INTRODUCTION

The management of pregnant women with mechanical heart valves is challenging. This has created a huge problem for physicians managing pregnant women with prosthetic heart valves because the alternatives, heparin and warfarin, are problematic. Women with mechanical heart valves have a high risk of both adverse fetal and maternal experiences, primarily due to thromboembolic complications and the anti thrombotic therapy given to prevent these complications. Pregnant women (and often women of child bearing potential) are usually excluded from trials that involve evaluation of drugs [1, 2].

Patients with mechanical valves need close monitoring of warfarin therapy during pregnancy. 2 regimens were commonly recommended in pregnant women with mechanical heart valves: (1) warfarin, for most of the pregnancy, usually with substitution of UFH near term, and (2) UFH throughout pregnancy [3].

Phenindione provided safe and effective anticoagulation during Pregnancy. Antithrombotic therapy is essential, because the risk of valve thrombosis and death or systemic embolism is high if it is not given. With currently used warfarin, pregnancy in a woman with a mechanical heart valve carries a risk of maternal mortality from valve thrombosis estimated at 1 % to 4%. Many factors determine the risk of valve thrombosis, including valve type and position, presence of atrial fibrillation,

left atrial size, history of previous thrombosis, number of mechanical valves, and adequacy of anticoagulation [4, 5].

Women who need <5 mg of warfarin are probably at low risk for fetal warfarin embryopathy and may be able to receive warfarin throughout pregnancy. One group has shown that the risk of warfarin embryopathy was extremely low in women who needed 5 mg of warfarin to maintain an adequate INR. The low-dose (60 to 150 mg/d) aspirin therapy administered during the second and third trimesters of pregnancy was safe for the mother and fetus [5, 6].

Until properly designed, adequately powered trials of currently available agents are performed or new antithrombotic suitable for use in pregnant women are developed, recommendations for the management of pregnant women with mechanical heart valves must be based on case reports, case series, and expert consensus[7].

AIM OF THE WORK

The aim of this work is to determine the percent of pregnant females with mechanical prosthetic heart valves (MPHV) who will achieve the target INR *(2-3.5)* with a small daily dose of warfarin (< 5mg) & adjuvant l00mg Aspirin per day. Those non responders to warfarin will be substituted with phenindione. Fetal & Maternal outcomes of either therapy will be noted.

The anticoagulant dose necessary to achieve the target INR will be compared to that noted in a concomitantly followed up group of non pregnant females with MPHV following either warfarin or phenindione therapy & all receiving adjuvant 100mg Aspirin per day. This group will be selected randomly from those fulfilling inclusion & exclusion criteria of our pregnant patients group.

MECHANICAL HEART VALVES

Development of prosthetic heart valves

The development of reliable, quality-controlled prosthetic heart valve devices had risen in the late 1950s and early 1960s. In 1952, Hufnagel used aortic valve ball and cage prosthesis heterotopically in the descending thoracic aorta to treat aortic insufficiency [8].

Currently, over 290 000 heart valve procedures are performed annually worldwide and that number is estimated to triple to over 850 000 by 2050. After the advent of cardiopulmonary bypass, initial attempts at AVR consisted of replacement of the individual aortic cusps with Ivalon gussets sewn to the annulus. When successful, these prostheses often calcified and results were short-lived. Shortly thereafter, surgical pioneers Starr, Braunwald, and Harkin began replacement of the aortic valve in the orthotopic position. The first successful prosthetic mitral valve replacement was a device implanted by Nina Braunwald at the National Institute of Health in 1959. This was a homemade device with artificial chordae made of polyurethane **[9]**.

Two years later the first generation prosthetic valves (1961) was produced on a commercial basis. This was the Starr-Edwards ball-and-cage mitral valve that resulted from the collaboration of Albert Starr, a cardiac surgeon in Portland, and Lowell Edwards, a mechanical engineer in Southern California.

This prosthesis was a great success and became the "gold standard" for many years, until the late 1960s, Multiple modifications ensued including: changing the material of the ball from Silastic to Satellite, changes in the shape of the cage, depression of the ball occluder, the addition of cloth coating to the sewing ring and the cage, and changes in the sewing ring itself [(10)].

Although it was reliable hemodynamically, the Starr-Edwards valve had significant thromboembotic potential, particularly in the small ventricle, and aggressive anticoagulation was required to control thromboembolic events. Hemodynamic performance was compromised, as there were three areas of potential outflow obstruction: the annular size of the sewing ring (the effective orifice area of the valve), the distance between the cage and the walls of the ascending aorta (particularly in the small aortic root), and obstruction to outflow by the ball itself distal to the tissue annulus. Flow patterns were also abnormal. In the early 1970s, the Second generation prosthetic valve started to appear, the Björk-Shiley tilting-disk valve, which was developed by Viking Björk in Stockholm and Earl Shiley in California. This valve had better hemodynamics (larger cross-sectional area and less hemolysis) than the Starr-Edwards valve and consequently had a lower thromboembolic potential. The low-profile configuration simplified surgical implantation. Problems with the tilting disc valve included stasis and eddy current formation at the minor flow orifice, and sticking or embolization of the leaflet, the latter leading to

discontinuation of the Bjork prosthesis in spite of otherwise good long-term results. Moreover, problems with thrombosis occurred when the anticoagulation was altered. When an engineering change was made to correct this problem in a later model (a concave-convex disk), a fracture in the strut ensued and the Björk-Shiley prosthesis was taken off the market. Third-generation prosthetic valve appeared in late 1970s by development of bileaflet prosthetic heart valves with the Advantages of improved hemodynamics compared to older valves with less stagnation of blood, more complete opening of the leaflets, and reduced incidence of thromboembolism. In 1977, the SJM prosthesis was developed and implanted by Nicoloff and associates. Over the following decades, the dramatic step of bileaflet prosthesis nearly obviated the use of all other kinds of mechanical prosthetic valves in the United States and to a large extent elsewhere [(11)].

SJM's has developed a new "HP" valve, which permits a greater flow orifice for any given valve size. This is because the sewing ring is placed further up the annulus rather than in the annulus, meaning that less of the sewing ring is needed to seat the valve, thus the orifice can be bigger. Each size of the SJM's HP valve corresponds to one size up of the regular SJM's valve, i.e. a 19 mm HP St. Jude's valve corresponds to a 21 mm regular St. Jude's valve. This corresponds to approximately 25% greater flow through any given valve using the HP valve. Newer St. Jude's valves however, also can rotate. The most recent development in bileaflet valve design was the

introduction of the SJM regent valve in aortic position. This valve model not only modified the sewing ring, but also redefined the external profile in a no intrinsic structural portion of the valve, increasing the effective flow orifice area. Thus, a larger prosthesis could be implanted for any given tissue annulus diameter. This was the first mechanical prosthesis to demonstrate left ventricular mass regression across all valve sizes. The Regent valve is seated supra-annular with only the pivot guards protruding into the aortic annulus. Anticoagulation continued to be necessary but to a lesser extent than with previous design models. Because of the low-profile design and lesser need for orientation, surgical implant was further simplified. In addition, The SJM valve in aortic position demonstrated low aortic gradients, minimal aortic insufficiency, and low rates of TE .Following the introduction of the SJM valve, several other third generation models of bileaflet prostheses were introduced, including the Sulzer Carbomedics valve, the ATS Medical prosthesis, and the On-X prosthesis The bileaflet Carbomedics valve was developed in 1986. Carbomedics is similar to the St. Jude's valve with the exception of a hinge modification and the fact that the valve can be rotated to allow for different orientations of the valve within the annulus once seated. The sewing ring of the Sulzer Carbomedics valve has been modified such that this valve is implanted in a supravalvular position (top hat model)[(12)].

The ATS mechanical prosthesis has been in clinical use in the United States since 2000. The ATS Medical valve

changed the *"rabbit ears"* pivot style of other bileaflet prostheses, incorporating a convex or open-pivot design allowing more complete washing of the moving parts of the valve and possibly a quieter valve closing. The prosthesis most recently approved by the FDA (2002) is the On-X valve. The On-X valve incorporates advanced pyrolytic carbon technology using a purer, more flexible coating to allow flanging of the inflow portion of the valve housing, mimicking the normal flow pattern[9]. All steps are summarized in figure (1).

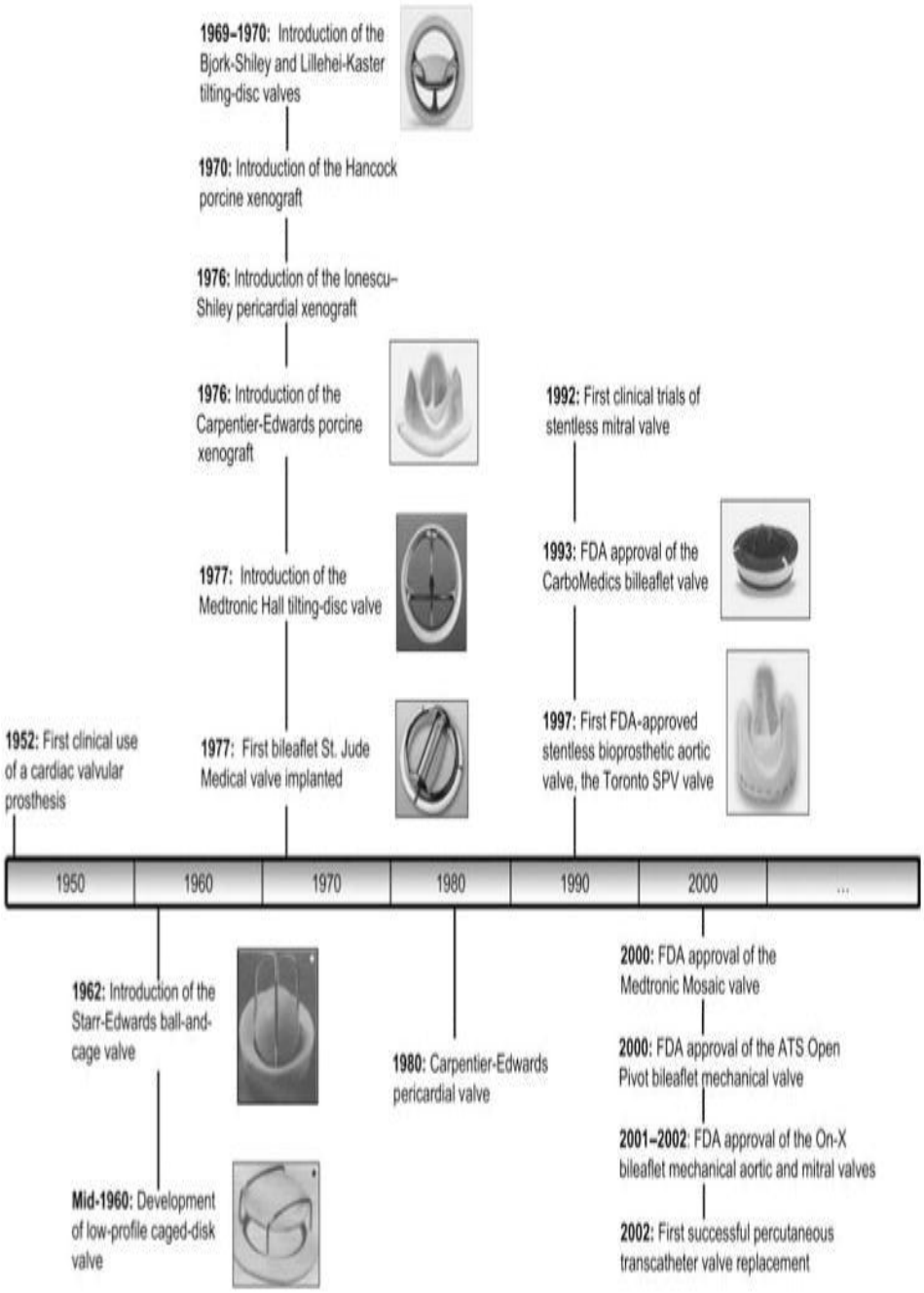

Figure (1): Towards the ideal prosthetic heart valve. Timeline of significant milestones in the history of prosthetic heart valve development **[13].**

Physics for mechanical heart valves:

Artificial heart valves have been in use for over five decades to replace diseased heart valves. Since the first heart valve replacement performed with a caged-ball valve, more than 50 valve designs have been developed, differing principally in valve geometry, number of leaflets and material. To date, all artificial heart valves are plagued with complications associated with haemolysis, coagulation for mechanical heart valves and leaflet tearing for tissue-based valve prosthesis. For mechanical heart valves, these complications are believed to be associated with **non-physiological blood flow patterns**. Mechanical heart valve designs have evolved significantly, with the most recent designs providing relatively superior haemodynamics with very low aerodynamic resistance. However, high shearing of blood cells and platelets still pose significant design challenges and patients must undergo life-long anticoagulation therapy. Bioprosthetic or tissue valves do not require anticoagulants due to their distinct similarity to the native valve geometry and hemodynamic, but many of these valves fail structurally within the first 10–15 years of implantation. These shortcomings have directed present and future research in three main directions in attempts to design superior artificial valves: (i) engineering living tissue heart valves; (ii) development of advanced computational tools; and (iii) blood experiments to establish the link between flow and blood damage.

One of the main afflictions of the cardiovascular system is heart valve disease, which is generally caused by congenital birth defects, ageing or diseases such as rheumatic fever. Such heart valve disease compromises the functionality of the valve by restricting the motion of the valve leaflets or by damaging its supporting structure. This leads to either valve stenosis (calcification of the leaflets associated with narrowing of the valve, resulting in greater resistance to blood flow and a greater cross-valvular pressure drop) or regurgitation (failure of the valve to close completely), both eventually leading to valve failure. Clinicians have therefore developed two parameters to quantify the degree of stenosis/regurgitation to better assess valve performance: (i) the effective orifice area which is a measure of the effective valve opening during the forward flow phase; and (ii) the regurgitant volume, which is a measure of the back flow (or regurgitation) during the leakage flow phase. A low effective orifice area, commonly resulting from valve stenosis, is usually associated with a higher net blood pressure loss across the valve and therefore an increased workload for the pumping heart. The EOA is traditionally computed from measured flow and pressure drop using the Gorlin relation, which is based on the principle of energy conservation:

$$EOA(cm^2)=\frac{Q_{rms}}{51.6\sqrt{\Delta\bar{p}}}$$

Where Q_{rms} is the root mean square systolic/diastolic flow rate (cm^3/s) and $\Delta\bar{p}$ is the mean systolic/diastolic pressure drop (mmHg) [14].

Conversely, the regurgitant volume corresponds to the total volume of fluid that leaks back across after closure and is related to valve shape and leaflet closing dynamics. A high regurgitant volume indicates that the net cardiac output is reduced and the heart has to contract more to meet the demands of the body. Thus, a small regurgitant volume is preferable because it indicates a good coaptation of the valve. More recently, turbulence stress levels, which are a surrogate measure of the shear stress experienced by blood cells and platelets in a turbulent flow environment, have been used to assess the potential of the valves towards causing thromboembolic complications. Turbulent stress levels from 10 to 100 Pa are considered to trigger platelet activation, with a more precise threshold known as *Hellums criteria*, which states that platelets will activate if the product of shear stress and its time duration is above 3.5 Pa. However, the threshold for haemolysis is much higher at 800 Pa .Note, the values cited in this paper are all *in vitro* measurements because these measures have not been quantified *in vivo* [15].

Heart valve mechanics:

Despite the widespread use of artificial heart valve designs, neither mechanical nor bioprosthetic heart valves are free from complications. The overall complications associated

with prosthetic heart valves can be divided into six main categories: structural valvular deterioration, non-structural dysfunction, valve thrombosis, embolism, bleeding and endocarditis. On the one hand, bioprosthetic heart valves are plagued with leaflet calcification and leaflet tearing. On the other, mechanical heart valves are associated with haemolysis, platelet activation and thromboembolic events arising from clot formation and their subsequent detachment. These complications are believed to be associated with non-physiological blood flow patterns in the vicinity of heart valves. In fact, the potential of abnormal flow patterns to promote blood cell damage has long been recognized, because they may initiate thrombus formation by: (i) imposing forces on cell elements (regions of high shear stress cause tearing of the blood elements, thus leading to haemolysis and platelet activation); and (ii) changing the frequency of contact (recirculation and flow stagnation regions increase the contact time between blood elements, in particular activated platelets, thereby promoting thrombus formation). In addition, these abnormal flow patterns may induce leaflet calcification and tearing in tissue and polymeric valves by creating elevated regions of shear in the immediate vicinity of the leaflet surfaces [16]. The Figure (2) illustrates what is hypothesized to be the problem with artificial heart valves. Shown is a bileaflet mechanical heart valve in the aortic position during the leakage flow phase. As mentioned previously, bileaflet heart valves in the closed position are not perfectly sealed and leakage flow may occur. Red blood cells and platelets leaking back from the aorta into the left ventricle.

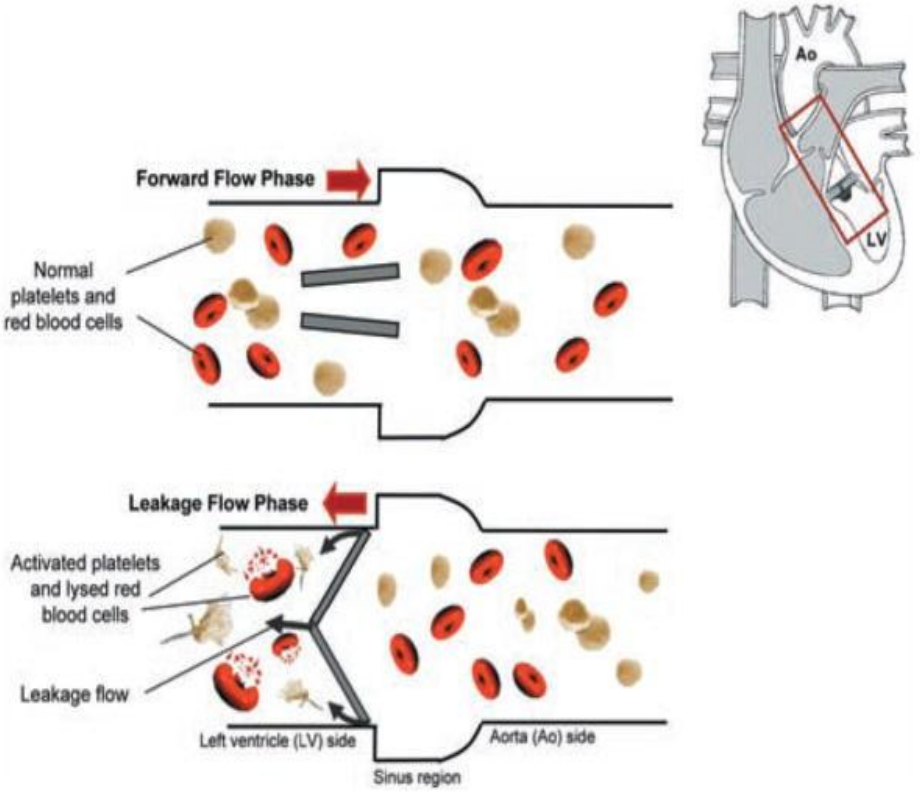

Figure (2): Schematic of a bileaflet mechanical heart valve implanted in the aortic position during the leakage flow phase. Shown are the blood cells damaged from the high shear environment experienced within the leakage gaps (not to scale). Top panel: forward flow phase; bottom panel: leakage flow phase. Grey arrows, leakage flow; red arrows, bulk flow direction; Ao, aorta; LV, left ventricle [(13)].

While flowing through the valve prosthesis these cells are subjected to non-physiological flows, leading to rupture or activation, the first step towards initiation of the coagulation response. It is therefore clear that the EOA and the regurgitant volume alone do not sufficiently reflect the potential of artificial heart valves in inducing thrombus formation and thus the clinical performance of the valve. Hence, it is essential to assess the fluid mechanics of prosthetic heart valves to

understand clinical valve successes or failures and improve the designs of these devices by minimizing the procoagulant potential and increasing valve durability. Therefore, the following paragraphs concentrate on the fluid mechanics of major prosthetic heart valves in the scope of establishing a relationship between fluid mechanics and valve success rate. The focus will be placed on the ball-and-cage valve, the tilting-disc valve, the bileaflet mechanical heart valve and the trileaflet valve. The flow fields downstream of these four valve designs during both the forward and leakage flow phases seen in figures (3-4).

Ball-and-cage valve

During the forward flow phase, the flow emerging from the valve forms a circumferential jet that separates from the ball, hits the wall of the flow chamber and then flows along the wall. At peak forward flow, a maximum velocity as high as 2.20 m/s was reported near the annulus in this forward flow jet under aortic conditions. This velocity decreases to 1.80 m/s 30 mm downstream of the valve. Immediately downstream of the apex of the cage, a wake develops and a region of low-velocity recirculating flow is present throughout the forward flow phase. A region of high-velocity gradient, and thus of high shear, exists at the edge of the forward flow jet and the recirculation region. A maximum turbulent shear stress up to 1850 dyn/cm^2 was measured in this region. Turbulent shear stresses reach as high as 3500 dyn/cm^2 in the annular region between