

A Simple Individualized Method for Dose-Responsive Heparin and Protamine Administration

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While increasing credibility is being granted to the use of Activated Clotting Time (ACT) determinations¹⁻⁶ and to dose-responsive administration curves^{2,3} for heparin and protamine therapy during cardiopulmonary bypass, many open heart surgery teams continue to calculate these dosages upon such typical parameters as percentages of original anticoagulation doses, or to elapsed time on bypass; with anticoagulant reversal doses of protamine calculated as percentages of the original pre-pump (and sometimes including supplemental) heparin doses.

These protocols do not in general recognize or consider:

- the marked variability of patients in their sensitivity to heparin^{3,7,8}
- the often substantial variability in the potency of different batches of heparin, both within and between laboratories^{9,10}
- changes in *circulating* blood volume upon initiation of bypass^{3,8}
- metabolism of heparin by the body, at different rates, over time
- the fact that, of the administered heparin, not all is or remains necessarily active⁷
- the prospect that both over-heparinization^{2,7,11} and over-protaminization^{2,7,12} can be significant contributors to insidious post-op coagulopathy

Some of these variables can be controlled and some cannot; most can, at least to some extent, be minimized or compensated for.

In an attempt to devise a suitable individualized, dose-responsive regimen for open heart heparin and protamine administration, we have modified one of several available anticoagulation protocols. Additional requirements for any such technique are that it be simple and amenable to use in the operating room environment.

The graph shown in Figure 1 is plotted for each patient on cardiopulmonary bypass (or is indeed useful for any patient requiring systemic heparinization for whatever reason). The graph can be simply reusable if placed under glass and marked with a grease pencil, or a permanently marked paper copy can be maintained as part of the patient's chart.

Plotting the concentration (in Mg/Kg) of a heparin dose against the ACT achieved by that dose establishes a heparin sensitivity value for that particular patient. Successive

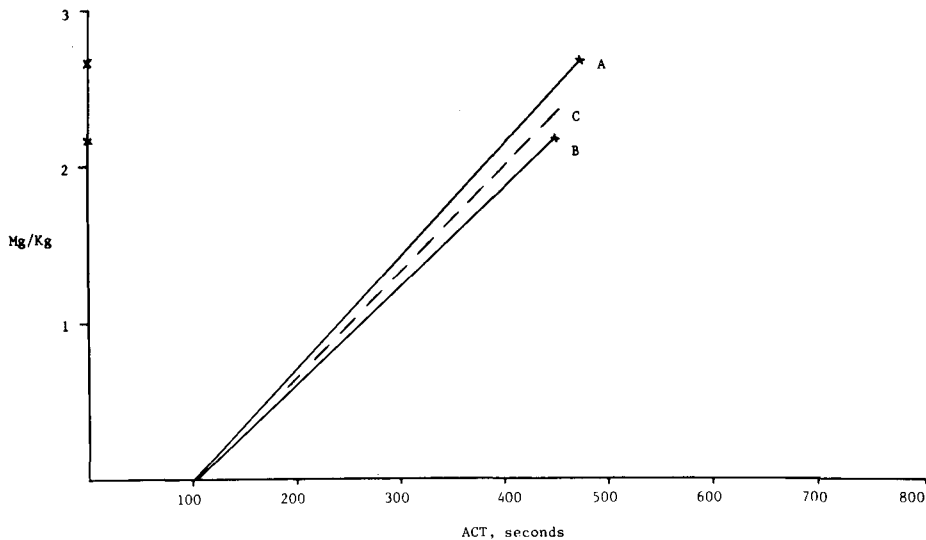


Figure 1.

or simultaneous multiple determinations may be employed and then “averaged” in an attempt to further minimize sampling variation (Bull, et al.,³ describe a probable ten percent maximum in statistical testing variation). We use a Hemochron* instrument in measuring the ACT, for sake of the safety and simplicity of its automation while occupied at the pump. Though it may be that this device yields ACTs several seconds longer than those of manual determinations, we feel that it achieves a more objective and consistent endpoint.

Consider then a hypothetical application of the method, given:

patient weight = 82 Kg

patient total blood volume = 5250 ml

pump prime volume = 2000 ml (1000 whole blood + 1000 fluid)

patient’s pre-op ACT = 100 seconds

Presently our initial total heparin dose is predicted upon 3 Mg/Kg of patient weight. Thirty milligrams of that dose is retained in the pump as a safety measure and to heparinize prime blood, the remainder is administered intravenously by the anesthesiologist. Then,

$$82 \text{ Kg} \times 3 \text{ Mg} =$$

a dose of 246 Mg rounded to 250; 220 Mg administered I.V., 30 Mg administered via

*International Technidyne Corporation, Metuchen, New Jersey

pump prime. Volume concentration of the 220 Mg I.V. dose, immediately pre-bypass is

$$220 \text{ Mg} \div 82 \text{ Kg} = 2.68, \text{ rounded to } 2.7$$

A mark is made on the Y axis at 2.7 (Figure 1). An ACT determination is made at this time, yielding perhaps 475 seconds. This value is found on the X axis and raised to place it opposite the concentration of 2.7 (A). What this indicates is that a dose concentration of 2.7 Mg/Kg (which as you recall neglects the pump prime complement) achieves an ACT of 475 seconds, for *that* patient, and at *that* circulating blood volume. A line is drawn from point A to the pre-op unheparinized ACT standard of 100 seconds.

Initiating bypass, however, immediately changes the circulating blood volume by 2000 ml. Additionally there is 30 Mg more heparin circulating. Heparin concentration has thus changed by virtue of both these effects. These changes can be calculated and displayed on the graph. The pump volume of 2000 ml is 38% of the hypothetical patient's total blood volume ($2000 \div 5250 = .38$). To establish a new circulating blood volume figure that is useful to the graph, the patient Kg index is modified by an equal amount:

$$82 \text{ Kg} \times .38 = 31 \text{ Kg}$$

82 "patient" Kg plus 38 "pump" Kg equals 113 Kg, an analog to describe the revised circulating blood volume.

Referring back to the Y axis, with the total 250 Mg of heparin now diluted into a new hypothetical circulating blood volume analog of 113 Kg, we use the same calculation used to arrive at the 2.7 mark, only this time using the volume adjusted values:

$$25 \text{ Mg} \div 113 \text{ Kg} = 2.21, \text{ rounded to } 2.2$$

2.2 is marked on the Y axis.

A second ACT is now taken, several minutes after the initiation of bypass, yielding perhaps 450 seconds. Similarly this value is found on the ACT X axis and raised to place it opposite the revised concentration of 2.2 (B). As before, a line is drawn from point B to the unheparinized pre-op standard of 100 seconds.

Line C is now drawn, bisecting A and B, to assist in averaging uncontrollable variation (at times, points A and B will be perfectly linear with the pre-op baseline value). In point of fact, any number of determinations may be extrapolated and used to establish an average (however, long time intervals between sampling introduce discrepancies due to heparin metabolism).

What has now been achieved is this: Line C describes, experimentally, how sensitive that particular patient is to heparin anticoagulation, that is, what dose of heparin, in Mg/Kg (Y axis) will achieve what degree of anticoagulation in seconds of ACT (X axis). This degree of sensitivity can be hereafter calculated from any point upon Line C. Furthermore the "sensitivity extrapolation" of C has been adjusted to reflect the variation in circulating blood volume (less effective, of course, in nonhemic primes devoid of clotting factors), as well as having been averaged for random fluctuations. It is now used as an

established, individualized *heparin activity value* regardless of further volume fluctuations.

It also becomes apparent that, for any patient, a qualitative look at the steepness of extrapolation C can quickly tell you how relatively sensitive a particular patient is to the heparin you are using.

Theoretical inference would also show that, when the time for supplemental heparin arrives, the *activity* difference between the point on Line C (in Mg/Kg) at present ACT, and that point on C describing the desired ACT, will, by subtraction, indicate what dose of heparin is required to achieve the desired ACT level. In practice we find ourselves typically giving less than any such calculated dose; partly because any ACT attenuating metabolic effects of hypothermia are not compensated for by the method, and in part because the dilution of platelets and clotting factors on bypass may also prolong ACTs.¹³ We give 20–40 Mg supplemental heparin at a time when required, and immediately afterward consult the ACT again. We also find that larger supplemental doses are required during rewarming.

The greatest usefulness of the graph, however, becomes apparent at the time of protamine administration.

We attempt to neutralize heparin with a one-and-one-third (1:1.3) ratio protamine dose, a typical formula. But it is not necessary to neutralize the amount of heparin given as the original anticoagulation dose; only the amount of heparin that is *active* upon termination of bypass needs neutralizing. Thus, an ACT is obtained immediately upon termination of bypass. Let us assume this value to be 400 seconds and refer again to Figure 1. Finding point C at 400 seconds reveals (on the Y axis) that only 2.0 Mg/Kg of circulating heparin is active, not 3 Mg/Kg, the original systemic anticoagulation dose. This *activity value* of 2.0, in this case, is the variable in the protamine dose calculation:

$$(2.0) \times 1.3 \times \text{patient Kg}$$

or

$$2.0 \times 1.3 \times 82 = 213 \text{ Mg}$$

The 82 Kg value is used because the circulating volume we are now concerned with neutralizing is that of the patient's alone, not any amount including the pump volume (the prior total of 113 Kg). Of course, if large amounts of heparinized pump reservoir blood are subsequently transfused, additional fractional doses of protamine will be required. At any point up until the desired post-op ACT is achieved, supplemental protamine doses, if required, may be calculated upon new ACTs which will determine how much heparin still remains active. We feel it important that the protamine dose be administered slowly in an I.V. drip; or at least injected slowly in small increments.

This protocol has been used at our institution over a period of two years with an improvement in the postoperative hemostasis of open heart patients. Less controllable effects resulting from hemodilution, hypothermia, platelet depletion plus coagulation mechanism deficiencies¹³, and the uncertain rates of heparin metabolism over time, still moderate the effectiveness and repeatability of the dose-responsive procedure, and of the ACT determination itself.

As everywhere, we do experience the occasional obstinately bleeding patient, for which our surgeons tend to prescribe additional protamine, aquamephyton, premarin,

or amicar in hyperfibrinolytic states. These patients will sometimes be seen to bleed irrespective of the ACT level.

In any case, where situational variables can, to some extent, be quantified and manipulated, their effects can be significantly minimized; furthermore this protocol allows for the heparinization and reversal of patients according to their individual metabolic needs, rather than to the needs of arbitrary formulae. If coagulopathies are encountered postoperatively, greater confidence can be had in ruling out over-protaminization as a possible cause.

This protocol is presently expressed in dose/concentration terms of milligrams, as a convenience, in that most perfusionists still use Mg determinants of dosage. It is recognized that the use of *units* is more precise, in terms of heparin. The method is also clearly amenable to dosage in units, and remains to be tested on that basis.

One can quickly become familiar with the essentials of what may, at first, seem a complex protocol. An understanding of the basic principles of the method will allow its adaptation to any system regardless of prime volume, initial and reversing dose concentrations, or other variables offering some degree of control to the perfusionist.⁴

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