

Can Regurgitant Flow Damage the Left Atrial Endothelium in Patients with Prosthetic Mechanical Heart Valves?

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Background and aim of the study: Previous in-vitro studies of mechanical heart valves (MHVs) in the closed position demonstrated the formation of regurgitant flows, with bubbles and jets forming vortices during each systole. The study aim was to determine whether the regurgitant flow observed in patients with MHVs can damage the left atrial endothelium, due to shear stresses exerted on the endothelial layers. This objective has been accomplished by appropriate in-vitro simulation experiments.

Methods: In these experiments, leakage flow through several commercial MHVs was investigated. The geometry of the set-up closely resembled that of the left atrial anatomy. Water was forced through the slit of a closed MHV and directed toward the hemispherical cup coated with fluorescent paint. The flow field between the valve and the cup was photographed using high-speed videography, from which local velocities were measured, using digital particle imaging velocimetry. Qualitative damage to

the surface of the cup was assessed from the amount of fluorescent paint removed from the cup.

Results: The experimental results and calculations indicated that flows through the gaps of the closed valves were sufficient to generate strong vortices, with velocities near the atrial wall in the range of 0.5 to 4.0 m/s, depending on the valve. This led to high shear stresses on the left atrial wall, which far exceeded physiologically acceptable levels.

Conclusion: The calculated shear stresses exceeded by orders of magnitude the maximum physiologically tolerated stresses. This suggests that shear stresses associated with regurgitant jets in MHVs may damage the endothelial cells, leading to the activation of the inflammatory reaction, enhanced procoagulation, platelet activation and aggregation, and mechanical cell denudation.

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The closing phase of mechanical heart valves (MHVs) is a rather stormy event. Indeed, in patients with mitral MHVs, clinicians have observed bright, intense, high-velocity and persistent echoes (high-intensity transient signals, HITS), which resembled bubbles both in appearance and movement. The suspected bubbles were seen by Doppler echocardiography at the instant of valve closure (1). Although the phenomenon of cavitation seems to trigger the mechanism by which bubbles are formed, this proposal could not be proven in humans until recently, when Paulson et al. (2) measured high-frequency pressure fluctuations up to 67 Pa in patients with St. Jude Medical and CarboMedics MHVs in the aortic position. Experiments with patients with normal aortic valves,

as well as with bioprosthetic valves, resulted in very low pressure fluctuations of about 0.5-0.8 Pa. In-vitro studies have also demonstrated the presence of bubbles in the vicinity of MHVs, but not in bioprosthetic valves (3-6).

Bubbles are formed when the local pressure is reduced below the vapor pressure of the liquid. In the case of MHVs, abrupt pressure changes are associated with valve closure. When the fluid returns to a high-pressure region, the bubbles collapse violently, releasing very high energy which may damage the nearby blood elements. High-frequency pressure oscillations have been shown to be associated with bubbles on MHVs (4-6).

Another phenomenon that occurs after mechanical valve closure is that of vortex formation, which was recently observed in vitro (6). However, vortex formation has not yet been observed in patients, nor are there any reports from animal experiments in which vortices have been detected.

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In a recent study, Rambod et al. (6) simulated the gap of a closed St. Jude Medical valve, and showed that flow and pressure conditions of a magnitude which was measured clinically in patients, led to vortex formation. This finding confirmed the present authors' previous suspicions of a potentially damaging occurrence associated with valve closure, with unknown clinical implications. The question posed is whether conditions exist during the first 25-35 ms of systole to enable vortex formation and, if so, how far from the valve does this vortex reach, and whether its impact on the walls of the left atrium results in damage to the endothelial layer.

Materials and methods

Experimental set-up

A schematic of the experimental set-up is shown in Figure 1. The set-up was designed to reproduce the backflow conditions that occur in a closed MHV. The equipment consisted of a test chamber (shown schematically in Fig. 2) in which a mitral valve could be mounted below a transparent hemispherical cup. To simulate the geometrical relationship of the mitral valve and the left atrial wall, the distance between the valve and the hemisphere was set at 3 cm. At the base of the hemisphere, four openings were made to simulate the four pulmonary veins.

Five medical-grade 29-mm mitral MHVs were tested in the experiments, namely, St. Jude Medical, ATS, Mira by Edwards Life Sciences, Medtronic-Hall single leaflet, and CarboMedics valves.

Flow visualization was performed using two methods, one qualitative and one quantitative. Qualitative visualization was carried out by micrometer-sized hydrogen bubbles produced from the hydrolysis of water. The bubbles were generated on the tip of a needle electrode and used as tracers. This is a well-known technique for flow visualization (6). The position of the needle electrode could be adjusted by a micrometer screw, such that the small bubbles passed through the gap of the closed valve and were entrained in the vor-

tex that formed distal to the valve, serving as tracers for the flow.

Quantitative visualization was carried out by digital particle imaging velocimetry (DPIV). Silver-coated glass spheres (10 μm diameter) dispersed in the water were used as tracers; the method for this is described below.

A third set of experiments was designed in order to simulate potential damage to the left atrial walls. In these experiments, the concave side of the hemisphere was covered with a thin layer of fluorescent paint of thickness ~ 0.1 mm. When the painted surface was placed in quiescent water, the paint layer remained intact. However, when hit by a water jet the paint would partially detach from the surface and dissolve in the water, thus reflecting the amount of damage to the painted surface.

The water for the experiments was de-ionized and kept under pressure in a pressure vessel. The working temperature was 22°C. The flow of liquid was con-

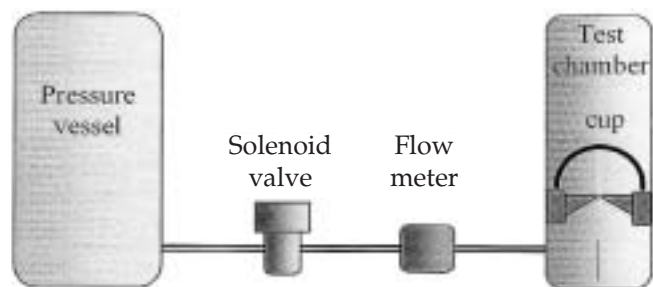


Figure 1: Schematic representation of the experimental set-up.

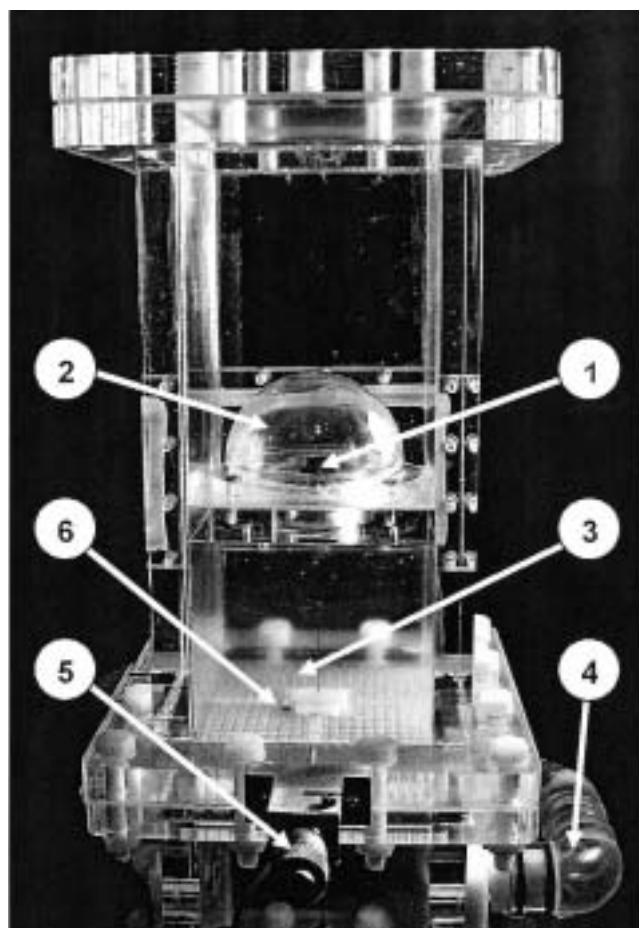


Figure 2: Experimental set-up. 1. Closed mechanical heart valve. 2. Transparent cup simulating left atrial wall. 3. Needle electrode for bubble generation. 4. Pulsed flow inlet tube. 5. Electrode adjustment screw. 6. Perforated plate for flow equalization.

trolled by a high-speed solenoid valve, the operation of which was monitored by a solenoid drive unit set at a 35 ms opening time, which was sufficient and suitable for the purposes of this study.

The pressure inside the vessel was kept constant, leading to leakage jet velocities through the gaps of the valves in the range 1-4 m/s depending on the valve design. This range corresponded to the backflow velocities measured in MHVs in patients.

Experimental procedure and data acquisition

The flow field between the valve and the hemispherical cup was photographed by high-speed videography, using a 1000 frames per second Kodak Digital Motion Analyzer (model HR1000; Kodak, Rochester, NY, USA) at a spatial resolution of 512x384 pixels. A video camera equipped with a Tamron TeleMacro 90 mm, f/2.5 lens connected to a 12-bit A/D board (MacADIOS ADPO; GW Instruments, Somerville, MA, USA) was used to visualize the flow field downstream from the valve gap and up to the wall of the hemisphere. Approximately 1,500 digital images were recorded for every experiment, and downloaded onto 2.3 GB magneto-optical discs (EDM-2300B; SONY Oradell, NJ, USA) for analysis.

Flow rates were monitored and recorded by a four-crystal clamp-on 16C ultrasonic flow probe (Transonic Systems, Ithaca, NY, USA), placed downstream of the solenoid valve. The flow probe was connected to an ultrasonic flow meter (T110; Transonic Systems) generating an output signal of ± 1 V. The solenoid was activated, releasing a short pulse of liquid, which entered the lower section of the test chamber and passed through the narrow gap between the leaflets of the closed mitral valve, creating a high-velocity jet.

Results

Initially, the leakage backflow through the different closed valves was measured. Figure 3 shows flow rates through the valves as a function of time, from opening of the solenoid valve and up to some time after it was closed, with positive flow rates indicating backflow through the valves. The shapes of the curves for the different valves were similar, with maximum flows of 5 to 5.5 l/min. It should be noted that the St. Jude Medical and Medtronic valves exhibited some forward flow after the solenoid had shut off; this phenomenon may represent a recoil effect due to the higher pliability of the sewing rings and lower firmness of the mountings in these two valves.

Before performing the quantitative studies, an experiment was conducted with the 29 mm St. Jude Medical mitral valve and without the hemispherical cup, in order to obtain a general qualitative view of the flow field distal to the closed valve. Figure 4 shows the sequence of events during the first 10 ms from the time the solenoid valve was opened. The flow is seen to start as a jet, and then to develop into a vortex, which is formed in the retrograde direction to the closed valve (7); following this, the vortex dissipates.

Figure 5 shows a typical sequence of photographs with the cup in position retrograde to the closed St. Jude Medical valve, depicting development of the vortex. The flow is seen to start perpendicular to the cup and then, as the fluid approaches the cup surface, to change direction such that it becomes parallel to the surface (Fig. 5h), exerting a shear stress on the surface.

In the quantitative set of experiments, DPIV was used to determine the velocity at the valvular level, as well as close to the surface of the hemisphere. The experiment was repeated three times for each valve. During the experiment, the procedure consisted of following a specific tracer particle through several photographic frames, as it approached the hemisphere surface and changed direction from normal to parallel, thus simulating the flow near the left atrial wall. Using this procedure, the velocities near the cup surface and parallel to it were found (Table I). In some of the valves there was a variation in leakage flow velocities during

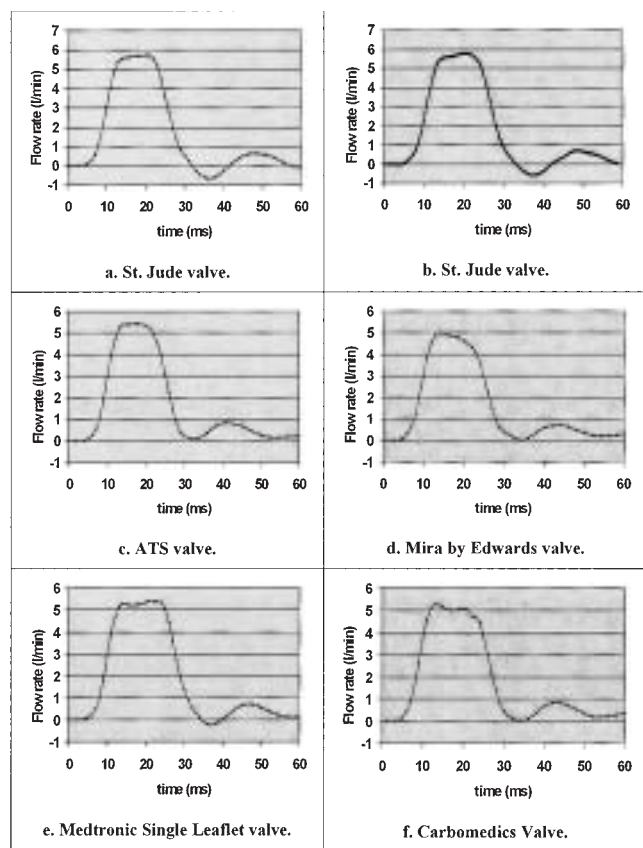


Figure 3: Flow rates through the various valves as a function of time. Positive flow rates indicate backflow.

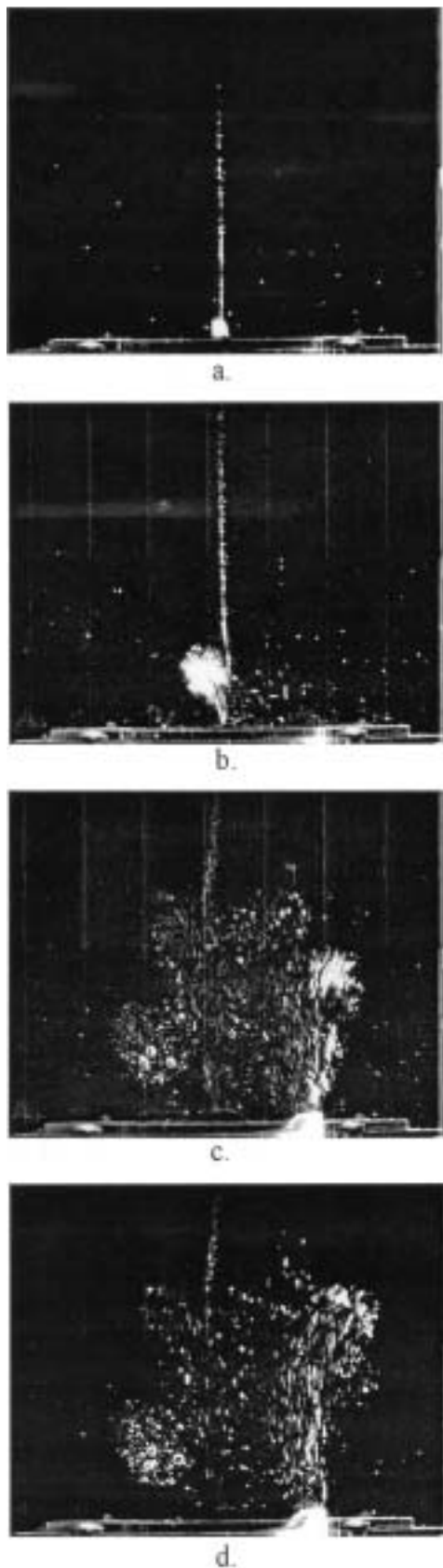


Figure 4: Sequence of events during vortex formation in a closed valve.

Table I: Velocities near the cup surface for leakage flow through different valves.

Valve type	Velocity (m/s)
St. Jude Medical #29	3-4
St. Jude Medical #29	2.5
ATS	2.0
Mira by Edwards	0.75-1.5
Medtronic-Hall single leaflet	0.5
CarboMedics	1.25-1.5

the repeated experiments, indicating a different gap width at each closure of the valve.

In the third set of experiments, which were performed with all the tested valves, the transparent hemispherical cup was covered with a thin layer of fluorescent paint and mounted in position (see Fig. 2). Before each experiment, the painted cup was photographed using a digital camera. The experiments were run by releasing 10 consecutive flow pulses, each of 35 ms duration, after which the cup was removed from the set-up and re-photographed.

Figure 6 includes three pictures of the cup from experiment with the 29-mm St. Jude Medical valve: (a) before the experiment; (b) after the experiment; and (c) the digitally obtained difference between (a) and (b), indicating the damage caused by the impact of water vortices exerted on the cup during the 10 consecutive flow pulses. The illustration shows clearly the extent of damage caused to the wall of the cup, there being discrete areas in which the damage is more severe than on the remainder of the surface, which points to there being impact sites of the vortices. It should also be noted that the damage on the circumference of the cup (see Fig. 6c) attests to the existence of secondary jets on the circumference of the valve, and indicates leakage on the periphery of the valve, near the hinges. Although this is a design feature of the valve - the purpose of which is to wash the hinges and prevent settling of blood clots on them - the jets still cause damage to the surface of the cup.

Calculation of wall shear stress

The estimation of the wall shear stress τ_w is based on the vortex velocity, as measured from the particle imaging velocimetry. To find the wall shear stress resulting from the flow impinging on the cup inner surface, the equation for stagnation flow as given by White (8) was used:

$$\tau_w = U_o F''(0) \sqrt{\mu \rho B} \quad (1)$$

where U_o is the free stream velocity, $F''(0)$ is the normalized wall shear stress function, μ the fluid dynam-

ic viscosity, and ρ its density.

The constant B is given as $4/\rho B U_0 =$ where $D = 5.0$ cm is the diameter of the cup. U_0 is found from the axisymmetric stagnation flow solution (8) as $U_0 = 1.3F$. Hence, substitution of B and U_0 into Eq. (1) yields:

$$\tau_w = 2.6U_0^{3/2} \sqrt{\frac{\mu\rho}{D}} \quad (2)$$

For water, viscosity $\mu = 1 \text{ cp} = 0.01 \text{ g}/(\text{cm}\cdot\text{s})$ and density $\rho = 1 \text{ g}/\text{cm}^3$, such that the following is obtained:

$$\tau_w = 2.6U_0^{3/2} \sqrt{\frac{0.01 \times 1}{5.0}} = 0.1163U_0^{3/2} \frac{\text{dyne}}{\text{cm}^2} \quad (3)$$

where the units of U_0 are cm/s.

The wall shear stress for the flow through the different valves is now calculated using Eq. (3). For comparison, the wall shear stress is recalculated using an approximate method, in which a boundary layer thickness is assumed, given by White (8) as:

$$\delta = 2.4 \sqrt{\frac{\nu}{U_0}} = 1.2 \sqrt{\frac{\nu D}{U_0}} \quad (4)$$

The wall shear stress is calculated for this case as follows:

$$\tau_w = \mu \left. \frac{\partial u}{\partial y} \right|_{y=0} \approx \mu \frac{\Delta u}{\Delta y} \Big|_{y=0} = \mu \frac{U_0}{\delta} = \frac{U_0}{1.2} \sqrt{\frac{\rho\mu}{D}} \quad (5)$$

The fluid velocity at the edge of the boundary layer is assumed to be the one measured by the DPIV

method. Hence, the wall shear stress is calculated for water as:

$$\tau_w = \frac{U_0^{3/2}}{1.2} \sqrt{\frac{\rho\mu}{D}} = \frac{U_0^{3/2}}{1.2} \sqrt{\frac{1 \times 0.01}{5}} = 0.0373U_0^{3/2} \quad (5)$$

The data on measured velocities and calculated shear stresses in close vicinity to the cup surface are summarized in Table II.

Equation (6) yields shear stresses which are approximately one-third of those obtained from Eq. (3). As both equations represent approximations to the actual flow conditions, the results of the calculations should be taken as indicative of the order of magnitude, rather than exact data.

Data correction for blood flow

The data obtained in experiments with water are now corrected for blood. Equations (2) and (5) may still be used to calculate shear stresses for blood issuing from a slit and changing direction to parallel flow near a surface. However, the properties of blood must be substituted and the velocity in Eqs. (2) and (5) adjusted.

The velocities used in Eqs. (2) and (5) for experiments with water were measured directly using the DPIV method. To adjust the velocities to blood flow, the equation is used of a plane jet issuing from a slit into a stagnant fluid, according to Schlichting (9). For this case, the centerline jet velocity is:

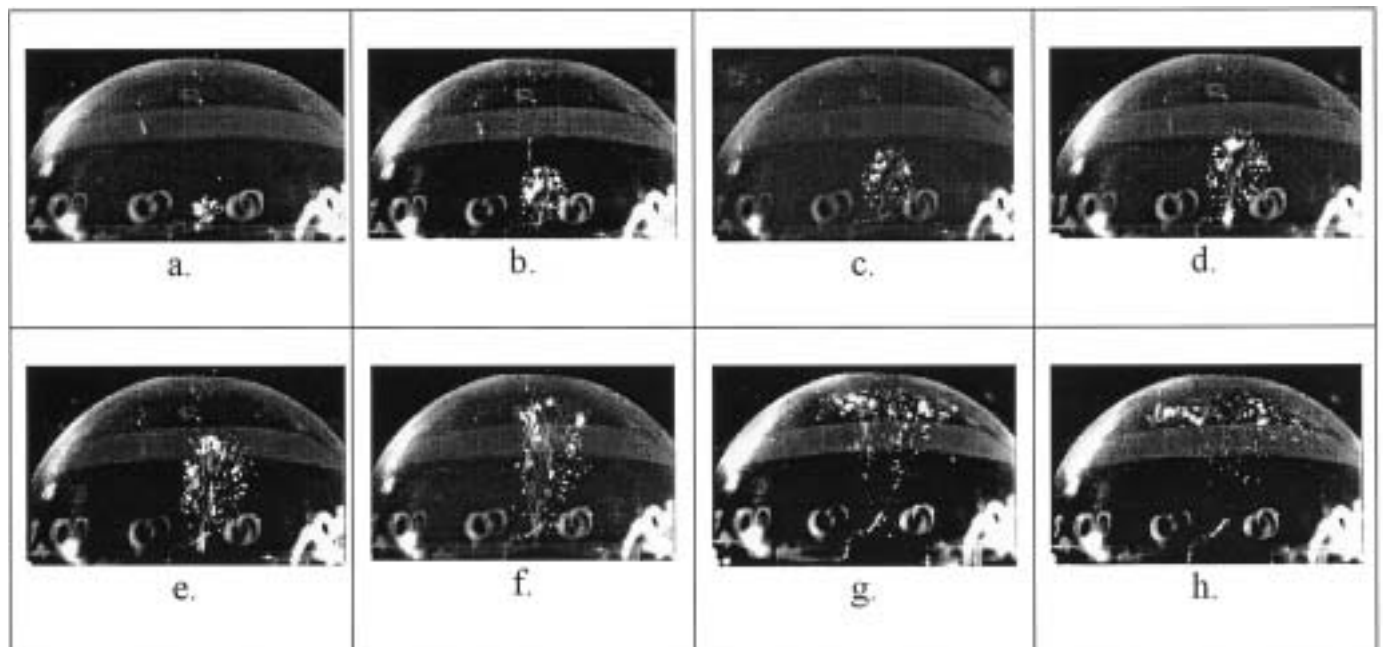


Figure 5: Sequence of photographs depicting development of the vortex with the cup in position retrograde to the closed valve.

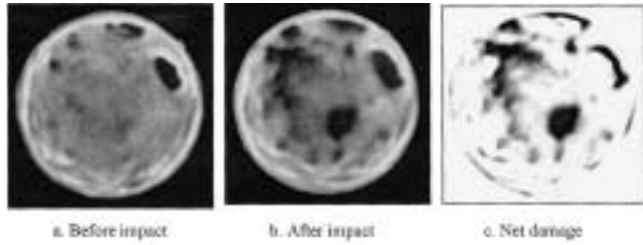


Figure 6: Damage due to vortex impact on the hemisphere surface.

$$U_0 = 0.4543 \left(\frac{\rho K^2}{\mu x} \right)^{1/3} \quad (7)$$

where K is the kinematic momentum of the jet and x its distance from the slit. Hence, the velocity depends on fluid properties as $1/3(\rho/\mu)U_0 \propto$.

The ratio of blood-to-water shear stress at the wall can now be computed using either Eq. (2) or (5) as:

$$\frac{\tau_{\text{blood}}}{\tau_{\text{water}}} = \left(\frac{U_{\text{blood}}}{U_{\text{water}}} \right)^{3/2} \sqrt{\frac{(\rho\mu)_{\text{blood}}}{(\rho\mu)_{\text{water}}}} = \left(\frac{(\rho/\mu)_{\text{blood}}^{1/3}}{(\rho/\mu)_{\text{water}}^{1/3}} \right)^{3/2} \sqrt{\frac{(\rho/\mu)_{\text{blood}}}{(\rho/\mu)_{\text{water}}}} = \frac{\rho_{\text{blood}}}{\rho_{\text{water}}} \quad (8)$$

Equation (8) indicates that the shear stress ratio is directly proportional to the density ratio of the fluids, and for blood with a density 1.04 g/cm^3 this ratio is therefore 1.04. Hence, the shear stress data given for water in Table II are approximately valid for blood also.

Discussion

The phenomenon of regurgitant jets in patients with MHVs has been well established from the time that diagnostic echocardiography was introduced into cardiology, and has been studied by leading groups in vitro (10,11). Jet velocities in the range of 2-5 m/s have been reported in the literature (12). These jets are considered by many as an integral part of the normal 'physiological function' of a prosthetic mechanical valve.

One clinical aspect of these regurgitant jets is their interaction with blood elements, more specifically with blood platelets. Recent clinical and laboratory data have hinted toward one important adverse effect due to the high velocities of these jets and their flow patterns, especially of vortices that generate high shear stresses, which lead to the activation of platelets that is believed to contribute to a state of hypercoagulability in the vicinity of the valve (13).

During a previous in-vitro study of bubble formation in MHVs (7), it was noted that the jets tended repeatedly to form vortices as they developed and advanced during each systole from the prosthetic mitral valve towards the left atrial wall. In the present study, the question was posed as to what effect these vortices have on the atrial endothelial cell layers or, more precisely, was the magnitude of the shear stresses exerted by these vortices sufficiently high to impart sustained damage to the endothelial layers?

In order to answer this question, a series of in-vitro experiments was designed and performed with water. The data obtained from these experiments enabled assessments to be made of the shear stresses exerted on the endothelial layer during each systole through the gap between the leaflets of a closed mechanical mitral valve. The experimental results obtained, and the calculations based on the data indicated the following findings:

The velocities measured on the axes of the jets close to the hemispherical surface were, for the different valves, in the range of 0.5-4.0 m/s. Marked differences were found between the various valves, with the single-leaflet Medtronic valve having the lowest leakage flow.

In spite of the variability in the leakage flows through the gaps of the closed valves, the flow conditions were sufficient in all cases to generate strong vortices.

The vortices seen in these experiments were not limited to the central gap between the leaflets, but also appeared in the peripheries near the hinges.

The high velocities measured in these experiments led to high shear stresses in the blood, which have previ-

Table II: Leakage flow velocities and shear stresses near the cup surface for different valves.

Valve type	Velocity (m/s)	Shear stress from Eq. (3) (dyne/cm ²)	Shear stress from Eq. (6) (dyne/cm ²)
St. Jude Medical #29	3-4	604-930	192-298
St. Jude Medical #29	2.5	460	147
ATS	2.0	330	105
Mira by Edwards	0.75-1.5	76-214	24-68
Medtronic-Hall single leaflet	0.5	41	13.2
CarboMedics	1.25-1.5	163-214	52-68

ously been recognized as having an adverse effect on the platelets, resulting in platelet activation and aggregation.

Even if the lower shear stresses calculated from Eq. (6) were representative of the actual stresses, they were far in excess of the maximum physiologically tolerated levels, which are known to be in the range of 7-14 dynes/cm² (11).

These high shear stresses may result in activation of the endothelial cells in various forms, of which enhancing procoagulation is the more relevant. They may also lead to mechanical endothelial cell denudation along with activation of the inflammatory reaction (14).

In this report, attention was focused on the potential adverse mechano-transduction effects of periodic damage to the left atrial endothelial cell layer by the wall shear stress (WSS), rather than on its better-recognized effects on the platelets and their activation. However, in order to emphasize the importance of the proper function of the endothelial cells and the other blood elements, current understandings of WSS and its effects must be reviewed (15).

The majority of research into the effects of shear stress on endothelial cells has been conducted in relation to atherosclerosis of the arterial tree, which is a high-pressure system. The present study revealed the existence of high shear stresses as a result of the impact of high-velocity vortices on the endocardial endothelial cell layers of the left atrium, which is a low-pressure system. To the best of the present authors' knowledge, this phenomenon has not been investigated to date.

In being located at the interface between the blood and the vessel wall throughout the circulatory system, endothelial cells are strategically positioned to respond to hemodynamic forces, which manifest themselves as shear stress and strain. Strain is the abluminal stretching that results from wall shear (the force which would 'tear' a cell from its adherent state), leading to vascular distention that affects endothelial cells and subendothelial components (e.g. smooth muscle cells and extracellular matrix). Flow-induced hemodynamic forces signal endothelial cells to modulate the synthesis and release of a variety of vasoactive antithrombotic substances, the net effect of which is to promote blood fluidity. The phenomenon of flow-induced adaptive vasodilatation (16) is mediated by the release of vasoactive products, such as prostaglandin I₂ (PGI₂, prostacyclin) and endothelium-derived relaxing factors or nitric oxide (NO), from shear-stimulated endothelial cells (17).

Endothelial cells may act as shear sensors in their role of regulating flow by means of changing the arterial diameter under normal and pathological condi-

tions (18). Moreover, shear stresses induce endothelial cells to release platelet inhibitory and fibrinolytic products which, in the presence of an intact endothelium, tend to counterbalance the pro-aggregatory effects of pathologically elevated shear stresses in the arterial circulation (19).

The steady-state release of prostacyclin by endothelial cells subjected to pulsatile shear stresses is more than double that of cells exposed to constant shear stress (20). These findings indicate that endothelial cells release bursts of PGI₂ in response to step increases in shear stress (21). PGI₂ is likewise produced by endothelial cells subjected to the cyclic strain or stretch, which occurs with each pulse wave (22).

The release of NO from endothelial cells is stimulated by the cyclic shear stress (23) and the resulting strain (16). The response to shear stress is greater when flow is pulsatile (20).

Tissue plasminogen activator (tPA)-generated plasmin is not only fibrinolytic but can also proteolyze large von Willebrand factor multimers and, under certain conditions, inhibit platelet function (24). As noted previously, tPA and plasmin inhibit shear-induced platelet aggregation. Arterial levels of shear stress (>15 dynes/cm²) stimulate the secretion of tPA by endothelial cells, whereas the secretion of plasminogen activator inhibitor type 1 (PAI-1) remains unaffected by shear stress over the physiological range (25). This enhancement of the fibrinolytic potential of endothelial cells in response to hemodynamic forces is at least partially transcriptionally regulated, as tPA mRNA is increased by shear stress (26).

The mechanisms by which the principal hemodynamic forces of cyclic shear stress and strain transduce signals to alter the structural and functional properties of endothelial (and other) cells are poorly understood. Moreover, cyclic fluid shear stress and strain may use different signaling pathways, because gene regulation and protein secretion are quite different in response to these mechanical stimuli (27).

In summary, shear stress can directly activate platelets. Under normal circumstances, however, intact endothelial cells exposed to strong flow-induced forces produce a potent array of vasodilatory and platelet-inhibitory mediators that mitigate the activation of platelets by shear stress to preserve blood fluidity. However, when the vessel wall component of Virchow's triad is perturbed, these endothelium-derived factors cannot oppose direct shear stress-induced platelet aggregation that occurs subsequent to initial platelet-subendothelial adhesion. The result is platelet thrombus formation, associated - if it occurs in a coronary artery - with downstream tissue ischemia and infarction.

In the presence of a MHV, the fine balance between

procoagulant and anticoagulant factors is steadily tipped towards thrombus formation, due to the fact that the high shear rates encountered in these valves are entirely outside the physiological range. This fact should alert us to the major violation of this delicate balance.

It is further believed that the high shear stresses may lead to sustained damage of the left atrial endothelial layer, which might be expressed in several ways. On the mechanistic level - and especially in the presence of gas bubbles - it may lead to abrasion and denudation of the cells from the basal laminae (15), whilst physiologically it constitutes a steady insult on the endothelial layer. This results in a further tipping of the balance towards hypercoagulability in the vicinity of the mechanical valve, and leads to continuous stimulation of the inflammatory reaction and activation of the clotting cascade.

Although modern mechanical heart valves have saved many lives and have been proven very beneficial to patients, there remain many areas where valve design could be improved. The phenomena of vortex shedding and bubble formation (6,7) are unique to the operation of the current generation of MHVs, and have not been observed in bioprosthetic valves.

Based on the findings of the present study, the design of future prosthetic heart valves should be considered so as to minimize the shedding of vortices from these valves in the closed position, to dissipate the velocities, and to reduce the shear stresses thereof. This is indeed a formidable challenge, which requires the coupling of high-quality clinical understanding with some ingenious engineering thoughts.

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