Transcatheter Aortic Valve Implantation: Clinical, Interventional, and Surgical Perspectives

Part 1 – Pathophysiological and translational perspectives

1.8 Hemodynamic issues with transcatheter aortic valve implantation

Jacob Salmonsmith, *MSc, Assistant Researcher, ucemjas@ucl.ac.uk*

UCL, Torrington Place, London, WC1E 7JE, UK

Anna Maria Tango, *MSc, PhD Research Student, a.tango@ucl.ac.uk*

UCL, Torrington Place, London, WC1E 7JE, UK

Andrea Ducci, *PhD, Senior Lecturer, a.ducci@ucl.ac.uk*

UCL, Torrington Place, London, WC1E 7JE, UK

Gaetano Burriesci, *PhD, Reader in Biomedical Engineering, g.burriesci@ucl.ac.uk*

UCL, Torrington Place, London, WC1E 7JE, UK

Ri.MED Foundation, Palermo, Italy

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Abstract

Transcatheter aortic valves are typically implanted inside the native (or failed bioprosthetic's) leaflets, permanently forcing the old leaflets open into a pseudo-cylindrical condition. Due to the passive nature of heart valves, the dynamics of the surrounding fluid environment is critical to their optimum performance. Following intervention, the haemodynamics of the region would ideally be returned to their healthy, physiological state, but major alterations are currently inevitable, such as increased peak flow velocity, the presence of stagnation regions, and increased haemolytic fluid environments. These leaflets reduce the volume of and restrict the flow into the Valsalva's sinuses, and minimise the development of vortices and associated flow structures, which would aid washout and valve closure.

Despite these differences to the healthy condition, implantation of these devices offers much improved flow from that of a moderately stenotic valve, with reduced transvalvular systolic pressure drop, peak blood velocity, and shear stress, which normally outweighs the disadvantages highlighted above, especially for high risk patients.

Key Words

In vitro; In simulo; Haemodynamics; Vortex; Stagnation; Transcatheter Aortic Valve

Abbreviations

ΔP	Change in Pressure (i.e. Aortic Transvalvular Pressure Gradient)
EOA	Effective Orifice Area
GOA	Geometric Orifice Area
PVL	Paravalvular Leakage
RBC	Red Blood Cell
SAV	Surgical Aortic Valve
SAVR	Surgical Aortic Valve Replacement
SCLT	Sub Clinical Leaflet Thrombosis
STJ	Sinotubular Junction
TAVI	Transcatheter Aortic Valve Implantation
TAV	Transcatheter Aortic Valve
WSS	Wall Shear Stress
ViV	Valve-in-Valve

Introduction

Heart valves ensure unidirectional blood flow throughout the cardiac cycle, and their operation is directly controlled by the pressure difference and local flow dynamics upstream and downstream of the valve. This passive mechanism implies that the interaction between the valve components and their surrounding fluid environment is critical to optimal valve function. As a consequence, the haemodynamics, or blood motion, within the aortic root provides crucial information and indicators about the performance and prognostication of heart valves. Analyses of these haemodynamics enable improved design of prosthetic replacement heart valves by enhancing the valve performance. Taking inspiration from the flow dynamics observed in healthy, physiological valves, such as vortex generation patterns, may aid the improvement of the valve performance as well as improving less quantifiable flow properties such as turbulence levels or stagnation zones. In fact, non-physiologically high blood shear can result in blood damage in the form of haemolysis and/or platelet activation, whilst at the other extreme, low shear can lead to blood stagnation and thrombosis, with coagulation occurring more quickly on artificial surfaces[1].

Native valve pathologies, such as senile calcification, can severely alter the local flow downstream of the aortic valve, impairing its function. When the haemodynamic performance is deemed to be insufficient and the native valve is replaced with a prosthetic valve, the haemodynamics of the region would ideally be returned to the healthy physiological state, but the current level of clinical intervention does not allow a full recovery of the optimum valve haemodynamics, and results in increased peak blood flow velocity, formation of stagnant regions within the Valsalva sinuses, and/or local flow characteristics that increase the risk of haemolysis.

The non-invasive nature of transcatheter aortic valve implantation (TAVI) provides treatment for patients who would be too weak for surgery, but also results in the calcified native leaflets being left in the aortic region, left in a forced open position between the prosthetic valve and the sinuses of Valsalva. As a consequence, beside the non-optimum haemodynamics comparable to those of a surgical aortic valve (SAV) procedure, TAVI results in further changes to the local flow dynamics. In order to fully clarify and interpret these changes, some basic review of the critical haemodynamic factors affecting the valve safety and performance is necessary, as well as a summary of the haemodynamic conditions occurring in healthy and pathological native valves and after correction with bioprosthetic SAVs and TAVs.

Haemodynamic Considerations

The pulsatile nature of blood flow results in four distinct stages of the cardiac cycle for the aortic valve – opening, open, closing, and closed.

As valve opening is initiated, it is important that the valve provides minimal resistance, promptly reconfiguring to offer the largest possible orifice area of the valve and, hence, conserve as much of the energy and pressure of the flow as possible[2]. In this stage, the valve resistance is related to the energy needed to reverse the leaflet curvature between the shut and open configurations. A ready opening, requiring lower pressure differences across the valve leaflets, results in minimum flow energy loss, and lower levels of strain and stress in the leaflets[2].

During the ejection phase, the widest valve opening is desirable, as it would utilise as much of the aortic lumen as possible, reducing the energetic losses. The valve opening is quantified by the Geometric Orifice Area (GOA), defined as the smallest transversal section encompassed within the open leaflets at the maximum systolic pressure. However, this parameter is difficult to measure in clinical environments and is not directly related to the systolic performance of the valve. In fact, the effective dimension of the ejected flow does not only depend on the area of the valve passage, but also on the downstream jet contraction due to leaflet profile and the extension and location of the vortices generated at the valve exit. Hence, a more indicative quantification the haemodynamic efficiency during valve opening is provided by the Effective Orifice Area (EOA), which corresponds to the cross-sectional area of the blood streamtube (a tubular region of fluid delimited by streamlines, i.e. lines locally parallel to the flow) ejected through the valve during systole, at the downstream point of its maximum contraction (*vena contracta*)[3,4]. The EOA is directly proportional to the systolic flow rate and inversely proportional to the transvalvular pressure drop (ΔP) across the valve and can be easily estimated in vivo and in vitro. GOA and EOA are directly related to the cross-section geometry of the jet flow contraction. Another factor that may introduce fluid energy losses, concurring to increased ΔP, is the presence of turbulence generated by non-physiological peak blood velocities[5].

Valve closure is determined by a combination of reverse transvalvular pressure, associated with the drop in pressure in the left ventricle due to diastolic relaxation, and the action of the vortices in the sinuses, which guide the leaflets profile before and during closure[6]. The synergy between these two mechanisms reduces the closing regurgitant volume, and the loss of flow energy. Similar to valve opening, a reduced resistance to the change in leaflets' curvature also contributes to reduce the stresses in the leaflets and minimise the energy consumed during closing.

Once the valve is fully closed, the main factor responsible for the loss of performance is the leakage of blood from the aorta to the ventricle. In the case of native valves, this is typically due to valvular incompetency (intravalvular leakage). For prosthetic valves and, in particular, TAVI devices, paravalvular leakage (PVL) external to the functional leaflets, occurring through potential gaps between the implanted valve and the surrounding host tissues, can be a major contributor to the regurgitant volume.

In summary, the overall left ventricular energy loss during the valve function is primarily associated with the ΔP across the aortic valve during systole, also related to the EOA, and with regurgitation during diastole[7]. However, other fluid dynamic parameters acting at a more local scale need to be taken into account, in order to evaluate the safety and efficacy of heart valves. As mentioned above, alteration of the physiological flow may induce turbulence, which is related to chaotic velocity fluctuations, and leads to increased aortic wall and leaflet

stresses and an elevated risk of haemolysis. Also, during the cardiac cycle the levels of shear rate and shear stress experienced by the blood vary greatly, with undesirable phenomena resulting at both non-physiologically high and low shear rates[1], promoting red blood cell (RBC) damage[8]. High blood shear rate results into haemolysis, especially when exacerbated by prolonged exposure, with the rupture of RBCs releasing their contents, and increasing the platelet activation levels and thrombogenicity of the blood[1,9]. Activated platelets are complementary to the aggregation of RBCs, and have been identified as the primary cells involved in cardioembolism, via haemostasis and thrombosis[10,11]. As the flow has a significant role in platelet activation, any deviation from the healthy, physiological behaviour is of clinical concern[10]. The magnitude of which specific shear stress, such as turbulent viscous shear stress (calculated the viscous dissipation of turbulent energy) or Reynolds shear stress (derived from the effect of convective acceleration upon the mean velocity profile), to be identified for the threshold of haemolysis is not yet agreed upon in the literature, but it is agreed that the higher the shear stress and the longer the exposure, the greater the amount of haemolysis[9,12,13]. In addition, the presence of turbulent blood flow, with associated high levels of turbulent stress, can also result in platelet activation and endothelial cell damage to the vessel walls[14,15].

On the other end of the scale, shear stresses below a threshold of 0.4 Pa increase the likelihood of thrombosis and cell aggregation, with platelets adhering to the surfaces leading to the formation of thrombi in sizes inversely proportional to the shear forces produced in static and low-flow conditions[1,16–18]. As well as the amount of flow stasis, thrombogenicity is affected by the amount and type of non-native material in contact with the blood, and the blood coagulability, dependent upon blood properties such as hematocrit and protein levels and any anticoagulation regimen[18]. Washout of a region will decrease the risk of thrombosis, with a RBC residence time less than 10 s significantly reducing the chance of cell aggregation, and blood flow speeds higher than 0.05 m/s drastically reducing any persistent stagnation[18,19]. The washout effect associated with the vortices shed from the aortic leaflets during systole reduces the prolonged presence of activated platelets in the sinuses of Valsalva[18]. Once thrombi form and grow, portions may break away from the primary site and block cardiovascular vessels, causing downstream areas of the body to become starved of oxygen and other nutrients, with potentially fatal consequences, such as a stroke or myocardial infarction[20]. Even if not detached, thrombus formation upon the bioprosthetic leaflets has been identified as the primary event resulting in reduced leaflet motion[21], potentially causing sub-optimal valve performance and flow separation downstream of the valve.

Physiological Haemodynamics

Healthy

The proper operating function of the native healthy valve is directly controlled by the interaction between the leaflets and the structural/fluid dynamics established in the aortic root (Figure 1.8.1A)[6,22,23]. The valve opens under the effect of an essentially radial flow, directed from the valve inflow towards the Valsalva's sinuses and following the root wall so as to realign with the root axis towards the sinotubular junction (STJ)[24]. This mechanism supports a prompt leaflet motion towards the open configuration, with the leaflets pushed into the sinuses until they assume an approximately circular orifice shape[25]. During this stage, a jet with a nearly flat velocity profile is ejected into the aortic root, with very little reverse flow back through the aortic annulus during systole[25,26]. Since the beginning of systole, the interaction between this fast jet and the low inertial flow in the developing boundary layer of the root results in the formation of vortices at the valve exit [26,27]. These vortices are captured in the sinuses throughout the forward flow phase, up to the early stages of diastole, disappearing only after complete valve closure[26]. As the vortices are confined, the central jet flow is unrestricted as it spreads out across the aortic root at the STJ, occupying most of the root section[26]. The presence of the vortices in the sinuses also contribute to stabilise the leaflets' position during the forward flow phase, keeping them away from the aortic lumen[27]. The flow becomes more complex further downstream in the aortic arch[25,26].

In late systole and early diastole, the pressure difference inversion and reverse flow generate a vortex ring spinning in the opposite direction to that observed after valve opening. Though axial pressure alone is sufficient to close the valve, this vortical structure promotes a swift and efficient closure[27],[28], minimizing the closing regurgitation. The location and size of these vortices affect the pressure within the sinuses, with optimal position aiding the coronary flow and pressure gradient across the coronary ostia[28]. The closing vortex fills the whole sinus throughout diastole, providing continuous washout of the region, even when the overall blood velocity is zero.

Physiological flow conditions are also essential in maintaining the healthy mechanical properties and function of the tissues of the leaflet tissue and root. In fact, together with the annulus expansion and contraction during the cycle, the physiological opening and closing mechanisms described above minimize the levels of shear and bending stresses in the leaflets, high levels of which would typically result in tissue degradation[29]. Moreover, it has been reported that the majority of aortic valve diseases occur on the aorta side of the valve, which might be directly linked with the more unstable flow conditions and shear rate present on the downstream side of the valve, as opposed to the comparably more uniform and regular ventricular flow[27]. Altered velocity gradients (i.e. shear rate) leading to abnormal viscous forces at the root wall have been shown to potentially change gene expressions, resulting in endothelial remodelling and alterations of the root geometry[30]. Healthy aortic root regions experience an average wall shear stress (WSS) of 13.3 Pa at peak systole, with an increase in WSS towards the leaflet tips[31]. Oscillating shear stress at a magnitude lower than that experienced physiologically is associated with regions prone to atherosclerosis, resulting in a far more aggressive and proliferative phenotype[17].

Pathological and surgically corrected

Various pathologies can affect the performance of the aortic valve, with degenerative aortic valve stenosis due to senile calcification currently the most prevalent valvular disease, affecting about 3% of individuals over the age of 65[32] and more than 10% of adults over the age of 75[33]. Treatment of calcific aortic stenosis via pharmacological therapies is currently limited and palliative, being unable to reverse or prevent the progression of aortic stenosis[34]. As a result of the increased leaflet stiffness due to calcification, the resultant haemodynamics are altered, with a reduction in EOA and less complete closing of the valve[27]. As the main jet cross section reduces in size, the peak velocity correspondingly increases – for example, a mildly stenotic valve of orifice area 1.5 cm^2 (for a reference STJ diameter of 2.5 cm) results in a ΔP of 20 mmHg and peak jet velocities up to 70% faster than in the healthy condition[35,36]. Consequentially, the elevated levels of shear stress and turbulence intensity increase the likelihood of damage to the root walls and blood, whilst the jet itself is asymmetrical and typically angulated[36]. Combined with typically asymmetrical leaflet calcification across the aortic valve leaflets, this can result in very complex patient specific conditions, especially when surface irregularities of calcified leaflets are taken into account[27].

For a more severe stenosis, the ΔP may rise above 40 mmHg and the EOA may drop beneath 1 cm^2, with the outflow jet diameter significantly decreased at the base of the aorta, reducing the size of the central jet and increasing the flow's peak velocity by up to four times that of the physiological condition[27,35]. This is accompanied by increased flow separation and highly turbulent shear layers between the central jet and the walls of the root, enough to cause damage to RBCs and platelets within the flow, and endothelial cells on the aortic walls[27]. In addition to the elevated risk of thrombosis and thromboembolism, the altered wall shear stress can lead to dilation of the ascending aorta, whilst the increased force of the faster jet can weaken the distal portion of the ascending arch[36].

Valve stenosis can also significantly alter the flow in the Valsalva sinus, with the systolic vortices becoming larger and more distorted, and located further from the leaflet tips soon after generation[31]. As a result, rather than being confined within the sinuses during valve closure, improving valve closure, these vortices leave the sinus region during late systole[26],[31], causing further deterioration to cardiovascular performance. In addition, the reduced recirculation in the sinus might be linked to the decrease in coronary flow, which is has been encountered alongside an increase in leaflet stiffness[37].

Surgical valve replacement via bioprosthetic substitutes aims to restore healthy functional conditions and physiological haemodynamics. However, whilst biological tissue valves are more biomechanically compatible than their mechanical counterparts, they are still not able to reproduce the healthy physiological state (Figure 1.8.1B)[2,26]. In fact, the presence of the supporting stent and the implantation strategy determine a mismatch between the aortic root and the shape and position of the prosthetic leaflets. The presence of the sewing ring and pledget-armed sutures used to fix the valve into place at the basal annulus, together with the restriction due to the stent thickness, result in a reduction of the GOA[38]. Similarly, the structures of the man-made commissures and the increased stiffness of the crosslinked tissue determine the formation of a non-physiological vortex above the commissures, which expands as the flow rate decreases in late systole, impinges upon the central jet flow[26], and affects the flow in the sinus[39]. Depending on the proportion between the bioprosthetic and the host root, the start-up vortex generated in early systole remains in the sinus, as in the physiological case, or migrates into the aortic root, narrowing the flow and decreasing the potential performance of the valve[26]. In

its stead, a second vortex forms in the sinus, with a direction of rotation opposite to that of the initial vortex, which is still effective in providing washout of the sinuses and supporting valve closure - the configuration produces similar levels of regurgitation to a larger surgical valve with vortical structures more closely aligned to those observed physiologically[26].

All these factors contribute towards producing a slightly stenotic valve performance, characterised by an increase of peak jet velocity and ΔP of 70% and 60% respectively, whilst the EOA reduces by 30%, when compared to that of a native valve in the same size aortic root[26,40]. The smaller leaflet lengths appear to reduce the closing regurgitant volume, mitigating some of the loss due to smaller EOA[26]. Bioprosthetic valve performance can be improved by using stentless configurations, which give less forward flow obstruction and improved haemodynamic performance to their stented equivalents[40]. However, their production and implantation procedure are more complex, and their performance can be affected by the irregularity of the host anatomy, and by procedural inaccuracies. In fact, the leaflets are normally designed to operate properly in a regular circular configuration, which is difficult to attain in the absence of a supporting stent. Generally, stentless valves are reported to restore flow velocities closed to the physiological ones, and better coronary flow than their stented equivalents, due to the resultant lower transvalvular pressure drop, and the decreased turbulence downstream of the valve[41].

The leaflets of bioprosthetic valves are usually constructed out of porcine or bovine tissue[42], which makes them vulnerable to calcification, resulting in valve stenosis and associated higher ΔP and peak blood flow velocity[40]. Leaflets have been constructed from polymeric materials to prevent calcification, but these tend to have more constricted flow orifices, reducing valve performance, decreasing the central jet diameter, and increasing the shear stresses experienced by the blood flow[43]. A sharp flow separator such as this would could result in a location with a high residence time of RBCs, increasing the thrombogenicity of the region[19].

TAVI Haemodynamics

Transcatheter valves merge some of the features of stented and stentless bioprosthetic valves, maintaining the presence of a frame which support and leads the prosthetic leaflets' attachment line, but minimizing its thickness to about 0.5 mm[44,45]. Due to the presence of the pathological native leaflets, the functional orifice area of the TAV may be limited by the irregularly calcified native valve leaflets, and operate at a configuration that is suboptimal, normally smaller than the fully expanded design geometry [46,47]. In fact, the nature of the implantation procedure, whether trans-femoral, trans-apical, or otherwise, implies an inherently increased level of variability of prosthetic valve positioning than in an equivalent Surgical Aortic Valve Replacement (SAVR) procedure[48]. Deviation from the ideal position by a few millimetres can potentially result in alteration of valvular haemodynamics, decreased ventricular performance, decreased TAV durability, seal zone mismatch leading to severe PVL, coronary artery obstruction, conduction abnormalities, and/or increased wall stress potentially resulting in valve embolization or annulus rupture[48,49]. Moreover, implanting the TAV into an annulus with a relatively high degree of ovality, exacerbated by heavy calcification or an inhomogeneous implantation layer, can result in the TAV itself being warped and/or deployed with an oval shape, without the possibility to correct this imperfection, which is possible during SAVR[46,50]. High level of eccentricity may lead to large increase in regurgitation, probably due to the lack of leaflet apposition[46,51]. Oversizing is commonly used to overcome this issue and attain more secure valve anchoring, but it can adversely affect the valve haemodynamics[52,53]. In fact, excess leaflet tissue relative to the stent orifice area results in severe/moderate stenosis of the TAV, increasing ΔP by up to three times[54].

Despite the mentioned limitations, transcatheter valves still result in reduced patient prosthesis mismatch compared to SAV, as the valve expands to fit into an annulus which, in turn, distends to an extent, accommodating a better valve fit[45]. As a result, the procedure is normally characterized by a larger increase in the systolic performance, with ΔP below 10 mmHg and EOA up to 2.0 cm^2, for a reference STJ diameter of 2.5 cm, with this performance maintained at follow-up[45,55].

Nevertheless, the fluid dynamics of the region after TAVI are different to both the healthy native aortic region and a post-SAVR aortic region (Figure 1.8.1C), with some of the prominent complications observed being flow separation regions downstream of the valve, energy losses across the valve, non-physiological coronary flow, and PVL[42]. Further complications can also occur further downstream of the valve, and TAVI is associated with an increased risk of stroke, cerebral embolism, and silent ischemic lesions post-implantation[56–59].

The difference in flow pattern is mainly due to the fact that the calcified leaflets are not removed during the implantation, but rather radially displaced into the Valsalva's sinuses, in a permanently open position. As a result, the volume of these sinuses is reduced by the presence of the displaced native leaflets, and radial flow during systole is confined to the upper regions of the sinus, around the free edges of the native leaflets[60]. Consequently, average flow velocity in the sinuses of Valsalva is reduced to a quarter of the physiological velocity, and the peak velocity in the region is halved[61]. This reduction in the fluid velocity and shear rate increases the chance of formation of thrombi[24,62], whose fracture and downstream transportation can eventually lead to neurological pathologies[56–59].

The space between the native leaflets and the TAV stent can be regarded as a neo-sinus, with a size dependent upon not only the geometry of the native region and the prosthesis, but also the angular orientation of the TAV – non-alignment of the TAV with the commissures may further reduce the flow within sinuses[63]. Flow in the

neo-sinuses may be particularly prone to stagnation and associated thrombosis, so lowering the heart rate whilst increasing the stroke volume maintains the cardiac output but improves the flow in this region, reducing the chance of leaflet thrombosis[63]. As previously mentioned, the flow within the Valsalva sinuses play a key role in blood supply to the coronary arteries and sinus washout[6,22,64].

The described configuration of the implant also determines major variations in both the fluid mechanics and operating mechanisms of the valve[24]. In the case of TAVI devices, the start-up vortices generated during opening do not hold in position at the tip of the dynamic leaflets inside the upper part of the sinus, but form further downstream at the edge of the native leaflets, which act as a continuous wall[24]. This is associated with reduced washout of the sinuses[24],[51] and some delay of around 10 ms in the opening of the valve[61,65]. During systole, in most designs the valve stent prevents the operating leaflets from opening beyond 90°, resulting in a narrower, centrally located systolic jet[61,65], characterised by higher peak velocities, up to double that in healthy native valves[5,25,64]. The raised central jet velocities result in higher viscous shear stresses, up to 6 Pa [51], which is still below the haemolytic threshold[60].

During valve closing, the return of fluid in the axial direction is not accompanied by the vortical structures observed in the physiological configuration, reducing wash-out of the sinuses[24]. The presence of the static native leaflets also alters the effect of the fluid suction generated by the closing leaflets upon the fluid within the sinuses[60]. Consequently, valve closure is delayed by about 10 ms [61,65], and extended and prolonged stagnation zones develop between each sinus and its corresponding native leaflet throughout the entire cardiac cycle, with a shear rate below 100 s^{-1}[24,48].

During the closed stage, PVL is far more common than in SAV, due to the elliptical shape of the native annulus combined with heavy calcification of the region, which can lead to a reduction of annular sealing[41,75,76,77]. Asymmetrical deployment may also result in intra-valvular leakage, as full closure of the leaflets is inhibited by the deployed frame shape[46,66]. The high level of PVL is mitigated to an extent by redilation of the prosthesis and, in more recent devices, by the use of external skirts around the upstream base of the valve frame[65,67]. Despite these improvements, moderate and severe PVL is still frequent in TAVI, and is associated with increased mortality[66]. This produces substantial energy losses in diastole, imposing a higher workload upon the left ventricle[54]. This PVL may be reduced in the months post-procedure by tissue overgrowth from the surrounding physiology and/or coagulation of blood filling in the gaps between the prosthesis and host tissue. However, mild leakages are reported as remaining constant, and the statistics indicating decreases in severe or moderate PVL over time may be biased by the increased mortality associated with higher levels of PVL[66,68].

The regions of flow stagnation described as a result of TAV implantation can lead to thromboembolic complications[60,64]. In particular, the regions of permanent low level of shear rate observed at the base of the Valsalva's sinuses, associated with the rheology of blood, lead to a substantial increase in the local dynamic viscosity, prolonging residence time and producing thrombogenic conditions [24]. This effect is mitigated in the coronary sinuses, as the flow accessing the coronary arteries slightly increases the shear stress in the sinus[39]. The sinus flow alterations can have a detrimental effect upon the coronary reserve, with reductions of up to 20% of the coronary flow [22,69,70]. This is not necessarily a critical problem, as myocardial demand typically reduces as a result of improved left ventricular performance, but this may depend on the long-term myocardial needs of the individual patient[41].

The effect of TAV upon coronary artery flow is not agreed upon in the literature. There are reports that the post-TAV implantation flow of some coronary arteries is increased from the pathological level, thanks to decreased central flow velocity, reducing the resultant Venturi effect during systole, and improved coronary bed pressure gradients[41]. However, there are also reports that sinus flow alterations as a result of TAVI in aortic roots with low positioned coronary ostia may have a reduction in coronary flow by up to 20%[68]. Coronary ostia have an increased risk of being obstructed when in the vicinity of native leaflets thickened due to calcification, a problem exacerbated by using an oversized TAV relative to the native region[62,71]. The implantation procedure itself can also cause obstruction, whether due to fragmentation of the calcified native leaflet during TAV insertion, high implantation of the TAV, or as a consequence of a balloon expansion method[55]. Non-ideal positioning of the TAV also increases the risk of coronary ischemia and conduction abnormalities of the heart, with atrioventricular block occurring after 16% of procedures, compared to 1% of SAVR[44,72–74]. Increased blood residence times have also been observed close to the leaflets and around the non-physiological neo-sinus zone in general, resulting in more thrombotic conditions[75]. As a result, risk of clinical thrombotic events is not insignificant after TAVI, particularly in the first 3 months following the implant, with most cases occurring within 6 months; although the variance in manifestation is large, with some events occurring within 2 weeks of the procedure and others not becoming present for over 9 months[76,77]. If the thrombosis does not directly affect the valve performance, this may be undetected for some time, as sub clinical leaflet thrombosis (SCLT) results in the presence of lesions and reduced leaflet motion, but not to the extent that the valve performance is noticeably affected[78,79]. Though the performance of the valve is not affected, SCLT can be associated with transient ischemic attacks and strokes, so prevention may improve long-term clinical outcomes[78]. Clinical thrombotic behaviour is observed when the thrombosis reduces the mobility of the prosthetic leaflets, thus increasing the transvalvular pressure drop[76,77]. Clinical thrombosis is treatable by oral anti-coagulation, such as Heparin or Warfarin, which restores both TAV function and, correspondingly, haemodynamic performance for 75% of patients, although this anti-coagulation treatment is not a viable option for all patients[64,76]. The increased level of co-morbidities of the older patients who require TAVI is possibly an important contributing factor to thrombosis[79], though it is plausible that the valve thrombosis is caused by the leaflets themselves, due to the high levels of inflammatory cells in the thrombus. In fact, leaflet damage occurring during crimping and balloon expansion can result in native leaflet fissuring, perforation, and endothelial denudation[76,77] increasing the likelihood of thrombosis[78,79]. It is still debated if the metallic frame of TAVs may act as a nidus for thrombi until endothelialization occurs, although it is plausible that the level of turbulent shear stresses in the region should provide sufficient washout[64,76,79]. Folding or geometric confinement of the leaflets may increase the blood residence time, indicated as a permissive factor in TAV leaflet thrombosis, with no preference to occurrence on the leaflet associated with the non-coronary sinus[75]. The lower rate of thrombosis in bioprostheses when the native valve is excised suggests that the lack of native leaflet ablation for TAVI may be another source of thrombosis, as their presence causes a reduction of sinus washout during systole[24,63].

Valve in Valve

Another relevant application of TAVI is their use for the treatment of dysfunctional or underperforming surgical valves[55,66,71], by expanding the device inside a previously implanted bioprosthetic valve, in a valve-in-valve (ViV) configuration.

The approach further narrows the orifice area, and therefore it may not be indicated for patients requiring small prostheses, as this additional reduction may result in critically reduced valve performance[66,80,81]. Supra-annular positioning can help to reduce this negative effect, allowing the transvalvular pressure drop to halve, but increase the risk of further reduction of the flow in the sinuses[82]. In fact, as the flexibility of the stent posts of the host prosthetic valve is greater than the annulus, they tend to splay outwards, resulting in a 'flower pot' arrangement[53] which results in a less constrained operating configuration for the operating leaflets, especially at their free margin. Moreover, this provides a wedge effect which improves the security of the valve, especially in the case of balloon expandable devices, where the post-ballooning recoil results in the radial forces being reduced as the prosthesis is fitted into the rigid section at the base of the host stent[83].

Though effective in dropping the energetic losses during systole, the 'flower pot' arrangement narrows the available access to the Valsalva's sinuses, resulting in further reduction of the sinus washout[80]. However, the increase in stagnation is less severe in the coronary sinuses, as the flow towards the ostia generates some motion in the region[39]. Still, the chance of coronary obstruction is raised after ViV treatment, especially when the original prosthesis had badly calcified leaflets, the ostia are located close to the annulus, the aortic region and STJ have a narrow diameter, and/or the sinuses themselves are particularly narrow[41,68,71,80].

Blood residence time is reported to increase also in the neo-sinuses, in proximity of the TAV leaflets, with a longer residence time during systole (about 40% longer) and higher mean value of residence time from the end of systole until mid-diastole (about 150% longer), elevating the thromboembolic risk of the valve[75]. In addition, other ViV issues include bad positioning of the TAV (15% of procedures), leaflet thrombosis (4%), coronary artery obstruction (3.5%), and increased conduction issues for ViV configurations than for TAVI within a native valve[66,80].

Conclusion

Being able to circumvent the necessity of surgery when replacing the aortic valve is the vital value of TAVI, enabling weak patients who would be at high risk of morbidity from surgery to receive life changing improvements to their cardiac function. However, this primary benefit necessarily comes with some drawback, which need to be fully understood, appreciated and assessed when pondering the opportunity to expand the crucial advantages of TAVI to lower risk patients and devising new generation valves.

The presence of the native leaflets reduces the sinus volume[60], restricting the flow in the Valsalva sinus chambers[61] and minimising the development of vortical structures and associated flow, especially at the basal end of the sinuses[24]. Coronary arteries with particularly low ostia seem to be at higher risk of reduced flow or blockage by either the native leaflet or a detached thrombus from the basal portion of the sinus [62,71]. Similarly, the region between the native and the bioprosthetic leaflets is also particularly prone to stagnation and thrombus formation[75]. In the case of valve-in-valve procedures, the functional orifice area is further reduced, whilst blood residence time in the sinuses is increased again due to even more diminished sinus washout[66,80,81]. These thrombogenic conditions could be linked to the increased rates of strokes and transient ischemic attacks[56–59], as well as the more recent concern of subclinical leaflets thrombosis[78,79]. Anticoagulation treatment can be used to control these thrombotic concerns, although this comes with the inherent risks and management of the anticoagulant drugs themselves[64,76].

In terms of orifice area, the TAV's design and method of expansion enables a better fit into the annulus it is being implanted into than the rigid SAV[45]. However, the positioning of transcatheter devices is currently less precise and affected by the asymmetries of the host region[46,50], and these factors have been linked to increased leakage of the bioprosthesis[46,51].

Despite these drawbacks, the resultant blood flow through a TAV after implantation is much improved from that of a moderately stenotic valve – blood velocity is decreased[5,64], and the shear stress of the aortic region is below the haemolytic threshold[51,60]. The bioprosthetic produces acceptable pressure gradients, generally below 10 mmHg[45,55], and these benefits normally outweigh the disadvantages highlighted above, especially in high risk patients.

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Figure Captions

1.8.1 – Schematics of fluid flow within aortic root throughout cardiac cycle for physiological (A), post-surgical (B), and post-transcatheter valve implantation (C) configurations.

A) i – As the valve opens, radial flow directed towards the sinuses from the valve inflow supports leaflet motion towards the open configuration; ii – the leaflets assume an approximately circular orifice shape, as a jet is ejected through the valve and vortices are generated at the leaflets' edge – these vortices are subsequently captured within the Valsalva sinuses; iii – at the end of systole, the pressure difference inversion and reverse flow generate a vortex ring with the opposite rotation, aiding valve closure; iv – the vortex fills the whole sinus in diastole, washing out the region.

B) i – The flow is similar to that in A, although the presence of the sewing ring reduces the orifice area and results in a vortex at the base of the sinus; ii – a non-physiological vortex forms above the commissure stent post, impinging the jet flow, whilst the sinus vortex either remains in the sinus or migrates into the aortic root, depending on the relative size of the surgical valve. If the vortex migrates, a second vortex forms in its stead, with opposite rotation direction; iii – this counter vortex is still effective in washing out the sinus and supporting valve closure; iv – similar to A, during diastole the vortex fills the whole sinus and washes out the region.

C) i – the native leaflets form a permanent pseudo-cylindrical structure around the bioprosthetic, decreasing the sinus volume, reducing flow in the lower regions of the sinus throughout the cycle, and potentially preventing the bioprosthetic from fully expanding to its designed geometry, narrowing the geometric orifice; ii – the vortices generated by the opening of the valve do not remain at the bioprosthetic's leaflets' edges, but rather at the tip of the stationary native leaflets, delaying the opening of the valve and reducing sinus washout; iii – during valve closure, the vortical structures observed in the physiological configuration are not present, reducing wash-out of the sinuses and delaying valve closure; iv – the sinus filling vortex observed in A and B is not present, reducing washout during diastole