may be another alternative, although associated with increased risk of perioperative death, but this risk could be reduced by omentopexy around the tube graft. Subtotal oesophageal resection followed by gastric or jejunal interposition as a second stage surgical intervention could minimize the hazard of graft infection. For feeding, transdiaphragmatic or transthoracic gastrostomy are reliable solutions that both avoid further opening of the abdomen for a separate gastrostomy or jejunostomy and minimizes damage to the stomach, but maintains patency of the upper gastrointestinal tract. Another interesting complex solution to prevent late thoracic interposition graft infections has been described by Aleksic *et al.* and Aizawa *et al.* Although with different etiology, they both demonstrated reasonable long-term results after implantation of an extraanatomic ascending-descending aortic interposition tube graft bypass with stump closure of the affected descending aorta, with or without omentopexy around the descending stump. Müller *et al.* have investigated 33 patients with anatomic and extraanatomic repair following mycotic aneurysms of the thoracic and abdominal aorta, their conclusion shows that in situ reconstructions did not carry a higher risk of morbidity and mortality than extraanatomic counterparts.

Similar conclusions to our therapeutic considerations were drawn by the so far largest multicentric database analysed by Japanese Association for Thoracic Surgery in 2014. 47 AOF cases were reported from whole Japan, their conclusion was that TEVAR alone for AOF management is associated with high mid-term mortality and does not improve mid-term outcome; therefore, not be considered as a definitive stand-alone therapeutic option. In addition, oesophageal reconstruction might be acceptable for single stage operations in patients with stable condition, as no significant differences were observed between patients treated with oesophageal reconstruction at the same or a different occasion.

#### ***Study IV - Age-related considerations in acute type A aortic dissection***

TAAD is more common from seventh decade of life, albeit it is an unexpected pathology in healthy subjects; and represents one of well recognized causes of sudden death in young people. Our data entirely support previous findings reporting that among patients undergoing TAAD repair 6% are younger than 40 years, and 20% is aged less than 50 years. Several triggers including hypertension, smoking habit, cocaine abuse and amphetamine have been

associated with occurrence of this catastrophic event in the young, but the presence of underlying connective tissue disorder has been extensively recognized as a fundamental predisposing factor strongly bound to this population. It is not surprising that patients with known connective tissue disorders came to our attention at a significantly lower age than those without any syndromic disease and presenting with a tricuspid aortic valve. An inherited pathology of the aortic wall leads to faster development of aortic aneurysms and to higher risk of aortic complications. This early pathologic evolution does not characterize only syndromic patients, who represent only a small subgroup in surgical series, and a minority among young patients. IRAD investigators reported that people under 40 years with positive family history showed a significantly increased size of aortic root and ascending aorta when compared with older patients. This finding was common both in Marfan and non-Marfan patients. Several non-syndromic genetic conditions can lead to early development of thoracic aortic aneurysms, which are further characterized by rapid dilation, and high risk of dissection. These non-syndromic Familial Thoracic Aortic Aneurysms are related to genetically heterogeneous disorders, and are estimated to represent 20% of cases in diagnosed thoracic aneurysms. Mutations in five genes (MYH11, TGF $\beta$ 1, TGF $\beta$ 2, MYLK, and ACTA2) have been identified so far with all autosomal dominant inheritance. From molecular point of view, consequences of genetic alterations translate into a degenerative remodelling of the aortic medial extracellular matrix resulting in progressive loss of elastic properties. Clinical, anatomical, genetic and molecular evidences suggest that prevalence of inherited aortic wall disorders in young people presenting with aortic complications is probably higher than expected and diagnosed.

This pathologic background can have an important role in extension of dissection. In our series, a significantly lower mean age characterized the presentation with a more prominent involvement of the aortic root and distal aorta. Even after excluding patients from the analysis having syndromic disorders or bicuspid aortic valve, we found that more severe involvement of the aortic root and coronary sinus(es) were present in younger than in patients having a proximal dissection flap involving just the ascending aorta and limited to the non-coronary sinus. Association of lower age and dissection of coronary sinus(es) may further account for the preoperative presenting sign of myocardial ischaemia. This event has been associated with aortic root complication after dissection repair and can be seen as a marker of severe proximal aortic tissue disruption.

Intimal tear at the level of the aortic root is a feature of the younger subgroup and this result was additionally confirmed via analysis following exclusion of patients with known connective tissue disorders or bicuspid aortic valve. Alongside genetic and metabolic alterations, the aortic flow properties play a key role in progression of the wall disease, and maybe an active variable in promoting the onset of dissection. Recent studies investigated on aortic flow patterns and wall stress with the aid computational fluid dynamics. Wall shear stress seems to have a significant impact in triggering and progression of medial degeneration, and represents a mechanical force able to separate aortic layers once imbalance between the tissue strength and flow-induced wall stress occurs. Numata *et al.* investigated on six different anatomical models of aortic disease. In all patients the oscillatory shear index (a parameter describing the deviation on wall shear stress from its mean direction) was higher close to the sinotubular junction (STJ), near the origin of innominate artery, and on the lesser curvature of proximal descending aorta. All these areas are predilection points for intimal tears. Clinical evidences are limited, but suggest that different patterns of aortic segment dilatation and blood flow properties across the aortic valve can promote development of intimal tear in different areas of proximal aorta; with major involvement of the lesser curvature of ascending aorta in patients with preserved or not extremely dilated STJ; the right lateral side of the aorta in case of diffusely dilated proximal aorta; and the sinus(es) of Valsalva/STJ in presence of a dilated aortic root.

Different pathologic and pathogenetic substrates between young and elderly patients - the latter are affected by long-standing hypertension and a progressive atherosclerotic process - require a significantly different approach in proximal repair of aortic dissection. We found that full root replacement was regularly performed in younger patients, while elderly patients underwent a more conservative proximal repair. The literature reports an average rate of 23%-25% full root replacement in the overall population of patients undergoing TAAD repair, around 40%-60% in people under the age of 50, 10%-20% in septua- and 5%-10% in octogenarians. Isolated aortic valve associated with interposition graft replacement of the ascending aorta is nowadays reserved in case of valve leaflet degeneration or calcification, and reported in about 5% of cases; mostly in people aged over 70 years. There is no doubt that younger people deserve more radical aortic resection, but besides clinical and prognostic reasons we should recognize the importance of pathologic background and anatomic features in determining the surgical strategy for proximal repair. Nevertheless, recommendation for a full root replacement in case of connective tissue disorders, dilated or severely dissected

aortic root, and in presence of an intimal tear in the aortic root, is nowadays widely accepted aiming a safe procedure in an acute setting and reduction of risk of reoperation in mid- and long-term. Evaluation of anatomical characteristics can also explain similar prevalence of arch procedures in young and elderly patients in the literature; more extensive distal repair is usually reserved in case of an intimal tear situated in the aortic arch or in presence of an aortic arch aneurysm.

Clinical presentation and occurrence of dissection related malperfusion syndrome were not associated, apart from presence of signs of myocardial ischaemia and syndromic connective disorders, with the age of patients presenting with TAAD. More extensive involvement of the proximal and distal aorta characterized the younger patients. Different pathologic background triggering the onset of TAAD in young and elderly could explain this finding. Higher rate of connective tissue disorders and wide prevalence of undiagnosed intrinsic underlying disease of the proximal aortic wall might be accountable for this peculiar presentation in the young. Intimal tear in the aortic root is also more common at lower age of presentation. This finding associated with prognostic reasons is strongly supports a higher prevalence of full root replacement in younger patients.

## ***Conclusion***

### ***Study I - Central cannulation by Seldinger technique in type A aortic dissection repairs***

Ultrasound-guided direct cannulation on the concavity of aortic arch applying Seldinger technique is a reliable method in dissection repairs. Prompt antegrade perfusion provides not only cerebral, but also peripheral organ and tissue protection, which is an advantage in this high-risk group of patients.

### ***Study II - Body temperature measurement sites in aortic surgery***

We conclude that tympanic temperature measurements correlate with arterial blood temperature monitoring during aortic surgery with HCA and ACP and, therefore, should replace bladder and rectal measurements.

### ***Study III - Management options for aortooesophageal fistula***

Eliminating the source of bleeding as an emergency, resecting the oesophagus urgently to prevent sepsis and reconstructing the gastrointestinal continuity as an elective case after having the inflammatory processes settled seems to justify the sequence of endovascular

aortic repair and subtotal oesophageal resection, followed by a gastro-oesophageal reconstruction, as an effective surgical approach.

***Study IV - Age-related considerations in acute type A aortic dissection***

More frequent proximal and distal progression of the dissection flap occurs in younger patients with acute type A aortic dissection. Older age is associated with a lower probability of an intimal tear at the level of sinus of Valsalva. These findings, associated with prognostic implications, account for the choice of more radical proximal procedures for repair of aortic dissection in younger patients.

### *Summary of new findings*

1. Minimal invasive central cannulation by Seldinger method on concavity of the aortic arch is technically feasible and safe. It may avoid cerebral embolization and organ malperfusion; therefore, may reduce the rate of neurological and malperfusion complications. This alternative arterial inflow technique can be applied for prompt establishment of CPB in type A dissections or other aortic emergencies, especially during haemodynamic instability. SACP provides more homogenous perfusion to both haemispheres than UACP, reducing the risk of overperfusion of the right, and relative hypoperfusion on the contralateral side.
2. We have proven that tympanic temperature monitoring is highly reliable as a guide to temperature changes of the brain during HCA and rewarming, as best correlating with arterial and brain temperatures. We recommend multiple temperature measurement sites - additional bladder or rectal - during aortic surgery applying HCA and SACP to be able to assess homogenous cooling and rewarming of the patient.
3. Early diagnosis and aggressive surgical approach without delay is a key factor in effective treatment for AOF. TEVAR treatment is essential to save the patient, but as the process is usually situated in an infected environment due to communication with the inner body surface, TEVAR as a stand-alone procedure would often end-up with life threatening mid-term graft infection. Therefore, following short-term vital stabilization, the oesophagus should be removed, and the infected posterior mediastinal area cleared. After sufficient recovery period, a second stage interval gastrooesophageal reconstruction may lead to the most optimal long-term results.
4. We have demonstrated that more extensive involvement of proximal and distal aorta, myocardial ischaemia and syndromic connective disorders characterize younger patients. Different pathologic background promoting onset of TAAD in young and elderly patients could explain this finding. Intimal tear localized in the aortic root is also more common at lower age of presentation. These findings associated with prognostic reasons support the necessity for radical surgical approach in younger patients.

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***List of publications related to subject of thesis***

- I. **Göbölös L**, Philipp A, Foltan M, Wiebe K: *Surgical management for Stanford type A aortic dissection: direct cannulation of real lumen at the level of the Botallo's ligament by Seldinger technique*. *Interact Cardiovasc Thorac Surg*. 2008;7(6):1107-1109.
- II. **Göbölös L**, Foltan M, Ugocsai M, Thrum A, Philipp A, Livesey SA, Tsang GM, Ohri SK. *Recent advances in the management of Acute Aortic Syndrome*. In: Nazari S (editor): *Front lines of Thoracic Surgery*. Milano: 2012; ISBN 978-953-307-915-918.
- III. **Göbölös L**, Miskolczi Sz, Pousios D, Tsang GM, Livesey SA, Barlow CW, Kaarne M, Shambrook J, Lipnevicius A, Ohri SK. *Management options for aorto-oesophageal fistula: case histories and review of the literature*. *Perfusion*. 2013;28(4):286-290.
- IV. **Göbölös L**, Philipp A, Ugocsai P, Foltan M, Thrum A, Miskolczi Sz, Pousios D, Khawaja S, Budra M, Ohri SK. *Reliability of different body temperature measurement sites during aortic surgery*. *Perfusion*. 2014;29(1):75-81.
- V. **Göbölös L**, Ugocsai P, Foltan M, Philipp A, Thrum A, Miskolczi Sz, Malvindi PG, di Gregorio V, Pousios D, Navaratnarajah M, Ohri SK. *Central cannulation by Seldinger technique: A reliable method in Type A aortic dissection repairs*. *Med Sci Monit*. 2014;20:2386-2393.
- VI. **Göbölös L**, Tsang GM, Curzen N, Calver AJ, Ohri SK. *Transapical perfusion for peri-arrest salvage during transcatheter aortic valve implantation*. *Perfusion*. 2015;30(8):650-652.
- VII. Miskolczi S, Sheppard MN, Bogáts G, **Göbölös L**. *Double-locus lymphoplasmacytic aortitis*. *Asian Cardiovasc Thorac Ann*. 2018;26(3):231-233.
- VIII. Malvindi PG, Votano D, Ashoub A, Modi A, Miskolczi Sz, Velissaris Th, Barlow CW, Ohri SK, Tsang GM, Livesey SA, **Göbölös L**. *Age-related presentation of acute type A aortic dissection*. *Asian Cardiovasc Thorac Ann*. 2018;26(9):659-666.
- IX. **Göbölös L**, Bajwa G, Ramahi J, Bergonzi PC, Bhatnagar G. *An aortic “supravalvular shelf” is not always innocuous*. *NEMJ*. 2020;2(1):3-5. ISSN: 0250-6882.
- X. **Göbölös L**, Bonatti J, Bogáts G. *A comprehensive guide to new directions in thoracic aortic surgery*. In: *Horizons in World Cardiovascular Research*. Nova Science Publishers Inc., Hauppauge, NY: 2020; ISBN 978-1-53617-615-5. (In Press)

### *Glossary of terms and abbreviations*

AAS	Acute Aortic Syndrome
ACP	Antegrade Cerebral Perfusion
AHA	American Heart Association
AOF	Aortooesophageal Fistula
AxS	Axillary/Subclavian Artery
BSA	Body Surface Area
CAD	Coronary Artery Disease
COPD	Chronic Obstructive Pulmonary Disease
CPB	Cardiopulmonary Bypass
CT	Computed Tomography
ECC	Extracorporeal Circulation
ECG	Electrocardiogram
FTAA	Familial Thoracic Aortic Aneurysms
GERAADA	German Registry for Acute Aortic Dissection Type A
HCA	Hypothermic Circulatory Arrest
ICU	Intensive Care Unit
IMH	Intramural Haematoma
IRAD	International Registry of Aortic Dissection
MMP	Matrix Metalloproteinase
MRI	Magnetic Resonance Imaging
NIRS	Near Infrared Spectroscopy
PAU	Penetrating Atherosclerotic Ulcer
SACP	Selective Antegrade Cerebral Perfusion
STJ	Sinotubular Junction
TAA	Thoracic Aortic Aneurysm
TAAD	Type A Aortic Dissection
TBAD	Type B Aortic Dissection
TEVAR	Transcatheter Endovascular Aortic Repair
TOE	Transoesophageal Echocardiogram
TTE	Transthoracic Echocardiogram
UACP	Unilateral Antegrade Cerebral Perfusion