Age-Related Effects of Acidosis in Isolated Cardiac Muscle

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Acidosis is associated with myocardial ischemia and several reports indicate the greater vulnerability of the aged heart to ischemic dysfunction. We investigated the effects of hypercapnic acidosis on isolated heart (n = 14) and papillary muscle (n = 10) from adult and senescent rats. Acidosis (pH from 7.36 to 6.91) induced a decrease in left ventricular developed pressure together with an increase in left ventricular end-diastolic pressure, but was significantly more evident in senescent than in adult hearts (p < .01). The return to normal pH induced a further increase in the end-diastolic pressure parallel to the development of arrhythmias that were greater in senescent than in adult hearts. In isolated papillary muscle, acidosis confirmed its greater negative inotropic effect on senescent than adult muscles (p < .01), while intracellular sodium activity (a:v) increased to a similar extent in both adult and senescent papillary muscles (p = NS). 5-(N,N-dimethyl)-amiloride hydrochloride (DMA), a specific inhibitor of Na+/H+ exchanger, produced similar modification of tension and a:v, in both adult and senescent muscles. When DMA was superfused in acidic solution, the contractility was markedly compromised in senescent than in adult muscles (p < .01), but the a:v modifications were similar in adult and senescent muscles (p = NS). Our results show that acidosis induced a greater reduction of contractility in senescent than in adult hearts. The similarity of contractility during DMA administration between adult and senescent muscle and of modifications of a:v, suggests that depression of contractility with acidosis may be related to pathophysiological mechanisms other than the Na+/H+ exchanger.

MYOCARDIAL ischemia is characterized by the development of an intracellular acidosis that may play a determinant role in the depression of cardiac contractile function observed in this pathophysiological condition (1). It is well known, moreover, that aging heart is more susceptible to deleterious effects of myocardial ischemia (2–5).

Acidosis is known to provoke a modification of intracellular and extracellular ionic homeostasis and sensitivity of calcium to myofilaments (1,6-12) via a reduction of cardiac contractility by reducing the sensitivity of contractile protein to calcium and modifying the release of this ion at the sarcoplasmatic reticulum. Acidosis-induced negative cardiac inotropism is, however, partially counteracted by Na+/Ca2+ exchanger; the increase in intracellular hydrogen concentration induces an increase in intracellular sodium that increases intracellular calcium and therefore contractile force via an altered Na+/Ca2+ exchange (13–17). The recovery from an intracellular acid load is also produced by Na+/HCl cotransport which accounts for ~30% of total acid-equivalent efflux (18).

Solaro et al. (19) demonstrated a different response to hypercapnic acidosis in adult compared to neonatal ventricular muscle. In the adult ventricular muscle, a rapid fall in developed tension is followed by slow recovery to a steady state while in neonatal muscle there is no initial fall in developed tension but during recovery developed tension reaches a lower level than that obtained in adult muscle. The authors suggested an age-related difference in the effect of acidosis on the myofibrils and Ca2+ transport.

The aging heart is characterized by a modification of contractile protein configuration which could be responsible for age-related difference in cardiac inotropism in response to different pathological conditions (20,21). Myosin ATPase activity reduces progressively with age shifting in the myosin heavy chain from the α (V1) to the β (Vv) isoform (22). The age-associated modification of the Ca2+ pump function of cardiac sarcoplasmic reticulum is also well known (23,24). Some authors have hypothesized an age-related modification of ionic exchanger (such as Na+/Ca2+ or Na+/H+) that may contribute to a different contractile response in the presence of acidosis (20). However, we have recently demonstrated that Na+/Ca2+ is probably not altered by aging processes (25).

The aim of the present study was to investigate ionic, electrical, and mechanical responses to metabolic acidosis in hearts and papillary muscles from adult and senescent rats. Moreover, in order to verify the hypothetical involvement of Na+/H+ exchanger, membrane potential, a:v, and contractile force were simultaneously recorded in papillary muscle.

MATERIALS AND METHODS

Male normotensive Wistar–Kyoto rats aged 6 (adult; n = 12) and 24 (senescent; n = 12) months weighing 290 ± 30 g and 495 ± 34 g, respectively (mean ± SD), were used. Animal care was performed according to the “Position of the American Heart Association on Research Animal Use” adopted by the American Heart Association on November 1998, Vol. 53A, No.1, B42–B48

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The electrical signal was obtained from a bioelectric amplifier and perfused at constant pressure of 70 mmHg, as described previously in details (4, 26). Heart weight was 770 ± 23 mg at 6 months and 995 ± 70 mg at 24 months. Left ventricular pressure was measured using an intraventricular balloon attached to a 1-mm diameter hollow cannula and connected to a Statham (Hato Rey, PR) P 23 pressure amplifier and to a low-level pre-amplifier (OTE Biomedica, model 2080 pressure meter; Vienna). Isovolumic loading conditions were established by setting left ventricular end-diastolic pressure at 5 mmHg. Heart electrogram was obtained by an atraumatic epicardial electrode (.8 mm diameter, silver wire) attached to the free wall of the right ventricle (to avoid affecting left ventricular function). The electrical signal was obtained from a bioelectric amplifier (OTE Biomedica model 2077 ECG amplifier). Pacing wires were fixed to the pulmonary outflow tract, and the hearts were paced at 6 Hz and turned off after the equilibration period. Coronary flow rate was measured in graduated cylinders at intervals of 5 min, and related to wet ventricular weight (ml/min/g) in both groups. Cardiac electrode (mV) and left ventricular pressure (mmHg) were monitored, and recorded on a Harvard oscillograph (Harvard Apparatus, Inc., Chelmsford, MA) at a paper speed of 0.1 mm/sec at intervals of 5 min.

Arrhythmias were analyzed according to the Lambeth Convention guidelines (27). To permit correlation analysis, arrhythmias were scored as follows for each heart: 0, no arrhythmias; 1, single ventricular premature beats; 2, couplets and salvos; 3, ventricular tachycardia; 4, nonsustained ventricular fibrillation; and 5, sustained ventricular fibrillation.

Isolated and perfused rat papillary muscle. — Anterior papillary muscle was dissected from left ventricle and transferred to a tissue bath. At the end of each experiment, the muscles length was measured and then blotted dry, and weighed. Cross-sectional area was determined from muscle weight and length, assuming a uniform cross-section and a specific gravity of 1.05. Cross-sectional area was 1.05 ± 0.21 mm² in adult (n = 5) and 1.18 ± 0.13 mm² in senescent (n = 5) papillary muscle (p = NS). Great care was required to minimize muscle contraction to maintain microelectrode impedances for many hours. For this reason, one end of the papillary muscle was tied by means of a short silk thread to a stainless steel rod attached to a force transducer (Harvard Apparatus, model no. 52-9545, 50–60 Hz). The other end of the strand was immobilized by means of one of the stainless steel pins used as stimulating electrodes. Another L-shaped insect pin was placed ~1 mm away from the stimulating electrode to lightly press the muscle to the bath floor to maintain the muscle in a stable position throughout the experiment. The muscle portion between the distal end of the muscle, connected to a force transducer and delimited by L-shaped pin, could move freely during contraction. The papillary muscle was continuously driven at a frequency of 60 beats/min (1 Hz) by means of electrical stimuli (5 msec pulses at a voltage 10% above threshold) delivered by a WPI stimulator (model A 310 Accupuls; WPI Instruments, Waltham, MA). The stimulated papillary muscles were stretched to ~30% of their resting length and were equilibrated for a minimum of 1 hr in Tyrode solution prior to the experiments. Resting force and developed force in response to excitation were normalized for muscle cross-sectional area (g/mm²) and expressed as resting tension and developed tension. Intracellular sodium activity (aNa) was measured with Na⁺-selective microelectrodes made with neutral carrier ETH 227. The construction and calibration of Na⁺-selective microelectrodes have previously been described in details (25). Papillary muscles were impaled with conventional microelectrodes and Na⁺-selective microelectrodes. In the text, Vm represents the filtered voltage of the action potential measured with the conventional microelectrode. In several cases, when the perfusion changes (for example, from normal to acidic solution) it is possible to observe an abrupt change in Vm that, of course, does not represent a membrane potential modification but only an electrical artifact. In order to measure continuously aNa of electrically driven muscles, two identical low pass filters (with a fixed frequency of .24 Hz) were used as described previously (25). Both Na⁺-selective and conventional microelectrodes actually measure voltage fluctuations caused by action potentials of the papillary muscles driven at constant rate. The voltage fluctuations were removed with the low pass filter before Vm was electrically subtracted from ENa. Contractile force, aNa, and Vm were recorded simultaneously and continuously at slow speed (.05 mm/sec) with a Gould (Cleveland) recorder (model no. 2400).

Solutions. — Both isolated heart and papillary muscle superfused with Tyrode solution at 37 °C for heart and 30 °C for papillary muscle. The composition of the standard Tyrode solution was (in mM): 120 mM NaCl, 5.9 mM KCl, 1.2 mM MgCl₂, 25 mM NaHCO₃, 1.2 mM NaH₂PO₄, 1 mM CaCl₂, and 11.5 mM glucose. When equilibrated with 5% CO₂ and 95% O₂, the pH of this solution was 7.36; when equilibrated with 15% CO₂ and 85% O₂, the pH was 6.91. The acidification lasted 10 min in isolated heart (Table 1 and Figure 1) and 20 min in isolated papillary muscle (Table 2 and Figures 2–4). pH out (pHₗ) was measured continuously with a small probe placed near to the papillary muscle (Hamilton, model Minitrode, Carlo Erba, Milan, Italy).

Drugs. — 5-(N,N-dimethyl)-amiloride hydrochloride (DMA) from Sigma Chemical Co. (St. Louis, MO) was dissolved directly in the perfusate (10⁻⁵ M). The DMA solution was stored at 5 °C, protected from light and diluted to the concentration needed shortly before each experiment.

Statistical analysis. — The results were reported as mean values ± SD of absolute values, and analyzed with two-way analyses of variance (ANOVA). If the F ratios were significant, post hoc Scheffé test was applied to assess the specific significance. Interactions between age and different
of the heart to metabolic acidosis. Basal condition was more evident in senescent than in adult hearts, and indicated an age-related greater sensitivity (Table 1). Thus, reduction in myocardial contractility and occurrence of arrhythmias was more evident in senescent hearts. The increase in end-diastolic pressure and the presence of ventricular arrhythmias in both adult and senescent papillary muscle changes were considered as significant. 

### RESULTS

**Isolated and perfused rat heart.** — During acidosis (pH reduction from 7.36 to 6.91 for 10 min) developed pressure decreased more significantly in senescent than in adult hearts (-66.5% and -47.7%, respectively; p < .01). End-diastolic pressure increased more in senescent than in adult hearts (+488.2% and +187.5%, respectively; p < .01) (Figure 1, Table 1). When pH returned to the physiologic range (from 6.91 to 7.36), end-diastolic pressure increased more than in the acidotic condition with a parallel development of ventricular arrhythmias in both adult and senescent hearts. The increase in end-diastolic pressure and the presence of arrhythmias was more evident in senescent hearts (Figure 1, Table 1). The interaction between age and acidosis was significant for each parameter investigated (p < .05) (Table 1). Thus, reduction in myocardial contractility and ventricular arrhythmias development (when pH returned to basal condition) was more evident in senescent than in adult hearts, and indicated an age-related greater sensitivity of the heart to metabolic acidosis.

**Isolated and perfused rat papillary muscle.** — Figure 2 shows data from adult and senescent from papillary muscles exposed to acidosis (from pH 7.36 to pH 6.91 for 20 min). Slow speed recordings were made for $a_{in}$, $V_m$, and tension (T) in adult and senescent papillary muscle. In adult muscle active T decreased 55.5% and then recovered, but at steady state it was still lower than baseline (-24.6%); resting tension in adult papillary muscle remained unchanged. In senescent muscle, active $T$ showed a progressive decrease more pronounced than adult (-50.5%) while resting tension progressively increased (+66.2%). After an initial and transient decrease $a_{in}$ increased in both adult and senescent papillary muscles to the same extent (from 8.5 mM to 9.7 mM and from 8.7 mM to 9.8 mM, respectively). During the recovery, resting $T$ showed a further increase in senescent but not in adult muscle (+25.3% vs + 1.7%). The recovery in senescent muscle was accompanied by the insurgence of repetitive activity which lasted 5.2 ± 3.1 min. We did not observe significant changes on $V_m$ during exposure to acidic solution. DMA ($10^{-4}$ M), a specific inhibitor of Na°H+ exchanger (voce), was administered in both adult and senescent muscles (Figure 3). After an initial and transient increase in both adult and senescent papillary muscle (+7.8% and +11.6%, respectively) active tension decreased (-21.6% and -26.2%, respectively) and resting tension increased (+8.5% and +11%, respectively) in both adult and senescent papillary muscle. There was a similar decrease in $a_{in}$ in both adult and senescent papillary muscle (from 8.6 mM to 7.7 mM and from 8.8 mM to 7.0 mM, respectively). $V_m$ initially shifted to less negative values indicating a membrane potential depolarization in both adult and senescent muscles. When DMA was administered simultaneously with acidic solution (Figure 4), active tension showed a progressive decrease (-40.2% and -61.5%) while resting tension increased (+25.3% and +41.6%) more evident in senescent than in adult papillary muscle. On the contrary, $a_{in}$ decreased similarly in both adult and senescent papillary muscle (from 8.4 mM to 7.8 mM and from 8.7 mM to 7.8 mM, respectively). $V_m$ remained stable throughout the procedure.

Results from different single experiments are expressed by average results and shown in Table 2. Senescent muscle is more sensitive to acidosis than adult muscle. The absence of difference in $a_{in}$ between adult and senescent muscle during the different procedures suggests that Na°H+ exchange is not modified by the aging process. This is also confirmed by the absence of different contractile responses during the DMA-mediated inhibition of Na°H+ exchange. However, acidosis simultaneously with DMA administration decreased myocardial contractility more in senescent than in adult muscle confirming the greater sensitivity of muscle to pH reduction. This is also demonstrated by the significant interactions between age and acidosis except for the experiments performed with DMA alone (Table 2).
Table 2. Average Results (Mean ± SD of Absolute Values) of Developed Tension (DT, g/mm²), Resting Tension (RT, g/mm²), and $a_{in}$ (mM) in Isolated Papillary Muscle from Adult (n = 5) and Senescent Hearts (n = 5)

<table>
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<tr>
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<th>Adult</th>
<th>Senescent</th>
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<tr>
<td></td>
<td>DT (g/mm²)</td>
<td>DT (g/mm²)</td>
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<tr>
<td>Baseline</td>
<td>3.5 ± 0.2</td>
<td>3.9 ± 0.6</td>
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<tr>
<td>pH 6.91</td>
<td>2.8 ± 0.6$^a$</td>
<td>1.6 ± 1.1$^{bc}$</td>
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<tr>
<td>Recovery</td>
<td>3.6 ± 0.3</td>
<td>4.6 ± 1.2$^c$</td>
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<tr>
<td>Baseline</td>
<td>3.4 ± 0.5</td>
<td>3.6 ± 0.5</td>
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<tr>
<td>DMA</td>
<td>2.7 ± 0.7$^a$</td>
<td>2.3 ± 0.6$^a$</td>
</tr>
<tr>
<td>Recovery</td>
<td>3.5 ± 0.6</td>
<td>3.9 ± 0.8</td>
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<tr>
<td>Baseline</td>
<td>3.5 ± 0.2</td>
<td>3.7 ± 0.7</td>
</tr>
<tr>
<td>pH 6.91 + DMA</td>
<td>2.0 ± 0.9$^a$</td>
<td>1.1 ± 0.5$^{bc}$</td>
</tr>
<tr>
<td>Recovery</td>
<td>3.6 ± 1.0</td>
<td>3.9 ± 0.8</td>
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DMA, 10$^{-5}$ M. Interaction between age and acidosis (pH 6.91) = p < .01, between age and DMA = p < NS, and between age and DMA + pH 6.91 = p < .05. $^a$p < .01 vs baseline; $^b$p < .05 baseline; $^c$p < .01 vs adult; $^d$p < .05 vs adult.

DISCUSSION

Our results show that acidosis induced a decrease of cardiac contractility more evident in senescent than adult hearts and papillary muscles while $a_{in}$ was similarly increased in both adult and senescent papillary muscles. The normalization of pH reduction induced the development of arrhythmias that were more evident in senescent hearts. The inhibitor of Na$^+/H^+$ exchange DMA induced a similar reduction of contractile force and $a_{in}$ in both adult and senescent heart. However, when DMA was administered in hypercapnic acidosis, contractility decreased more in senescent than in adult muscle while $a_{in}$ was reduced to a similar extent in both adult and senescent heart. Moreover, we found a significant interaction between age and acidosis (except for the experiments performed with DMA alone)
indicating that results obtained during acidosis primarily depending on different age between groups.

The results in both experimental models (isolated and perfused papillary muscle and heart) clearly demonstrate that the negative inotropic effect of acidosis is more pronounced in senescent than adult cardiac muscle. Similar patterns for $\alpha_n$ in adult and senescent muscle and the experiments performed with DMA suggest that the Na$^+/\text{H}^+$ exchange does not seem to contribute to this phenomenon. The higher development of arrhythmias in senescent heart during recovery from pH reduction could indicate an age-related difference in intracellular Ca$^{2+}$ movements.

**Acidosis, myocardial ischemia, and aging.** — A drop of intracellular pH is observed during myocardial ischemia mainly because the anaerobic metabolism of glucose terminates in lactic acid (28). Acidosis contributes to a decrease in cardiac contraction observed during myocardial ischemia and this should be attributed to the modifications of myofilaments and sarcoplasmic reticulum induced by pH reduction (29). In this condition, the Na$^+/\text{H}^+$ exchanger is activated and the increase in intracellular sodium activates Na/K pump that in turn increases ATP consumption. These events lead to energy depletion, cellular Na$^+$ overload and finally cellular Ca$^{2+}$ overload (30). However, experimental studies have demonstrated that an episode of myocardial ischemia determines a more severe myocardial dysfunction in senescent than in adult hearts (3). Aged hearts exhibit a greater accumulation of Ca$^{2+}$ during ischemia although it was not a result of the difference of buffering capacity for ischemia-induced acidosis (2).

**Negative inotropic effect induced by acidosis.** — Acidosis is known to be associated with a decrease in the ability of the heart to generate tension (7–12). In particular, during hypercapnic acidosis produced by increasing the CO$_2$ concentration in the solution from 5% to 15%, contractile force rapidly fell and was followed by a slow recovery that did not reach the baseline. In experiments performed with aequorin, the initial decrease in force occurs without change in Ca$^{2+}$ transients while the recovery phase is associated with an increase in the systolic rise of transients (1). It is reasonable to suggest that the initial drop in contractile force is due to a reduction of sensitivity of Ca$^{2+}$ to myofilaments; skinned-fiber experiments have demonstrated that Ca$^{2+}$ sensitivity to myofilaments diminished during acidosis (7). Moreover, the recovery phase seems to depend on the Ca$^{2+}$ accumulation in cytoplasm and release from sarcoplasmic reticulum (1,31).

Solaro et al. (19) demonstrated that acidosis induces a completely different response in adult and neonatal ventricular muscle. The initial fall in contractile force observed in adult muscle, in fact, was significantly reduced in neonatal muscle, but at the same time it was observed a contractile force during steady-state lower than that of adult muscle. Myofibrillar Ca$^{2+}$ sensitivity in neonatal ventricular muscle is less susceptible to acidosis than adult muscle and this phenomenon might explain the reduction of initial fall observed in neonatal muscle. On the contrary, the difference in the lower development of contractile force during steady-state in neonatal muscle is not clear. One explanation could be that calcium accumulation and release from sarcoplasmic reticulum decreased because of the small amount of sarcoplasmic reticulum in neonatal muscle.

In the present study, senescent muscle shows a biphasic response during hypercapnic acidosis quite different from adult muscle: the initial fall was more pronounced than in adult muscle. This phenomenon could be ascribed to a greater sensitivity to pH reduction in myofilaments of senescent muscle which show a marked shift in myosin heavy chain (22). Cardiac muscle, in fact, shows a marked increase in the expression of β myosin heavy chain (V, isoform) and a reduction of α myosin heavy chain (V, isoform) (22). The contractile response in the second phase of exposure to acidosis also presented significant difference between adult and senescent cardiac muscle. In adult muscle contractile force slowly increased after the initial fall. In senescent muscle, on the contrary, there was a significant increase in end-diastolic pressure in isolated heart and resting tension in papillary muscle. The increased contractility observed in adult muscle is related to intracellular calcium increase, and thus to Ca$^{2+}$ uptake and release from sarcoplasmic reticulum (7,19). The absence of systolic and the presence of diastolic increase in senescent muscle could be ascribed to age-related modifications in sarcoplasmic reticulum. The rate of Ca$^{2+}$ uptake is reduced in isolated sarcoplasmic reticulum vesicles prepared from senescent rat hearts, reflecting a decreased Ca$^{2+}$ pump function of sarcoplasmic reticulum (23,24). Maciel et al. (32) have also demonstrated that aging induced a lower amount of Ca$^{2+}$-ATPase protein of sarcoplasmic reticulum by reducing mRNA levels.

**Na$^+/\text{H}^+$ exchange and acidosis.** — The increase in intracellular calcium responsible for the increase of cardiac contractility in adult muscle observed during the second phase could be related to activation of Na$^+/\text{H}^+$ exchange system (33). This seems to play a major role in maintaining an intracellular pH level within narrow limits and in the recovery from acidosis (33). Acidosis stimulates the Na$^+/\text{H}^+$ exchanger to extrude H$^+$ from the cell in exchange for extracellular Na$^+$ into cell. Na$^+$ entry via the Na$^+/\text{H}^+$ exchange leads to an accumulation of Na$^+$ which, in turn, accumulates Ca$^{2+}$ by inhibition of the Na$^+/\text{Ca}^{2+}$ exchange (34,35). It is well known that Na$^+/\text{Ca}^{2+}$ exchange is regulated by the sodium gradient (36). In controls, Na$^+$/Na$^+$ ratio was 14.4 in adult and 13.9 in senescent muscle while it is reduced during acidosis (12.3 in adult and 12.1 in senescent muscle). Thus, during acidosis, the sodium gradient decreases and therefore the activity of the Na-Ca exchanger is reduced. It should be considered that age-related difference in contractile response during the second phase of acidosis exposure is associated with a reduction in the Na$^+/\text{H}^+$ exchange system in senescent muscle. However, our data seem to exclude this possibility. During acidosis, Na$^+/\text{H}^+$ exchange extrudes H$^+$ from the cell in exchange for extracellular Na$^+$ which enters the cell. If the Na$^+/\text{H}^+$ exchange was modified by the aging process, there would be a difference in the $\alpha_n$ increase between adult and senescent muscles. In spite of different contractile response there is no difference in the
increase between adult and senescent papillary muscles. Experiments performed with DMA, a specific inhibitor of Na\(^+\)/H\(^+\) exchanger (37), seem to confirm that the Na\(^+\)/H\(^+\) exchange is not modified by aging process. According to other studies (38,39), at concentrations used in the present study, DMA reduces \(a_{in}\) and contractile force by blocking the Na\(^+\)/H\(^+\) exchange. Since \(a_{in}\) as well as contractile force were reduced to a similar extent in both adult and senescent papillary muscles, it appears very likely that this mechanism is not influenced by the aging process. In addition, DMA administered in acidic solution, counteracts \(a_{in}\) increase induced by hypercapnic acidosis to a similar level in both adult and senescent muscles. However, in adult muscle, DMA abolished the recovery of developed tension while in senescent muscle resting tension increased less than in absence of the Na\(^+\)/H\(^+\) exchange inhibitor. These results also suggest that the Na\(^+\)/H\(^+\) exchange contributes to increasing intracellular Ca\(^{2+}\) and that inhibition of this mechanism reduced the intracellular calcium increase leading to a reduced developed tension in adult muscle (in which the increased Ca\(^{2+}\) could be utilized by contractile apparatus) and reduced diastolic tension in senescent muscle (in which the increase of Ca\(^{2+}\) could not be correctly utilized by contractile apparatus).

Arrhythmias and acidosis. — During the recovery from hypercapnic acidosis, \(a_{in}\) slowly returned to control value in both adult and senescent papillary muscles whereas electrical and mechanical parameters showed a different response in both heart and papillary muscles isolated from senescent with respect to adult rats. The return to physiological pH determined an increase of developed pressure (greater than control value) with development of ventricular arrhythmias in senescent isolated hearts as well as an increase in developed tension with the development of repetitive activity in senescent papillary muscles; these phenomena were not present in preparations from adult rats. Increase in developed pressure and tension associated with the insurgence of arrhythmias suggest that in senescent heart intracellular calcium accumulates during acidosis in cytoplasm, as demonstrated by the increase in both end-diastolic pressure and resting tension observed during acidosis. During intracellular acidosis, although cytosolic Ca\(^{2+}\) is increased, sarcoplasmic reticulum pump, mithocondrial Ca uptake, and sarcocoleml Ca-ATPase (42).

In addition, although the contribution of the Na\(^+\)/HCO\(_3\) support for acid exclusion is still controversial (18,43), the hypothetical difference of this exchanger between adult and senescent hearts is not considered. Finally, the recovery of mechanical function after hypercapnia depends also on release of norepinephrine by the nerve endings (44). McLean et al. (45) demonstrated an age-related sympathetic axonal degeneration and therefore, if norepinephrine release is involved in response to the pH reduction, the age-related reduction of catecholamine content might explain the different response to acidosis in adult compared to senescent hearts.

Conclusions. — These results indicate that: (i) the senescent heart is more sensitive to acidosis than the adult heart (in terms of greater reduction of cardiac contractile parameters parallel to development of arrhythmias), and (ii) the greater sensitivity of the senescent heart to acidosis result from age-related modifications of mechanisms other than the Na\(^+\)/H\(^+\) exchanger.

Acknowledgments

The authors want to dedicate this study to the memory of Prof. Gaetano Salvatore (Naples, Italy), who died in June 1997.

This work was supported in part by grants 95.01023.PF40 from Consiglio Nazionale delle Ricerche (C.N.R.) Progetto Finalizzato Invecchiamento, and 95.40% from Ministero dell’Università e della Ricerca Scientifica e Tecnologica (M.U.R.S.T.).

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