A Rapid Method for Estimating Mean Platelet Survival Time

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Platelet survival studies were performed in 27 consecutive subjects, and mean platelet life span was derived by computerized calculations of radioactivity in blood samples obtained daily for 9–11 days. These computer derived estimates were then correlated with the raw whole blood radioactivity data obtained for the first 3 days of each study. Data from the 48-hr point correlates with the computer estimates so that platelet survival data can now be reported in 2 days with 93% precision of the long method and without visual curve fitting. Thus, one may take a "quick look" at the probable platelet lifespan, under steady state conditions, in order to evaluate therapy while avoiding problems of patient compliance.

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Both visual and computer aided techniques have been employed to fit platelet survival data into a clinically meaningful expression. Three decades of work suggest that observer bias complicates visual interpretation and it has been recommended that such methods be replaced (*1*). Interlaboratory comparisons remain tenuous because of platelet injury sustained during collection as well as many slight differences in labeling methodology. Reports of differences in isotope elution rates further confound comparisons between chromium-51 (^{51}Cr) and Indium-111 (^{111}In) data (*2*). Last, without a general consensus for the shape of the normal platelet survival curve, comparative data is difficult to interpret.

Regarding the shape of the platelet survival curve, some investigators favor a linear model while others believe there is a variable random component superimposed on the linear curve. Gamma function analysis appears to circumvent these arguments in that all the data points of the curve, regardless of shape, are fit by least square assuming a multiple hit model (*3*). For example, a one-hit curve, a gamma function of order 1 is exponential—reflecting a substantial insult to the platelet followed by its rapid removal from the circulation. The longer a platelet survives and circulates the greater the number of episodes or hits to which it is exposed—such survival is characterized by a more linear curve. A straight line platelet survival curve would represent a gamma function curve of infinite order.

Lotter et al. (*4*) evaluated 12 mathematic methods used to calculate mean platelet survival time. They concluded that the most reliable estimate of platelet survival can be obtained by fitting the data to either the modified weighted mean (when limited computing facilities were available) or the multiple hit model. Furthermore, they suggest advantages of fitting the data to at least two mathematic models.

The present studies were undertaken to modify and expedite the cumbersome current method of analyzing platelet survival. The data reported herein strongly suggest the effectiveness of employing the ratio of 2 hr to 48 hr platelet radioactivity as a shortcut for estimating platelet survival based on a conventional 9-day data analysis with computer curve fitting.

MATERIALS AND METHODS

Autologous platelet survival studies were performed in our laboratory using [^{111}In]oxine-labeled platelets. In view of the complexities of fitting platelet survival data to various computer models, we chose to analyze the data on a per day basis versus the fit by computer program (*5*). The data presented indicate that one may predict, with reasonable certainty, platelet life span from radioactivity remaining in the circulation 48 hr after injection of labeled platelets.

The data from 27 consecutive patients were used. Platelets were labeled according to the method of Klonizakis et al. (*6*).

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Thirty milliliters blood sample collected in acid citrate dextrose (ACD) was subjected to differential centrifugation to obtain platelet rich plasma. The platelet-rich plasma was then centrifuged on a cushion of autologous red blood cells. The platelet red cell mixture was re-centrifuged at 100 *g* in dextrose saline to obtain a reasonably pure platelet suspension. Cytospin preparations from the platelet suspension revealed <0.01% white cell contamination. Indium-111 oxine, 350 μCi. was added to label the platelets. The unbound indium was removed by centrifugation through autologous citrated plasma containing 0.2 volume of autologous red cells. The platelets were re-suspended in autologous citrated plasma and re-injected intravenously. Blood samples were collected at 15 min, 1 hr, 2 hr, 3 hr, and daily thereafter for 9 days.

Radioactivity was measured in a well counter using aliquots of whole blood and plasma. The data was fit by a computer program supplied by Dr. Edmond Murphy (*7*). Linear, exponential, and multiple hit models were used for formal curve fitting and the residual sum of squares was used as a measure of precision of the fit. A mean and weighted mean were also provided by the program. Four groups of subjects were studied; normal controls, patients with congestive splenomegaly, patients with arterial shunts, and patients with partially compensated idiopathic thrombocytopenia purpura (ITP). Raw data, that is radioactivity remaining in the circulation at 24, 48, and 72 hr after injection of ^{111}In-labeled platelets were divided by the 2-hr value then multiplied by 100. These terms, called percent of injected dose, were subjected to multiple regression analysis against computer derived estimates of platelet lifespan according to the various computer models (Table 3 and Fig. 1).

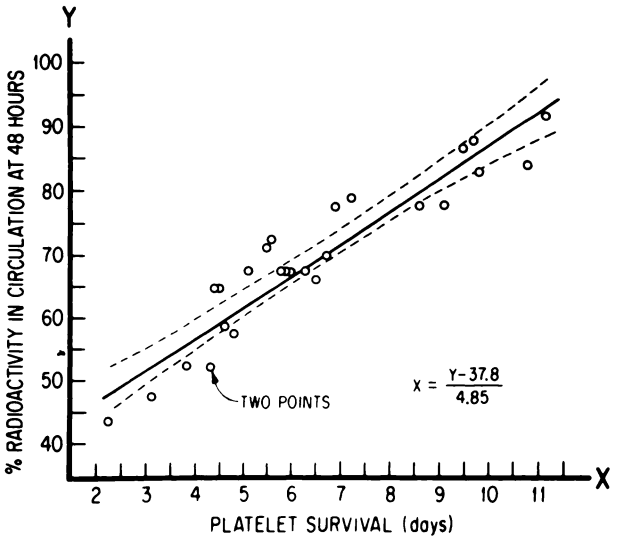

FIGURE 1
Forty-eight-hour regression with line of best fit (—) and the 95% confidence limits (- - - -). X = platelet survival in days; $y = \frac{\text{Radioactivity in peripheral blood at 48 hr}}{\text{Radioactivity in peripheral blood at 2 hr}} \times 100$; Radioactivity = CPM/ml.

RESULTS

Platelet survival data with mean and standard deviation for the four groups studied are presented in Table 1. Based upon the multiple hit model, platelet survival in normal subjects averaged 9.8 days with 70% of the labeled platelets returning to the circulation 2 hr after initial splenic sequestration. In patients with congestive splenomegaly, the 2-hr circulating recovery of labeled platelets was only 15% of injected dose.

Individual platelet survival values, according to computer model, are presented in Table 2. Based upon the multiple hit model, platelet survival ranged from 11.2 to 2.3 days. The multiple hit model provided the best fit in all but two subjects. These were two normals in whom the linear model provided the best fit since both had greater then 50 hits. In four patients the exponential model provided nearly as good fit as the multiple hit model; included herein were three patients with arterial grafts and one patient with ITP.

Table 3 depicts the statistical evaluation of the correlations between percent of injected dose remaining in the circulation 24, 48, and 72 hr after injection of labeled platelets and computer derived estimates of platelet lifespan according to each model-following multiple regression analysis. It is readily apparent that the multiple hit model provided the best survival estimates with 24-, 48-, and 72-hr data points as indicated by the lowest residual sum of squares, the highest F values and the highest r values. Moreover, the 48-hr data point provides the best correlation of the group showing the lowest residual sum of squares, the highest F value, and the highest correlation coefficient. When the other models were used, in all instances the F values and r values were all lower.

TABLE 1
Group Platelet Survival (Days)

	Linear	Exponential	Multiple Hit	Weighted Mean
Normal (7)*	10.1 ± 0.7†	4.3 ± 1.2	9.8 ± 1.0	9.8 ± 0.7
Splenomegaly (5)	10.2 ± 1.8	5.8 ± 1.1	4.8 ± 1.6	6.9 ± 0.9
Vascular prosthesis (11)	12.0 ± 1.2	5.1 ± 1.0	6.2 ± 1.5	7.0 ± 1.5
ITP (4)	8.3 ± 1.2	4.7 ± 1.9	4.3 ± 1.5	5.7 ± 2.4

*No. subjects.
† mean ± s.d.

TABLE 2
Individual Platelet Survival (Days) by Computer Model

Multiple hit	Exponential	Linear	Weighted mean
11.2	5.7	11.3*	10.6
10.8	5.4	10.9	10.7
9.8	7.7	13.6	9.8
9.7	4.0	10.2	9.8
9.5	2.5	9.6*	9.5
9.1	3.5	9.7	9.2
8.6	3.8	9.9	9.0
7.2	6.9	13.1	8.0
6.9	7.1	12.3	7.7
6.7	4.6	11.0	6.2
6.5	6.4*	12.5	7.7
6.3	6.5*	14.1	7.8
6.0	7.0	11.9	8.4
5.9	6.8	11.8	8.1
5.8	5.6*	10.7	6.9
5.6	5.4	11.0	5.8
5.5	5.3	11.6	5.5
5.1	5.0	11.3	5.1
4.8	4.8*	11.1	5.6
4.6	6.4	11.7	8.2
4.5	4.1	8.8	5.7
4.4	5.2	8.5	6.0
4.3	5.4	9.4	6.8
4.3	5.2	9.9	6.4
3.8	5.3	7.9	6.3
3.1	4.6	9.2	6.0
2.3	2.4	3.8	2.5

* Best fit if other than multiple hit.

TABLE 3
Statistical Interpretation

Model	Residual Σ Sq	F	r	P
Linear				
24*	1768	5.8	0.53	0.05
48	3051	7.9	0.49	0.01
72	1767	7.7	0.60	0.05
Exponential				
24	2408	0.3	0.13	N.S.
48	3956	0.4	0.13	N.S.
72	2015	5.0	0.51	0.05
Multiple hit				
24	812	30.3	0.82	0.0001
48	516	169.3	0.93	0.0001
72	538	57.3	0.90	0.0001
Weighted mean				
24	1293	13.4	0.69	0.0001–0.01
48	1619	37.1	0.77	0.0001–0101
72	1443	12.6	0.69	0.001–0.01

* Hours after injection of ^{111}In platelets.

Figure 1 graphically displays this 48-hr regression showing both the line of best fit as well as its 95% confidence limits. Usefulness of prediction is determined by r^2 which at the 48-hr data point show a value of 0.87 for the multiple hit model. Table 4 further refines the data using a Y^2 transformation which slightly improves the prediction to a value of 0.90, however, p values remain unchanged from the Y versus X data.

DISCUSSION

Mean platelet life span, derived by computer, show correlation against raw whole blood radioactivity data obtained over the first 3 days. The data clearly show an excellent correlation when using the 48-hr circulating radioactivity value, (percent of injected dose), as a predictor of a computer derived estimate of platelet life span. We realize that there can be considerable error in the use of a single-point projection for a platelet survival curve that is neither linear nor exponential. Obviously it is safer to use all data points to estimate the final outcome of the platelet survival. We have tested the data using a combination of Day 1 and Day 2 point and find no better correlation or prediction than using the Day 2 point alone. The most practical use of the 48-hr point is to obtain a "quick look" at the probable platelet life-span. If the life-span is very short then the survival curve may be completed within the first or second day thereby negating the need for this type of analysis. If the survival curve is erratic then all data points are needed to fit a curve. Although erratic survival curves have been mentioned in the literature, we have not encountered this phenomena in our studies. This may reflect the steady-state condition of our selected subjects. Clearly, platelet kinetics should not be attempted during the nonsteady-state. Mustard, Murphy, and colleagues have stressed these facts when discussing platelet survival prediction using two few points or using visual methods of curve fitting (7). In the clinical setting, where platelet lifespan may alter patient therapy or where patient compliance is in question, the value of the 48-hr point for predicting platelet survival becomes most apparent. It may also allow early testing of drug efficacy where prolongation of platelet survival is desired.

TABLE 4
Predictive Value of 48-hr Platelet Survival Data

	F	r	r^2	P
Y vs. X	169.9	0.93	0.87	0.0001
Y^2 vs. X	214.8	0.95	0.90	0.0001

REFERENCES

1. Murphy EA, Francis ME. The estimation of blood platelet survival. II. The multiple hit model. *Thrombos et Diathes Haemorrh* 1971; 25:53–80.
2. Peters AM, Lavender JP. Platelet kinetics with indium 111 platelets: comparison with chromium-51 platelets. *Semin Thromb Hemostasis* 1983; 9:100–114.
3. Murphy EA. The estimation of blood platelet survival. III. The robustness of the basic models. *Thrombos et Diathes Hemorrh* 1971; 26:431–448.
4. Lotter MG, Heyns AP, Badenhorst PN, et al. Evaluation of mathematic models to assess platelet kinetics. *J Nucl Med* 1986; 27:1192–1201.
5. Murphy EA. Platelet survival computer program. Department of Medicine, Johns Hopkins University School of Medicine Baltimore, Maryland 21205.
6. Klonizakis I, Peters AM, Fitzpatrick MI. Radionuclide distribution following injection of ^{111} indium-labeled platelets. *Br J Haem* 1980; 46:595–602.
7. Murphy EA, Francis ME, Mustard JF. The estimation of blood platelet survival, IV characteristics of the residual errors from regression. *Thrombos et Diathes Haemorrh* 1972; 28:447–456.