LETTERS TO THE EDITOR

Hemochron Versus HemoTec Activated Coagulation Time Target Values During Percutaneous Transluminal Coronary Angioplasty

We read with great interest the results of a study by Avendano and Ferguson (1) dealing with the target activated clotting time values determined by two different clot detecting systems. We agree with the authors on the main results of this study that activated clotting time results achieved by different machines cannot be used interchangeably, and further prospective research is needed to determine the level of correct anticoagulation.

The two systems use different clot detecting systems, which at least partly explains the finding that the HemTec system usually detects a shorter activated clotting time. The HemTec system detects the early appearance of the fibrin mesh, whereas the Hemochron system detects the time required for the formation of a firm clot capable of grabbing the magnet in a test tube and, hence, stops the timer.

Our main criticism concerns the statistical method used in this study. Linear regression analysis is not an appropriate statistical test for comparing two methods measuring the same clinical variable. The correlation coefficient is a measure of the strength of linear association between two variables and does not show the level of agreement and contributes no information as to whether the two methods can be used interchangeably. The correlation coefficient also depends on the random measurement error and the range of measurements (2). One of the correct statistical tests for comparison of methods was published by Altman and Bland in 1983 (2). They suggested a simple calculation of the difference between the results achieved by the two methods and plotted this against their mean value. The mean difference is the bias and the mean difference ±2 SD is the limit of agreement. If this limit of agreement is smaller than the difference with clinical significance, then the two methods can be used interchangeably. The interpretation of the limit of agreement must depend on the clinical circumstances, and it is not possible to use statistics to define acceptable agreement. This statistical test has widely been used for comparison of methods studies (3–5).

Statistical techniques provide the tools for assessing the validity of a finding. Use of the appropriate statistical method facilitates the correct interpretation of the results. It is a pity that >10 years after publication of an easy, clinically oriented statistical method, studies using incorrect statistical methods are still appearing in journals of international reputation.

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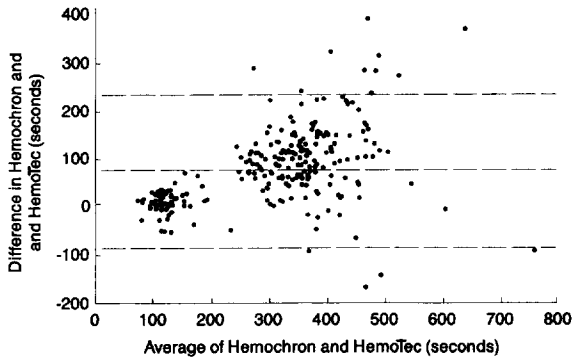
Reply

We appreciate the insightful comments of Varga et al. regarding the appropriate statistical techniques for comparing two different measurements of the same clinical variable. In response to their query, we have included an analysis of our data (1) using the technique published by Altman and Bland (2) (Fig. 1). This graph shows the difference between the two measurements plotted as a function of the mean of the two measurements. This type of analysis shows the variability of the two measurements over the entire range of application and is primarily useful for indicating whether one type of measurement can be used interchangeably with another. As is obvious from Figure 1 (and as stated in our original article), the Hemochron activated clotting time measurements tend to exceed HemoTec activated clotting time measurements; the degree of variability increases markedly after the administration of heparin. The implications are exactly the same as in the original article: Hemochron and HemoTec activated clotting time measurements cannot be used interchangeably. The regression equation mentioned in the article was intended only to illustrate that a relation existed and should not be used as a basis to "predict" one activated clotting time measurement on the basis of measurements using the other technique. We agree that prospective data for both

Figure 1. Difference between Hemochron and HemoTec measurements plotted as a function of the mean value of the two measurements. The degree of variability increases in the higher range of measurements, after the administration of heparin.



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HemoTec and Hemochron activated clotting times will be necessary to determine exactly what "adequate" anticoagulation is.

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Congestive Heart Failure and Sodium Dichloroacetate

I recently read with interest the excellent article by Bersin et al. (1) reporting on the metabolic and hemodynamic effects of sodium dichloroacetate in patients with congestive heart failure. Dichloroacetate, in a dose of 50 mg/kg body weight, resulted in an increase in minute work of 12.3% (from 1.38 to 1.55 kg-m/m^2), while at the same time myocardial oxygen consumption was reduced by 14.5% (from 19.3 to 16.5 ml/min), resulting in a reported 28% increase in left ventricular mechanical efficiency.

As the authors note, dichloroacetate stimulates pyruvate dehydrogenase activity by inhibiting pyruvate dehydrogenase kinase, enhancing glycolysis and increasing utilization of lactate, particularly in the myocardium. The concomitant inhibition of free fatty acid consumption leads to a shift of substrate utilization from predominantly free fatty acids—the usual preferred energy source of the myocardium—to glucose and lactate. The authors relate the improved mechanical efficiency of the heart to this shift in metabolic substrate.

Two points, though, are unclear in this explanation. The authors attribute the higher efficiency of glucose to its higher respiratory quotient without explaining how the respiratory quotient affects energy utilization. Furthermore, they state that glucose and lactate generate more adenosine triphosphate (ATP) per mole of substrate (3.0 and 3.2 mol, respectively) than fatty acids (yielding 2.8 mol of ATP per mole of substrate). However, fatty acids yield more ATP than glucose per mole of substrate. The complete oxidation of 1 mol of glucose yields 36 mol of ATP, not 3.0 mol (2), whereas the oxidation of 1 mol of palmitate, a 16-carbon fatty acid, yields 129 mol of ATP rather than 2.8 (2).

It appears more likely that the numbers 2.8 and 3.0 refer instead to the ratio, not of ATP to fuel substrate, but of ATP to oxygen requirements, a ratio that relates more directly to the issue of energy efficiency. For glucose, 6 mol of molecular oxygen (O_2) are necessary to yield 36 mol of ATP, giving an ATP/oxygen ratio (P/O) of 3.0 (2 atoms of oxygen per molecule). For palmitate, its complete oxidation yields 16 mol of CO_2 and 129 mol of ATP (2). The respiratory quotient of 0.7 indicates that it requires, 16/0.7 or 22.9 mol of O_2 to metabolize 1 mol of palmitate, yielding a P/O of 129/(22.9 × 2) or 2.8. These calculations may explain how the respiratory quotient affects the mechanical efficiency of the heart, without directly affecting ATP generation, per se.

One additional finding of this study requires further clarification. How does an increase in P/O from 2.8 to 3.0 (or even to 3.2) explain a 28% improvement in efficiency? It would seem that another mechanism must be invoked. Is it possible that the metabolic shift caused by dichloroacetate, or a direct effect of dichloroacetate itself, could change the mechanical properties of the heart, allowing it to perform more work for a given level of ATP consumption? Perhaps dichloroacetate does have vasodilating properties that effect this improvement in efficiency.

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Reply

In response to Koshkarian's letter regarding our article on dichloroacetate in congestive heart failure (1), I have the following reply.

Koshkarian raises two good points that require further clarification. First, he correctly points out that the ratios referred to in the Discussion section of the article represent the adenosine triphosphate (ATP)/oxygen ratios (P/O ratio), which refer to the number of moles of ATP generated per mole of *oxygen* consumed, not per mole of *substrate* consumed as stated in the article. The respiratory quotients, on the other hand, refer to the number of moles of carbon dioxide produced per mole of oxygen consumed during complete oxidation of substrate for aerobic respiration. The P/O ratio and the respiratory quotient of substrates for aerobic respiration tend to correlate such that substrates with the highest P/O ratios (glucose and lactate) tend to have the highest respiratory quotients. However, the P/O ratio most directly reflects the metabolic efficiency of a substrate.

Because lactate has the highest P/O ratio (3.2:1), a shift in substrate utilization by the myocardium from predominantly free fatty acid utilization to lactate consumption should improve cardiac mechanical efficiency. However, Koshkarian's second point is that even a complete shift from free fatty acid consumption to lactate consumption would only be expected to increase cardiac mechanical efficiency by 14%, yet a 28% increase in cardiac mechanical efficiency was observed. Therefore, the observed change in mechanical efficiency cannot be completely explained on the basis of a change in P/O ratios of substrate alone. A greater than expected change in mechanical efficiency observed with dichloroacetate may be explained by other effects that substrate and dichloroacetate have on cellular metabolism.

In isolated rat hearts perfused with solutions containing either glucose or free fatty acids (Hexonate), Burkhoff et al. (2) observed a greater than expected decrease in myocardial efficiency based on the P/O ratios of substrate. Although a 10% reduction in myocardial efficiency for excitation-contraction coupling occurred as expected, the efficiency of basal metabolic function in the KCl arrested state was reduced by nearly 30%. This led Burkhoff et al. to conclude that the changes in P/O ratios in switching from glucose to Hexonate could only account for a portion of the change of myocardial efficiency measured. The difference between the expected and observed efficiencies ap-