Mitral mechanical heart valves: in vitro studies of their closure, vortex and microbubble formation with possible medical implications

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Abstract

Objective: The goal of the present work was to create the closest possible in vitro fluid dynamic environment in which prosthetic mitral valves in the patients’ hearts function, in order to demonstrate whether microbubbles are generated, and if yes, under what conditions and at which stage of the cardiac cycle. Microbubbles were observed in the blood of patients with mitral mechanical heart valves (MHV) by means of echocardiography. The phenomenon, often referred to as high-intensity transient signals (HITS), appears as bright, intense, high-velocity and persistent echoes detected by Doppler echocardiography at the instant of valve closure. The question is no longer whether microbubbles are being formed in patients with MHV, as an inherent aspect of their design, but rather how they evolve and when. The answer to this question was the objective of the present paper. Methods: Hemodynamic conditions in which microbubbles were observed in patients with mitral MHV were simulated in our laboratory. We were able to describe the bubble formation process, as one consisting of nucleation and microbubble growth. While mild growth of nuclei is governed by diffusion, extensive growth of microbubbles is controlled by pressure drop during deceleration of the leaflets on the housing on the atrial side of the mitral MHV. Results: The present study has shown that bubbles form in a fluid at the instant of closure of mechanical valves. The formation of vortices after valve closure, although clinically not yet observed, was also demonstrated in the present in vitro studies. We believe that impact of such vortices on the endothelial layer of the left atrial wall may have clinical significance. These two phenomena were not observed in bioprosthetic valves. Conclusions: As demonstrated, there exist two distinct phenomena characteristic of mechanical heart valves, which take place during valve closure, namely, that of vortex formation and that of microbubble growth. Both phenomena may have far reaching clinical implications.

Keywords: Mitral valve; Mechanical heart valve; Microbubble formation; Valve closure; High intensity transient signal

1. Introduction

The improvement made in recent years in echocardiographic technology enables us to observe new phenomena previously not seen or measured at regular heart catheterization. With the availability of better resolution and new approaches to view the heart, a closer scrutiny of the dynamics of mechanical heart valves became possible. Phenomena, termed at first as spontaneous echocardiographic contrast, seen at systole in patients with mechanical prosthetic mitral valves, were reported [1,2]. In 1992 Reisner et al. [2] reported that spontaneous contrast, as seen in patients with Carbomedics valves in the mitral position, is more likely to be the result of bubbles formed at valve closure. These bubbles were shortly afterwards observed by Doppler ultrasonography as bright, intense, and persistent high-velocity echoes, and were referred to as high-intensity transient signals (HITS) [3]. As HITS were detected by transcranial Doppler (TCD) studies in patients with mechanical heart valves (MHV) [4], reports of some degrees of neurological disorders followed [5]. This phenomenon has been observed [2] only on the tilting disc type and bi-leaflet valves. There was no evidence of bubble formation on bioprosthetic valves. Different Doppler-based methods have been developed for detection and characterization of the embolic material in blood, indicating that Doppler signal intensity of gas emboli differs
significantly from that of solid emboli. Recent reports showed clear distinction between gas emboli and echoes seen in low-flow states.

By the nature of valve design, transient transvalvular flows and pressures during and after closure cause a certain degree of retrograde flows termed regurgitation. This is a twofold process: The amount of backflow during the closure of the leaflet, is called the closing volume, and whatever leaks through the closed valve is the leakage volume.

Whereas valvular regurgitation has been studied both clinically and in-vitro [6], the exact dynamic events at the very last stage of the closure are still being debated [7,8]. Since the housing and the leaflets of the valve are considered rigid structures from the hemodynamic point of view, the closure of a mechanical heart valve may instigate a combination of forward squeezed flow, and backward water hammer together vortex cavitation on the atrial side of the valve [9,10], resulting at valve closure in areas of positive and negative pressures [12]. As the local pressure drops below the vapor pressure of the liquid, vapor filled microbubbles are formed. Moreover, after valve closure the leakage flow forms a jet, which may assume the form of a vortex, accompanied by a low pressure zone.

HITS were originally observed in the middle cerebral artery by means of TCD, in patients with visible high-velocity mobile echoes popping from their mitral MHV [13].

TCD images of the carotid artery in patients with MHV have displayed reflected signals similar to those observed upon mitral valve closure [11,12]. Similar Doppler signals have also been reported in patients with atrial fibrillation and carotid artery disease [1]. The gas-filled bubbles generated by mitral MHV closure can be of the order of 200–300 μm in diameter. The significance of steady showering of the brain by micro gas emboli is currently difficult to assess, due to lack of unambiguous clinical evidence [14,15]. Some reports have found a correlation between brain micro-emboli detected by TCD, and the decline in neuropsychological function in patients with MHV [16], irreversible neurological damage [3] and other consequences [5,17,18].

In the present work we describe the model we have postulated [19] for the closure of MHV in the mitral position, which results in the evolution of microbubbles and the formation of vortices. We present a hypothesis to correlate our findings with the various potential medical implications on patients, and draw some conclusions on the design of the next generation of MHV.

2. Materials and methods

The experiments consisted of two separate studies, namely that of vortex flow and that of bubble formation, and were carried out in the Cardiovascular Fluid Dynamic Research Laboratory at Caltech.

The fluid in all the experiments was de-ionized water at 37 ± 1 °C. It must be stressed that one should not overlook the different physico-chemical properties of water compared to those of normal blood. This may in fact raise some concerns about the one-to-one correspondence between the laboratory study and its medical implications. Still, based on the clinical experience of the authors, the results should closely resemble conditions as seen in patients.

The purpose of the first set of experiments was to demonstrate the formation of a vortex in flows through a stationary two-dimensional 80 μm slit, which simulates the slit between the valve leaflets in the closed position of an MHV. The second set of experiments was designed to demonstrate the formation of microbubbles during valve closure in a dynamic system, consisting of a left heart pulsed flow simulator. In this system clinical grade MHV were used.

While in the dynamic experiments the microbubbles were formed as a result of the valve closing process, in flow through a closed stationary slit there were very few visible bubbles observed.

2.1. Vortex formation

Regurgitant flows through the mitral mechanical prosthesis often form a vortex ring structure. The vortex studies were performed in a setup shown schematically in Fig. 1, with the two-dimensional valve model shown in Fig. 2. The setup was designed to simulate the flow conditions that occur at the peak of backflow after valve closure, in the first 25–35 ms of the systole, when high-speed leakage passes through the narrow gap that remains between the closed leaflets of the valve. It consisted of a test chamber, in which a stationary two-dimensional valve model was mounted.

The flow of the liquid was controlled by means of a high-speed solenoid valve. The opening time of the solenoid valve was set to 35 ms and the pressure inside the pressure vessel was adjusted such as to achieve a maximum velocity through the gap of around 12 m/s, which corresponds to the velocities measured in MHV in patients.

For flow visualization, micrometer sized hydrogen bubbles were generated by electrolysis of water in a microbubble generator, and used as tracers as well as nuclei. This is a well known technique for flow visualization [19]. The flow field was photographed by high-speed videography, two centimeters above the 80-μm gap. The
Video camera was operated during the 35 ms opening time of the solenoid valve. The visualization of the vortex was facilitated by the presence of hydrogen bubbles in the flow, which acted both as tracers and as nuclei.

2.2. Bubble formation

In this set of experiments, we used a left heart pulsed flow simulator, shown in Fig. 3. The setup consists of four major components: a positive displacement pulsatile pump (Superpump SPS3891, Vivitro Systems, Canada) with a physiologic waveform generator; a left ventricular (LV) compartment; two pressurized chambers which mimic the systemic compliance and peripheral resistance, connected through a variable resistor to an open-to-atmosphere ‘venous’ reservoir. The detailed description of the system has been published elsewhere [19].

In these experiments we attempted to generate similar physiological conditions (cardiac output, heart rate, ejection fraction) to those of a patient with a 29-mm mitral St. Jude Medical (SJM) bileaflet mechanical valve [20], mounted in the anatomical orientation. Other valves that were studied were the 29-mm Carbomedics (CAR), 29-mm Sorin BiCarbon (SOR), 29-mm Edwards–Tekna (ET), 29-mm Medtronic Hall (MH), and the 29-mm Bjork–Shiley Mono-Strut (BSMS). A 27-mm mitral Carpentier–Edwards (CE) bioprosthesis was used as the control valve. A 25-mm CE aortic valve was inserted into the aortic position.

Two different imaging techniques were used to view the immediate atrial surface of the mitral valve through the left atrial viewing window:

- high-speed videography at 1000 frame/s and a spatial resolution of $512 \times 384$ pixels;
- laser video imaging, using a $1024 \times 768$ pixels charge coupled device (CCD) camera, synchronized with a 25 MJ YAG:Nd double pulse laser beam, converted to a light sheet for planar illumination.

The pictures in both methods were taken at a plane parallel to that of the valve, on the atrial side. The images were recorded on a video disc.

3. Results

3.1. Vortex formation

The evolution of the vortex took around 10 ms. Fig. 4 depicts the sequence of events during vortex formation from time $t = 0$ to $t = 11$ ms. As seen, after 3 ms the vortex is already visible, while after 11 ms it is fully developed.

In order to quantify the results, digital particle imaging velocimetry (DPIV) was carried out starting at 0.8 ms after solenoid opening and until closure at 35 ms. Fig. 5 shows the velocity vector field, as obtained by DPIV, with the vortex clearly visible.

3.2. Bubble formation

While in the first set of experiments with a static valve described above, no bubbles were observed, the present tests with a closing valve resulted in bubble formation. Fig. 6 shows two views of a single frame of the high-speed videography of microbubble formation at the instant
Fig. 4. Sequence of events during vortex formation following valve closure.

Fig. 5. DPIV velocity vector field of the flow downstream of the gap in the two-dimensional flow model of the closed valve, demonstrating vortex formation.
of closure of a 29-mm SJM mitral MHV. The images were recorded simultaneously, with the front view shown in (a), and the side view in (b), at cardiac output, $CO = 5.0 \pm 0.2$ lpm, heart rate, $HR = 72 \pm 1$ bpm, systolic ratio, $SR = 33\%$ and a rate of pressure change, $(dP/dt)_{LV} = 2100$ mmHg/s. The images were synchronized with the mitral flow signal, shown at the bottom. The arrow on the flow signal in view (a) points at the corresponding video frame, while the arrows on the image point at five locations where additional microbubbles were detected. These corresponded to the four hinge locations. Fig. 6 demonstrates very clearly the existence of microbubbles, which are shown as bursts of microbubbles in the form of white clouds against a black background.

Fig. 7 depicts bubble formation during valve closure in two other valves that were tested, namely, a 29-mm SOR and a 29-mm ET. As seen, the results are similar, closely resembling those of the SJM mitral valve, and suggesting that bubble formation is an inherent feature of the mitral MHV.

We also performed an experiment with a 27-mm mitral CE bioprosthesis. As seen in Fig. 8, no bubbles were detected during experiments with this valve under the same conditions as with the MHV. Surprisingly, also in the experiments performed with the classical Starr–Edwards ball-in-cage valve, shown in Fig. 8b, no microbubbles were detected. This is a rather astonishing result, indicating that the different concept of valve closure has a profound effect on microbubble formation.

4. Discussion

When we embarked on this study, we postulated a hypothesis that the sequence of events leading to the formation of microbubbles on MHV is associated with valve closure. We further postulated that the formation of vortices is an inherent part of the leakage flow through closed MHV. To prove these hypotheses we created the closest possible in vitro fluid dynamic conditions in which prosthetic mitral valves function in patients’ hearts.

The study demonstrated the existence of the two distinct phenomena during valve closure, namely, that of vortex formation and that of microbubble growth. Both phenomena may have far-reaching clinical implications. Proving the existence of the vortex is important in evaluating potential mechanical damages to the endothelial layer of the left atrial wall opposite the prosthetic valve.

The formation of bubbles in patients with MHV has been established indirectly by means of transcranial Doppler echocardiography. The clinical significance of HITS associated with mechanical heart valves was studied in details by Dekunder et al. [3,13] and more recently by Kofidis et al. [21] revealing permanent neuropsychological impairment. HITS observed during extracorporeal circulation are also known to be associated with deterioration of episodic and working memory [22]. Moreover, HITS might be further associated with elevated risk of cerebral embolism [23] or cognitive dysfunction [24].

Another concern of the constant production of gaseous microbubbles in the vicinity of the valve is the creation of gas–blood interfaces, which activate the thrombocytes, thus causing a continuous state of hypercoagulability. Hence, it was important to find out how and when microbubbles are formed. A further goal of the present study was to find out whether microbubbles could be formed in patients with...
bioprosthetic valves, as clinical studies failed to detect microbubbles in such cases. Our laboratory studies did not show the formation of microbubbles in such cases as well.

The first set of our experiments demonstrated that under physiological conditions it is possible to reach vortex flow. Figs. 4 and 5 confirm our basic assumption that vortices are generated at mitral MHV, after closure within the first 20–30 ms of systole. In the stationary setup used in this set of experiments we did not encounter any bubble formation.

In the second set of experiments we tried to show that regurgitant flows at the final closing stage of MHV appear to be the main factor in instigating the onset of a chain of events, the result of which is nucleation and growth of gas-filled bubbles. Numerical solutions [19] for our experimental conditions also predict the generation of vortices and a sudden reduction of local pressure that appears at the peak of backflow during valve closure, which leads to the formation and growth of microbubbles.

Once a microbubble is formed, the growth takes place over a short period of time. Our laboratory experiments indicate that large bubbles seem to be unstable and disintegrate into smaller and more stable bubbles, which stay in the simulation system for numerous cycles. Formation of gas microbubbles in patients with mitral MHV, probably follows similar steps. Hence, it is the stable bubble that is detected by echocardiography, and when it reaches the cranial circulation is detected as HITS by the TCD.

The chemical composition of bubbles in patients with mitral MHV is of considerable importance. To measure it, one would have to perform experiments with blood under clinical conditions. Because of its high solubility in blood, CO₂, if contained in microbubbles, would probably not last long enough to leave the heart. The lowest solubility in blood is that of N₂, and is 4.8 times lower than that of O₂. The literature describes an experiment in which patients with MHV were given to breathe pure oxygen, with the result of near disappearance of the monitored HITS [25]. This suggests that HITS are the signals of gaseous bubbles, which contain mainly nitrogen. Since nitrogen is the predominant gas in bubbles detected within the vascular bed of patients suffering from decompression sickness (DCS) [26], relevant information can be derived from this medical field. Stirring of platelet-rich plasma with N₂ microbubbles, causes a decrease in the number of free platelets. Platelets and aggregates of platelets adhere to the surface of the N₂ microbubbles. Transmission and scanning electron microscopy studies reported in the literature [27] revealed structural changes in the platelet, which support the argument that N₂ microbubbles in fact activate platelets. In vitro laboratory studies also showed the activation of human complement by nitrogen bubbles [28]. These laboratory studies correlate well with blood cell changes seen in asymptomatic divers.

We showed in the present study that vortex formation although not yet seen clinically in patients, does occur in flows through closed prosthetic valves. The physiological implications of this intra cardiac phenomenon in terms of the cascade of clotting and impact on the inflammatory reaction is needed to further assess the clinical as well as neuropsychological long-term impact on patients.

Meanwhile, we may draw some important conclusions regarding the design of future generations of mechanical heart valves. In order to reduce the potential damage to the endothelial layer of the left atrium, valve design has to be such that the vortex is dissipated as much as possible, which can be achieved by redesigning the shape of the leaflet edges. This is a rather formidable task, requiring a combination of high powered analysis of the fluid dynamics of this complicated flow, together with well-designed experiments with prototype valves with optimized edges, using the system and visualization techniques developed in the present study. The rewards of such a study are well worth the challenge, and are left for a future effort.

The present study has also shown that bubbles form in a fluid at the instant of closure of mechanical valves, while in the case of bioprosthetic valves with their benign closure no bubbles are formed. We have also shown that in the absence of the impact of closure, as in the stationary experiment, no bubbles could be observed. Similarly, no bubbles were detected in experiments performed with the classical Starr–Edwards ball valve. We believe that the formation of bubbles is strongly related to the manner in which the valve closes. It is conceivable that bubble formation is closely linked to hypercoagulability of blood near the valve, requiring lifelong intake of anticoagulants. It seems like the classic Starr–Edwards ball valve design with its feature of no bubble generation is less susceptible to thrombus and emboli formation. This finding is supported by clinical evidence demonstrating that patients with Smeloff–Cutter ball valves in the aortic position survived emboli free without anticoagulation for periods of over 5 years [29].

Hence, soft closure should be an important item in the design of future heart valves. This can be achieved by a combination of softening the closure process and improving the timing of events during closure, by moving the beginning of the closure from the beginning of systole more towards the end of the diastole. This would closer mimic the sequence of closure of the natural mitral valve.

References

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