LETTERS TO THE EDITOR

Comments on "Role of Glycolytic Products in Damage to Ischemic Myocardium" which appeared in Circ. Res. 55: 816-824, 1984

Neely and Grotyohann (1984) provided experimental evidence that lactate accumulation may play a major role in irreversible damage to ischemic myocardium in the perfused rat heart. They suggested that the effect of lactate on cardiac muscle may be mediated by changes in cellular pH. This may be either an incomplete or an erroneous suggestion. As early as 1970, Pannier and Weyne studied the effects of lactate on the mechanical performance of isolated cat papillary muscle. They demonstrated that, besides a possible effect by cellular pH changes, lactate has by itself a direct and specific action on cardiac muscle. As these latter experiments were performed at the unphysiological temperature of 25°C, we repeated them at 37°C.

Seven right ventricular cat papillary muscles were set to l\textsubscript{max}, i.e. the length at which maximum active force is developed. The Krebs-Ringer bathing solution was gassed with a mixture of 95% O\textsubscript{2} and 5% CO\textsubscript{2}; pH was 7.4, [Ca\textsuperscript{++}]\textsubscript{o} 2.5 mM, stimulation rate 0.2 Hz, and temperature 37°C. The entire bathing solution was replaced by a Krebs-Ringer solution at the same temperature, containing 20 mM lactate. A correction for pH was made by adding NaOH and for osmolarity by lowering NaCl concentration.

Lactate progressively lengthened the overall duration of the contraction (Fig. 1). It had a slow but marked effect on all time and velocity parameters of the isotonic and isometric contraction. The effect of isometric force was biphasic. There was an initial depression, which was maximal after 4 minutes. However, time-to-peak force continued to lengthen to such an extent developed force was isolated above control level after 20 minutes, despite a slower rate of force development. Depression of isotonic peak shortening, after an early rapid fall, slowly continued with time in the lactate solution. Despite a diminished isotonic lengthening velocity during the relaxation phase, load dependence of relaxation (Brutsaert et al., 1980, 1984) was enhanced due to the markedly delayed isometric relaxation. Twenty minutes after the addition of lactate, the time parameters recovered very slowly, whereas the velocity parameters did not.

Our results at 37°C are consistent with those of Pannier and Weyne (1970) at 25°C. On the other hand, species' differences in response to lactate may exist. Yatani et al. (1981) studied the influence of 20 mM lactate buffered at pH 7.4 on isometric contractions of frog atrial muscle. They reported a rapid and severe depression of developed force, without changes in time-to-peak force. The experiments by Neely and Grotyohann (1984) were performed in rat hearts, in which ischemic and hypoxic myocardium is known to develop irreversible contracture more easily than in any other mammalian myocardium.

Changes in the overall duration of the contraction or in time-to-peak force, as observed by us and by Pannier and Weyne (1970) in isolated cat myocardium, are not observed by changing cellular pH (Pannier and Leusen, 1968; Cingolani et al., 1970). Therefore, contrary to the opinion of Neely and Grotyohann (1984), the lactate ion probably has a direct and specific effect on mammalian cardiac muscle.

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INDEX TERMS: Lactate • Contractility • Cardiac muscle • Ischemia

Reply to the Preceding Letter

Thank you for the opportunity to respond to the “Letter to the Editor” by Dr. Brutsaert and co-workers. They have, in my opinion, misinterpreted the manuscript by Neely and Grotyohann in Circulation Research 55: 816–824, 1984, on “Role of Glycolytic Products in Damage to Ischemic Myocardium.” Their reason for writing the “Letter to the Editor” is their belief that we attribute the harmful effects of glycolytic products during ischemia to decreased pH rather than to high lactate. They present some data on the direct effects of lactate on contraction of isolated papillary muscle, with the purpose of showing that lactate has a direct effect on muscle contraction that is not mediated by changes in cellular pH.

My response to their letter is that our paper throughout discusses a role of glycolytic products during ischemia on recovery of function during reperfusion. We measured lactate, but in the Summary of the paper, we state that the data suggest a major role of anaerobic glycolytic products (lactate, hydrogen ion, or NADH). This is because the available data do not allow us or, in my opinion, anyone else, to distinguish the direct effects of lactate from that of hydrogen ion or NADH. When lactate accumulates during ischemia or is added to muscle, it may change both intracellular pH and NADH. The only other mention of pH in our paper is on pages 823 and 824 in the Discussion, where we point out that the effects of lactate accumulation during ischemia or addition of lactate to ischemic myocardium could be mediated by changes in cellular pH, and we explain why. We think this is a possibility that must be pointed out in the discussion of any paper such as ours, but the paper does not make the claim that the effects observed are due to hydrogen ion. Another point that Dr. Brutsaert and co-workers appear not to appreciate is that our data found an association between accumulation of lactate during ischemia and the inability of the heart to recover mechanical function when reperfused. We clearly point out that this depressed mechanical function during reperfusion is not due to the presence of lactate during the reperfusion period, but, rather, to damage that occurred during ischemia. The data Dr. Brutsaert and co-workers have presented in their letter relate to changes in contractility of isolated muscle fibers in the presence of high concentrations of lactate. Their data, like ours, will not allow a change in cellular pH due to protonated lactate entering the cell to be distinguished as a direct effect of lactate on contractility.

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