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Non-physiologic closing of bi-leaflet mechanical heart prostheses requires a new tri-leaflet valve design

Thierry Carrel [a,*], Walter P. Dembitsky [b], Bas de Mol [c], Dominik Obrist [d], Gilles Dreyfus [e], Bart Meuris [f], Bernhard Vennemann [d,g], Didier Lapeyre [h], Hartzell Schaff [i]

[a] Department for Cardiovascular Surgery, University Hospital and University of Bern, Switzerland
[b] Department for Cardiovascular Surgery, Sharp Memorial Hospital, San Diego, CA, USA
[c] Technical University, Eindhoven, the Netherlands
[d] ARTORG Center, University of Bern, Bern, Switzerland
[e] Cardiothoracic Center, Monaco, Monaco
[f] Department of Cardiovascular Surgery, Gasthuisberg, University of Leuven, Belgium
[g] Institute of Fluid Dynamics, ETH Zurich, Zurich, Switzerland
[h] Novostia SA, Neuchâtel, Switzerland
[i] Department for Cardiovascular Surgery, Mayo Clinic, Rochester, USA

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ABSTRACT

Mechanical heart valve prostheses are based on older designs without changes during the last 40 years. Today, there is an unmet need for less thrombogenic mechanical prostheses. Analysis of the relationship between flow characteristics and thromboembolic complications is possible using numerical and biomolecular flow studies that have shown that the reverse rather than the forward flow is responsible for local platelet activation and thrombosis. After peak flow, leaflets experience flow deceleration and the leaflets are still widely open when the flow becomes zero. The closure of the valve starts with the onset of reverse flow. Therefore, the valve closes extremely fast with most of the leaflet traveling angle occurring in <10 ms with excessively high reverse flow velocities. The pivoting spaces, so-called "Hot Spots" should be eliminated to prevent pathologic shear stress that result in thrombosis. A novel tri-leaflet valve combines favorable hemodynamics with the durability of mechanical heart valve. This valve closes within 60 ms, much slower than bi-leaflet valves and similar to the closing mode of a tissue valve. Micro-particle image velocimetry did not show critical regions of flow stagnation and zones of excessive shear in the pivoting region suggesting low potential for thrombogenic events that should allow to avoid long-term anticoagulation.

Current bi-leaflet mechanical valves based on a design developed in the early 1970s with the assumption that damage to blood cells and thrombogenic activation occur during forward flow. In contrast to the energy efficient central flow of human valves, caged-ball valves of the 1960s obstructed central flow and were replaced by tilting-disc valves and later by bi-leaflet pyrolytic carbon valves; the latter became the gold standard [1]. Since then, there has been little progress in the design of mechanical heart valves.

Minimizing the energy required to eject the blood through the valve did not eliminate activation of the coagulation cascade. Therefore, current bi-leaflet mechanical valves still require life-long anticoagulation. Although inexpensive, Warfarin increases bleeding risk and does not address the real problem of mechanical heart valves. New anticoagulants were recently disqualified by clinical trials [2].

Advanced experimental, numerical and biomolecular blood flow studies have shown that the reverse rather than the forward flow phase is responsible for local platelet activation and thrombosis [3,4]. These insights on thrombogenicity of mechanical heart valves have been overlooked so far. Indeed, the medical community still believes that oral anticoagulation in patients with mechanical heart valves is required because foreign material is exposed to the blood flow.

Modifying closing characteristics and hinge mechanisms by a tri-leaflet mechanical valve design may reduce thromboembolic complications and will make need for long-term Warfarin therapy unnecessary.

Soluble agonists of the coagulation cascade initiate platelet aggregation and thrombus growth ("*biochemical coagulation*") in mechanical heart valves. High resolution intra-vital imaging techniques and numerical hydrodynamic analyses confirm that platelet aggregation is

* Corresponding author at: Department for Cardiovascular, Surgery University Hospital, University of Berne, CH-3010 Bern, Switzerland.
E-mail address: thierry.carrel@insel.ch (T. Carrel).

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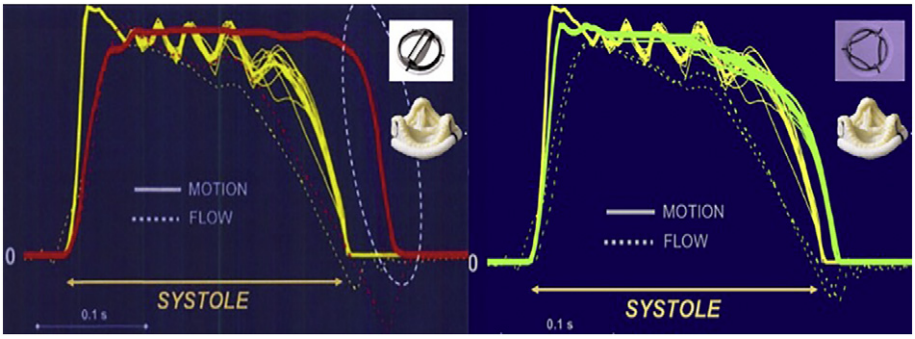

Fig. 1. Left. Closing mode comparing a tissue valve (yellow) with a mechanical bi-leaflet valve (red). The St Jude valve is wide open at zero flow while the tissue valve (CE) is fully closed. Right. Closing mode comparing a tissue valve (yellow) with a mechanical tri-leaflet valve (green). The tri-leaflet valve closing mechanism is rather similar to that of a tissue valve (CE). Left is valve opening and right valve closure.

primarily driven by changes in blood flow parameters ("*shear-induced thrombosis*") [5].

Shear stresses during valve closure of current bi-leaflet prostheses are much higher than those required to stimulate platelet activation [1]. Platelets exposed to excessive shear stress instantaneously develop membrane tethers, leading to transient platelet aggregates. Upon subsequent exposure to low-flow conditions or flow stagnation, filamentous tethers physically restructure, increasing the strength and stability of platelet aggregates, thereby promoting thrombus growth. Simultaneously, large thrombi form on substrates that are not covered by endothelial cells from local release and conformational changes of von Willebrand factor with explosive (<10 microsec) binding to specific platelet receptors (*20,000 GPI b sites on each platelets*) and "Velcro-like" capture of billions of platelets.

The bi-leaflet valve cannot close without reverse flow because flow deceleration in late systole does not generate sufficient closing pressure. Unlike the leaflets of a native or tissue valve, the carbon leaflets start closing with the onset of reverse flow (Fig. 1) which accelerates rapidly due to the low pressure in the relaxing ventricle. This non-physiologic closing mode leads to significant backflow during the closing process. Moreover, the valve closes extremely fast and exhibits leaflet rebound. Experimental studies report 75% of the leaflet traveling angle occurring in <3 ms and reverse flow velocities as high as 200 m/s (approximately 700 km/h) [3]. For a short period of time, this leads to extremely low pressures. When pressure goes below the vapor pressure, blood is "boiling" for few microseconds – a process known as *cavitation* - and the formed micro-bubbles "implode" when pressure recovers with a considerable energy release that can damage or even destroy solid surfaces. At the same time, nitrogen and carbon dioxide are extracted from the blood and bubbles with a longer lifespan are detected downstream in the brain (HITS: High Intensity Transient Signal) [6].

After closing, aortic pressure leads to a leakage flow through the narrow gaps in the hinge recesses of bi-leaflet valves. Like the non-physiologic closing mode, this leakage flow leads to shear-induced thrombosis in the hinge region, which may immobilize one leaflet or the entire valve [4]. This phenomenon has been thoroughly investigated by modern computational methods and high-velocity jets in the hinge regions were identified with velocities higher than 5 m/s leading to shear stresses beyond 100 Pa. Platelets are activated in these high shear regions and get trapped in low shear regions in the vicinity of the hinges.

Better design of mechanical valves must ensure smooth closing during flow deceleration to prevent reverse flow and eliminate high-shear hinge flow during diastole. Tissue valves addressed the problem of thromboembolic complications of mechanical valves and the disadvantage of anticoagulation. The concept consisted in retaining the design advantages of the native valves. The tissue valves do not carry such a risk because of the soft closing mode during flow deceleration (Fig. 1) and because there is no leaking hinge for the leaflets. Their low thrombogenicity is not material related. Glutaraldehyde fixation makes biologic tissues hydrophobic similar to foreign materials commonly used in mechanical valves; its toxicity results in poor endothelial cells adhesion and therefore cross-linked bovine or porcine collagen materials have no bioactive protection against thrombosis. This is the reason why oral anticoagulation is still recommended in the early phase (3–6 months) following tissue valve implantation.

A new tri-leaflet valve design (Lapeyre-Triflo Valve, Novostia, Switzerland) is much more similar to that of a biological valve than a bi-leaflet valve (Fig. 1). It combines the favorable hemodynamics of bioprosthetic heart valves with the durability of mechanical heart valves. Computational and in vitro studies indicated that this valve closes much slower than bi-leaflet valves and similar to the closing mode of a tissue valve (Fig. 1) [7,8]. Studies using micro-PIV were unable to identify any critical zones of excessive shear in the pivoting region, suggesting a lower thrombogenic potential compared to classical recessed hinge designs [9].

Recent efforts have focused on development of tissue valves for trans-catheter implantation only. However, there is still a worldwide unmet need for more durable and less thrombogenic heart valves, particularly for younger patients including children and women in child-bearing age suffering from congenital or rheumatic valve disease.

The Tri-Flo valve is a novel valve concept towards a Warfarin-free mechanical heart valve that combines optimal function, minimal blood particle injury and predictable long-term performance. This will challenge the trans-catheter valves.

Declaration of Competing Interest

D. Lapeyre, is the founder of Novostia and hold stocks. T. Carrel, W. Dembitsky, B. de Mol, G. Dreyfus, B. Meuris are members of the Advisory Board of Novostia. B. Meuris, D. Obrist and B. Vennemann received research funding. H. Schaff has no conflict of interest to declare.

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