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LETTERS TO THE EDITOR

Inotropic Effect of Methylxanthines

In his recent review article on the mechanisms of action of inotropic drugs, Scholz (1) makes a number of points that deserve further discussion. Scholz correctly dismisses the suggestion that methylxanthines exert their positive inotropic effect by an interaction with intracellular calcium stores. He cites the discrepancy between concentrations of methylxanthines producing such an effect and those concentrations achieved in vivo. However, the same quantitative discrepancy applies to the inotropic mechanism suggested by him, inhibition of phosphodiesterase. Inhibition of phosphodiesterase is negligible at a concentration of 10^{-4} *M*(2), whereas fatal theophylline poisoning may occur in humans at concentrations of approximately this level (3). Thus, it seems unlikely that phosphodiesterase inhibition plays any role in the suggested positive inotropic effect of methylxanthines in vivo.

A similar quantitative comparison raises doubts as to whether methylxanthines do, in fact, exert any positive inotropic effect in vivo. The threshold for positive inotropic effect of the methylxanthines approximates to 10^{-3} *M* (4,5). As just discussed, this concentration of theophylline, the most effective inotrope of the methylxanthines, is not achieved in humans. Therefore, any inotropic effect of the methylxanthines in humans is likely to be negligible at concentrations that can be safely achieved.

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Reply

Maximal therapeutic theophylline plasma concentrations are 10 to 20 μg/ml or 55.5 to 111 μmol/liter (1). At a concentration of 100 μmol/liter, theophylline increases myocardial force of contraction by not more than about 30% (2–5). It is therefore probably true that the methylxanthines do not exert a marked positive inotropic effect in vivo. However, the concentration-response curves for the positive inotropic and the myocardial phosphodiesterase-inhibiting effects of theophylline coincide when determined in the same tissue (3–5). Thus, *if* theophylline exerts a positive inotropic response, it seems safe to conclude that this is related to its effect to inhibit phosphodiesterase and therefore to increase cyclic adenosine monophosphate levels.

That theophylline may lead to sudden cardiac death is well known. In this context it is worth recalling that theophylline and other phosphodiesterase inhibitors increase the cardiac effects of beta-adrenergic agents. Thus, the fatal events just mentioned may ultimately also be due to particularly pronounced arrhythmogenic effects of endogenous catecholamines when these are increasedly released under certain circumstances; during exercise, for example.

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Precordial ST Segment Deviations During Acute Myocardial Infarction

Lew et al. (1) presented a graphic representation of the correlation between the maximal inferior ST segment elevation and the maximal ST segment depression in lead aVL. A Pearson correlation coefficient of r = 0.88 describes the strong linear relation presented in the graph. This is contrasted to the weak coefficient of r = 0.38, relating precordial ST depression anteriorly to ST elevation inferiorly. The authors conclude that while the ST depression in lead aVL generally represents a reciprocal reflections, the precordial ST depression is more complex. Based on angiographic and thallium studies, the authors support the view that precordial ST depression during an acute inferior myocardial infarction represents more extensive involvement of adjacent posterolateral or inferoposterior segments supplied by the artery of infarction. What