Hemolysis in Patients with the Cloth-Covered Aortic Valve Prosthesis

Changing Severity of Hemolysis and Prediction of Anemia

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This paper is addressed to two questions: (1) Is there evidence for increasing hemolysis in patients with a cloth-covered aortic valve prosthesis? (2) Is it possible to predict from the hematocrit, retriculocyte count, serum hemoglobin and serum lactic dehydrogenase (LDH) levels which patients are at risk of anemia? These screening studies were performed in patients attending the postoperative clinic from 1970 to 1973. Patients were classified into anemic and nonanemic groups. LDH values for the anemic group include all yearly values for that patient including preanemia levels. The median LDH levels showed a yearly increase in the anemic group and no change in the nonanemic group ($P < 0.005$). A subset of these patients had a mean 1 year increase of 3 LDH units for 15 nonanemic patients and 242 units in 17 anemic patients. The reticulocyte levels did not demonstrate any progressive increase in the anemic group. The LDH level was the most useful predictor of future anemia. A value of 250 units predicted anemia on the next yearly visit with 28 percent false positive and 4 percent false negative readings. The reticulocyte count of more than 2.5 percent also placed the patient at greater risk of anemia. A serum hemoglobin level in excess of 40 mg/100 ml was common in the anemic patients and was present in only 3 of 17 nonanemic patients. It is suggested that the serum LDH level should be monitored in all patients with the aortic totally cloth-covered prosthesis. Values in excess of 250 units (four times the upper limit of normal by other LDH methods) or increasing levels, or both, suggest future anemia.

Hemolytic anemia after aortic valve replacement with the totally cloth-covered aortic prosthesis has been well documented.[1-3] We found an initial incidence of 22 percent of severe hemolytic anemia in patients with the totally cloth-covered aortic prosthesis.[4] Because the anemia developed several years postoperatively in some of these patients we reviewed our data on patients with hemolysis after valve replacement with this aortic prosthesis in an attempt to answer the following questions: (1) Is there evidence for increasing hemolysis in patients with the cloth-covered aortic valve prosthesis? (2) Is it possible to predict in which patients anemia will develop from the hemolysis?

Methods

Since late 1970 we have been screening all patients with an aortic valve prosthesis for hemolysis. Patients were studied if they were at least 3 months postoperative and had no evidence of hepatitis. Laboratory examinations consisted of determinations of (1) hemoglobin and hematocrit, (2) reticulocyte count, (3) serum lactic dehydrogenase (LDH) (normal values 23 to 65

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TABLE I

Median LDH Values (units) for Each Postoperative Year

Group	Year 1	2	3	4
Anemic	383 (16)	478 (19)	560 (12)	653 (11)
Nonanemic	181 (20)	150 (18)	187 (11)	147 (5)

Figures in parentheses indicate sample size.

units),[5] (4) serum glutamic oxaloacetic transaminase, (5) serum haptoglobin concentration by electrophoresis and, since 1972, (6) serum hemoglobin and serum iron levels. The blood specimens were drawn in the hospital's central laboratory and were promptly processed.

The criterion for a diagnosis of a significant hemolytic anemia secondary to an aortic prosthetic valve was a reduction in hematocrit of 10 volume percent from the preoperative value. Mechanical hemolysis was confirmed by finding an increase in reticulocyte count, an increase in LDH levels with electrophoresis of the LDH enzymes demonstrating the increase to be due to the fast fractions, negative Coombs' test, elevation of the serum hemoglobin level above 5 mg/100 ml, a decrease in the serum iron concentration in the presence of a normal serum iron-binding capacity and, most importantly, evidence of red cell fragmentation on examination of peripheral film.

Only patients with a cloth-covered Starr–Edwards aortic valve prosthesis, series 2300, 2310 and 2320, were included in this analysis. Patients with multiple prosthetic valves, one of which was in the aortic position, and patients with paravalvular leakage were included in this study. In all patients whose diagnosis predated our study, a retrospective chart review was carried out to determine the onset of the anemia. Paravalvular leakage was considered present if there was a left sternal diastolic murmur. Definite leakage was considered present if it was at least grade 2/6.

Anemic and nonanemic groups: Patients with a diagnosis of significant hemolytic anemia as of June 1973 comprised the "anemic" group, and the remaining patients the "nonanemic" group. The two groups were compared for reticulocyte counts, serum LDH and serum hemoglobin levels for each postoperative year. Values obtained before the diagnosis of anemia are included in the appropriate postoperative year under the anemic group. Jonckheere's nonparametric test[6] was used to evaluate these results for evidence of increasing hemolysis in the anemic group in comparison with the nonanemic group. A subgroup of patients whose yearly sequential LDH levels were available were then compared with the anemic and nonanemic groups to again evaluate for increasing hemolysis. Preanemic hematocrit values, reticulocyte counts and LDH levels were then evaluated for their ability to predict future anemia.

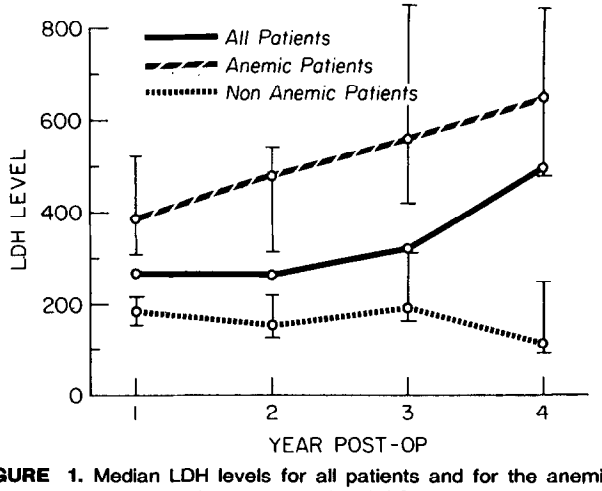

FIGURE 1. Median LDH levels for all patients and for the anemic and nonanemic groups by postoperative (POST-OP) year. Bars indicate approximate 90 percent confidence limits for the true group medians.

TABLE II

LDH Activity (units) in Patients with Proved Cloth Wear by Postoperative Year

Case no.	Year 1	2	3	4
1	434	622	870	653 (op)
2	320	...	...	2039 (op)
3	...	265	1490 (op)	
4	670	795 (op)		
5	...	...	...	1300 (op)

op = reoperation (replacement with another aortic valve prosthesis); ... = no values available.

Results

Serum LDH values: The yearly median LDH values for the two groups of patients are given in Table I. Medians rather than means are reported because the LDH values have skewed distributions, particularly in the anemic group. The difference between values in the anemic and nonanemic groups is statistically significant ($P < 0.01$) by the rank sum test. Figure 1 shows the median LDH values for the anemic and nonanemic groups and for all patients by postoperative year.

With these results in mind, Jonckheere's nonparametric test[6] for ordered alternates was employed to determine whether LDH remained unchanged, indicating a constant rate of hemolysis, or whether LDH levels rose, indicating an increase in hemolysis with time. The calculated data in the nonanemic group suggest a constant rate of hemolysis and the data in the anemic group indicate an increasing rate of hemolysis ($P < 0.005$).

Patients with proved cloth wear at reoperation often show a marked increase in LDH activity (Table II). If these patients were deleted from the anemic group and the nonparametric test employed, it is evident that the LDH levels would still tend to increase with time ($P < 0.05$).

LDH value comparisons over a 1 year interval indicated that the nonanemic group (15 patients) had a mean increase of 3 units of LDH activity and the anemic group (17 patients) a mean increase of 242 units. The greatest change in LDH activity in the nonanemic group was 67 units, whereas 8 of 17 patients in the anemic group had an increase of more than 70

TABLE III

Reticulocyte Counts (%) for Each Postoperative Year*

Group	Year 1	2	3	4	5
Anemic	4.8 (18)	6.1 (17)	6.1 (17)	9.2 (12)	4.7 (6)
Nonanemic	2.2 (28)	2.4 (12)	2.6 (14)	1.8 (7)	3.4 (4)

* Differences between groups are significant for the first 4 years ($P < 0.01$, t test).

Figures in parentheses indicate sample size.

units. However, since 5 of the 17 anemic patients had a decrease in LDH activity over a year, it is evident that false negative responses occur.

Reticulocyte count and serum hemoglobin: The reticulocyte counts (percent) were less skewed and therefore mean values for each postoperative year are shown for the two groups in Table III and Figure 2. The anemic group had significantly higher reticulocyte counts for each year ($P < 0.01$ by t test). The reticulocyte data do not support evidence for increasing hemolysis in either group by the nonparametric test. The serum hemoglobin data are limited because this determination was part of the routine screening studies for only 1 year; therefore, most of the values were obtained at the time of the evaluation for anemia. Table IV gives the mean serum hemoglobin values available. As expected, patients in the anemic

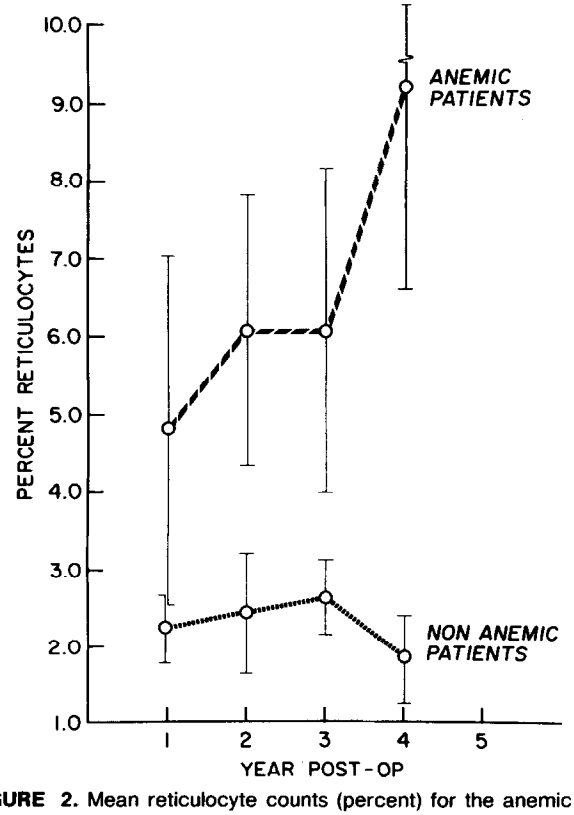

FIGURE 2. Mean reticulocyte counts (percent) for the anemic and nonanemic groups by postoperative year. Bars indicate approximate 90 percent confidence limits for the true group means.

TABLE IV

Mean Serum Hemoglobin Levels (mg/100 ml) by Postoperative Year*

Group	Year 1	2	3	4
Anemic	65 (7)	50 (7)	73 (8)	54 (10)
Nonanemic	10 (4)	24 (7)	25 (8)	5 (1)

* Differences between groups are significant only in the 3rd year ($P < 0.01$, rank sum test).

Figures in parentheses indicate sample size.

group had higher values that were significantly different only in the 3rd year ($P < 0.01$, rank sum test). These data cannot be used to evaluate increasing hemolysis.

Hematocrit: The predictive ability of sequential hematocrit values in the diagnosis of anemia was limited. Figure 3 gives sequential hematocrit levels before the diagnosis of anemia. In several patients the postoperative hematocrit values were lower than preoperative values. However, the hematocrit values in some cases dropped rapidly to anemic levels or stabilized for several years before anemia developed.

Predictive Value of Reticulocyte Count and Serum Hemoglobin

Using a screening rule of a reticulocyte count of 2.5 percent or greater to predict anemia within 1 year, based on a sample size of 10 preanemic values and 28 values in patients in whom anemia did not develop, one might expect a 10 percent false negative rate and a 35 percent false positive rate. Adequate preanemic

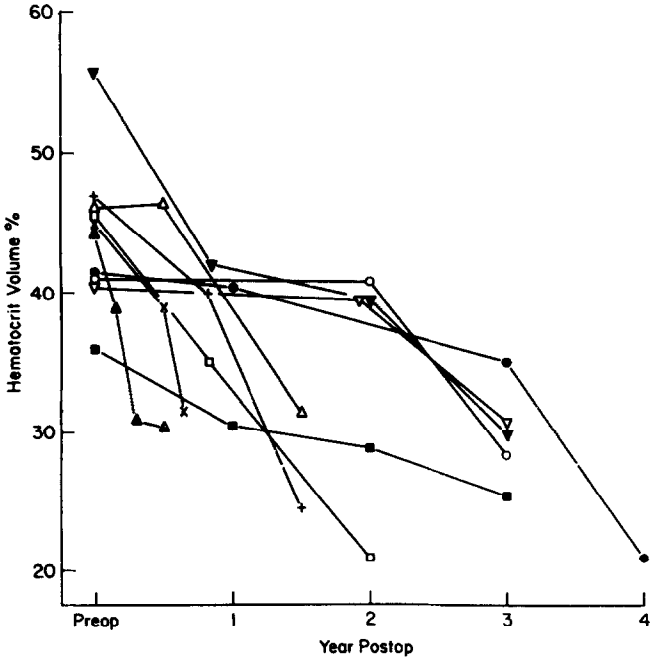

FIGURE 3. Sequential hematocrit values, by postoperative year, in patients who manifested anemia.

values for serum hemoglobin levels were not available to establish a predictive rule. However, 17 of 24 anemic patients had serum hemoglobin values in excess of 40 mg/100 ml, whereas only 3 of 17 nonanemic patients had values greater than 40 mg/100 ml.

Predictive value of LDH levels: Estimated probabilities of false positive and false negative results for various screening criteria based on LDH levels are shown in Tables V and VI. Here, a "false positive" occurs if the screening rule does not predict anemia for a patient who later has anemia. The rates in Tables V and VI were estimated by applying the indicated rule to data in patients in the specified postoperative years, then observing the proportions of patients misclassified at the end of the study period. Table V gives the estimated error rate for the rule that predicts anemia for patients with an LDH value exceeding 250 units. This rule will result in about 25 percent false positive and 5 to 18 percent false negative readings. All values that would have been false negative by this rule were obtained at least 1 year before the diagnosis of the anemia. Consequently, better estimates of the error rates might be obtained by considering only the latest LDH values for each patient. Estimated error rates for various screening rules based on the latest measurement are presented in Table VI. Using 250 units as the value to predict anemia would have resulted in 28 percent false positive and 4 percent false negative readings. The estimate of the false positive rate may be somewhat high, since anemia may still develop in some of these patients.

TABLE V

Estimated Error Rates (%) for Predicting Anemia on the Basis of LDH Level of 250 Units

Postoperative Year	False Positives (%)	False Negatives (%)
1 (16, 20)	25	19*
2 (19, 18)	28	5*
3 (12, 11)	27	17*
4 (11, 5)	20	9

* False negatives determined at least 1 year before diagnosis.
Figures in parentheses indicate number of anemic patients (first figure) and number of nonanemic patients (second figure).

TABLE VI

Estimated Error Rates in Percent Based on Last Preanemic, LDH Reading for Various Screening Rules for 11 Anemic and 40 Nonanemic Patients

Rule: Predict Anemia If LDH Greater Than (units)	False Positives (%)	False Negatives (%)
150	68	4
200	39	4
225	31	4
250	28	4
275	17	7
300	13	10

TABLE VII

Number of Diagnoses of Anemia by Postoperative Year and Valve Series

	Year				
Valve Series	1	2	3	4	5
2300	9 (7)	2 (18)	3 (16)	3 (16)	1
2310–2320	9 (29)	1 (19)	1 (7)	...	...

Figures in parentheses indicate number of patients studied in our clinic for that postoperative year. The number of patients with valve 2300 studied in postoperative year 1 is less than the number of diagnoses because this time interval antedated our routine screening program.

Comparison of 2300 and 2310–2320 valve series: Table VII gives the number of diagnoses of anemia by postoperative year and valve series. It is important to note that the mean follow-up period is approximately 4 years for the 2300 series and about 2 years for the 2310 and 2320 series. In the first postoperative year the number of patients studied in the 2300 series is smaller than the number of diagnoses of anemia because these diagnoses antedated our routine screening program. The presence of "definite" paravalvular leakage accelerated the onset of hemolysis, giving a mean onset time of 15 months in 10 patients as compared with 20 months in 18 patients without "definite" paravalvular leakage.

Discussion

Hemolysis and valve cloth wear: Iron depletion through urinary loss has been the usual explanation for anemia of late onset secondary to prosthetic valve hemolysis. We believe that our data indicate that increasing hemolysis is an additional factor in the late onset of anemia in patients with the cloth-covered aortic valve prosthesis. Increased rates of hemolysis may be evident during an anemic crisis; however, the majority of our patients had increasing LDH values in spite of a stable hematocrit. We believe that cloth wear is an important factor in the increasing hemolysis. We performed reoperations in six patients because of severe hemolysis, and only one had no evidence of cloth wear. Valve wear with increasingly severe hemolysis has been reported previously.[7]

Identifying patients at risk for anemia: Our data suggest that patients at increased risk of anemia can be identified. The postoperative hematocrit value is commonly lower than the preoperative value, but it may stabilize at this lower level until the onset of anemia several years later. This onset may be precipitous and iron depletion certainly is an important factor in this event. The reticulocyte level is commonly in excess of 2.5 percent in patients at risk of having anemia within the coming year. We do not have data for the predictive value of the preanemia

serum hemoglobin levels. However, a value in excess of 40 mg/100 ml was common in those patients with anemia, whereas only 3 of 17 patients without a present diagnosis of anemia had values greater than 40 mg/100 ml.

The serum LDH level is perhaps the most useful screening test available. If the patient's serum LDH activity is 400 units or greater, anemia is likely to develop or may already be present. Only 4 of 42 patients in the nonanemic group had values in this range. The future of these latter patients is, of course, still uncertain. An LDH activity of 250 units would identify a population at increased risk of anemia. A preanemia LDH level of 250 units in our study gave a 28 percent false positive, but only a 4 percent false negative result, which is acceptable for a screening test.

There is considerable variance in the manner of estimation for LDH activity in serum by laboratories. Variables such as direction of the enzymatic reaction, temperature (ranging from 37° C to 25° C) and endpoint vs. kinetic assays make interhospital transfer of units of LDH activity nearly impossible.[8] Because there is no satisfactory correction factor to standardize the unit of activity, the data presented here, particularly those relating to the serum LDH activity levels that indicate the patient is at risk, can be converted to use in other clinical settings by the following steps: (1) establish "normal" range of activity for the individual laboratory's technique of assay, and (2) multiply the upper limit of normal activity by 4. This method of expression avoids confusion over units and expresses abnormal activity in terms of "times normal." In the technique used in this report the critical activity level of 250 units is four times the established upper limit of normal for that assay and would correspond to 1,600 units as estimated by the LDH technique of Henry et al.[9]

Other methods for detecting the severity of hemolysis have been reported. The plasma hemopexin level was reported by Eyster et al.[10] as being a good indicator of severe hemolysis. Patients with a high level of hemosiderin in urinary sediment were found to have marked hemolysis.[11] However, the predictive ability of these findings has not been demonstrated, and the limited availability of these studies restricts their use. Since the LDH level correlated well with the degree of hemolysis and is easily available, we believe it offers the best present screening test for hemolysis.

Clinical implications: Routine monitoring of LDH levels in all patients with a cloth-covered aortic prosthesis should be carried out. A sudden rise in LDH activity of over 70 units should alert the physician to the possibility of cloth wear and risk of anemia. Values exceeding 250 units of LDH would place the patient in a high risk category. We believe that these patients should be followed up closely for the onset of anemia.

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