Correspondence

Heparin reversal protocol

To the Editor:

I was delighted to read the letter of Dr. David S. Pounder concerning the algebraic analysis of the heparin dose-response curve.¹ The graphic construction of a dose-response curve as described by Bull^{2,3} is a widely accepted and reliable method for managing heparin and protamine administration during cardiopulmonary bypass. However, this method is very cumbersome for routine use in the operating theatre. Three years ago, I made an algebraic analysis of the Bull curve in the same way as Dr. Pounder pointed out, and wrote a basic program for a pocket computer. Since then we have used this easy-to-handle and safe system during all the extracorporeal procedures performed in our institution (750 cases a year). To estimate the reliability of this program I compared the baseline ACT (Activated Clotting Time) before heparin and the ACT twenty minutes after protamine administration in a consecutive series of a hundred

patients scheduled for elective coronary revascularization. Using a paired Student's *t* test, I could not demonstrate a statistically significant difference ($P = 0.35$). To avoid inappropriate conclusions from these analyses, a calculation of statistical power was performed *a posteriori*.⁴ If a variation in ACT-level of five seconds is assumed to have no clinical relevance, analysis of this sample (100 subjects) showed with 95 per cent confidence that the ACT returned to its baseline level using this computer protocol.

This analysis and the computer program were presented at the Spring Meeting of the English Association of Cardiothoracic Anaesthetists in Cambridge, England (June 1987). A print-out of the basic-routine is enclosed (Figure).

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10 PRINT "HEPARIN: DOSE-RESPONSE CURVE"
20 PRINT "-----"
30 REM: WEIGHT (G) AND THE BASELINE ACT (B) ARE ENTERED
40 INPUT "WEIGHT (KG)";G:INPUT "BASELINE ACT (seconds)";B
50 REM: CALCULATION OF THE HEPARIN-DOSE (D) (300 I.U./KG) IN ML
60 D=G*.06
70 REM: A 5000 I.U./ML SOLUTION OF HEPARIN IS USED
80 PRINT USING "HEPARIN-DOSE=###.0 ml";D
90 REM: 5-10 MIN AFTER THE HEPARIN ADMINISTRATION A SECOND ACT (H) IS PERFORMED
100 INPUT "ACT AFTER HEPARIN:";H
105 REM: SLOPE (S) OF THE FIRST ESTIMATE OF THE DOSE-RESPONSE CURVE IS CALCULATED
110 S=(H-B)/D
120 REM: USING THIS FIRST ESTIMATE (DETERMINED BY POINT B AND H) AN EXTRA DOSE
    OF HEPARIN (E) IS CALCULATED BY EXTRAPOLATION IN ORDER TO REACH A PRESET ACT (T)
130 CLS:INPUT "TARGET ACT:";T
140 E=(T-H)/S
150 PRINT USING "EXTRA-DOSE=###.0 ml";E
160 REM: 5-10 MIN AFTER THE ADMINISTRATION OF THIS EXTRA DOSE A THIRD ACT (N) IS
    PERFORMED; THIS VALUE REPRESENTS A SECOND ESTIMATION OF THE DOSE-RESPONSE CURVE
170 INPUT "ACT AFTER EXTRA DOSE:";N
180 REM: SLOPE (W) OF THE BISECTING LINE OF THE TWO DOSE-RESPONSE ESTIMATES IS
    CALCULATED TO BE USED AS THE FINAL DETERMINANT OF THE HEPARIN DOSE-RESPONSE
    CURVE FOR FURTHER CALCULATIONS
190 W=((((T-N)/2)+N)-B)/(D+E)
200 CLS:INPUT "DO YOU WANT A TOP-UP DOSE ? (Y/N)";A$
210 IF A$="N" THEN GOTO 270
220 REM: TOP-UP DOSES OF HEPARIN (J) TO REACH THE PRESET TARGET ACT ARE
    CALCULATED DURING BYPASS (REPEATED)
230 INPUT "ACTUAL ACT:";Q
240 J=(T-Q)/W
250 CLS:PRINT USING "TOP-UP DOSE =###.0 ml";J
260 GOTO 200
270 CLS:INPUT "DO YOU WANT THE PROTAMINE DOSE ? (Y/N)";A$
280 IF A$="N" THEN GOTO 340
290 PRINT:INPUT "LAST ACT (after rewarming)";Z
300 REM: USING THE LAST ACT DURING BYPASS (Z) THE PROTAMINE DOSE (P) NECESSARY
    TO REVERSE THE CORRESPONDING HEPARIN-LEVEL IS CALCULATED IN A 1/1 PROTAMINE-TO-
    FREE-HEPARIN RATIO
310 P=(Z-B)/W
320 CLS:PRINT USING "PROTAMINE DOSE=###.0 VIALS OF 5 ML (1000 I.U./ml)";P
330 REM: IF ANOTHER PROTAMINE NEUTRALIZING FACTOR FOR REVERSAL IS REQUESTED THEN
    MULTIPLY THE FORMULA IN 310 BY THE RATIO YOU WANT [e.g. 1.3 -> P=1.3*(Z-B)/W]
340 END

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FIGURE

REFERENCES

- 1 Pounder DS. Heparin reversal protocol. *Can J Anaesth* 1988; 35: 321-2.
- 2 Bull BS, Korpman RA, Huse WM, Briggs BD. Heparin therapy during extracorporeal circulation I. Problems inherent in existing heparin protocols. *J Thorac Cardiovasc Surg* 1975; 5: 674-84.
- 3 Bull BS, Huse WM, Brauer FS, Korpman RA. Heparin therapy during extracorporeal circulation II. The use of a dose-response curve to individualize heparin and protamine dosage. *J Thorac Cardiovasc Surg* 1975; 5: 685-9.
- 4 Spriet A, Beiler D. When can non-significantly different treatments be considered as "equivalent." *Br J Clin Pharmacol* 1979; 7: 623-4.

REPLY

With regard to Dr. Himpe's letter, I have the following comments. He found that by using a computer-stored algebraic treatment of Bull's heparin dose-response curve he could successfully return the ACT to preheparin levels. I had similar success, and was also able to correct ACT's using doses of protamine significantly smaller than those used by most staff in our department. That is to say, both of us have found algebraic treatments of Bull's technique that work.

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Phaeochromocytoma

To the Editor:

The article on phaeochromocytoma by Pullerits *et al.*¹ in the September 1988 issue of the Journal was well organized and informative. I commend them for this, though I take issue with them on two points.

First, their contention that the incidence of "clinically significant cardiomyopathy" in patients with phaeochromocytoma is approximately 58 per cent may be an overestimate, as their reference (Van Vliet *et al.*)² does not support that figure in today's hospital practice. Van Vliet *et al.* studied the hearts of 26 patients with an autopsy diagnosis of phaeochromocytoma from 1928-1964. They found an incidence of cardiomyopathy at autopsy of about 58 per cent in 26 patients. Their study may not be representative of elective surgery for phaeochromocytoma in the 1980's for four major reasons. First, patients who die of their disease may be expected to have a relatively high incidence of severe complications related to their pathological condition. Second, in some of the patients in Van Vliet's study the diagnosis was not made before surgery. Third, only 1 of 26 patients showed clinical evidence of cardiomyopathy before surgery.

Finally, as Pullerits *et al.* point out, the study was conducted during a period before the widespread use of alpha-adrenergic blockade in patients with phaeochromocytoma.³ Hence the stated incidence of "clinically significant cardiomyopathy" in phaeochromocytoma patients of 58 per cent may be much higher than the true incidence today.

This is not simply an academic point, as it has obvious implications for anaesthetic management. Pullerits *et al.* suggest that a Swan-Ganz catheter should be used in phaeochromocytoma patients suspected of having abnormal left ventricular function - by inference, in approximately 58 per cent of patients. Some studies suggest that occasionally even the young, apparently healthy patient with phaeochromocytoma may be at risk of iatrogenic fluid overload.⁴ Mihm⁵ suggests that Swan-Ganz catheterization be routinely performed in all phaeochromocytoma patients. These studies support the caution of Pullerits *et al.* regarding the monitoring of pulmonary capillary wedge pressure in phaeochromocytoma patients but do not address the question of the incidence of clinically significant cardiomyopathy.

The second point relates to the suggestion that hypertension occurs in over 50 per cent of phaeochromocytoma patients postoperatively. This may be the experience at their institution but it is not supported either by the literature or their quoted reference.⁶ It is true that the concentration of plasma catecholamines may remain elevated postoperatively for seven to ten days, but the same investigators also point out that there is no correlation between the concentration of plasma catecholamines and blood pressure. Furthermore, a recent review suggests a much lower incidence of postoperative hypertension.⁷

In summary, the true incidence of "clinically significant cardiomyopathy" in phaeochromocytoma is not known; the incidence of hypertension after operation may not be as high as Pullerits *et al.* indicate. Furthermore, the zeal to monitor aggressively patients with phaeochromocytoma must be tempered with a realistic appreciation of the true incidence of complications.

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REFERENCES

- 1 Pullerits J, Sigmund E. Anaesthesia for phaeochromocytoma. *Can J Anaesth* 1988; 35: 526-34.
- 2 Van Vliet PD, Burchell HB, Titus JL. Focal myocarditis associated with pheochromocytoma. *N Engl J Med* 1988; 274: 1102-8.