Review Article

Starr–Edwards ball caged mechanical heart valves' reverberations – Need for a Phoenix of analysis with a critical mindset

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ABSTRACT

The mechanical heart valve prosthesis with a caged ball has been around for 60 years. It has since experienced changes and adjustments. The Starr–Edwards (SE) valve was a pioneer and was taken out of clinical use in the late 2000s. SE is reportedly close to or has reached the age of 50, according to numerous sources from around the globe. The author's observations and review of the literature about thrombogenicity, pannus formation, left ventricular outflow tract obstructions, and infective endocarditis in the SE valves, which were reportedly higher before its clinical ending, were only an overestimation and were not supported by scientific data. However, it was less discussed in the article, along with potential benefits. The main reasons for its demise were its obtrusive size and unattractive shape. There have been several successful implantations of these valves in Asian nations and reports of fewer primary failures and unexpected cardiac fatalities. Therefore, there is a need for extensive data gathering, documentation, and more recent studies on these valves to prepare for a prospective revival of use with newer research, mainly when long-term durability is considered.

Key words: Caged ball valves, Durability, Safety, Starr–Edwards, Thrombogenicity

The mechanical heart valve prosthesis is commonly used in the treatment of valvular heart disorders. The biophysics and models of these mechanical heart valves have undergone numerous changes and exist in their current form. Among many mechanical heart valve models, Starr–Edwards (SE) is a standard model, and its implantation dates back 60 years or more. The currently used models have replaced the SE valves, and it is no longer in clinical use. The article deals with some of the interesting aspects of the SE valves, their evolution, general performance, and discontinuation. The report also discusses the literature on clinical performance, thromboembolism, and echocardiographic characteristics.

HISTORY OF SE BALL CAGED MECHANICAL HEART VALVE

Albert Starr and Lowell Edwards worked and developed the first successful ball cage valve in Oregon medical school [1]. Albert Starr was a young surgeon, and Lowell Edwards was an experienced engineer. They made numerous modifications and finally arrived at the unshielded ball valve used in human

beings. Their work offered hope for a large number of patients with rheumatic heart disease and other valvular heart diseases requiring mechanical heart valve replacement. The last model was mitral-6120 extended non-cloth valves, and its aortic counterpart 1260. The metallic cage was made of stellite, and the ball was silastic, which is silicone with 2% barium. Later replaced, the ball with stellite to prevent ball variance. The sewing ring had knitted Teflon with polypropylene cloth. The valve had good durability and hemodynamics. Starr and Edwards founded a company – American Edwards Laboratory, in 1966 and manufactured the valves in the early stages (Figs. 1 and 2).

It was further marketed and developed by Edwards Life sciences till the late 2000s. The mitral prosthesis model 6120 and aortic prosthesis models 1200 and 1260 persisted till its discontinuation. The usage of SE' valves, known for their excellent long-term durability, was common in India and neighboring countries in the late 1980 and 90s and was stopped in clinical use in the late first decade of 2000. Many of the implanted patients during that time are doing well these days with these valves. These valves were often criticized for their bulky size (Figs. 1-3) and also the higher thrombogenicity, in which the tilting disk valves have largely reduced in the general purview.

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WHY WAS THE STARR–EDWARD VALVE ELIMINATED?

At present the SE valve is eliminated from the market in the early first decade of 2000. Extensive analysis of the published articles concerning increased thrombogenicity shows that the claims are attributed to the earliest and first-generation SE valves. In the subsequent years, many minor modifications were made to the SE valves [2]. By computational fluid-flow dynamics, turbulent annular shear stress has been shown to reach up to 3500 dyn/cm^2 in ball-caged valves. In contrast, in the tilting disk prosthesis, the maximum turbulent shear stress was 1850 dyn/cm^2 which is seen at the minor orifice [3]. Although this could be seen as a disadvantage, this hemodynamic could also give a potential vantage point by clearing or "self-cleaning" any microthrombi which happens spontaneously. There are general claims that thrombogenicity is higher in ball-caged valves [4]. However, large studies substantiating the claim with a head-to-head comparison between the valves are not available in reality. In a small single-center study involving 12 patients with SE valve replacement and 50-year follow-up, 66.6% survived. Among the patients

Figure 1: Picture of a Starr–Edward ball caged valve

with mortality, the event started occurring only after 7500 days after implantation [5]. An article which evaluated, the SE valves were published in 1983, which included 509 patients followed up for 10–15 years. In this paper, any event-free all valve-related morbidity and mortality were 38 ± 3%. About 22% of hospital deaths and 27% of late deaths were SE valve related. A small study in 1991 comparing the SE (149 patients) and 87 patients with St Jude valve prosthesis showed better 5 year survival statistics with St Jude valve – 94% versus 86% for SE valves. The study was small, and it was not matched with numbers [6]. In the aortic position the for the silastic ball valve, cumulative freedoms at 10 and 25 years were 59 and 20% from all deaths (crude survival), 85 and 80% from thromboembolism, 87 and 70% from bleeding, 98 and 94% from endocarditis, 96 and 95% from redo AVR, and 68 and 51% from all valve-related complications joined [7]. The published rate of ball variance in the aortic position was 6% and 0% in the mitral position [8]. In the initial stages, the results published by Starr and his team show that the patient survival rates were 80%, 58%, and 50% at 5, 10, and 15 years, respectively [9]. Furthermore, the report by Starr [10] in 1985, about 110 patients have shown good results, with valve thrombosis rates nearing 0% and embolism rates of 2.9% patient years in the mitral position and 1.8% in aortic models. The report also shows a significant improvement in the results from 1973 to 1984, compared to the period of implantation from 1965 to 1972. A study by the team of Christian Bernard published in 1977 shows thromboembolic free event rates, including three models of SE, was about 71% at 5 years; and interestingly, a subset of 52 patients who were not receiving anticoagulants for various reasons also almost had a similar thromboembolism free rates at 5 years [11].

In the clinical experience of the author, patients with the SE valves were performing well in the past and in the current juncture; and some patients also come for regular follow-up these days, and the higher thrombogenicity [12] claimed compared to patients with tilting disk valves and also stuck valves was not
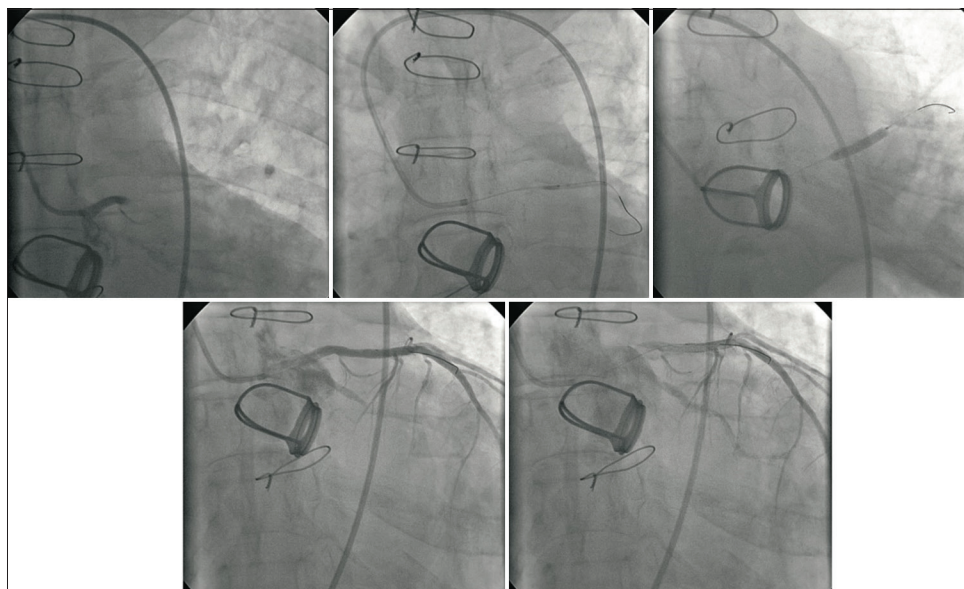

Figure 2: Primary angioplasty in a patient with Starr–Edwards' ball caged valve in aortic position during primary angioplasty
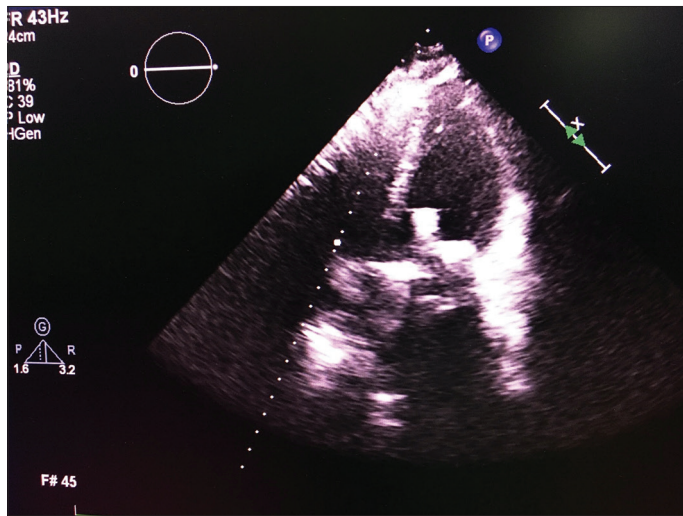
Figure 3: Echocardiography profile of Starr–Edwards valve in mitral position

seen. The fact is, in some of the patients who have lost follow-up, who had discontinued anticoagulants, and tend to show up in later days – about weeks/months and in some cases, even after many years of non-compliance with anticoagulants, the problems of stuck valve were not seen in the clinical observation of the author. Furthermore, this observation of non-compliance with anticoagulants was not uncommonly seen in the past, even in the mitral valve position of SE valves. Anecdotal case reports of normal valve functioning after medications default does exist with all types of valves, but the observation mentioned above is a significant number.

Before the stage of exit from the clinical use, the SE valves were used in numerous patients and hospitals in the lower socioeconomic strata population in the general hospitals of the Asian countries, and these patients' sudden cardiac deaths were not known. Furthermore, the primary valve failures after implantations were very few or hardly ever seen. Moreover, these patients being from a lower socioeconomic status were also prone to drug default. A thorough discussion from the older generation of cardiovascular surgeons and cardiologists performing echocardiography will shed more light on these caged ball valves and their abrupt ending. Furthermore, during routine follow-up, the usually criticized ball-caged valves for the left ventricular outflow tract (LVOT) tract causing LVOT obstructions were not seen in the echocardiography. Clinically, significant LVOT gradients elevations similar to hypertrophic cardiomyopathy were not observed. In the opinion of the author, when the tilting disk valves arrived, the generation of the cardiovascular surgeons was also changed by their age and retirement processes, and the newer generation of cardiovascular surgeons shifted to tilting disk valve usage. Furthermore, as indicated, the claims of higher thrombogenicity of SE valves are primarily concerning the initial models in the early 1960s, and the initial bad reputation silhouetted the SE valves and passed on to the subsequent generation of SE valves. Many modifications were performed in the later generations of SE, including heat treatment of the silastic ball at high temperatures to prevent ball variance [1]. The silastic ball

was changed to stellite alloy ball valve in the later days to prevent ball variance. In some patients presenting with subtherapeutic INR during the routine follow-up also, the thrombogenicity was not seen. Small and older published studies also do not indicate higher thromboembolism.

Freedom from thromboembolic events after the implantation of SE valves in the aortic position varied from 76% to 87% at 10 years and 90.8% at 5 years depending primarily on the time frame of the studies, which likely reflected evolutions in anticoagulation protocols [13-15]. In aortic position, the mortality is 12 ± 2 in 10 years [14]. Hence, it could be primarily the generation change and the mindset of the cardiovascular surgeons who adopted the tilting disk valves due to the thin profile and physiological appearance of the tilting disk valves than the actual benefit observed. Furthermore, the LVOT obstructions were not seen or over-emphasized, and the pannus formation was also not high in the SE valves.

The traditional recommendation of higher therapeutic INR of 3–4 was also based on the older or initial generation SE valves, and it was not supported by any large or randomized controlled studies.

AREAS OF CONTROVERSIES

When an extensive internet search was performed, even small recent studies were not available supporting the claim of increased thrombogenicity. Some of the studies showing head-to-head comparisons were small. A study by Zouaoui *et al.* [16] showed increased mortality in patients with SE valves in comparison with St Jude's valve. In this study, the comparison was performed with two groups – SE, 127 patients, and 109 patients on St Jude valves. In this study, the 30-day hemorrhagic, conduction abnormalities, infections, pleuropulmonary complications, and overall non-prosthetic-related complications were significantly lesser in patients on SE valves, though the late mortality was higher in SE (9.2%) compared to St Jude valves (4.6%). In this study, 67.7% of patients with SE had mitral valve disease versus 53.2% of patients on St Jude valve [16]. In the aortic valve position, the SE had a higher survival rate [14]. In one another study involving 122 patients in each arm, the results of SE and St Jude valves were the same, with the baseline characteristics matched in both arms [17]. In a study by Sezai *et al.* [18] comparing the SE, St Jude, and ATS valves, the results favoring St Jude valves, though the results were comparable and SE' patients the longest mean follow-up of 16.9 years, whereas patients with St Jude valves had a follow-up of 11.5 years. The survival rates after 10, 20, and 30 years were 62.3, 39.4, and 19.9% after aortic valve replacement and 75%, 36.5%, and 22.6% after mitral valve replacement. The freedom from all valve-related complications including valve-related causes of death after aortic and mitral valve replacements were – 70% at 10 years, 55.8% at 15 years, 39.4% at 20 years, and 19% at 30 years [19]. The 416 patients in this study were enrolled between 1963 and 1977 [19]. A large study [20] involving 4480 patients with St Jude valves, and the total follow-up was

7±5 years, and patients' freedom from late mortality was 61% at 10 years, 42% at 15 years, 28% at 20 years, and 20% at 24 years follow-up. The patients were enrolled between 1977 and 2002 [20].

The lack of large studies and randomized controlled studies evaluating the SE valves and other valves has also been acknowledged by studies [21]. Worldwide so far more than half a million SE valves have been implanted so far [22]. The higher thrombogenicity by the SE valves has not been a clinical observation by the author. Due to the less contact of the ball with surrounding structures, unlike the joints in tilting disk valves, the pannus formation is also lesser. Hemolysis and valve thrombosis rates were reported as low as 0.1% and 0.06% per patient years, respectively [9].

Compared with St Jude's valve, the Doppler gradient was highest in SE and lowest in St Jude. Mitral regurgitation was in the opposite direction – highest with St Jude, though both the gradients and regurgitation were acceptable levels of physiology in all the tested valves [23]. In comparison with carbomedics valve, for the carbomedics valve, the peak pressure gradient (PPG) was 26.1±8.2 mm Hg, and the mean pressure gradient (MPG) was 14.7±5.1 mm Hg; in the Starr–Edwards valve, the PPG was 32.8±9.1 mm Hg, and the MPG was 19.5±5.6 mm Hg [24]. In another study, the peak calculated transvalvular aortic gradients in normal subjects were 22±10 mm Hg in 33 Björk-Shiley valves, 23±10 mm Hg in 27 porcine valves, and 29±13 mm Hg in 6 Starr–Edwards valves [25]. Small studies indicate mildly increased gradients in SE compared to St Jude. However, in these studies, the number of SE valve patients tested was <10 numbers [26,27]. A large echocardiography study shows mild differences in flow velocities in the aortic position, 3.2±0.6 m/s versus 2.5±6 m/s in SE and St Jude valves, respectively [28]. In a large study involving all types of valves, the gradients across the valves were not significantly different across various valve types [29].

Another concern that eliminated the SE valves was the LVOT obstruction due to the larger size. When an internet search was performed, only three studies showed this concern. One was two case reports [30,31], another was an animal study involving five heart models and measuring LVOT after SE valve implantation [32]; and the third was a study published in 1973 concluding the possibility of low cardiac output syndrome in four patients in a sub-group of seven patients with smaller LVOT [33]. Hence, an extensive study on LVOT gradients is not available comparing the valves, especially when the implantation worldwide has crossed half a million to date.

The attractive thin profile of the tilting disk valves, a higher market cost and inadequate data, unnatural look of caged ball valves, and the thrill of the new arrival of tilting disk valves changed the mindset and emotions of the next generation of younger cardiovascular surgeons. Other parameters such as less experience in the initial stages with cardiovascular physicians regarding warfarin and other similar anticoagulants like drug interactions, general paucity of data concerning thromboembolism and bleeding, and the late identification of mechanism of warfarin, that is, epoxide reductase inhibition in the liver were demonstrated in 1978, which could have influenced the early clinical outcomes. It is indeed difficult for any valve to fulfill the "nine commandments" for best performance mimicking the native valves [2].

Nowadays, point-of-care (POC) devices are available for self-testing of INR. Bench testing of the valves is possible in the present times, which can give more information about the valves' performance to certain exact, though the exact physiology *in vivo* is slightly modified by biological processes such as endothelization, pannus, and biofilm formation which cannot be studied *in vitro*.

A similar mindset effect is also seen among cardiovascular surgeons for some of the excellent procedures like closed mitral valvotomies (CMVs), which are going out of vogue these days. Elliot Cutler and Samuel Levine performed the first commissurotomy in 1923 in Peter Bent hospital Brigham hospital in Boston, and later, the technique had minor modifications. CMVs yield excellent results in preserving natural anatomy when mitral balloon valvotomy is not suitable [3]. CMV also reduces the need for long-term anticoagulation. Post-CMV during echocardiography in long axis and 4-chamber views, the mitral valve tends to be narrow, but the real caliber is visualized in the short axis profiling only. CMV is often replaced by prosthetic valve insertion by the current generation of cardiovascular surgeons. Hence, whenever feasible, the time-tested SE valve needs to be evaluated in the present context in a blinded fashion with extensive long-term data and in-depth analysis, especially in the community at risk for non-compliance with long-term oral anticoagulants. The author feels the elimination of the SE valves from regular use with inadequate data and hemodynamics understanding needs more evaluation and possible revival of the valve, at least in a few patients who insist on long-term durability.

FUTURE RESEARCH PERSPECTIVES

For the mechanical prosthetic heart valves, warfarin or related anticoagulants is the treatment of choice. Non-vitamin K antagonist oral anticoagulants (NOVCs) are not very effective in these valves, with a higher rate of prosthetic mechanical heart valve failure, irrespective of the prosthetic valve models [34]. The Re-Align study, which was prematurely ended, had a majority of patients on high doses of dabigatran – 220 mg twice daily, and the mean trough level in the study was >100 ng/mL in the majority of the patients, and the minimum was about 75 ng/mL. The target trough level of dabigatran in the study was 50 ng/mL. Asprin or clopidogrel can potentiate the action of dabigatran/NOVCs [35,36]. It is worthwhile to evaluate moderate doses of the novel oral anticoagulants with SE valves in animal models, as their "self –cleaning" hemodynamics are different, especially with smaller doses of aspirin or clopidogrel on a daily or alternate day basis. This will be better to study 2–3 weeks of valve implantation, which is usually required for endothelization.

CONCLUSION

The traditionally durable and well-performing SE mechanical ball caged heart valves were withdrawn from the market and

clinical use in a preliminary and abrupt context of time. Hence, extensive studies are required to identify the benefits of the latest generation of the SE valves for better understanding and revival of its clinical use.

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