

Platelet Suppressant Therapy in Patients with Prosthetic Cardiac Valves

Relationship of Clinical Effectiveness to Alteration of Platelet Survival Time

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SUMMARY Platelet survival time (SURV) has correlated with thromboembolism in patients with prosthetic cardiac valves. Sulfipyrazone increases SURV. SURV (autologous labeling with $^{51}\text{Chromium}$) was measured in 126 patients who had aortic or mitral valve replacement. These patients were followed prospectively. Ninety-four with shortened SURV received sulfipyrazone; 32 with normal SURV were not treated with platelet suppressants. Eighty-seven patients were anticoagulated with warfarin — 67 with shortened SURV and 20 with normal SURV. Eleven patients have had thromboembolism, and all had shortened SURV (2.4 ± 0.08 days; average half-time \pm SEM; normal 3.7 ± 0.03 days; $n = 26$) none had an increase of SURV with sulfipyrazone (2.3 ± 0.09 days). Of 83 patients with shortened SURV who did not have embolism, sulfipyrazone increased SURV in 59 (71%) (2.6 ± 0.05 to 2.9 ± 0.06 days). Of 35 patients with shortened SURV who failed to increase SURV with sulfipyrazone, 11 (31%) had embolism; none of 59 (0%) with an increase of SURV with sulfipyrazone had thromboembolism. These results suggest that patients with thromboembolism after prosthetic cardiac valve replacement have shortened SURV and that patients treated with sulfipyrazone who have thromboembolism do not have an increased SURV.

THE USE OF PLATELET suppressant therapy to prevent thromboembolism in patients with prosthetic cardiac valves appears to rest on firm clinical and experimental grounds. Anticoagulation with warfarin does not appear to decrease the frequency of embolism in patients with mitral prosthetic valves,¹ although it may be beneficial in patients with both newer^{2, 3} and older aortic prosthetic valves.¹ In silastic arteriovenous shunts used for hemodialysis in uremic patients, platelet suppressant therapy decreases thrombosis, but warfarin had no effect;⁴ this model should be similar to prosthetic cardiac valve replacement. In patients with prosthetic aortic and mitral valves, platelet survival time is shortened, particularly in patients with a history of thromboembolism.⁵⁻⁸ Platelet suppressant therapy using either sulfipyrazone or dipyridamole increases platelet survival time in these patients.^{5, 6} In a controlled study in valve replacement patients, dipyridamole in combination with warfarin decreased the frequency of thromboembolism compared with warfarin alone.⁹ Warfarin does not alter platelet survival time.^{6, 7}

Evaluation of platelet suppressant drugs for antithrombotic treatment has been difficult because it is not known which, if any, laboratory test of platelet reactivity correlates with thromboembolism and which drug effect in these tests will be associated with

protection from thrombosis. Platelet survival time appears to be a sensitive indicator of involvement of platelets in thrombosis, but this test may be somewhat less sensitive in measuring platelet suppressant drug effects. For example, aspirin has been shown to decrease systemic embolism in patients with prosthetic aortic valves,¹⁰ but has only a modest effect on platelet survival time.^{6, 11} The present study was undertaken to clarify the value and limitations of measurement of platelet survival time and of platelet suppressant therapy in patients who have had cardiac valve replacement.

Patients and Methods

One hundred twenty-six patients (85 men and 41 women) with valvular heart disease underwent mitral or aortic valve replacement. Platelet survival time was measured 2 and 6 months postoperatively. Ninety-four of these patients (60 men and 34 women) had shortened platelet survival time, and were treated with sulfipyrazone. Eleven of these patients sustained an embolism while taking sulfipyrazone. These 11 patients were matched to patients who had shortened platelet survival time, but who did not have thromboembolism, did have the same underlying valvular disease, the same prosthetic valve, and were followed for at least 12 months with sulfipyrazone treatment (table 1).

Ten of the 11 patients who had a new embolic event and 57 of the 83 patients who did not have a new embolism were treated with warfarin in combination with sulfipyrazone (table 1). Patients treated with warfarin were seen at least monthly for measurement of prothrombin time. We tried to maintain the prothrombin time for 19–30 seconds, and almost all patients were anticoagulated within this range continuously. The patients who had undergone aortic

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TABLE 1. *Patients with Shortened Platelet Survival Treated with Sulfipyrazone*

	Patients with thromboembolism	Patients without thromboembolism
Mitral replacement		
CAD, Beall valve	2 (2)	7 (5)
RHD, Beall valve	2 (2)	21 (17)
RHD, Starr-Edwards valve, Model 6300	1 (1)	9 (9)
Aortic replacement		
Starr-Edwards, Model 1200-1260	2 (1)	16 (6)
Starr-Edwards, Model 2300-2320	3 (3)	17 (10)
Björk-Shiley	1 (1)	13 (10)
Total	11 (10)	83 (57)

Numbers in parentheses indicate number of patients who also received warfarin.

Abbreviations: CAD = coronary artery disease; RHD = rheumatic heart disease.

valve replacement had no clinical evidence of rheumatic heart disease. All had aortic stenosis that was thought to be either congenital or degenerative.

The 32 patients who had normal platelet survival time (and were therefore not treated with sulfipyrazone) were followed for at least 1 year. Twenty were treated warfarin and 12 were not anticoagulated (table 2).

Platelet survival time was measured 2–6 months after cardiac surgery and again after 3–6 months of treatment with sulfipyrazone, 800 mg/day orally. The patients with normal platelet survival had platelet survival measured again 3–6 months after the first measurement. This study was not controlled in that all patients with shortened platelet survival received sulfipyrazone and none of the patients with normal

TABLE 2. *Patients with Normal Postoperative Platelet Survival Time*

	Patients studied
Mitral replacement	
CAD, Beall valve	4 (2)
RHD, Beall valve	5 (5)
RHD, Starr-Edwards valve, Model 6300	2 (2)
Aortic replacement	
Starr-Edwards, Model 1200-1260	6 (3)
Starr-Edwards, Model 2300-2320	7 (4)
Björk-Shiley	8 (4)
Total	32 (20)

Numbers in parentheses indicate number of patients who received warfarin; patients were not treated with sulfipyrazone.

Abbreviations: CAD = coronary artery disease; RHD = rheumatic heart disease.

platelet survival were treated. However, this was a prospective study, and all patients with shortened platelet survival continued on sulfipyrazone after the second measurement of platelet survival.

Platelet survival time was measured by labeling the platelets from about 400 ml of the patient's venous blood with 100–150 μ Ci of 51 Chromium.¹² A single exponent was fitted to 6 or 7 days of platelet count-rate data to obtain the half-time. Normal platelet survival half-time averaged 3.7 ± 0.03 days (average \pm SEM), with a range of normal of 3.3–4.2 days (SD = 0.14 days; $n = 26$). These patients ranged in age from 26–47 years and had normal coronary arteriograms (performed for exclusion of coronary disease). The correlation coefficients for single exponent fit of the platelet count-rate data was always > 0.96 ; the SEE was ≤ 0.26 .

The averages of the groups were statistically compared by means of the paired t test. All patients gave informed consent to participate in this study and appreciated the experimental nature of antithrombotic treatment with sulfipyrazone.

Results

Platelet survival time was shortened (< 3.3 days half-time) in 94 patients and normal in 32 patients. Platelet survival was shortened in all 11 who subsequently had thromboembolism (2.4 ± 0.08 days; average half-time \pm SEM; normal half-time 3.7 ± 0.03 days; $n = 26$). In none of these patients did platelet survival time increase with sulfipyrazone treatment (2.3 ± 0.09 days; NS); one patient (9%) had a decrease of platelet survival of 0.2 days, and 10 (91%) had no change (± 0.1 days). Embolism occurred 10–47 months after initiation of sulfipyrazone (average 25 months), and 10 of these 11 patients were effectively anticoagulated with warfarin at the time of thromboembolism.

In patients treated with sulfipyrazone who did not have a new embolism, average platelet survival time was increased by sulfipyrazone ($2.6 \pm 0.05 - 2.9 \pm 0.06$ days; $n = 83$; $p < 0.001$). Fifty-nine of these patients (71%) had an increase (≥ 0.2 days) in platelet survival, 23 (28%) had no change in platelet survival, and one patient (1%) had a decrease in platelet survival.

Platelet survival was not altered with time in the patients with normal postoperative platelet survival. Although three (9%) had a decrease in platelet survival of at least 0.2 days, the value did not become abnormal in any patient. One (3%) had an increase in platelet survival and 28 (88%) had no change. In patients with normal postoperative platelet survival time, no embolisms have occurred.

Patients with shortened platelet survival who have not had new thromboembolism were grouped according to prosthetic valve (table 3). Patients with prosthetic mitral valves had shorter platelet survival time than those with aortic prosthetic valves (2.2 ± 0.11 days vs 2.8 ± 0.06 days; $p < 0.001$). The Björk-Shiley aortic valve was associated with a

TABLE 3. Platelet Survival Time and Effect of Sulfipyrazone in 83 Patients with Prosthetic Heart Valves

	Platelet survival time (days), ave $t_{1/2} \pm \text{SEM}$	Platelet survival time with SFP (days), ave $t_{1/2} \pm \text{SEM}$
Mitral prostheses		
CAD, Beall valve (n = 7)	2.2 \pm 0.15	2.7 \pm 0.11 ($p < 0.01$)
RHD, Beall valve (n = 21)	2.2 \pm 0.08	2.6 \pm 0.13 ($p < 0.001$)
RHD, Starr-Edwards, Model 6300 (n = 9)	2.3 \pm 0.13	2.7 \pm 0.21 ($p < 0.01$)
Aortic prostheses		
Starr-Edwards, Model 1200-1260 (n = 16)	2.7 \pm 0.10	3.1 \pm 0.15 ($p < 0.01$)
Starr-Edwards, Model 2300-2320 (n = 17)	2.8 \pm 0.05	3.1 \pm 0.09 ($p < 0.01$)
Björk-Shiley (n = 13)	3.0 \pm 0.03	3.2 \pm 0.10 ($p < 0.05$)

None of these patients had thromboembolism, and all had shortened survival time.

Results are average \pm SEM.

Abbreviations: CAD = coronary artery disease; RHD = rheumatic heart disease; SFP = sulfipyrazone; ave $t_{1/2}$ = average half-time.

significantly longer platelet survival time than either the Starr-Edwards model 1200-1260 ($p < 0.05$) or model 2300-2320 valves ($p < 0.05$) (table 3).

Discussion

The results of this study indicate that patients with prosthetic heart valves and shortened platelet survival time who do not have an increased platelet survival time with sulfipyrazone treatment have a greater risk of thromboembolism than patients who do have an increased platelet survival time (fig. 1). Of 35 patients who did not have increased platelet survival, 11 (31%) had thromboembolism, whereas none of 59 (0%) with an increase in platelet survival had embolism. In patients without thromboembolism, 30% did not have an increase in platelet survival time. Thus, the anti-thrombotic effect of sulfipyrazone in each patient appears to be predictable by the alteration of platelet survival time. We observed a similar relationship between the effects of sulfipyrazone on thromboembolism and platelet survival in patients with cerebral vascular disease and transient ischemic episodes.¹³ Platelet survival time was shortened in all 25 of the patients whom we studied. In 10 patients sulfipyrazone was very effective in decreasing the frequency of ischemic episodes, and platelet survival was in-

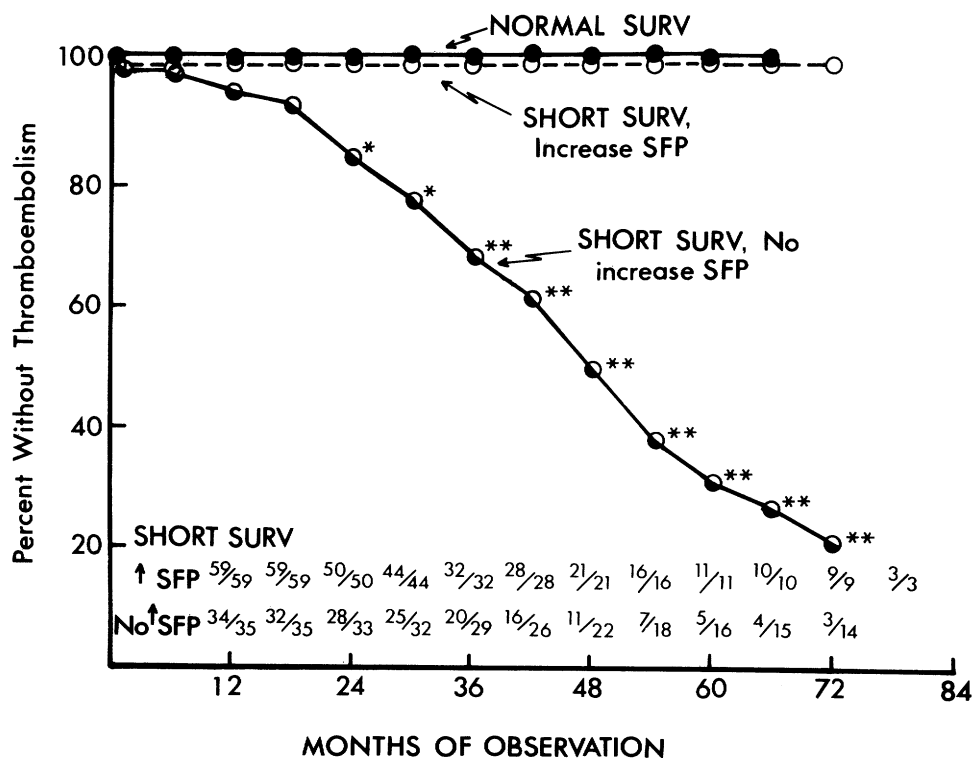


FIGURE 1. Occurrence of thromboembolism with time plotted for patients with normal postoperative platelet survival time (normal SURV), shortened platelet survival with an increase in platelet survival with sulfipyrazone (SFP) treatment (short SURV, increase SFP), and those with shortened platelet survival who did not respond to SFP (short SURV, no increase SFP). Chi-square analysis yields significant differences at 24-72 months (* $p < 0.05$; ** $p < 0.01$). Fractions are the number of patients without thromboembolism at each 6-month interval divided by the number followed and at risk. Standard errors at 24 months, 48 months and 72 months for shortened platelet survival without and increase with sulfipyrazone are 5%, 5% and 7%, respectively.

creased in seven (70%) of these patients.¹³ In three patients who had no benefit from the drug, platelet survival was not altered.¹³

Previous studies have suggested that shortened platelet survival time correlates with a history of thromboembolism in patients with prosthetic cardiac valves^{7, 8} and in patients with rheumatic mitral valve disease.¹⁴ The present study suggests that thromboembolism will not occur in patients with prosthetic cardiac valves who have normal postoperative platelet survival time. This conclusion may be too strong, as the duration of follow-up of these patients is relatively short with respect to the expected life of the prosthetic valve.

This study clearly shows that sulfinpyrazone is not completely effective in preventing embolism, even when administered with warfarin. Eleven patients with prosthetic cardiac valves treated with sulfinpyrazone sustained an embolism. The study design does not allow definitive assessment of the effectiveness of either sulfinpyrazone or warfarin in patients with prosthetic valves, because a control group receiving placebo was not included, and because most patients were treated with both warfarin and sulfinpyrazone. Sulfinpyrazone has been shown to decrease the frequency of thrombosis in dialysis patients with silastic arteriovenous shunts,⁹ and this clinical situation may be similar to prosthetic cardiac valve replacement. Sulfinpyrazone and dipyridamole have similar effects on platelet survival time¹² and dipyridamole has been shown to decrease thromboembolic frequency in patients with prosthetic cardiac valves.⁸ These studies suggest that sulfinpyrazone will prevent thromboembolism in patients with prosthetic valves.

Our data support the idea that platelet survival time is a relevant measurement of thromboembolic risk. Platelet survival seems to provide important information both for patient groups, e.g., prosthetic cardiac valve replacement, and for individual patients within the group. An increase of shortened platelet survival with platelet suppressant treatment appears to decrease thrombosis even though platelet survival time remains abnormal. This phenomenon could be due to the relative ineffectiveness of sulfinpyrazone as an antithrombotic agent; that is, a more effective drug would be associated with a further and more frequent increase in platelet survival and a further decrease in thrombosis. An alternative explanation might be that

platelet survival time does not specifically measure either thromboembolic risk or alteration of that risk with treatment, and a more specific laboratory test needs to be developed.

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