Effect of Hypercapnic Acidemia on Anisotropic Propagation in the Canine Ventricle

Vicken R. Vorperian, MD; Todd A. Wisiolowski, MS; Robert Deegan, MD; Dan M. Roden, MD

Background Impulse propagation in the ventricle depends on both sodium channel availability and cell-to-cell coupling through gap junctions. Sodium channel block has been shown to depress conduction velocity (θ) more longitudinal (LONG) than transverse (TRANS) to fiber orientation. Because exposure to CO₂ produces intracellular acidosis and decreased gap junction conductance in vitro, we tested the hypothesis that increased PCO₂ would result in preferential depression of transverse conduction in vivo.

Methods and Results In anesthetized dogs, when arterial pH was reduced to 6.70±0.04 by increasing the fraction of inhaled CO₂ to 40%, θTRANS fell from 0.23±0.04 to 0.19±0.02 m/s (-16±8%, P<.03), while θLONG was unchanged (-3±7%, P=NS). In contrast, with the same degree of acidemia produced by HCl infusion, only θLONG fell (-8±7%), coincident with a rise in serum K⁺.

Conclusions The observed effect of CO₂ on propagation in the intact heart is consistent with its previously described in vitro actions to uncouple cell-to-cell communication and may provide a model to study the role of cell-to-cell coupling in normal and abnormal propagation. (Circulation. 1994;90:456-461.)

Key Words • conduction • cells • excitation • waves • sodium

Impulse propagation in normal ventricular myocardium is determined by active current flow through transmembrane sodium channels and the passive effective resistance encountered along its path. The latter is anisotropic; that is, it demonstrates directional differences in magnitude1-3 and is composed of the resistivities of the cytoplasm, extracellular space, and junctional cell-to-cell connections (gap junctions). This anisotropy is explained, in part, by anatomic considerations of fiber geometry and distribution of gap junctions: more junctional resistances per unit distance of impulse propagation are present transverse to than longitudinal to the orientation of the long, thin ventricular myocytes. Therefore, when the ventricular epicardium is stimulated by a point current source, an excitation wave front propagates more than twice as fast along fibers (longitudinal direction) than across them (transverse direction). In experiments in which the effects of sodium channel blockers have been examined, the extent of conduction slowing has been consistently greater in the longitudinal direction.3,5-7 In contrast, medium-chain alcohols such as octanol and heptanol decrease gap junction conductance between cardiac cell pairs in vitro and have been shown to preferentially slow conduction transverse to fiber orientation in canine ventricular slices.8 However, reports of the effects of heptanol and octanol are inconsistent: in other studies,10 in which preferential and early block in transverse conduction was observed, longitudinal conduction was slowed to an equivalent degree to transverse conduction. This inconsistency may reflect the finding that heptanol blocks not only gap junction channels but also, at similar concentrations, cardiac sodium channels.11

Gap junctional conductance is also modulated in vitro by intracellular hydrogen ion concentration.12,13 One way to modulate intracellular pH (pHᵢ) is to increase extracellular carbon dioxide (CO₂). CO₂ rapidly crosses cell membranes and forms carbonic acid, thereby liberating hydrogen ions and so promptly lowering pHᵢ.14 Increasing the intracellular hydrogen ion concentration by exposure to CO₂ has been shown to abolish cell-to-cell coupling in early amphibian embryos13 and to increase gap junction resistance between isolated ventricular myocyte cell pairs.6 In contrast, when extracellular pH has been lowered by use of membrane impermeant strong acids, such as HCl, pHi is lowered to a far smaller extent than with CO₂.15,16 Moreover, the changes in pHi occur only after >30 minutes of exposure to the acid, in contrast to the prompt lowering of pH seen with CO₂ acidosis.

The objective of the present study was to test the hypothesis that acidosis produced by increasing CO₂ tension in vivo would preferentially slow transverse conduction, whereas that produced by the infusion of HCl would not. In the course of these studies, we have developed a model in which we believe gap junction conductance could be readily and reversibly inhibited. Our approach provides several advantages over the use of medium-chain alcohols in the study of anisotropic conduction in the intact heart: it appears to produce more selective depression of transverse conduction and, unlike heptanol or octanol, it can be used in the intact animal.

Methods

Preparation

Eleven mongrel dogs of either sex weighing 20 to 35 kg were anesthetized with sodium pentobarbital (30 mg/kg IV), intubated, and ventilated with room air (Harvard respirator) supplemented by oxygen to maintain PO₂ ≥100 mm Hg. A left lateral thoracotomy was performed in the fifth intercostal
space, and a pericardial cradle was created. A Lucite ring for placement of the recording electrode described below was then sutured to the left ventricular epicardium lateral to the left anterior descending artery. The right femoral artery was cannulated to continuously monitor blood pressure and to obtain blood samples. A 7F pigtail catheter was advanced into the left ventricular cavity and used to measure left ventricular pressure and its first derivative. Pressures were measured with fluid-filled catheters with a 52 dB strain gauge with zero reference taken at the midchest. Arterial blood gas samples were analyzed in the laboratory within 2 minutes (model 158, Corning), and ventilator settings were adjusted as described below. The right femoral vein was cannulated to obtain venous blood samples and to infuse HCl in isotonic saline as described below. Surface ECG leads I, II, and III were monitored continuously.

Data Acquisition

The methods of data acquisition and analysis have been described previously7 and are repeated here. A planar electrode array (Fig 1) with four pairs of closely spaced bipolar silver electrodes (interbipole distance of 1.5 mm) along two perpendicular axes was used to record direction-dependent propagation. A central titanium stimulating electrode was used as the cathode, and a stainless steel wire sewn to the rib cage was the distant anode.

To measure longitudinal and transverse conduction, the electrode array was introduced into the Lucite ring. The orientation of the array within the ring was adjusted by rotating the electrode, while pacing from the cathode, until the time difference between the signals at bipoles 4 and 8 was maximized (Fig 1), thereby defining the direction of fastest (longitudinal) and slowest (transverse) epicardial propagation. The electrode array was then fixed in place via setscrews on the Lucite ring for the duration of the experiment. Finally, a gauze moistened with saline was placed over the heart, and the edges of the thoracotomy were apposed.

Data were acquired during steady-state pacing (pulse width, 0.5 milliseconds; 2 mA) for at least 30 seconds at a cycle length of 300 milliseconds with a programmable stimulator (model DTU-110, Bloom Associates). The signals from each of the eight bipolar electrodes (four in the longitudinal and four in the transverse direction) were processed with high-gain amplifiers (×100) and band-pass filtered between 7 Hz and 1 KHz. Eight processed signals were then collected simultaneously by a stand-alone digital acquisition unit (model MDAS 7000 TransEra Corp) at a sampling rate of 8 KHz per channel. The signals were output over an IEEE-488 standard parallel bus (model HP1B, Hewlett Packard) to a 16-bit microcomputer for storage and further analysis.

Experimental Protocols

In all animals, serum electrolyte values were determined and conduction velocity data were acquired in triplicate during each study phase (baseline, graded acidemia, washout [for hypercapnia]). Left ventricular systolic and end-diastolic pressures as well as an isovolumic index of contractility (peak positive dp/dt) were monitored and recorded on photographic paper (Honeywell/E for M). All ECG intervals were recorded at a paper speed of 100 mm/s.

Hypercapnic Acidemia (n=7)

Control phase. Immediately after intubation (before any instrumentation), the endotracheal tube was connected to the Harvard respirator. End-tidal CO2 tension, which closely approximates arterial CO2 tension and the fraction of inhaled oxygen (FiO2), was monitored via a gas sampling probe interposed between the respirator and the endotracheal tube (Puritan-Bennett Corp/Datex Monitor). The ventilatory gas monitor was calibrated with the provided calibration gas samples; measured end-tidal CO2 during this phase was 5.3±0.4% (SD). The initial settings on the respirator were a tidal volume (TV) of 15 mL/kg and a respiratory rate of 12 to 14 per minute. Animals were allowed to stabilize for 30 minutes after end of instrumentation, before data collection. During this period, arterial blood gases were measured and respiratory rate was adjusted to achieve a pH of 7.4 (actual value, 7.40±0.03). Oxygen 2 to 4 L/min was supplemented to keep the arterial oxygen tension ≥90 mm Hg. After 15 minutes of equilibration at this pH, control data acquisition was begun.

Hypercapnic acidemia phase. After control data were acquired, the endotracheal tube, with PCO2 probe still attached, was connected to a modified closed ventilatory circuit anesthesi machine (Ohio Anesthesia Ventilator) equipped with two gas cylinders (100% O2 USP and 100% CO2 USP), and the absorbent was removed. The system was flushed with 100% O2, and the ventilator settings were kept identical to control settings. The following concentrations of admixed CO2 were then administered sequentially for 15 minutes each at 1 atm: 10%, 20%, and 40% CO2, achieving arterial pH values of 7.20±0.03, 7.02±0.04, and 6.70±0.05, respectively (see Table 1; Fig 2, left panel). In vitro studies14 suggest that 15 minutes is sufficient for equilibration of pH; as described further below, FiO2 was maintained at the highest value for 60 minutes, without further decreases in pH (Fig 2, right panel).

Washout phase. At the end of the hypercapnic phase, the endotracheal tube was connected back to the Harvard respirator and forced hyperventilation at 25 per minute, and 90% FiO2 was started until control pH and PCO2 levels (monitored by arterial blood gases and end-tidal PCO2) were reestablished, within 45 to 60 minutes. When control pH was reestablished, 15 minutes of further equilibration was allowed before washout data acquisition was begun.

Hydrochloric Acid Infusion (n=4)

In a separate group of dogs, the same control data were obtained. A continuous infusion of HCl in isotonic saline (12
TABLE 1. Arterial Blood Gases

A. During Hypercapnic Acidemia

<table>
<thead>
<tr>
<th>pH</th>
<th>Pco₂, mm Hg</th>
<th>PO₂, mm Hg</th>
<th>Fico₂, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.40±0.04</td>
<td>40±3</td>
<td>170±20</td>
<td>(5.3*)</td>
</tr>
<tr>
<td>7.20±0.03</td>
<td>72±7</td>
<td>285±60</td>
<td>10</td>
</tr>
<tr>
<td>7.03±0.04</td>
<td>142±10</td>
<td>251±50</td>
<td>20</td>
</tr>
<tr>
<td>6.70±0.04</td>
<td>284±20</td>
<td>180±25</td>
<td>40</td>
</tr>
<tr>
<td>7.40±0.05</td>
<td>34±7</td>
<td>270±70</td>
<td>(4.5*)</td>
</tr>
</tbody>
</table>

B. During Continuous HCl Infusion

<table>
<thead>
<tr>
<th>pH</th>
<th>Pco₂, mm Hg</th>
<th>PO₂, mm Hg</th>
<th>HCl, mEq/kg</th>
<th>Cumulative Total Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.40±0.04</td>
<td>37±7</td>
<td>180±30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7.20±0.06</td>
<td>35±4</td>
<td>146±50</td>
<td>1.5</td>
<td>15</td>
</tr>
<tr>
<td>7.00±0.05</td>
<td>35±2</td>
<td>180±50</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>6.70±0.05</td>
<td>36±4</td>
<td>180±30</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>6.70±0.06</td>
<td>38±5</td>
<td>170±40</td>
<td>12</td>
<td>145</td>
</tr>
</tbody>
</table>

Pco₂ indicates arterial carbon dioxide tension; PO₂, arterial oxygen tension; and Fico₂, fraction of inhaled carbon dioxide administered.

*Expired CO₂; † fixed ventilation.

mEq/kg IV) was then administered over a period of 145 minutes at the rate of 0.10 mEq/kg per minute for 100 minutes and 0.04 mEq/kg per minute for 45 minutes. A concentration of 0.5N HCl was used to limit the amount of fluid administered to less than 5% of estimated total body water. With this regimen, arterial pH values of 7.20±0.04, 7.00±0.04, and 6.70±0.06 were achieved at approximately 15, 60, and 100 minutes, respectively, after the start of infusion (Table 1B), at which times data were acquired.

Our rationale for allowing little time for equilibration is based on findings that it takes 30 to 40 minutes for pH to be minimally modified when extracellular pH is lowered by buffered HCl solution (HEPES/HCl). When the pH reached 6.70±0.05 at 100 minutes, equilibration was allowed for 45 minutes to examine any possible effects on propagation. No washout was possible with this protocol, presumably because total buffering capacity that amounts to approximately 15 mEq/kg was acutely replaced by fixed acid.

Data Analysis

To calculate conduction velocity, arrival times at each bipolar and the distance of each bipolar from the central cathode were used. In this way, events (such as latency or the virtual cathode effect) surrounding the launch of an impulse wave from the cathode do not affect the calculation of the subsequent velocity of the propagating wave. For each data set, a least-squares polynomial fitting routine was performed on each bipolar signal to determine the peak voltage, defining the arrival time of the propagating depolarizing wave front under the bipolar. The distance between the recording electrode and the stimulating cathodal electrode was plotted (ordinate) as a function of the time difference between the end of the stimulus and the arrival of the peak of bipolar signal (abscissa). A linear, least-squares fit to these distance versus arrival time data (r²≥.95, P<.001) was then used to determine longitudinal (θlong) and transverse (θtrans) conduction velocities.

Additional Measurements

Measurements of the QRS and QT intervals from the surface ECG recordings were averaged over five consecutive complexes. The QT interval was measured to the final return of the repolarization wave to baseline. QTc was calculated according to Bazett's formula (QTc=QT/[RR]½). We measured the threshold current of pacing by gradually increasing the current output of a stimulus with a pulse width of 0.5 milliseconds until consistent capture (>10 seconds) was noted. The ventricular effective refractory period (ERP) was determined by pacing at a cycle length of 300 milliseconds at twice diastolic threshold for eight beats followed by a premature extrastimulus. The longest coupling interval failing to result in capture was defined as the ERP.

Statistical Analysis

ANOVA for repeated measures was used to detect significant differences between means of variables in the control, washout, and various acidic phases of the experiment. A value of P<.05 was sufficient to reject the null hypothesis. Tukey's pairwise comparison procedure was performed on data sets for which significant differences were detected by ANOVA. All data are presented as mean±SD.

Results

Hypercapnic Acidemia

There was a linear relation between the concentration of inspired CO₂ and arterial pH (Fig 2, left panel: n=7 at each data point, r=.98, P<.001). The data in Fig 2, left panel, were obtained after 15 minutes at each Fico₂. When Fico₂ was maintained at 40% for 60 minutes, pH was stable (Fig 2, right panel), indicating that changes in Fico₂ rapidly achieved new values of Pco₂ and pH.

Hypercapnic acidemia reversibly depressed transverse conduction velocity (Fig 3). At pH 6.70±0.05, mean transverse conduction velocity decreased by 16±8%, from 0.23±0.04 m/s at baseline to 0.19±0.02 m/s (P<.03). At this pH, longitudinal conduction velocity decreased by 3±7%, from 0.53±0.07 to 0.50±0.04
m/s (P=NS). When pH was maintained at 6.7 for 60 minutes (Fig 2, right panel), no further slowing of transverse conduction velocity was noted (Fig 3). When increased CO₂ was washed out and pH returned to control values (7.40±0.05), transverse and longitudinal conduction returned to control values.

Hydrochloric Acid

The effects of continuous HCl infusion on longitudinal and transverse conduction are shown in Fig 4. HCl infusion had no effect on transverse conduction over the same pH range as that studied with hypercapnic acidemia (7.40±0.04 to 6.70±0.05). However, longitudinal conduction velocity fell significantly from a mean control value of 0.57±0.02 m/s to 0.52±0.05 m/s (−8±7%) at 30 minutes (P<.05) and 0.46±0.06 m/s (−19±10%) at 45 minutes at pH 6.7 (P<.03).

Other Electrophysiological Effects

As shown in Table 2, hypercapnic acidemia produced no significant changes in the QRS interval, the corrected QT; threshold current (I₉), or measured ERP. In contrast, prolonged acidemia induced with continuous HCl infusion resulted in a significant prolongation of the QRS interval. Significant increases from baseline in threshold current and ERP also were noted.

Acid-Base Alterations

The effects of hypercapnic acidemia and HCl infusion on electrolytes and acid-base balance are summarized in Table 3. With hypercapnic acidemia there was a significant rise in serum HCO₃⁻, presumably reflecting maximal acute buffering capacity. There also was a small but significant rise in serum potassium level with acidosis, which did not return to baseline upon washout; serum K⁺ did not rise above the normal range. There was no significant change in serum chloride concentration.

With HCl infusion, there was a significant rise in serum chloride concentration with a marked decrease in serum HCO₃⁻ at peak acidosis. Moreover, serum K⁺ rose to a greater extent with HCl than with hypercapnia, although some of this increase may reflect hemolysis, which has been reported with HCl infusion.¹⁸

### Table 2. Electrophysiological Effects of Hypercapnia and HCl Infusion

<table>
<thead>
<tr>
<th>Condition</th>
<th>QRS, ms</th>
<th>QTc, ms</th>
<th>ERP, ms</th>
<th>I₉, mA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercapnic acidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>65±7</td>
<td>360±20</td>
<td>160±11</td>
<td>0.19±0.05</td>
</tr>
<tr>
<td>Acidemia, pH 6.7, 60 min</td>
<td>66±10</td>
<td>340±17</td>
<td>170±17</td>
<td>0.23±0.07</td>
</tr>
<tr>
<td>Washout, pH 7.4</td>
<td>60±8</td>
<td>350±31</td>
<td>170±12</td>
<td>0.27±0.10</td>
</tr>
<tr>
<td>HCl infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control, pH 7.4</td>
<td>58±2</td>
<td>360±19</td>
<td>177±14</td>
<td>0.14±0.03</td>
</tr>
<tr>
<td>Acidemia, pH 6.7, 45 min</td>
<td>76±5*</td>
<td>347±12</td>
<td>238±49*</td>
<td>0.60±0.08*</td>
</tr>
</tbody>
</table>

QTc indicates corrected QT; ERP, effective refractory period; and I₉, threshold current. *P<.05 vs control.
infusion, although the extent of the rise in LVEDP was smaller.

**Discussion**

In the present study, we have shown that hypercapnic acidemia selectively and reversibly slowed transverse conduction in the dog. In contrast, the same degree of acidemia with HCl infusion had no effect on transverse conduction velocity and slowed longitudinal conduction, an effect we believe is attributable at least in part to hyperkalemia (Table 3) and consequent decreased sodium channel availability. Moreover, the HCl experiments also resulted in QRS prolongation and increases in LVEDP, ERp, and ERP that are consistent with this sodium channel effect. We also observed that induction of acidosis to the same degree by both methods resulted in small decreases in myocardial performance, although to a lesser degree with HCl infusion; this decline was not accompanied by hypotension, impaired gas exchange, or arrhythmias.

**In Vitro Effects of Elevated PCO2**

Previous in vitro studies have demonstrated that exposure to CO2 resulted in reduction in pH,14 and, in both early amphibian embryo cells and in isolated adult rat ventricular myocyte pairs,8,13 resulted in decreased cell-to-cell coupling. In contrast, membrane-impermeant strong acids did not display this effect.13 The mechanism underlying these changes in cell-to-cell coupling with CO2 exposure is thought to be an increase in intracellular H+, a major modulator of gap junction conductance.8,13 pHi was not measured in this study, but work both in vitro and in perfused mammalian hearts indicates that, with CO2 perfusion, pHi is linearly correlated with extracellular pH, allowing for a 15-minute equilibration.14,19,20 These previous studies indicated that pHi changes 0.4 to 0.5 units per unit change in extracellular pH.19,20 Thus, in our experiments, we infer a drop of pHi of approximately 0.3 units, or a pHi of 6.8 when extracellular pH was 6.7 in the hypercapnia experiments. In previous in vitro studies, this change in pHi resulted in a 30% reduction in gap junction conductance.21 Moreover, at this pHi, other investigators have reported that the sodium current is uninfluenced.22

**Longitudinal Versus Transverse Propagation**

Impulse propagation in the normal ventricle is thought to be determined by the magnitude of the fast inward sodium current and by cell-to-cell propagation through gap junctions. The heart is a highly anisotropic structure; as a result, side-to-side impulse propagation between adjacent cells encounters more gap junctions per unit length than does longitudinal conduction.4 Previous experiments, in our laboratory and by others, have demonstrated that sodium channel-blocking drugs depress longitudinal conduction proportionately more than they depress transverse conduction.3,5,6,7 On the other hand, Balke et al9 found a preferential drop in transverse conduction in thin canine ventricular epicardial slices exposed to the medium-chain alcohol heptanol. In other experiments, however, heptanol also decreased longitudinal conduction,10 a finding that may be attributed at least in part to the compound's sodium channel-blocking activity.11 In contrast, in the present experiments, induction of intracellular acidosis by CO2 resulted in a significant decrease in transverse conduction only. Indeed, even the small change in longitudinal conduction we observed is compatible with the observation that internal longitudinal resistance, assessed by cable analysis, is reduced by intracellular acidosis.23 Thus, even for the small, nonsignificant changes observed in longitudinal conduction in the hypercapnia experiments, an effect on sodium channels need not be evoked. In these experiments, QRS duration was increased only when longitudinal propagation was impaired during the HCl experiments and not when transverse propagation was affected in the CO2 experiments. Thus, the utility of prolonged QRS duration as a surrogate marker for impaired conduction may be limited to those interventions, such as sodium channel blockade, which affect longitudinal propagation.

**Table 3. Electrolyte Changes During Hypercapnia and HCl Infusion**

<table>
<thead>
<tr>
<th>Condition</th>
<th>pH</th>
<th>Serum Na+, mEq/L</th>
<th>Serum K+, mEq/L</th>
<th>Serum Cl−, mEq/L</th>
<th>HCO3−, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercapnic acidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7.40±0.03</td>
<td>147±3</td>
<td>3.6±0.3</td>
<td>112±5</td>
<td>21±2</td>
</tr>
<tr>
<td>Acidemia, 60 min</td>
<td>6.71±0.05</td>
<td>150±3</td>
<td>5.1±0.9*</td>
<td>110±6</td>
<td>31±3†</td>
</tr>
<tr>
<td>Washout</td>
<td>7.40±0.05</td>
<td>146±6</td>
<td>5.7±1.7*</td>
<td>111±7</td>
<td>24±3</td>
</tr>
<tr>
<td>HCl infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7.40±0.04</td>
<td>150±4</td>
<td>3.6±0.2</td>
<td>112±4</td>
<td>20±3</td>
</tr>
<tr>
<td>Acidemia, 45 min</td>
<td>6.70±0.06</td>
<td>147±6</td>
<td>7.6±0.4‡</td>
<td>131±5‡</td>
<td>4±1‡</td>
</tr>
</tbody>
</table>

*P<.05 vs control; †P<.05 vs control and washout; and ‡P<.01 vs control.

**Table 4. Hemodynamic Effects of Hypercapnia and HCl Infusion**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate, min−1</th>
<th>LVSP, mm Hg</th>
<th>LVEDP, mm Hg</th>
<th>Peak dP/dt, mm Hg/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercapnic acidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control, pH 7.4</td>
<td>142±20</td>
<td>149±51</td>
<td>2±3</td>
<td>2541±493</td>
</tr>
<tr>
<td>Acidemia, pH 6.7, 60 min</td>
<td>96±15*</td>
<td>134±60</td>
<td>16±6*</td>
<td>1487±356†</td>
</tr>
<tr>
<td>Washout, pH 7.4</td>
<td>120±12</td>
<td>140±54</td>
<td>4±3</td>
<td>1973±497</td>
</tr>
<tr>
<td>HCl infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control, pH 7.4</td>
<td>135±12</td>
<td>107±5</td>
<td>5±1</td>
<td>1844±232</td>
</tr>
<tr>
<td>Acidemia, pH 6.7, 45 min</td>
<td>103±10‡</td>
<td>107±5</td>
<td>8±2‡</td>
<td>1512±68‡</td>
</tr>
</tbody>
</table>

LVSP indicates left ventricular systolic pressure and LVEDP, left ventricular end-diastolic pressure.

*P<.05 vs control and washout; †P<.05 vs control; and ‡P<.01 vs control.
Limitations of the Present Study

Detailed histological studies to confirm that what we term longitudinal and transverse conductions do indeed correspond to these fiber orientations were not performed. However, other studies using this technique in our own laboratories as well as other studies of direction-dependent propagation in other laboratories confirm the relation between superficial subepicardial fiber orientation and these orthogonal conduction velocity differences. We can make no inference on transmural conduction, which may be especially dependent on side-to-side (or “transverse”) propagation. Moreover, the calculation of value for conduction velocity assumes a linear and constant conduction pathway. We recognize that discontinuities at the cellular level exist and may not be detected by our method of measurement. However, because the bipolar signals recorded did not display irregular contours, the recording sites are fairly close (1.5 mm), and we are studying normal myocardium, we believe the use of the term conduction velocity is appropriate.

In some animal models of anisotropic reentry, as well as in patients with sustained ventricular tachyarrhythmias thought to be dependent on a reentrant mechanism, sodium channel-blocking drugs have not been very effective. An alternative method of perturbing such reentrant pathways would be desirable, and interventions directed at gap junction conductance seem reasonable candidates. Other studies have used heptanol to test this hypothesis, but, as discussed above, heptanol also blocks cardiac sodium channels, reduces longitudinal conduction velocity in some models, and cannot readily be used in an intact animal. Thus, we propose that CO₂ acidosis will provide a new tool to test the role of gap junction-dependent conduction in tachyarrhythmias. An obstacle to this approach may be adequate delivery of CO₂ to the infarct zone. However, abnormal delivery of any antiarrhythmic intervention to a reentrant circuit subserved by inadequate coronary flow is a problem for all such studies. Certainly, viable cells within a reentrant circuit must receive sufficient coronary flow to ensure their viability; nevertheless, it is possible that gradients of intracellular acidosis might result with the use of a technique such as this in experimental animals.

Summary

In this study, we have found that hypercapnic acidemia selectively depresses transverse conduction velocity in the intact canine heart. Induction of the same degree of acidemia with HCl infusion did not show this effect. These findings, along with available in vitro data, suggest that cytoplasmic acidosis selectively decreases gap junction conductance with no demonstrable effect on sodium current. Hypercapnic acidemia therefore may be a tool to test the role of gap junctions in models of reentrant tachyarrhythmias in which directional differences of propagation are implicated in arrhythmogenesis.

Acknowledgments

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