Platelet Survival Time Following Aortic Valve Replacement

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SUMMARY

Thromboembolism continues to complicate the course of patients following aortic valve replacement. In patients with prosthetic and homograft mitral valves, platelet survival time has been shown to correlate with occurrence of thromboembolism. This study extends these observations to patients with aortic valve disease. Platelet survival time was measured (by the chromium-51 method) in 73 patients with aortic valve disease. Eighteen patients were studied preoperatively and had platelet survival times of 3.4 ± 0.14 days (mean ± standard error of the mean), almost the same as normal (3.7 ± 0.4 days). Platelet survival time was shortened (P < 0.001) following aortic valve replacement with Starr-Edwards prostheses — Model 1000: 2.5 ± 0.13 days (N = 6); Model 1200–1260: 3.0 ± 0.10 (N = 14); Model 2300–2320: 3.0 ± 0.15 days (N = 9) — and with stented aortic homografts: 3.0 ± 0.10 days (N = 16). Platelet survival time was normal following aortic valve replacement in patients with directly sewn aortic homografts 3.7 days ± 0.24 days (N = 10). Eleven patients with Starr-Edwards prostheses had a history of thromboembolism and all also showed shortened platelet survival time (2.7 ± 0.12 days, P < 0.001), a measurement which was significantly different (P < 0.01) from the 18 patients with Starr-Edwards prostheses and no thromboembolism (3.0 ± 0.09 days). Platelet suppressant therapy prolonged platelet survival in eight patients with Starr-Edwards devices, thromboembolism, and shortened platelet survival time. These results suggest that insertion of Starr-Edwards valves and stented aortic homografts alter platelet survival time but that direct homografts do not. A correlation between occurrence of thromboembolism after aortic valve replacement and shortened platelet survival time has been shown.

Additional Indexing Words:
Thrombosis Prosthetic aortic valves Homograft aortic valves
Valvular heart disease Platelet suppressant (inhibitor) therapy
Platelet function

THROMBOEMBOLISM continues to be a major complication of prosthetic aortic valve replacement. With improvement in valve design and materials, the incidence of thromboembolism following prosthetic replacement of the aortic valve has steadily fallen, but when the numbers of patients with these valves are considered, even low rates of thromboembolism will result in a high incidence of these complications.

Anticoagulants, although generally thought to be beneficial in reducing thromboembolism in patients with prosthetic aortic valves, remain incompletely effective and carry a definite risk of their own. With the valves currently manufactured, the risk of a complication of anticoagulant therapy approaches that of thromboembolism, and controlled trials of the efficacy of warfarin in recipients of newer prosthetic aortic valves are being undertaken. A test that would predict whether or not thromboembolism is likely to occur in patients with prosthetic aortic valves and a drug which would completely prevent thromboembolism are needed.

We have reported that altered platelet survival time is present in recipients of older types of mitral prosthetic valves, valves associated with high rates of thromboembolism. Platelet survival is normal in patients with the Beall mitral valve and with aortic homografts placed in the mitral position, valves associated with low rates of thromboembolism. Further, platelet survival time is shortened in patients whose mitral valves have been replaced and who have a history of thromboembolism, and the survival is

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significantly different from those without thrombosis.8

The purpose of this investigation was to examine whether platelet survival time correlates with thromboembolism in a similar way in patients with aortic valve replacement.

Patients
Seventy-three patients with isolated aortic valve disease, including 67 men and six women, ranging in age from 23–64 years, were studied. None had clinical, angiographic, or echocardiographic evidence of mitral stenosis. Patients included 18 studied prior to surgery and 55 evaluated at least three months following aortic valve replacement. Seven of the 18 studied preoperatively had repeat studies following valve replacement.

The 18 men studied prior to surgery had aortic stenosis of varying severity (peak systolic gradient of 15–100 mm Hg) with or without aortic regurgitation; none had a history of thromboembolism. The 55 patients studied after aortic valve replacement included 29 with Starr-Edwards Ball valve prostheses and 26 with aortic homograft valves. Those with Starr-Edwards valves had either the older models 1000 (N = 6) or 1200–1260 (N = 14), or newer cloth-covered metal-ball valves, Model 2300–2320 (N = 9).

Eleven of the total group had a history of thromboembolism and all groups were represented. Thromboembolism occurred twice in one patient. Platelet survival studies were done from 4–8 years (average, 67 months) after implantation for patients with the Model 1000 valve. For the Model 1200–1260 valve, studies were performed two to five years (average, 38 months) after placement, and eight episodes of thromboembolism were noted in seven patients. Patients with Model 2300–2320 valve were studied between one and three years (average, 21 months) after placement of the prosthesis and three patients had had thromboembolism. None of these patients had had atrial fibrillation. Thromboembolism was manifested as stroke in 11 incidents (10 patients) and as iliofemoral arterial occlusion in two incidents (two patients, one of whom also had stroke).

In the 26 patients with homograft valves, ten had directly sewn valves, and the remaining 16 had stented valves, that is, the homograft aortic valve was placed on a metal stent prior to its placement in the aortic ring. None of the patients with homografts had a history of thromboembolism. These patients were studied between one and five years following valve replacement (average, 35 mo).

Methods
Platelet survival time was measured by labeling the platelets from 450 ml of the patient’s blood with chromium-51. By computer-assisted least-squares analysis a single exponent was fitted to seven days of platelet count-rate data to obtain the half-time. Platelet survival half-time in a group of 18 normal subjects has been found to be 3.67 ± 0.04 days (mean ± SEM) with a range of 3.3–4.2 days.8

The patient’s informed consent was always obtained prior to study. Most of the patients who had received prosthetic valves were anticoagulated with warfarin, but none was taking a drug known to alter platelet function; in particular, special care was taken to inquire about and prohibit use of aspirin. None of the patients with homograft valves or the patients studied preoperatively were anticoagulated at the time of study.

Student’s t-test was used to compare the means for statistical significance.

Results
Mean platelet survival half-time was not significantly different from normal for the 18 patients with aortic valve disease studied prior to valve replacement with the average, 3.4 ± 0.14 days (fig. 1). Platelet survival did not correlate with patient age, sex, the severity of aortic stenosis or regurgitation, the amount of aortic valvular calcification or the presence of congestive failure.

Twenty-nine patients were studied following prosthetic aortic valve replacement with Starr-Edwards valves. Average platelet survival half-time was significantly shortened in the groups of patients with each of the Starr-Edwards valves, and in general, the degree of shortening correlated with the reported incidence of thromboembolism for that valve model. Average platelet survival half-time for the six patients with the Model 1000 valve was abnormally shortened (2.5 ± 0.13 days), a value which was significantly different from normal (P < 0.001) (fig. 1). All six had shortened platelet survival time. These patients had undergone aortic valve replacement from four to eight years prior to study and one patient (platelet survival, 2.3 days) had had two episodes of cerebral embolism.

The 14 patients with the Model 1200–1260 Starr-Edwards valve had an average platelet survival that was shortened (3.0 ± 0.10 days) and significantly different from normal (P < 0.001) (fig. 1). Seven patients had a history of thromboembolism and all seven had shortened platelet survival time (mean: 2.7 ± 0.37 days) (P < 0.001). Average platelet survival

![Figure 1](http://circ.ahajournals.org/doi/fig/10.1161/01.CIR.51.2.359)

Platelet survival half-time plotted for patients with aortic valve disease and following aortic valve replacement. The horizontal bars represent the means. The normal range (3.3–4.2 days) is identified at the left. Closed circles indicate patients with thrombosis and open circles are patients without thrombosis. Model 1000, 1200, and 2300 are the types of Starr-Edwards prosthetic aortic valves inserted.
half-time for the seven without a history of thromboembolism was 3.2 ± 0.09 days; three had normal platelet survival.

Average platelet survival time in nine patients with the entirely cloth-covered Model 2300-2320 valves was shortened (3.0 ± 0.15 days) and significantly different from normal (P < 0.001) (fig. 1). Thromboembolism had occurred in three, all of whom had shortened platelet survival (mean: 2.7 ± 0.33 days) (P < 0.001). Of the six without a history of thrombosis, three had normal platelet survival and in three the time was shortened.

Platelet survival time did not correlate with patient age, sex, the preoperative aortic valve lesion, anticoagulant usage, prosthetic valve size, or the length of time the valve had been in place.

Average platelet survival time was somewhat shorter for the patients with the older, Model 1000, valves than with newer Model 1200-1260 and 2300-2320 valves. The averages paralleled the reported rates of thromboembolism for these valves5, 4, 9, 9–22 (table 1).

Of the 29 patients with Starr-Edwards valves thromboembolism had occurred in 11. Average platelet survival half-time for all 11 was shortened (2.7 ± 0.12 days), significantly different from normal (P < 0.001). Average platelet survival for the 18 patients with Starr-Edwards aortic valves who had not had thromboembolism was 3.0 ± 0.09 days, which was significantly different (P < 0.01) from the average of those with a history of thrombosis (fig. 2).

Anticoagulation was not effective in preventing thromboembolism in these 11 patients with prosthetic Starr-Edwards aortic valves. Nine of the 11 patients with thromboembolism were effectively anticoagulated at the time of embolization. The two nonanticoagulated patients had cloth-covered valves (2310, 2300) and had had warfarin discontinued six and eight months prior to embolization.

Twenty-six patients were studied following homograft replacement of the aortic valve.19–21 Ten of these had directly sewn homografts and their average platelet survival half-time was normal (3.7 ± 0.24 days). Eight had normal values and two had shortened platelet survival (fig. 1). Average platelet survival for the 16 patients with stent aortic homografts (18) was abnormal (3.0 ± 0.10 days) and significantly different from normal (P < 0.001) (fig. 1). None of the 26 homograft patients have had thromboembolism. Thus, directly sewn homografts do not alter platelet survival, but the stented valve seems to be associated with increased platelet consumption.

Eight patients with prosthetic aortic valves, shortened platelet survival time, and a history of thromboembolism were treated with platelet suppressant drugs — six received sulfinpyrazone, 800 mg per day, and two received dipyridamole, 100 mg, and aspirin, 1200 mg per day. A platelet survival test was performed before and after three months of treatment. Average platelet survival time was significantly prolonged by sulfinpyrazone from 2.5 ± 0.18 to 3.4 ± 0.14 days (P < 0.001) and five of the six had prolongation of platelet survival and three had normalization of platelet survival time. Dipyridamole and aspirin prolonged platelet survival in one of the two patients.

None of these eight patients has had thromboembolism while taking platelet suppressants. They had been on therapy for an average of 18 months (6–38)

### Table 1

**Relationship of Platelet Survival Time to Reported Rates of Thromboembolism for Substitute Aortic Valves**

<table>
<thead>
<tr>
<th>Valve</th>
<th>Platelet survival time, days (Ave ± SEM)</th>
<th>Reported incidence of thromboembolism, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starr-Edwards, Model 100</td>
<td>2.5 ± 0.13</td>
<td>0–29%; ave 19%</td>
</tr>
<tr>
<td>Starr-Edwards, Model 1200–1260</td>
<td>3.0 ± 0.10</td>
<td>0–10%; ave 5%</td>
</tr>
<tr>
<td>Starr-Edwards, Model 2300–2320</td>
<td>3.0 ± 0.15</td>
<td>0–10%; ave 2%</td>
</tr>
<tr>
<td>Stented aortic homograft</td>
<td>3.0 ± 0.10</td>
<td>0%</td>
</tr>
<tr>
<td>Directly sewn aortic homograft</td>
<td>3.7 ± 0.24</td>
<td>0–1%</td>
</tr>
</tbody>
</table>

Ave = average; SEM = standard error of the mean.

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and were given the anticoagulant warfarin while taking platelet suppressants. Bleeding complications were not noted. The dosage of warfarin necessary to prolong the prothrombin time to therapeutic range was invariably less than that prior to sulfipyrazone therapy. The dosage of warfarin was readjusted, based on frequent determinations of prothrombin time, until restabilization occurred. Dipyridamole and aspirin may alter the prothrombin time in patients on warfarin and careful monitoring is required when initiating treatment.

Three patients with prosthetic aortic valves and two with stented homografts who had normal postoperative platelet survival time and were anticoagulated with warfarin were studied while anticoagulated and again three months after discontinuation of warfarin. Platelet survival half-time was not altered by more than 0.2 days. Thus warfarin does not alter normal platelet survival time after aortic valve replacement.

Discussion

These data suggesting that platelet survival time is altered in patients following prosthetic aortic valve replacement are in agreement with the findings of other investigators. Lander et al. reported shortened platelet survival in one of two patients with an early Model Starr-Edwards aortic valve.23 Harker and Slichter reported shortened platelet survival time in all of seven patients with Starr-Edwards aortic valves (model was not specified).24 In two patients with aortic homografts, platelet survival was normal. Selective consumption of platelets in the prosthetic valve patients was demonstrated by normal fibrinogen survival and by prolongation of platelet survival with dipyridamole.24

The average platelet survival times for the three models of Starr-Edwards prosthetic valves bear a rough relationship to the thromboembolic rates observed with these valves. Thus, patients with the older Model 1000 valve had a substantially lower than normal mean platelet survival time of 2.5 days; the time shortened in all. Platelet survival was only moderately shortened in patients with the newer Model 1200-1260 aortic valves and in the current Model 2300-2320 completely cloth-covered valves. The modern cloth-covered caged-ball prosthetic valve (Model 2300-2320) and the improved siliconized ball valve (Model 1200-1260) seem to be associated with less platelet consumption than the original Model 1000 valve.

Platelet survival time was normal following aortic valve replacement with a directly sewn aortic homograft, a not unexpected finding since no foreign materials are in contact with the blood. The stented homograft, a procedure in which a foreign surface can be exposed to blood, seems to consume platelets at about the same magnitude as the newer Starr-Edwards prosthetic valves.

More important than the correlation of average platelet survival rates with thromboembolic rates of the various valves is the correlation of occurrence of thromboembolism with shortened platelet survival time. All eleven patients with Starr-Edwards valves and a history of postoperative thromboembolism had shortened platelet survival. Although one might expect, on the basis of associated shortened survival time, that patients with stented aortic homografts also to have an increased incidence of postoperative thromboembolism, to date this has not been the case. As in substitute mitral valves, platelet survival time is altered by substitute aortic valves and correlates with a history of thromboembolism. Turbulence does not seem to be a factor, as normal platelet survival is seen in patients with severe aortic stenosis, and the shortened platelet survival time following aortic valve replacement is probably due to interaction of platelets with the abnormal valve surface.

The directly sewn homograft would seem to be superior to both the current prosthetic and the stented homograft from the standpoint of platelet consumption. These results support the hypothesis that platelets play a role in the thromboembolism of prosthetic aortic valve replacement and suggest a place for platelet suppressant therapy in patients with thrombosis. The frequent occurrence of shortened platelet survival in patients without a history of thromboembolism is disturbing. Patients with shortened platelet survival may be at risk of thromboembolism and measurements of platelet survival times may identify this risk. Thus, platelet suppressant therapy may be found to be an appropriate therapy in these patients as well.

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