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Influence of Temperature upon the Inotropic Effect of Metabolic Acidosis in Cat Papillary Muscles[1] (37921)

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Even though the negative inotropic effect of respiratory acidosis has been clearly established, some controversy still exists regarding the effect of metabolic acidosis upon cardiac inotropism. Changes in pH at constant P_{CO_2} have been reported to produce a decrease (1–3) or no change (4–6) in myocardial contractility. It is possible that this discrepancy could be explained in part on the basis of differences in level of sympathetic tone (7–9), oxygen availability to the cell (10), integrity of the cardiovascular reflexes (11, 12), and severity of the acidosis produced (13). Still, even in isolated preparations where systemic influences are eliminated, contradictory results have been reported (1, 3, 4).

The present experiments were performed to study the influence of temperature upon the inotropic effect of metabolic acidosis in isolated cat papillary muscles.

Methods. Cats were anesthetized with sodium pentobarbital (35 mg/kg) administered intraperitoneally. After a thoracotomy, the heart was rapidly removed and placed in a reservoir with oxygenated Ringers'. A papillary muscle was excised from the right ventricle and mounted in a glass chamber filled with Ringer's solution equilibrated with 5% CO_2, 95% O_2. The composition of the control Ringer's solution in m*M* was: NaCl = 120, $NaHCO_3$ = 21.2, KCl = 4.0, KH_2PO_4 = 1.0, $MgSO_4$ = 1.0, $CaCl_2$ = 2.5, glucose = 5.0. The mural end of the muscle was fixed with a clip attached to the chamber. The tendinous end was attached to an isometric force transducer by fine-silk suture. The muscle was then stretched to a resting tension of approximately 300 mg. Electrical stimulation was started approximately 2 hr after mounting the muscle in the chamber. Stimuli at a frequency of 10/min were delivered through two platinum electrodes immersed in the solution. Intensity of stimulation was set at 50% above threshold. Resting tension was maintained constant throughout the experiment.

Isometric developed force (DF) and rate of change of developed force (dF/dt) were recorded with an Electronics for Medicine photographic recorder. The natural frequency of the Grass force transducer was 85 Hz. The electronics differentiator was capable of differentiating rates of force change up to 1500 g/sec with an amplitude error of less than 1%. Thus the characteristics of the transducer, differentiator, and recorder were more than adequate for the parameters measured. Time to peak force (t-PF) was measured from records obtained at 200 mm/sec. DF was expressed as g/mm^2 and dF/dt as g/mm^2/sec. Muscle length was measured at the resting tension and cross-sectional area calculated assuming the muscle to be a cylinder with a density of 1. The chamber had a double wall for circulation of water maintained at the desired temperature. Temperature of the solution was continuously recorded and could be rapidly altered by the use of two heat exchangers kept at different temperatures. When DF and dF/dt showed stable levels, the solution was switched to another equilibrated with the same gas mixture, but in which $NaHCO_3$

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was lowered to obtain a pH of 6.90. Osmolarity of the solution was maintained by reciprocal changes in $NaHCO_3$ and NaCl. The procedure of exposing the muscle to solutions with normal and acid PH was performed at three different temperatures of the solution: 25, 30, and 38°. The muscle was exposed to the different solutions in a random sequence and maintained in a given solution for approximately 30 min, a time that proved adequate to reach a steady DF, *dF/dt*, and t-PF. Since the solubility of CO_2 is temperature dependent, the control and acid solutions at different temperatures had slight differences in the $NaHCO_3$ concentration, in order that they always yielded pH's of 7.40 and 6.90, respectively. Paired differences between control and acid were analyzed for statistical significance by the Student's *t* test.

Results. The results obtained in 8 experiments are summarized in Fig. 1. At 25° a decrease in pH from 7.4 to 6.9 at constant P_{CO_2} was not followed by a significant change in DF or *dF/dt*. A significant decrease in time to peak force of 28 msec was observed. Induction of acidosis at 30° was accompanied by significant decreases in DF, *dF/dt*, and t-PF of 0.4 g/mm², 1.3 g/mm²/sec, and 27 msec, respectively. At 38° acidosis resulted in significant decreases in: DF of 0.34 g/mm², *dF/dt* of 3.8 g/mm²/sec, and t-PF of 26 msec. Of interest is the observation that the absolute changes in DF accompanying acidosis were comparable at 30 and 38°. However, because of the lower control (pH = 7.4) developed force at 38° in relation to DF at 30°, the percentage change at 38° is more than twice that observed at 30°. Examination of the t-PF data indicates that the absolute decrease in t-PF engendered by acidosis was independent of the initial value.

Discussion. The effect of temperature per se on the mechanics of myocardial contraction at pH 7.4 are similar to those reported by Buccino and coworkers (14) in that a progressive decrease in t-PF was observed with increasing temperature. In our experiments, *dF/dt* increased from 25 to 30° and decreased slightly when the temperature was increased to 38°. Since the isometric developed force is directly related to both *dF/dt* and t-PF, the interaction of the changes in these two variables resulted in a lack of change in DF at 30° and a decrease at 38°.

The present results show that the temperature of the medium is not only capable of affecting the contractile characteristics of the myocardium, but that it also influences the negative inotropic effect of metabolic acidosis. At 25° metabolic acidosis did not affect myocardial contractility, whereas a significant decrease in contractility was observed at 30 and 38°. Furthermore, the depressant effect of metabolic acidosis was more marked at 38 than at 30°.

The mechanism by which temperature influenced the inotropic effect of acidosis is not clear. Evidence has accumulated in the past few years suggesting that intracellular pH is a major determinant of contractility during acid–base alterations (2, 4, 15). For our results to be explained on the basis of changes in intracellular pH, it would be necessary to assume that metabolic acidosis did not result in a decrease in cell pH at 25°, but was followed by intracellular acidosis at 30 and 38°. Several possibilities could be considered in this respect. Recent experiments from our laboratory have demonstrated that metabolic acidosis is followed by cellular acid–base changes compatible with a net HCO_3^- outflux (submitted for publication). If temperature increases transmembrane HCO_3^- and/or H^+ flux, it would be expected that during metabolic acidosis, intracellular H^+ concentration would be increased with increasing temperature. An alternative mechanism would be that increased metabolism and acid production associated with increased temperature could result in a higher intracellular H^+ concentration at the higher temperatures during metabolic acidosis (16). Finally, it is possible that an increase in myocardial oxygen consumption would result, in this nonperfused preparation, in a limitation of oxygen availability to the cell. The potentiating effect of hypoxia on metabolic acidosis has been previously described in more intact preparations (10). The interaction of these possible mechanisms cannot be discarded.

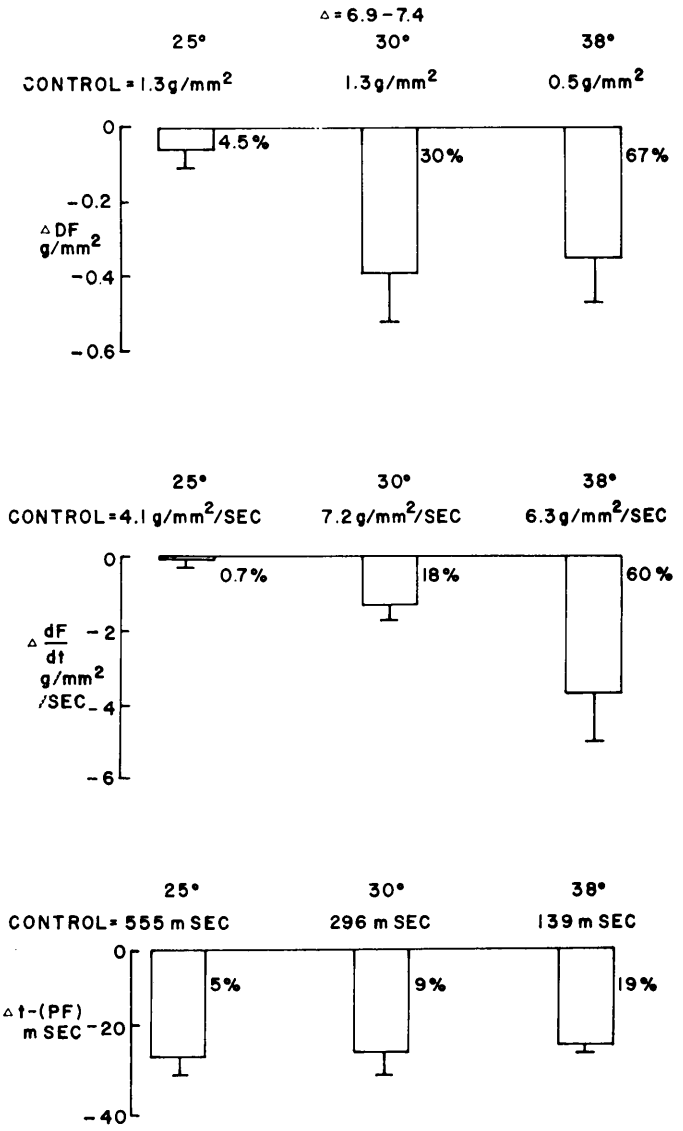

FIG. 1. Changes in developed force (ΔDF), rate of rise of the force ($\Delta df/dt$), and time to peak force (Δt-PF) with acidosis at 25, 30, and 38° in 8 experiments. Vertical bars represent 1 SEM. Percentage changes from the control are shown at the side of the vertical bars.

It is possible that the effect of temperature described in the present experiments could account in part for the discrepancies concerning the inotropic influence of metabolic acidosis found in the literature.

Summary. Isolated cat papillary muscles immersed in Ringer's solution were subjected to metabolic acidosis (pH 6.9, P_{CO_2} = 40 mm Hg). Acidosis was produced at three temperatures of the bathing solution: 25, 30, and 38°. Acidosis at 25° was not followed by significant changes in contractility, whereas a negative inotropic effect was observed at 30 and 38°. The deletereous effect of acidosis was more marked at higher temperatures. It is possible that this effect might account in part for some of the controversies observed in the literature.

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