JECT. 2005;37:153–156
The Journal of The American Society of Extra-Corporeal Technology

Can Lean Body Mass Be Used to Reduce the Dose of Heparin and Protamine for Obese Patients Undergoing Cardiopulmonary Bypass?

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Abstract: Increasing numbers of obese patients are presenting for cardiac surgery. The convention for heparin dose dictates that a bolus of 300 IU heparin per kilogram of total body weight (TBW) is administered before CPB. During CPB, the activated clotting time (ACT) is maintained for longer than 480 seconds. At the end of the procedure, protamine is administered to neutralize heparin and achieve hemostasis. Both of these drugs can have serious side effects: heparin can induce thrombocytopenia, and protamine has been known to cause reactions in patients allergic to fish, vasectomized men, and some patients with insulin-dependent diabetes. The calculation of lean body mass (LBM) may be a more accurate method of determining drug doses as opposed to TBW and may avoid giving obese patients a relative overdose of heparin, which must subsequently be neutralized with protamine. LBM can be determined by different methods. This study used bio-electrical impedance analysis as a simple, quick, and accurate method of calculating LBM. A comparison was made between two groups of patients whose body mass index (BMI) was >27 kg/m^2: Group 1, n = 13, mean BMI = 32, mean body fat = 36% received the conventional dose of 300 IU/kg heparin for their TBW. Group 2, n = 14, mean BMI = 31, mean body fat = 35% received a dose of 300 IU/kg heparin for their calculated LBM. ACT was conducted before and after heparin administration. Additional heparin was administered as required to achieve target ACT > 400 s. Mean ACT results and total heparin doses were analyzed using unpaired two tailed t tests. Our results indicate that with care, a reduction of as much as 25% in the doses of heparin (p = 0.0001) and protamine can be achieved for a substantial number of patients classified as overweight or obese. **Keywords:** obesity, cardiopulmonary bypass, hemostasis, lean body mass, bio-electrical impedence, heparin, protamine. *JECT. 2005;37:153–156*

The association between obesity and coronary disease has long been recognized by clinicians, and the number of overweight patients presenting for cardiac surgery has increased noticeably during the last decade. Obesity is most commonly defined by clinicians in terms of the body mass index (BMI), which is calculated as follows:

$$\frac{\text{Weight in kilogrammes}}{(\text{Height in metres})^2} = \text{BMI (kg/m2)}$$

A desirable BMI is considered to be in the region of 20–25. Anything greater than 25 but less than 30 is defined as overweight, and a BMI greater than 30 is defined as obese. According to UK Department of Health statistics, in the 15 years between 1980 and 1995 the prevalence of obesity in England more than doubled (1). At present 46% of men and 32% of women are overweight. Of these, 17% of men and 21% of women are defined as obese (Figure 1) (2). In the United States, 50% of the population is said to be overweight, and this worrying global trend looks set to continue.

Two methods for prebypass systemic heparinization are used in this unit. The conventional regime involves administering a bolus dose of 300 IU/kg heparin on the basis of the patient's body weight; the other empirical method involves giving patients an initial dose of 20000 IU (20 KIU) heparin. In each method, a further dose of heparin is administered if the prebypass ACT fails to reach the target value of 400 seconds. Surprisingly, many overweight and obese patients receiving the 20 KIU dose achieve target ACTs despite, on the basis of their body weight, being administered an apparently inadequate dose of heparin. The purpose of this study was to determine whether this phenomenon demonstrates that some patients in the overweight and obese category who, by receiving the conventional dose, may be given a relative overdose of heparin and subsequently protamine. Evidence suggests that overweight and obese patients have a greater percentage of body fat, which receives less blood flow per gram than fat

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The senior author has stated that authors have reported no material, financial or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

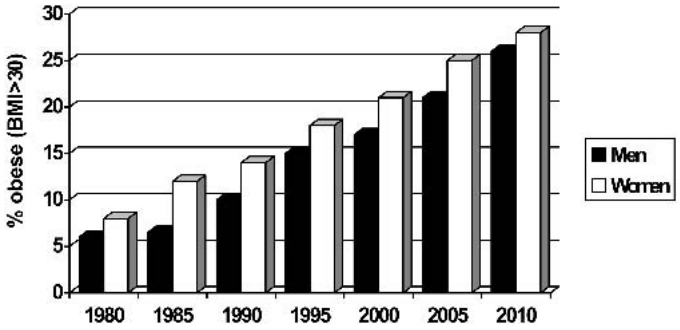

Figure 1. National Audit Office analysis of data from the *Health Survey for England*. Obesity statistics accurate to 1997 have been extrapolated to 2010. By then, it is estimated that 26% of men and 28% of women in England will be obese with a BMI greater than 30.

of nonobese individuals (3). Given the well-recognized side effects associated with heparin and protamine (4–7), it could be beneficial to give this group of patients a tailored dose that is effective but not excessive. Studies in adults in which dosage based on lean body mass (LBM) has been evaluated, has shown LBM to be superior to other measures of body size as a predictor of drug dosage (8). We decided to evaluate LBM as a predictor of pre-CPB heparin bolus dosage.

METHODS AND MATERIALS

Upon receiving Nottingham City Hospital Ethics Committee approval for a prospective randomized study, we obtained informed consent from elective patients with calculated BMI >27 who presented for a first-time coronary artery bypass grafting procedure. Because previous exposure to heparin can affect sensitivity (9), patients with previous heparin experience were excluded. Patients who might be expected to receive aprotinin also were excluded because of its effect on ACT tests performed using Celite (Hemochron, ITC, Edison, NJ) test tubes. All patients had been treated with aspirin, but this dose was stopped 7 days before surgery. A standardized intravenous anesthetic technique with fentanyl and propofol induction followed by propofol maintenance was used. After induction, bioelectrical impedance analysis (BIA) was used to determine the amount of fat and lean tissue present in each patient. The extracorporeal circuit and hollow fiber membrane oxygenator (COBE Laboratories, Arvada, CO) was primed with Hartmann's Solution containing 10 KIU heparin. Procedures were conducted using moderate hypothermia at 28°C.

Patients were computer randomized into two groups (Table 1): the total body weight (TBW) group was administered a prebypass bolus of heparin calculated at 300 IU heparin/kg total body weight, whereas the LBM group received a heparin dose of 300 IU/kg of lean body mass as calculated using BIA. Because heparin potency can be variable, one single batch was used for priming, pre-CPB bolus, and subsequent doses as required. ACTs were measured using the Hemochron Response (International Technidyne, Nevsky, NJ) presternotomy (baseline) and 3 minutes after the bolus dose (pre-CPB). Failure to reach the target ACT of 400 seconds prebypass resulted in the administration of additional heparin. Results were analyzed using GraphPad Prism Software (GraphPad Software, San Diego, CA) and are shown as mean ± SD.

Lean Body Mass and Bioelectric Impedence Analysis

LBM is described as muscle, bone, water, and tissue. Evidence is growing to suggest that LBM may be a better predictor of drug dosage than either total body weight or body surface area and that LBM can be used to accurately calculate the loading dose required for some drugs to attain a target peak plasma concentration (8). The average 70-kg male is composed of approximately 15% fat, whereas the average 57-kg female is composed of approximately 27% fat. BIA calculates body fat by measuring the voltage drop across the body as a harmless electrical current is applied via two pairs of small electrodes located on the right wrist and ankle. The body's ability to conduct an electrical current reflects the total amount of water present. In general, a high percentage of body water indicates a larger amount of muscle and lean tissue. Mathematical equations are used to translate the percentage of body water into an indirect estimate of body fat and lean body mass. The Bodystat 1500 (Bodystat (USA) Inc., Tampa, FL) body composition analyser was used to provide a simple, quick and accurate calculation of LBM, and results obtained by this method correlate closely with other more elaborate methods of measuring body fat such as deuterium dilution or densitometry.

RESULTS

No statistical differences existed in the baseline mean ACTs; TBW = 130 ± 9, LBM 135 ± 18, p = ns. However, the difference between the mean pre-CPB doses of heparin administered to the two groups was highly statistically significant; TBW 27 KIU ± 2.7, LBM 17 KIU ± 3.5 $p <$ 0.0001 (Figure 2). Analysis of mean pre-CPB ACT results

Table 1. Patient demographics.

	Total Body Weight	Lean Body Mass	p Value
No. patients	13	14	ns
Age (years)	62 ± 7	64 ± 11	ns
Gender (m/f)	9/4	10/4	ns
Height (cms)	167.2 ± 7.7	168.5 ± 9.5	ns
Weight (kg)	89.69 ± 9.1	88.5 ± 12.2	ns
BMI (kg/m^2)	31.92 ± 3.4	31.07 ± 3.5	ns
% body fat	36.39 ± 9.2	35.14 ± 10.2	ns

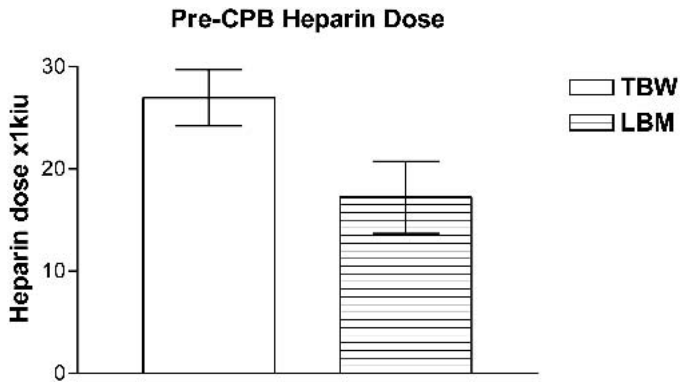

Figure 2. Pre-CPB heparin doses as calculated using conventional method and LBM. LBM, lean body mass; TBW, total body weight.

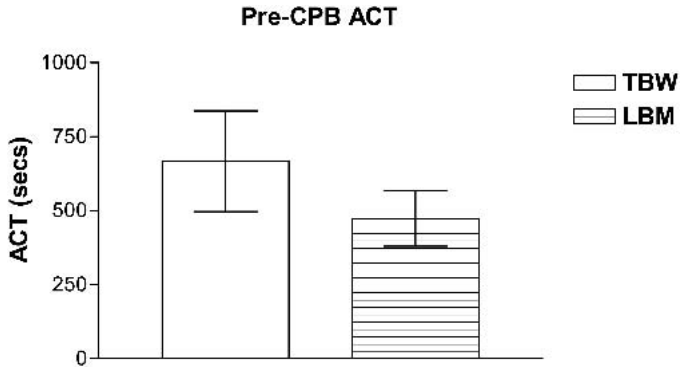

Figure 3. Pre-CPB ACT. LBM, lean body mass; TBW, total body weight.

reveals that both groups were adequately heparinized and achieved target values. There was a significant difference ($p < 0.001$) in the mean pre-CPB ACT; TBW = 667 ± 47, LBM = 473 ± 25 (Figure 3). These results suggest that patients dosed using LBM as a predictor of heparin dose achieved adequate ACT results, which correlated much more closely with the target value of 400s. Only two patients, both in the LBM group failed to meet the target ACT of 400s. Each patient received an additional 10 KIU heparin. However, even taking this additional 20 KIU heparin into consideration for the LBM cohort, (mean dose = 19 KIU ± 3.6), there is still a highly statistically significant difference between the doses administered to the two groups, $p < 0.0001$ (Figure 4), reflected in the doses of protamine used for heparin neutralization (1 mg: 100 IU).

DISCUSSION

Conventional dosing regimes for patients using weight surface area or BMI may be suitable for some patients, but for overweight and obese patients, using weight or surface area may result in overdosing. The key to safely determining which patients could benefit from a reduced dose lies

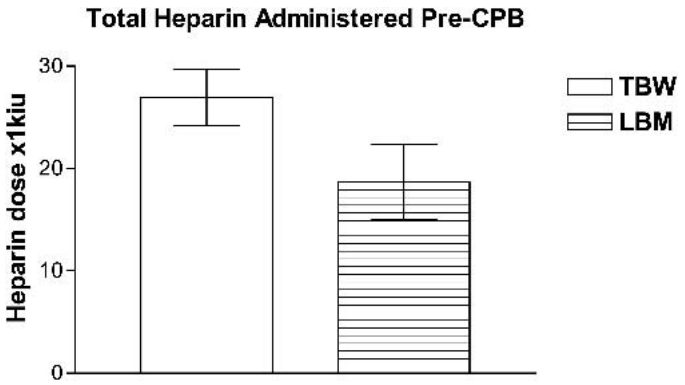

Figure 4. Total heparin dose including additional 20 KIU to two patients in LBM cohort. LBM, lean body mass; TBW, total body weight.

Table 2. Relationship between half life (t½) of heparin and dose.

Dose	100 iu/kg	200	400
t½ mins	56	96	152

not in using the BMI as an indicator of fatness but in measuring the LBM of individual patients. BMI is a measurement of relative weight for height; in large groups of subjects, there is a good relationship between excess weight and fatness. However, some individuals may have a relatively high BMI but remain lean. For instance, a body builder with a very well-developed musculature would register excess weight that is greater than reference figures but be composed of predominantly lean tissue rather than fat. Conversely, old people may have a normal or low BMI but have a high proportion of fat because lean tissue mass decreases with age. Therefore, BMI alone does not give enough information to correctly determine the body composition of individuals to determine drug doses.

CONCLUSIONS

Some overweight and obese patients presenting for cardiac surgery may require as much as 25% less heparin and subsequently protamine than previously thought. LBM could be used as a predictor of pre-CPB heparin bolus to calculate an individual dose that is effective, produces ACTs close to target values, whilst not being excessive. With care, LBM estimations can be used to reduce the amount of heparin and protamine administered by as much as 25% in overweight and obese patients presenting for cardiac surgery. On a cautionary note, it should be remembered that the half life of heparin is proportional to the dose administered (Table 2) (10). Using LBM, we can reduce the conventional dose from 300 to 225 IU/kg; as a result, the half-life of heparin also may be reduced. Therefore, frequent monitoring of the ACT is essential.

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