

Activated Coagulation Time Method for Control of Heparin is Reliable during Cardiopulmonary Bypass

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The ability of the heparin dose-activated coagulation time (ACT) response curve to predict doses of heparin during open-heart operations has been debated since its proposal. The dose-response method was examined in a statistically rigorous manner in 23 patients. The ACT response to 3 mg/kg heparin varied among patients from 308 to 520 s. Although at the start of bypass, ACTs often increased beyond the linear part of the dose-response curve (500 s), they returned to 483.7 ± 176.8 s (SD) within 1 h. After this first hour, one to four additional data points fit the initial two-point dose-response curve closely, and additional points did not significantly change dosage calculations for heparin and protamine. After a dose of protamine calculated to exactly neutralize heparin, the average ACT returned to within $7 \pm 11\%$ (SD) of control values. A two-point dose-response curve, generated for each patient before bypass begins, remains statistically valid and clinically useful throughout open-heart operations as long as the ACT is less than 500 s. The dose-response method is a simple, valid way to control coagulation during open-heart operations. (Key words: Blood: anticoagulants, heparin; coagulation, protamine. Heart: cardiopulmonary bypass. Surgery: cardiac; cardiovascular.)

FEW DRUGS are as nontoxic when given in excess, and as potentially lethal when not given in adequate amounts, as is heparin during open-heart operations. The catastrophic consequences of massive coagulation during cardiopulmonary bypass, or of inadequate restoration of normal coagulation thereafter, compel us to control the effect of heparin as accurately as possible during these procedures. Toward that end, a variety of fixed-dosage protocols have been developed¹; however, these regimens fail to take into account the wide variation in the response to heparin, which exists not only between patients but also within each patient during open-heart operations.² Specifically, the variation in the potency of heparin preparations, the depressive effect of temperature on heparin's rate of decay,³ the nonlinear effect of body mass on heparin's volume of distribution,³ shifts in circulating blood volume due to extracorporeal circulation,⁴ and genetic variations in the coagulation system⁵ all conspire to render the effects of heparin unpredictable.

Bull *et al.*⁶ proposed that the appropriate dose of heparin for any individual should be based on that individual's activated coagulation time (ACT) response to an initial

dose of heparin. The curve describing each person's dose-response relationship then could be used to compute additional doses of heparin needed to maintain ACT at a level necessary to prevent fibrinogen consumption (400 s)⁷ or to compute the dose of protamine necessary to neutralize circulating heparin.

The seeming simplicity of the dose-response method has made it very attractive for controlling heparin during open-heart surgery. Although widely used, this method has been criticized as inherently inaccurate for several reasons: 1) the profoundly variable biologic response of the ACT to heparin,^{2,5,8-12} especially in the presence of endocarditis or intraaortic balloon counter pulsation¹³; 2) errors in determining the initial dose-response coordinates, a consequence of the unpredictable rise in ACT during open-heart operations¹⁴; 3) interference with the predictive value of the ACT by errors intrinsic to measuring ACT during cardiopulmonary bypass, especially those induced by hypothermia¹² and hemodilution; and 4) difficulty identifying and reproducing the end point of the ACT.¹⁵ These factors have the potential to alter the individual's dose-response relationship and thereby to invalidate it as a predictor of heparin or protamine dose.

The use of the dose-response method is in direct conflict with the diverse criticisms lodged against it. This study was designed to evaluate the predictive value of the heparin dose-ACT response relationship during open-heart operations.

Methods

PATIENT SELECTION

Twenty-three patients were selected at random for this study from those undergoing open-heart operations. The patients ranged in weight from 6.9 to 118.3 kg (mean = 49.6 kg \pm 32.8 SD). The selection of patients was approved in compliance with the standards of the institutional review board.

DOSE-RESPONSE ALGORITHM

The heparin dose-ACT response curve, constructed for each patient by the method of Bull *et al.*,⁶ was used to compute doses of heparin to keep the ACT at a selected level. First, a control value for ACT was determined by placing 2.5 ml whole blood into a Hemochron® tube (International Technidyne, Edison, New Jersey) containing

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a magnet and a diatomaceous earth activator. The tube immediately was placed in the well of a Hemochron®, which determines coagulation to have occurred when the magnet within the Hemochron® tube stops moving through the blood. After this, the patient was given 3 mg/kg of Upjohn beef lung heparin and the ACT determination was repeated after 5 min. Then, the initial regression curve was plotted (fig. 1) from the two data points representing the ACT before (control) and after (response) the administration of the heparin.

Subsequently, the dose-response curve was used to compute the additional doses of heparin needed to keep the ACT at the selected value greater than 400 s (fig. 1). The ACT was reevaluated 5 min after each dose of heparin. Then, the new dose-response point was added to the plot, and the regression line was recalculated using least-squares linear analysis of variance. ACTs > 500 s and those obtained during the first hour of cardiopulmonary bypass were not used for dose-response calculations because they are not related linearly to heparin level.^{15,16}

To neutralize heparin, the same algorithm was followed, except that a dose of protamine equal in milligrams to the remaining heparin was given.

To avoid computational errors, a calculator was programmed and used to cue appropriate data in the correct sequence, to generate and update the regression curve,

to compute heparin or protamine dose, and to perform the statistical evaluation (regression coefficient, per cent error, and mean per cent error \pm SD of each predicted ACT).

PUMP PRIMING COMPOSITION

The composition of the pump prime varied in volume and composition from patient to patient. The basic priming solution was Normosol® (Abbott Laboratories, North Chicago, Illinois). For each unit of blood included in the priming solution, 2,000 units of heparin also were added. The priming solution was kept at 37° C until hypothermia (15–27° C) was induced. The duration of hypothermia varied considerably from patient to patient.

STATISTICS

A Hewlett-Packard Series 80 Statistical Program was used to perform analyses comparing data between patients: means, standard deviation, correlation coefficients by least-squares multiple linear regression analysis, Student's *t* test for paired data ($P \leq 0.05$ was considered significant), and one-way analysis of variance.

Results

After a 3-mg/kg dose of heparin was administered, control ACTs increased from a mean (\pm SD) of 111 ± 15

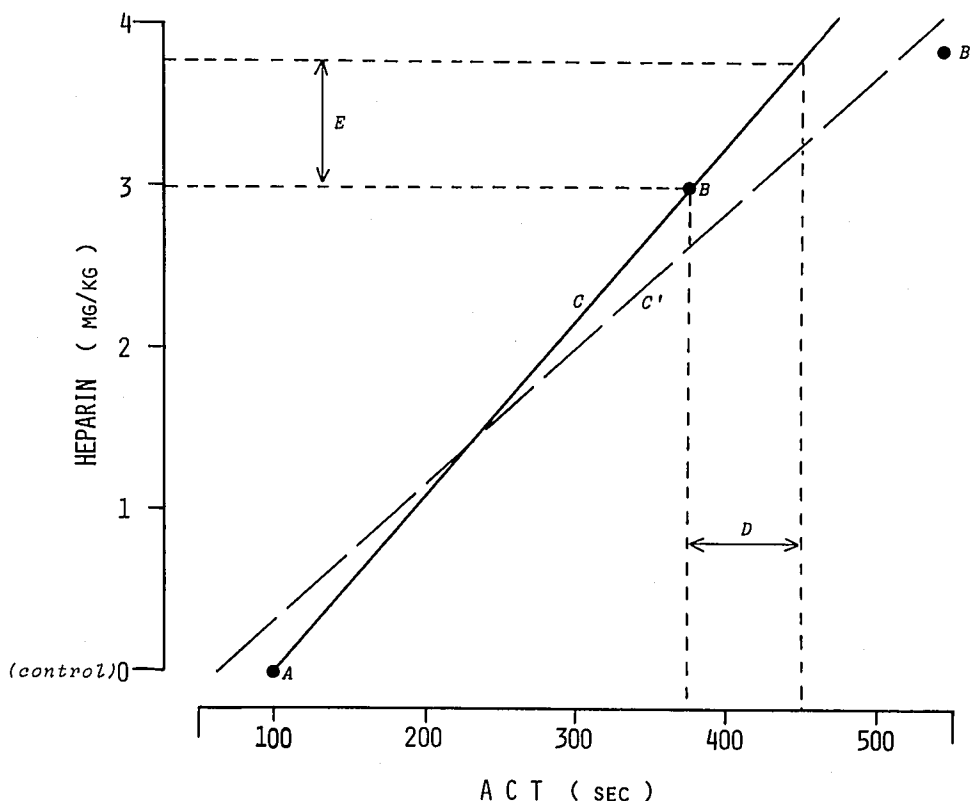
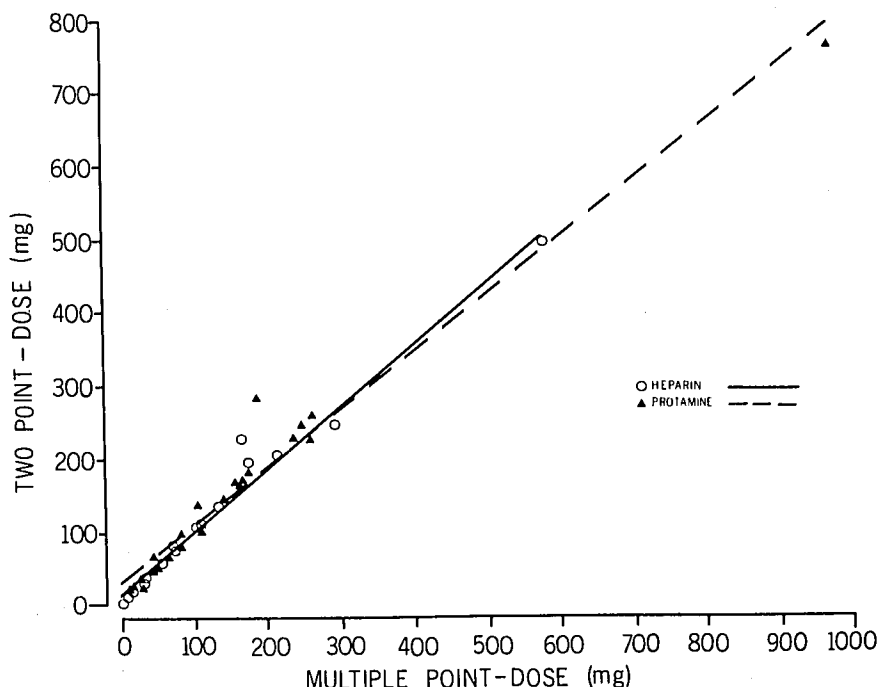


FIG. 1. Construction and use of the heparin dose-activated coagulation time (ACT) response curve. A) Plot ACT control versus no heparin. B) Plot ACT response versus initial heparin dose. C) Draw dose-response curve. D) Locate desired ACT increase. E) Locate corresponding change in circulating heparin and administer this dose. B') Plot new ACT response versus expected circulating heparin. C') Revise dose-response curve. Repeat D-C' as needed.

FIG. 2. Agreement of the total dose of heparin (circles) or protamine (triangles) calculated from a two-point and a multiple-point regression curve. No statistical difference in calculated total dose resulted when more data, obtained after 1 h of bypass, were used to construct the dose-response curve.



s (range: 72–139 s) to 351 ± 76 s (range: 308–520 s). The average ACT 5 min before cardiopulmonary bypass was 423 ± 73 s. After bypass began, ACTs increased without additional heparin, frequently above 1,000 s, well beyond the linear portion of the dose-response curve, and then decreased during the first hour to 484 ± 177 s, which neither correlated with ($r = 0.07$) nor was statistically different from the ACTs 5 min before bypass.

Two statistical tests were used to measure the precision of the dose-response method. 1) The average difference between the predicted and the observed ACT after the administration of a dose of heparin computed from the updated dose-response curve was $5.6 \pm 14.3\%$. This error was not changed significantly by increasing the number of data points used to generate the curve. 2) The average correlation coefficient of the dose-response relationship was 0.98 ± 0.03 (74% of the time, $r = 0.99$; 95% of the time $r = 0.95$; and 100% of the time, $r = 0.81$). This correlation coefficient was not related to the total number of dose-response pairs.

After the administration of the protamine calculated to completely neutralize the heparin, the ACT returned to baseline levels: 116 ± 12 s (range: 90–137 s). The average difference between the control ACT before heparin and the ACT after protamine was 8 ± 23 s, which was statistically and clinically insignificant.

The total dose of heparin and protamine resulting from the use of only the initial two points of each dose-response curve was calculated. If the other points had not been added to the data base, an average of $5.4 \pm 14.2\%$ less heparin (excluding the loading dose) and $2.3 \pm 17.3\%$

less protamine would have been calculated for each patient. Neither of these differences was clinically or statistically significant ($P > 0.50$). The close correlation ($r > 0.98$) of doses calculated by these two methods is shown in fig. 2.

Discussion

The variation in the response of the ACT to a dose of heparin among patients in this and other studies^{2,5,8,10,11} (table 1) is relevant only because these differences emphasize the need to individualize the construction of the dose-response relationship. However, this variation within each patient during open-heart operations has been observed and cited as valid evidence that the dose-response relationship constructed before cardiopulmonary bypass is an unreliable predictor of heparin or protamine requirements after bypass begins.^{12-14,17}

In this study, the dose-ACT response relationship was unreliable during the first hour of cardiopulmonary bypass and hypothermia: the ACTs, often increased above

TABLE 1. ACT before and after Heparin (3 mg/kg) as Measured By Different Investigators

Investigators	ACT (seconds)			
	Before Heparin		After Heparin	
	Mean	Range	Mean	Range
Cohen	111	72–139	351	308–520
Others	104^2-116^5	55^7-150^{10}	447^5	$245-810^5$

the linear part of the dose-response curve, were five times more variable than those 5 min before bypass and were unrelated to the ACTs before bypass. Because of these changes, the dose-*ACT* response data obtained before bypass were not expected to correlate with those after bypass began. The dose-response relationship was expected to deteriorate. Dosages of both heparin and protamine were expected to be different from those that would have resulted from a method based on two data points obtained before bypass.

In fact, the effect of the first hour of bypass on the dose-response relationship was transient. Neither dosage calculations nor errors in prediction changed significantly as each subsequent pair of dose-response data was used to update the regression curve, the coefficient of which remained consistently high, 0.98 ± 0.03 (SD). As a result, the ACT returned to within $7 \pm 11\%$ (SD) of control after the administration of a dose of protamine calculated from all of the dose-response data. This dose was not statistically different from that calculated from the initial two data points obtained before bypass. The continued fidelity of these dose-response statistics after the initial hour of cardiopulmonary bypass is surprising, considering the acute effect of bypass on platelet consumption, procoagulant levels, and the volume of distribution of heparin as well as the tendency of hypothermia to artifactually prolong ACT.^{12,17} Nevertheless, the validity and the reproducibility of the dose-response relationship are reflected clearly here by both the consistently high correlation of heparin dose to ACT response and the low error in the predicted ACT within each patient.

This study demonstrates several important principles in the successful use of the dose-response method: 1) the dose-response relationship must be generated before bypass begins and not during the first hour of cardiopulmonary bypass; 2) during the first hour of bypass the ACT is a valid indicator of anticoagulation but is not a reliable predictor of heparin; 3) ACTs greater than 500 s are not related linearly to dose and therefore are useless in performing dose-response calculations; and 4) errors in defining the ACT end point must be avoided when using the dose-response method. The ACT end point in this study was assumed to be represented by the smallest insoluble clot that stopped the timer. The continued fidelity of the dose-response relationship, as data were incorporated into the data base, demonstrates that this can be considered the valid end point of the ACT. Previous reports that failed to demonstrate the validity of the dose-*ACT* response method may not have observed all of these methodologic principles.

Although the ACT response to heparin varies widely among patients during open-heart surgery, a dose-response curve generated for each patient before bypass begins is statistically valid and clinically useful throughout that patient's operation, except for the first hour of bypass,

as long as the ACT is less than 500 s. When performed with methodologic consistency, even the simple two-point ACT dose-response method is accurate. The dose-*ACT* response method, therefore, should be regarded as a reliable, useful predictor of dosages of heparin and protamine during open-heart surgery.

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