行政院國家科學委員會補助專題研究計畫成果報告

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※臺大醫院異種生物組織心瓣膜置換病例之長期追蹤※
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計畫編號：NSC90－2314－B－002－432－
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本成果報告包括以下應繳交之附件：
- □赴國外出差或研習心得報告一份
- □赴大陸地區出差或研習心得報告一份
- □出席國際學術會議心得報告及發表之論文各一份
- □國際合作研究計畫國外研究報告書一份

執行單位：台大醫學院

中　華　民　國　91 年　10 月　4 日

中文摘要

前言：風濕性心臟病在台灣、中國大陸、東南亞及亞洲其他地區，自１９５０年以來一直是盛行率高且嚴重影響健康的主要疾病。幸賴 1950-1960 年醫療技術發達，使得開心手術及瓣膜置換成為可能，使得這些病患重拾健康。本計劃就這病人群之長期追蹤結果作一報告，以明瞭這種組織瓣膜在風濕性人體內之表現。

病患資料：在１９７５－１９９９年之間，共計８７２名病患於本院接受ＣＥＳ組織瓣膜置換手術。其中女性略多於男性（53% vs. 47%），單獨僧帽瓣置換占 60%。單獨主動脈瓣膜置換占 19%。合併主動脈及僧帽瓣置換占 21%。平均手術年齡各為４０，４３及４５歲。手術死亡率約為 5.9%。

追蹤：(1)長期存活率：在２０年之追蹤調查結果顯示，１０年存活率為 83.8±1.5%，２０年存活率為 35.8±6.4%。(2) 瓣膜耐用率：本調查顯示出ＣＥＳ於國人體內１０年及２０年之耐用度各為 63.7±2.1%及 7.7±1.5%。從年齡上來看，似乎年齡越大，ＣＥＳ組織瓣膜葉鈣化速度越慢，因此損壞率越低。(3) 栓塞發生率：在２０年的追蹤中，栓塞發生率為 0.86%/每人x每年。（簡言之，若一個病人存活１０年，則栓塞平均發生機率為 0.86%x10=8.6%）。

結語：Carpentier-Edwards Standard 豬心組織瓣膜在國人體內有好的長期表現，平均瓣膜堪用時間約為 11-12 年。

英文摘要

OBJECTIVES The clinical results of CES bioprosthesis have been extensively studied for valvular heart surgery in American and European countries. However, the data of long-term performance of CES porcine valve in area with high prevalence of rheumatic heart disease are still lacking. In this study, we assessed the clinical performance of Carpentier-Edwards standard (CES) porcine bioprostheses in a patient group with high prevalence of rheumatic heart disease.

METHODS A total of 872 patients underwent valvular heart surgery with CES porcine bioprostheses replacement between 1975 and 1999 was analyzed. Rheumatic etiology counts for ninety-five percent of the patients. Mean age of operation was 40±14 years (mitral valve) and 43±19 years (aortic valve) and 45±13 years (double valve). Follow-up was 95.6% complete and up to 24 years (total 7017 patient-years) with mean of 8.9 ±5.1 years

RESULTS The operative mortality rate was 5.85%, Actuarial patient survival rate after discharge at 5, 10, 15, and 20 years were 92.5%, 83.8%, 72.3% and 35.8%, respectively. A total of 442 cases received re-operation due to failure of bioprostheses. The mean duration to valve failure is 12.2 ± 0.4 years. Actuarial estimate of freedom from structural valvular failure at 5, 10, 15, 20 years were 96.3%, 63.7%, 24.4%, and 7.7%, respectively.

CONCLUSION The long-term result of CES bioprostheses in the present patient group is satisfactory. However, freedom from valve failure is lower than that of Western series, Younger operation age and higher prevalence of rheumatic etiology in this area are possible causes.

計劃緣由及目的

自 1970 年起，異種生物組織心瓣膜即開始被廣泛地應用於心瓣膜置換手術，一般相信異種生物組織心瓣膜較金屬機械瓣膜（mechanical valve）有較好的抗栓塞率及抗感染率，據國外大型長期追蹤資料顯示，此類瓣膜的長期耐用率與瓣膜置換位置、病人年紀有關，但未有研究顯示是否與人種差異有關。

本院於 1965 年及 1968 年分別首先植入生物組織心瓣膜於二尖瓣即主動脈瓣位置，1970 年至 1990 年間，共經歷的心瓣膜置換手術約 2000 例，但這些病例中，於本院接受再次置換瓣膜的比例，粗略估計僅 1/5 至 1/10，如此推論絕大部分病例均失去追蹤，究竟這些病人的長期

存活率為若干？異種生物組織心瓣膜在華人體內的耐用度與國外報告有無差異？因無相關研究，均不得而知。 本計劃即為針對這些病例，作一全面性的調查，以明瞭異種生物組織心瓣膜在國人體內的耐用度。

結果與討論

Patients. There were 406 men (46.6%) and 466 women (53.4%). There were 161 (18.5%) aortic valve replacement (AVR), 523 (60.0%) mitral valve replacement (MVR), and 188 (21.6%) both aortic and mitral valve replacement (DVR). The age ranged from 9 to 81 years; mean age of operation was 40 ±14 (MVR) and 43 ±19 years (AVR) and 45±13 (DVR). The total follow-up was 95.6% complete during the 6-month closing interval before our study period. The total cumulative follow-up were 7017 patient-years, with mean of 8.94 ±5.08 years.

Patient survival. The overall operative mortality was 5.85% (51 of 872 patients). As divided by decades, the operative mortality rate were 6.36%, 6.28%, and 0.00% in the periods before 1980, between 1980 and 1990, and after 1990, respectively. The overall late mortality was 154 of 785 cases (2.19% per patient-year). The causes of early and late mortality were listed in Table 1. The actuarial survival rate of all discharged cases at 5, 10, 15, 20 years were 92.5%, 83.8%, 72.3%, and 35.8%, respectively (Fig.2a). The survival rate of patients receiving DVR was initially similar to that of single valve replacement, but it got worse than that of patients receiving either MVR or AVR since about eight years after operation ($p=0.03$ and <0.01; respectively, Fig. 2b). Patients younger than 40 years were with better survival curve than those older than 40 years (Fig.2c). Both sexes had similar survival curves ($p = 0.21$).

Structural valve failure. During follow-up period, 442 cases (56.3%) received re-operation due to bioprostheses failure. The linearized rate was 6.30 per patient-year. The predominant pathology at re-operation of explanted valve was calcification on the leaflets, making the leaflets thickened and fused. Another major finding was linear tear of leaflet, which was usually associated with valve imcompetence. Occasionally, perforation holes in leaflets were found, in whom history of prosthetic valve endocarditis (PVE) sometimes could be traced. The mean duration to valve failure is 12.2 ± 0.4 years. Actuarial freedom rates from valve failure at 5,10,15,20 years were 96.3%, 63.7%, 24,4% and 7.7%; respectively (Fig 3a). Actual rate of freedom from reoperation was also plotted (Fig.4). Difference of results by these two methods began to show differences only after 10 years because of relative small number of mortality cases to valve failure cases. Male and female patients were with similar freedom from valve failure rate ($p=0.80$). The patients were sub-grouped as (1) ≧ 60 years (2) between 40 and 60 years (3) between 20 and 40 years and (4) ≦20 years. The median valve survival duration was 13.08, 12.30, 11.96, and 10.86 years in group 1, 2, 3, and 4, respectively (Fig. 3b). Only group 1 and group 4 was statistically significant ($p=0.03$). Valvular sites (mitral, aortic, and both) also affected the mean survival duration of CES porcine bioprostheses (Fig. 3c). Mean survival duration of DVR (11.07 years) was worse than either AVR (12.26 years) ($p=0.003$) or MVR (11.96 years) ($p=0.03$). Whether warfarin use or not did not influence freedom from valve failure rate ($p=0.29$). Freedom from reoperation rate among valves replaced before 1980 was not different from those replaced after 1980 ($p=0.11$) (Fig 3d).

DISCUSSION

Patient survival. The present study documented better survival and worse freedom from valve failure rate in our patient group than several published big series[1-4]. Age difference is the most possible cause. Long term actuarial survival estimates at 5, 10, and 15 years have been reported by Fann et al. [4] to be 77 ± 1, 54 ± 2, and 32 ± 3% respectively for the AVR with porcine bioprosthesis (Hancock valve) and respective rates for MVR are 70 ± 1, 50 ± 2, 32 ± 3%. Similar data have also

been reported by Fiane et al.[11] that actuarial survival rates at 5 and 10 years were 73.2 ± 5.2 and 52.1 ± 6.6 for AVR with CES bioprosthesis and respective rates are 76.7 ± 4.2 and 61.6 ± 4.8 for MVR. In the present study, long-term actuarial survival estimates at 5, 10, and 15 years were 94.4, 88.5, and 82.7 respectively for AVR and the respective rates for MVR are 91.6, 88.5, and 82.7%. The mean age of patients in the present study is younger than those of others [table2, 40 ±14 (MVR) and 43 ±19 years (AVR)]. According to the data reported by Fann et al,[4] mean age of operation was 58 ±13 (MVR) and 60 ±15 years (AVR). The age discrepancy between this report and that of other major series can be attributed to the etiology of valvular heart disease. In our hospital, most of the patients (95%) underwent valvular replacement at that time is due to rheumatic origin[12], while rheumatic disease only accounts for 47% in western series.[1] This younger age of rheumatic patients cohort is also documented by other series, such as John et al and Duran et al[13;14], both of which were also based on patients of rheumatic etiology. The main reasons for the high prevalence rate of rheumatic fever and rheumatic heart disease in these Asian areas are sub-tropic climate, crowded population, poor economic status at that time, as well as prevalence of streptococcal infections.[15] By analyzing respective peri-operative mortality rate in three separate decades (before 1980: 6.36%, 1980-1990: 6.28%, and after 1990: 0.00%), no differences of operative outcome could be found between self-formulated or commercialized cardioplegic solution (separated by early-1980), while marked improvement could be found after 1990, due to advance in operative technique, cardiopulmonary bypass, myocardial protection, as well as ICU and ward nursing techniques.

Structural valve dysfunction On the other hand, age was discovered to be a significant risk factor for primary tissue failure of bioprosthesis by many authors.[4;9] In the present report, our data were compatible with those series, either by actuarial or actual rate. The mean age of operation was younger in this study and it could explain why the freedom from structural valvular dysfunction is lower than those of the Western series (table 2).

To compare structural valve failure rate on specific age group, we pick out a subgroup of 40-50 years old with either MVR (case number=121) or AVR (case number=22) to study. In MVR cases, the freedom from structural valve failure at 5, 10, 15, 20 years are 99.1±0.9%, 63.1±5.1%, 16.6±4.3%, and 13.3±4.0%, respectively, which are quite similar to that reported by Fann et al[4] (97%, 65%, 21% at 5, 10, 15 years, respectively) and by Jamiesson et al[2] (12%, 0% at 15 and 20 years, respectively) for the same age MVR subgroup. While in AVR cases, the freedom from structural valve failure at 5, 10, 15, 20 years are 100±0.0%, 80±10%, 44±13%, and 7.5±7%, respectively, which are also similar to that reported by Fann et al[4] (100%, 70%, 47% at 5, 10, 15 years, respectively) and by Jamiesson et al[2] (42%, 26%, at 15 and 20 years, respectively) for the same age subgroup with AVR. This finding suggests age to be an important determining factor of structural valve failure in both Western and Eastern world.

High prevalence of rheumatic heart disease may partially explain the progression of structural valve dysfuncton, which was supported indirectly by the pathology of xeplanted valves (calcification, linear tear, and perforation). Valvular sites (mitral, aortic, or both) also affected the mean survival duration of CES porcine bioprostheses in this study. Mean durability of AVR (12.26 years), MVR

disease in the Orient. Jpn Heart J. 1979;20:237-252.

(11.96 years), and DVR (11.07 years) was better than those reported by Bernal et al (92.9 months for AVR, 101.6 months for MVR, 84.3 months for DVR).[16]

Later year of operation was with higher rate of structural valve dysfunction by our data (Fig. 3d), which is compatible with that reported by Fann et al. [4]. One possible explanation is the early detection of structural valve dysfunction by improved technology. (The 2D and Doppler echocardiography was generalized in our hospital since mid-1980, so many of the patients in the first time period (1975-1980) could not be followed by this method.) Besides this, it also implies that structural valve failure rate is not inversely related to economic status. (Gross national income in Taiwan at 1976-1979 and 1980-1985 were 850 and 1846 NTS, respectively.)

Limitation Due to many of our data were collected brfore 1996, when Edmunds et al.[8] publishesd the guideline for reporting the long-term results of valvular surgery, some parameters might not be wholly the same with suggested formats.

Another limitation is that since ninety-five percent of our cases were rheumatic in nature, no sufficient non-rheumatic cases can be compared to elucidate whether disease nature is one factor influencing structural valve dysfunction rate.

One another limitation is quite homogenicity of valve used in our hospital (CES), so no comparison can be made with other major types of first or second generation bioprostheses with respect to the durability of different valves in rheumatic patients.

The other limitation is young age group in our early operation population (Fig.1). This makes most patients older than 60 years were censored at less than five years, so we cannot obtain reliable CES reoperation rate in that age group. This is one possible explanation why structural valvular failure rate of AVR in the present study is higher than that by other reports.

計劃成果自評

(1) 在２１世紀初，我們回顧了本院過去２０年來的資料結果，其目的乃在期望能建立本國自己的資料庫。現在隨著醫療科技的進步，新一代的組織瓣膜已陸續問世。本資料庫所提供的數據，正可作為新一代組織瓣膜於國人體內適用度的比較標準。(2) 資料庫的開發與維護，可解決醫療決策上的迷思。

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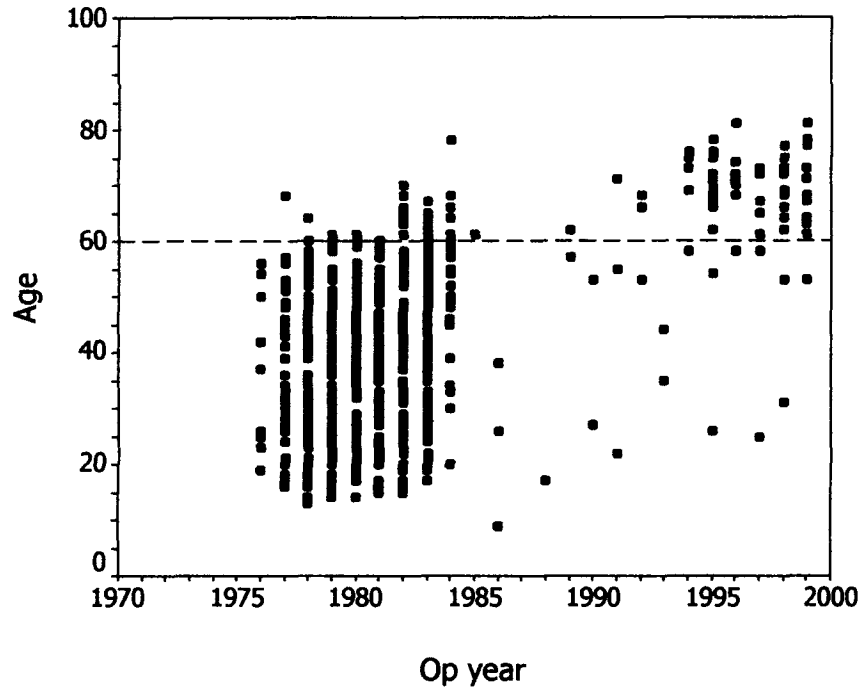
*請參閱拙著 **Long-Term Evaluation of Carpentier-Edwards Porcine Bioprosthesis for Rheumatic Heart Disease. Journal of Thoracic and Cardiovascular Surgery, accepted, unpublish.**

Fig. 1: Individual cases in the present study, plotted against operative year and age



Figures 2a. Actuarial survival after C-E bioprosthesis implantation

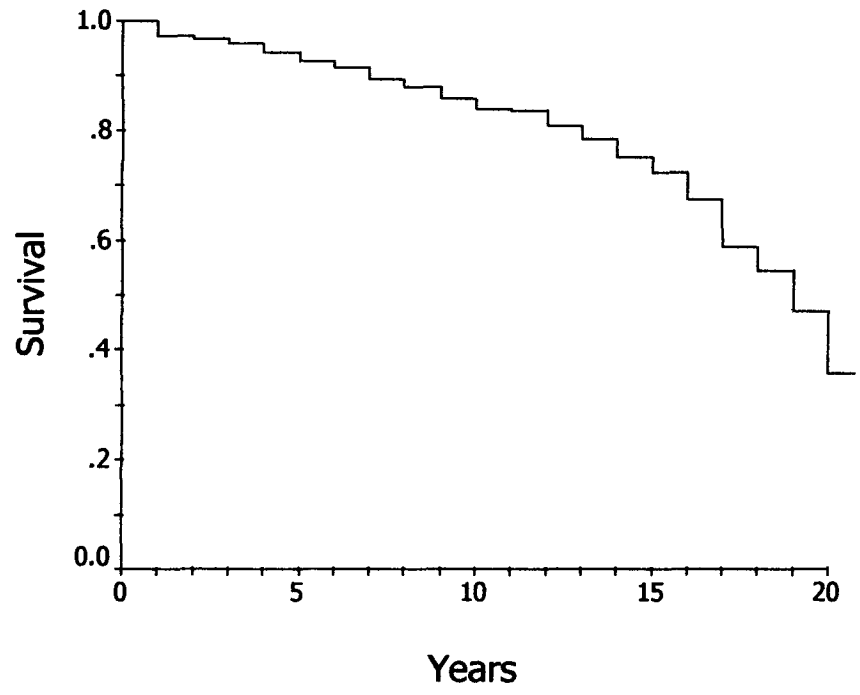
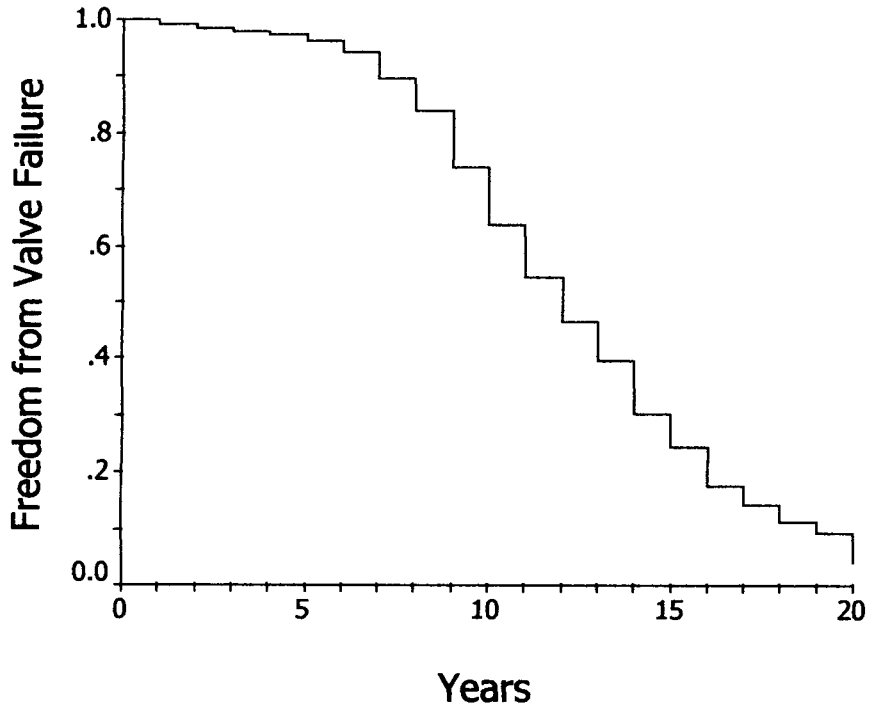


Figure 3a. Actuarial survival curve for freedom from valve failure needing re-operation


Freedom from Valve Failure
1.0
.8
.6
.4
.2
0.0
0
5
10
15
20
Years