VOLUME 20, No. 3 SEPT 1979 (SUPPLEMENT 1)

PLATELET SURVIVAL IN PATIENTS WITH ARTIFICIAL HEART VALVES AND THE EFFECT OF ANTI-PLATELET AGENTS

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One of the major causes of morbidity and mortality in patients with prosthetic heart valves is thromboembolism. The frequency of thromboembolism in some series can be as high as 20% even in patients who are judged to be adequately anticoagulated (1). Akbarian (2) reported a frequency of 13% of thromboembolism in those who are well anticoagulated, rising to 22% in those who are poorly anticoagulated, and 49% in those who are not anticoagulated. There is clear evidence that thromboembolism might occur even in well anticoagulated patients. The problem is compounded by the fact that it is not easy to achieve adequate anticoagulation. Using an arbitrary criteria of having not a single prothrombin time less than 1½ times the control value (in seconds) after the attainment of the initial therapeutic level, Duvoisin et al from the Mayo Clinic reported that only 98 patients out of a total of 405 patients (24%) were adequately anticoagulated (1). Because of the various problems associated with anticoagulation, it was decided to investigate the platelet survival time in patients with artificial heart valves and the effect of anti-platelet agents in order to evaluate the possibility of using anti-platelet agents in a large scale clinical trial for the prevention of thromboembolism in these patients.

PATIENTS AND METHODS

Platelet Survival. Platelet survival study was done using ^{51}Cr labelled autologous platelets according to the method of Abrahamsen (3). 90 min after the ^{51}Cr labelled platelets were injected into the patients, blood samples were taken and platelet rich plasma prepared for counting in a counter. This process of preparing platelet rich plasma for counting was repeated every day for 5 days. The results were used to calculate the platelet survival T/2. Surface scanning over the spleen and the heart was also carried out daily for 5 days. A spleen/heart ratio was obtained by the formula:

$$\text{Spleen/Heart ratio} = \frac{\text{radioactive count per min over the splenic area}}{\text{radioactive count per min over the cardiac region}}$$

Patients. Five healthy adults served as normal controls for the platelet survival study. Twenty-five patients with prosthetic heart valves were studied. Twenty of them had had no history of thromboembolism, and of these seventeen were not on any anticoagulants, while three were taking warfarin. Five had a past history of thromboembolism and were on warfarin 2 mg to 6 mg a day. Sixteen patients had mitral valve replacement with Starr-Edward valves and one had mitral valve replacement with the Beall valve. Five had aortic valve replacement with Starr-Edward valves and three had double valve replacements with the Starr-Edward valves. Their ages ranged from fifteen to sixty-two with a mean of 37.9 years.

Anti-platelet Agents. In some patients, platelet survival T/2 and surface scanning were done before and four to six weeks after they were put on various anti-platelet agents singly and in combinations. The drugs and dosage used were (1) pentoxifylline (Trental) 200 mg t.d.s.; (2) pentoxifylline (Trental) 400 mg t.d.s.; (3) dipyridamole 50 mg t.d.s.; (4) aspirin 600 mg b.d.; (5) dipyridamole 50 mg b.d. plus aspirin 600 mg b.d.; and (6) pentoxyfylline 200 mg t.d.s. plus aspirin 600 mg b. d.

RESULTS

The patients' clinical histories, platelet count, platelet survival T/2 and maximum spleen/heart ratios are summarised in Tables 1 to 3. It can be seen that compared with normal controls, patients with artificial heart valves had a lower platelet count and shorter platelet survival T/2. In the case of patients who were not on anticoagulant, the spleen/heart ratio was also higher.

TABLE 1

DETAILS OF CLINICAL DATA AND RESULTS OF PLATELET STUDIES

HEALTHY CONTROL

PATIENT	SEX/AGE	VALVE CHANGED	YEAR OF OPERATION	PLATELET T/2 IN DAYS	PLATELET COUNT X 10^9/L	SPLEEN/HEART RATIO
1. YT	M/35	—	—	4.09	278	1.65
2. LKT	M/30	—	—	4.11	197	1.84
3. TYL	F/25	—	—	3.72	188	1.25
4. WCW	M/32	—	—	4.00	220	1.19
5. YKP	M/40	—	—	4.09	231	1.20

PATIENTS WITH PROSTHETIC VALVES. NO HISTORY OF EMBOLISM. NOT ON DRUGS.

6. LCK	F/39	M	1977	2.40	178	1.97
7. SCH	M/21	A + M	1972	2.71	151	2.58
8. TCK	F/31	M	1970	1.58	184	—
9. CYT	F/40	A	1970	2.17	148	1.60
10. CNB	M/62	A + M	1978	2.95	185	2.65
11. TWY	F/44	A	1976	2.27	120	3.73
12. FSM	M/60	M (BEALL)	1969	2.47	67	3.34
13. WYW	M/51	A	1974	2.33	143	0.97
14. TTC	M/44	A	1972	1.78	132	4.96
15. LCY	F/22	M	1972	1.33	221	6.26
16. WYS	F/28	M	1974	1.81	96	3.89
17. KSY	F/49	M	1974	1.18	233	2.94
18. LHY	M/50	M	1972	2.68	105	2.73
19. YSP	M/28	A + M	1973	1.61	86	1.61
20. STT	F/32	M	1962	2.02	150	1.24
21. LMW	F/25	M	1976	1.72	120	2.74
22. CM	M/22	M	1976	3.41	105	1.00

TABLE 2

PATIENTS WITH PROSTHETIC VALVES AND WHO ARE ON WARFARIN

PATIENT	SEX/AGE	VALVE CHANGED	YEAR OF OPERATION	PLATELET T/2 IN DAYS	PLATELET COUNT X 10^9/L	SPLEEN/HEART RATIO
23. HMK	F/37	M	1975	1.58	110	1.95
24. NKM	M/15	A	1977	1.66	127	2.90
25. KSM	M/60	M	1977	2.56	115	2.12
26* CW	F/33	M	1971	2.08	106	1.56
27 CC	F/23	M	1975	1.91	186	2.63
28* YKY	F/50	M	1974	1.60	83	2.83
29* WWC	F/27	M	1975	2.17	110	2.06
30* LCF	M/56	M	1978	1.78	106	0.92

* PATIENTS WITH HISTORY OF EMBOLISM
M = MITRAL VALVE REPLACEMENT
A = AORTIC VALVE REPLACEMENT
ALL VALVES WERE STARR-EDWARD VALVES EXCEPT PATIENT NO. 12.

TABLE 3

SUMMARY OF CLINICAL DATA AND RESULTS OF PLATELET STUDIES

	NORMAL CONTROLS	PATIENTS NOT ON DRUGS & WITH NO HISTORY OF THROMBOEMBOLISM	PATIENTS ON WARFARIN WITH HISTORY OF THROMBOEMBOLISM
NO. STUDIED	5	17	5
TYPE OF VALVES	—	MITRAL 10	MITRAL 7
		AORTIC 4	AORTIC 1
		MITRAL + AORTIC 3	MITRAL + AORTIC 0
YEARS AFTER SURGERY	—	5.3 ± 3.8	3.4 ± 2.5
PLATELET COUNT X 10^9/L	222.8 ± 35.4[a]	142.6 ± 46.3[b]	118.2 ± 39.4[b]
PLATELET T/2 IN DAYS	4.00 ± 0.16[c]	2.14 ± 0.60[d]	1.91 ± 0.23[d]
SPLEEN/HEART RATIO	1.43 ± 0.30[e]	2.76 ± 1.45[f]	2.00 ± 0.78
PLATELET RECOVERY		37% ± 13%	
	ab $p < 0.01$	cd $p < 0.001$	ef $p < 0.05$

Figure 1 shows that there is a significant relationship between the platelet count and the platelet survival T/2, and a significant inverse relationship between the platelet survival T/2 and the maximum spleen/heart ratio (fig. 2). When the spleen/heart ratios are followed over the 5 days of the experiment, from day 0 to day 4 (fig. 3), it can be seen that patients' spleen/heart ratios were significantly higher than that of the controls throughout the five days.

The effect of anti-platelet agents on platelet survival is summarised in figure 4. It can be seen that warfarin or aspirin alone had no effect on platelet survival while aspirin 1200 mg plus pentoxifylline 600 mg a day or aspirin 1200 mg plus dipyridamole 100 mg a day normalised the platelet survival T/2 and pentoxifylline 1200 mg a day caused a partial return to normal of the platelet survival T/2.

Figure 1

RELATIONS OF PLATELET SURVIVAL 51Cr T/2 WITH PLATELET COUNT

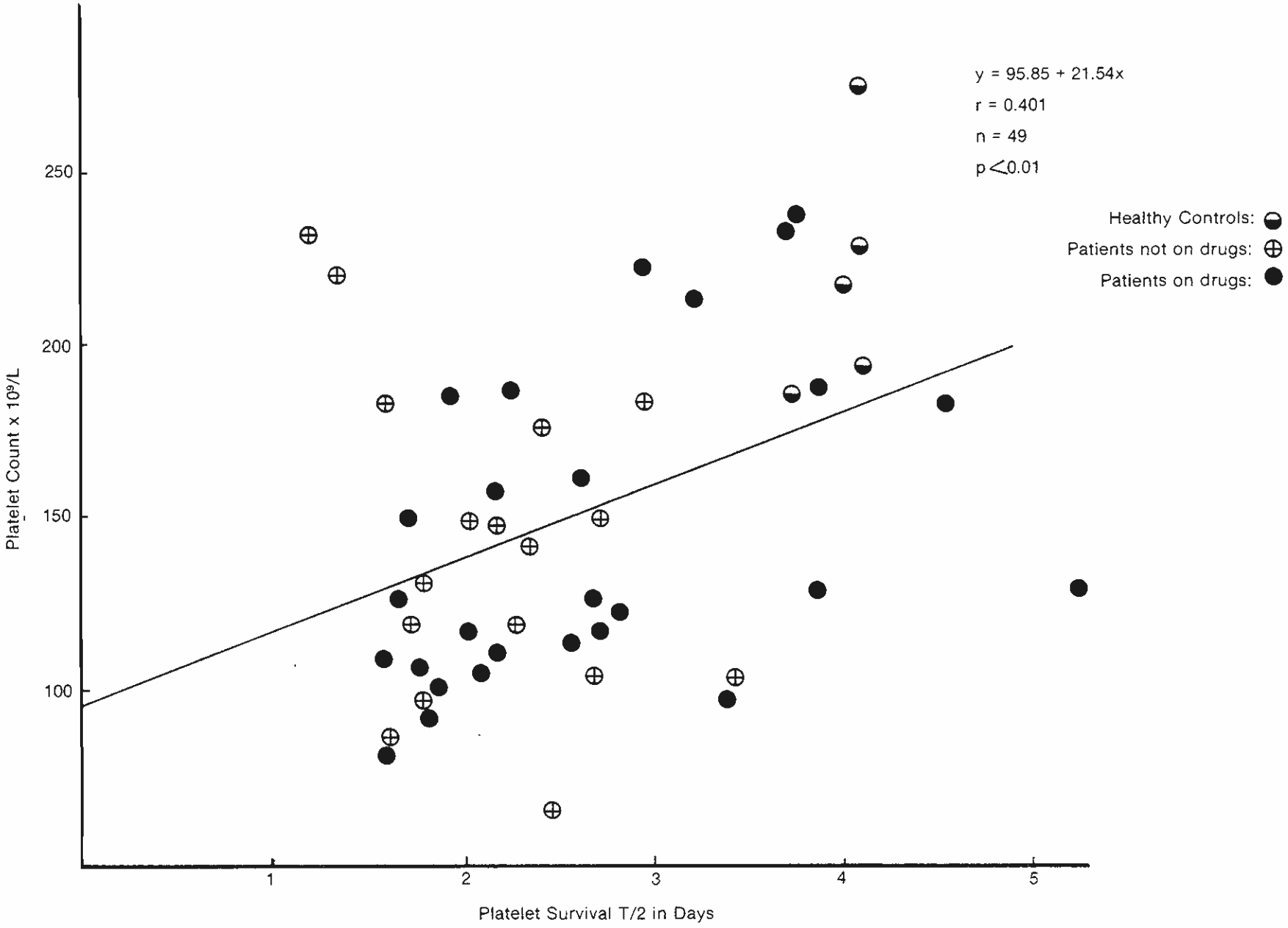


Figure 2

SPLEEN/HEART CPM RATIO IN PATIENTS AND CONTROLS AND PLATELET SURVIVAL T/2

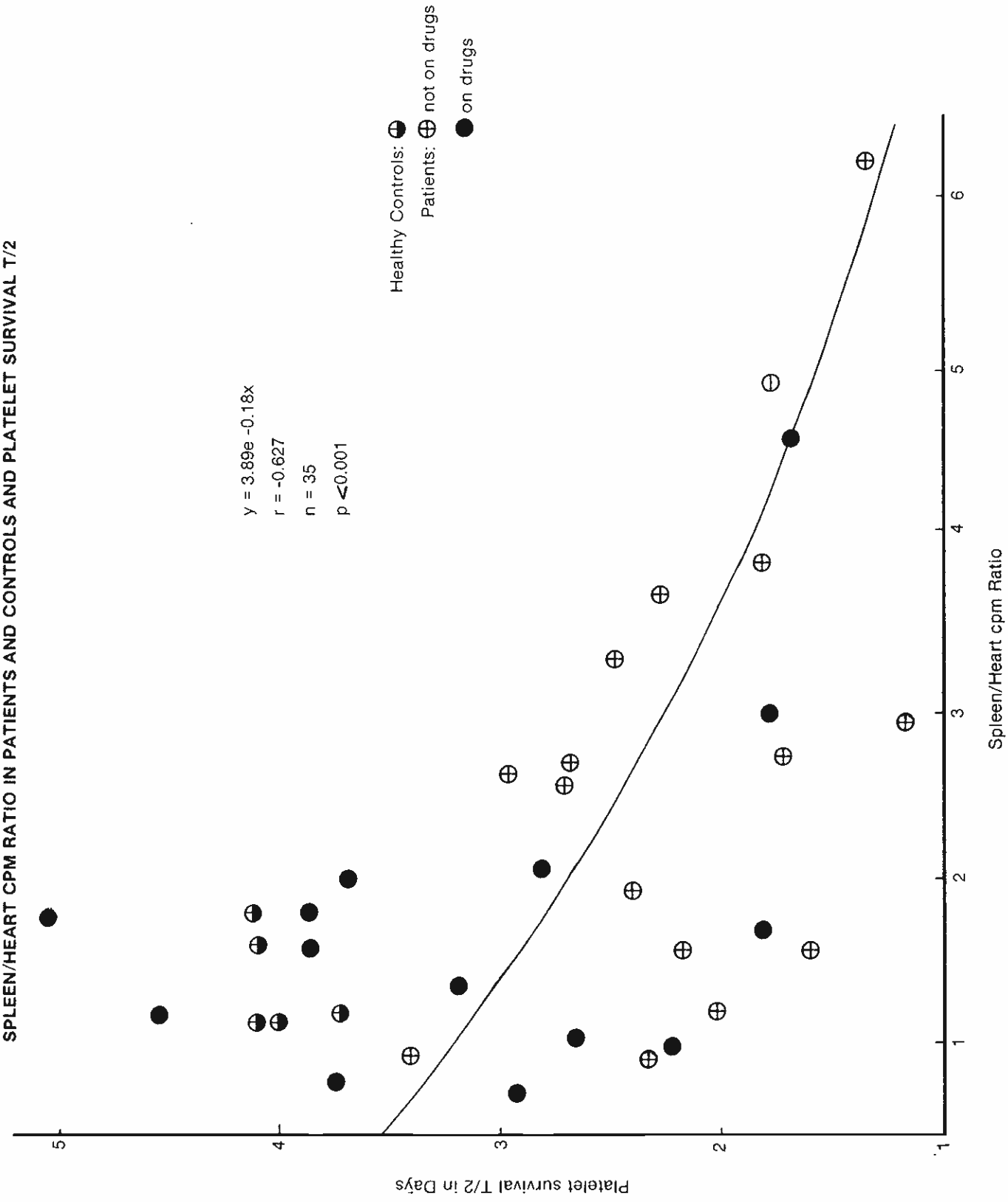


Figure 3

SPLEEN/HEART CPM RATIO ON CONSECUTIVE DAYS FOLLOWING THE INJECTION OF ^{51}Cr LABELLED AUTOLOGOUS PLATELETS.

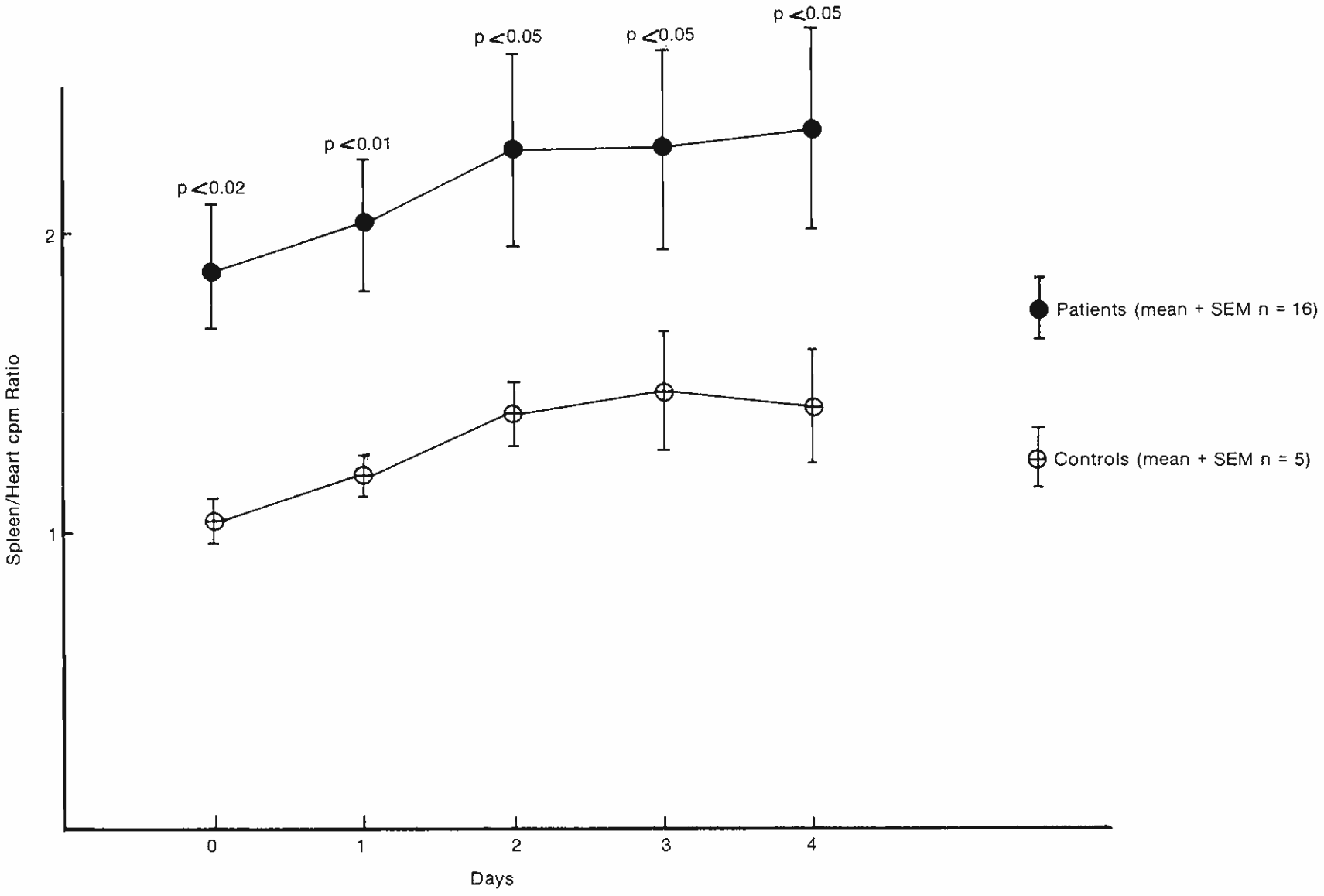
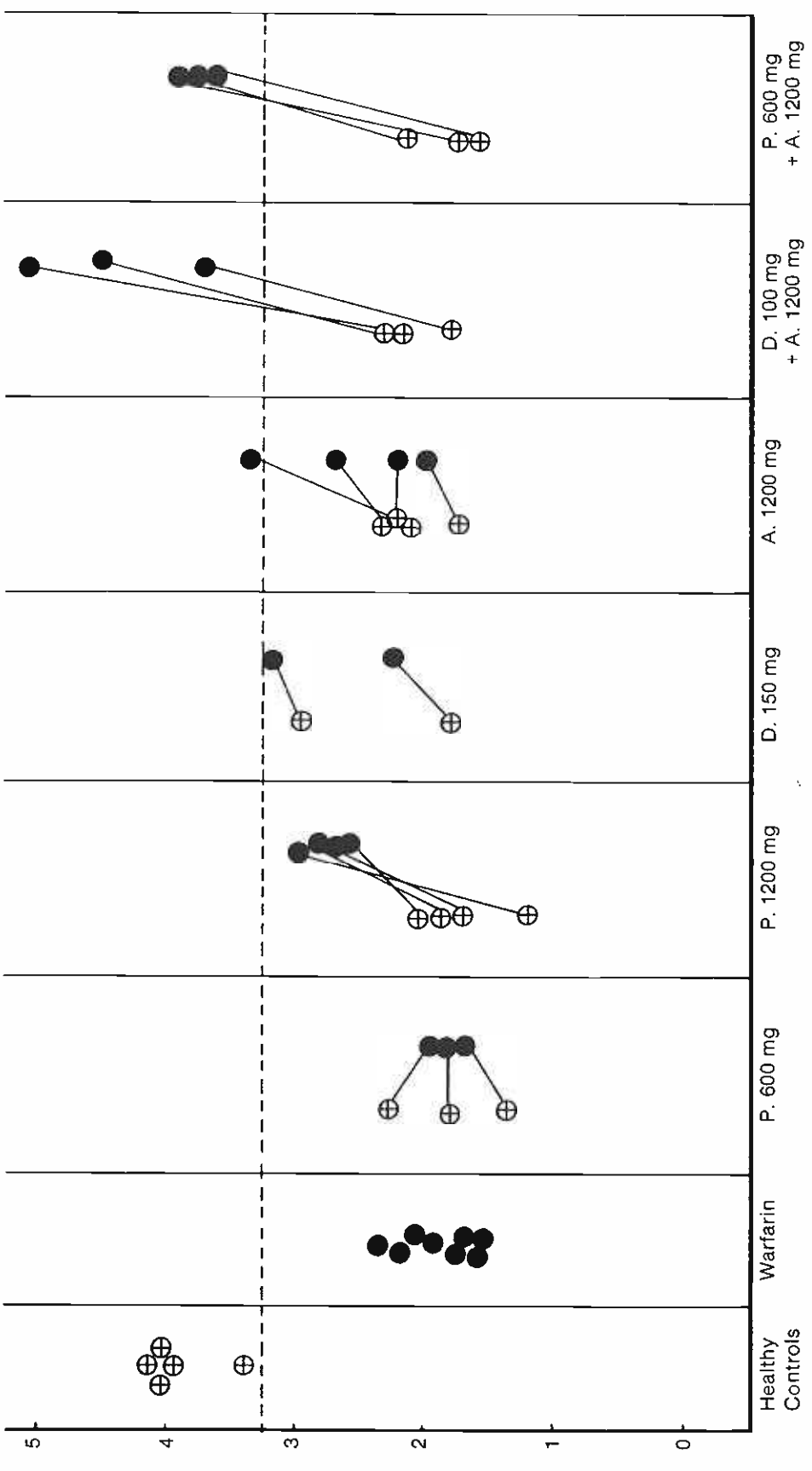


Figure 4

EFFECT OF DRUGS ON PLATELET SURVIVAL IN PATIENTS WITH PROSTHETIC HEART VALVES



DISCUSSION

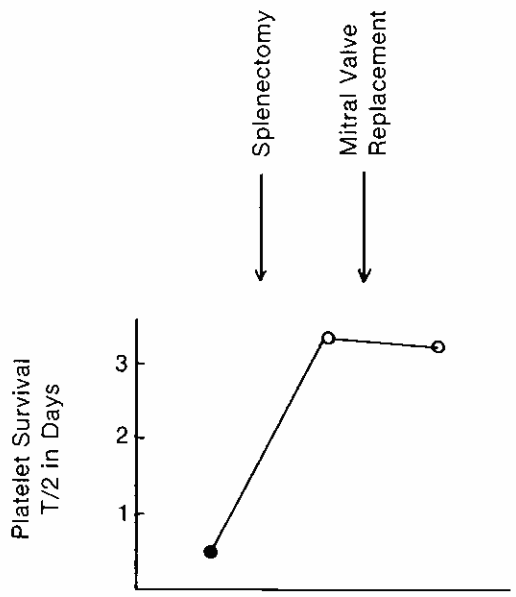
There has been some evidence that shortened platelet survival time in patients with artificial heart valves correlates with thromboembolic complications (4, 5). Harker & Slichter (6) reported that aspirin 3 gm a day had no effect on platelet survival time in these patients while dipyridamole 100 mg plus aspirin 1 gm a day normalised the platelet survival time. Our results are in agreement with their findings. In addition, we have shown that the combination of aspirin and pentoxyfylline (Trental), which is a phosphodiesterase inhibitor (7), also achieved the same effect.

Interestingly, we have also shown that a close relationship exists between the platelet survival T/2 and splenic sequestration of the platelets as indicated by a high spleen/heart radioactivity ratio. Figure 5 illustrates the case of a 48 years old woman with mitral valve disease, congestive splenomegaly and thrombocytopaenia due to hypersplenism. Her pre-splenectomy platelet count was 54 x 10^9/1 with a platelet survival T/2 of ½ day and spleen/heart ratio of 3.11. After splenectomy, the platelet count rose to 380 x 10^9/1 with a platelet survival T/2 of 3.1 days. She then had mitral valve replacement and both the platelet count and the platelet survivalT/2 remained normal. These results probably indicate the importance of the spleen in sequestering platelets which have been "partially" damaged by the prosthetic valves.

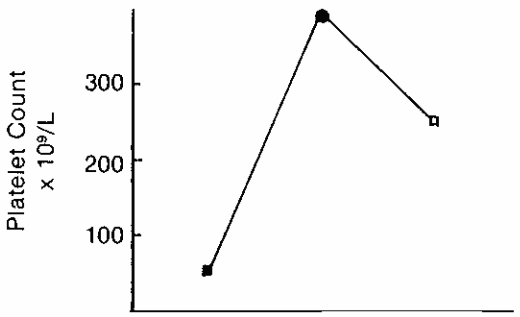
Figure 5

ILLUSTRATIVE CASE REPORT:

Normal Platelet Survival T/2 in a Splenectomised Patient with Prosthetic Heart Valve



M.S.Y. F/48
Known mitral valve disease for 25 years.
Chronic congestive heart failure with congestive splenomegaly.
Thrombocytopaenia, due to hypersplenism, prevented operation for valve replacement.
Initial spleen/heart cpm ratio was 3.11
After splenectomy, the platelet count and platelet survival T/2 became normal.
With the spleen removed, the platelet count and platelet survival T/2 remained normal one month after mitral valve replacement was done.



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Part of the paper has been presented at the 17th Congress of the International Society of Haematology, Paris, 1978.

The work has been supported by Wu Chung Medical Research Fund 311/030/8011/07 — 1978.