Anesthesiology
72:100–104, 1990

# *Cardiovascular Effects of Acute Changes in Extracellular Ionized Calcium Concentration Induced by Citrate and $CaCl_2$ Infusions in Chronically Instrumented Dogs, Conscious and during Enflurane, Halothane, and Isoflurane Anesthesia*

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**To study the cardiovascular effects of low blood ionized calcium ion concentrations [$Ca^{2+}$] induced by citrate infusion followed by high [$Ca^{2+}$], induced by $CaCl_2$ infusion awake and during enflurane (2.5% ET), halothane (1.2% ET), and isoflurane (1.6% ET) anesthesia, dogs were chronically instrumented to measure heart rate, aortic, left atrial, and left ventricular (LV) blood pressures, and cardiac output. In conscious dogs low [$Ca^{2+}$] (decreased 0.35 mM); increased heart rate (HR) and mean aortic pressure (MAP) and decreased stroke volume (SV) and LV $dP/dt_{max}$. Low [$Ca^{2+}$] increased HR during all three anesthetics and decreased LV $dP/dt_{max}$ except during isoflurane anesthesia. Low [$Ca^{2+}$] produced more hemodynamic depression during enflurane anesthesia than during anesthesia with halothane or isoflurane increasing left atrial pressure and decreasing MAP and SV. The differences seen were partially related to decreased systemic vascular resistance during halothane and isoflurane anesthesia. In conscious dogs following high [$Ca^{2+}$] (increased 0.37 mM); only MAP and LV $dP/dt_{max}$ increased. LV$dP/dt_{max}$ was also increased by high [$Ca^{2+}$] during all three anesthetics without a change in MAP. Cardiac output increased during halothane and isoflurane anesthesia but was unchanged during enflurane. It would appear that the hemodynamic sensitivity for the effects of changing [$Ca^{2+}$] was enflurane > halothane > isoflurane > awake. The results suggest that the effects of changes in [$Ca^{2+}$] induced by citrate and $CaCl_2$ infusion are modified by the three volatile anesthetics. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane; Heart: blood flow; ventricular function. Ions: calcium; citrate.)**

CHANGING THE IONIZED calcium concentrations [$Ca^{2+}$] has been reported to have important hemodynamic effects.[1] Such effects may be induced in patients receiving blood products anticoagulated with citrate (low [$Ca^{2+}$]) and infusions of $CaCl_2$ or Ca-gluconate (high [$Ca^{2+}$]). Inhalational anesthetics also have pronounced circulatory effects.[2] Price demonstrated in 1974 that increased [$Ca^{2+}$] reversed the myocardial depression caused by halothane.[3] Others have shown that volatile anesthetics cause complex alterations in intracellular [$Ca^{2+}$] control by the sarcolemma, the sarcoplasmatic reticulum and, possibly, other membranes of myocardial tissue.[4]

Most of the previous work on the hemodynamic effects of changing [$Ca^{2+}$] has been performed during anesthesia (especially halothane).[5–10] The purpose of this study was to investigate the hemodynamic effects of changes in [$Ca^{2+}$] induced by citrate and $CaCl_2$ infusions awake and during enflurane, halothane, and isoflurane anesthesia in chronically instrumented dogs.

## Methods

### INSTRUMENTATION

A description of the basic model has been previously published.[11–13] Briefly, seven healthy mongrel dogs, weighing 16.5–24.5 kg, were instrumented with the following: catheters (Tygon, Norton Inc., Akron, Ohio) in the left atrium and thoracic aorta, an electromagnetic flow probe (Micron Inc., Los Angeles, California) around the pulmonary artery, and a high fidelity pressure transducer (Konigsberg Inc., Pasadena, California) in the left ventricular cavity. All animals were studied at least 10 days after surgery when they were afebrile and trained to lie quietly. The details of the measurement techniques have also been previously published.[11–13] Aortic, left ventricular, and left atrial blood pressures and cardiac output were continuously recorded on a Gould polygraph (Gould Inc., Cleveland, Ohio) during the experiments. Cardiac output was measured using a Micron RC 1000 electromagnetic flow meter. Left ventricular $dP/dt_{max}$ was derived electronically.

### PROTOCOL

Each animal was studied awake and during enflurane, halothane, and isoflurane anesthesia. For each dog the experiments were performed on 4 different days. At least 48 h elapsed between experiments. The order of the experiments was randomized.

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Received from the Department of Anesthesiology, University of Texas Medical School, Houston, Texas, and the Department of Anesthesiology, Baylor College of Medicine, Houston, Texas. Accepted for publication August 10, 1989. Presented in part at the 1986 7th European Congress of Anesthesiology, Vienna, Austria.

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Following control measurements awake, citrate (46.7% trisodium citrate with *p*H adjusted with citric acid [Haemonetics, Braintree, Massachusetts]) diluted 1:5 with sterile water [*p*H 7.0 in solution] was infused using a pump (Harvard Apparatus, Millis, Massachusetts); a dose of 1 ml/kg administered over 10 min, followed by an infusion of 1.5 $ml \cdot kg^{-1} \cdot h^{-1}$ to produce a stable decrease in $[Ca^{2+}]$ of about 0.35 mM. Hemodynamic measurements and blood samples were taken after 5 min of infusion. The citrate infusion was stopped, and a rapid infusion of $CaCl_2$ (Calcium chloride USP 10%, Invenex Laboratory, Chagrin Falls, Ohio) 0.18 mmol/kg was then given over 2 min by pump to normalize $[Ca^{2+}]$, followed by an infusion of 0.4 mmol/kg to produce a stable increase in $[Ca^{2+}]$ of about 0.35 mM. Measurements were initiated after 5 min, and the infusion was continued for another 5 min to ensure stable hemodynamic values and $[Ca^{2+}]$.

On the day of the anesthesia experiments, anesthesia was induced by mask with nitrous oxide/oxygen and the corresponding inhalational anesthetic. When the animals were sufficiently anesthetized, the trachea was intubated, and ventilation was controlled with a Harvard ventilator (Harvard Apparatus, South Natwick, Massachusetts) at tidal volumes of 10–15 ml/kg with the rate adjusted to maintain carbon dioxide tension as in the awake animal. Immediately after tracheal intubation, nitrous oxide was discontinued and nitrogen was substituted, using a concentration that maintained arterial oxygen tension at approximately the same level as in the awake animal. Rectal temperature was monitored using a thermistor probe (Yellow Springs Instruments, Yellow Springs, Ohio) and maintained at 38° C using external heating if necessary.

During anesthesia end-tidal anesthetic (Beckman LB-2, Beckman Inc., Schiller Park, Illinois) and carbon dioxide (Lifespan 100, Biochem International Inc., Waukesha, Wisconsin) concentrations were continuously monitored using infrared absorption techniques. The experiments were not performed before at least 20 min of steady state end-tidal anesthetic concentration (concentrations that blocked the response to noxious stimuli). All measurements were done at zero airway pressure. Arterial blood gas measurements were made several times during anesthesia, including the times of hemodynamic measurements, using a Radiometer ABL electrode system (Copenhagen, Denmark). The animals were studied in a right lateral decubitus position awake and anesthetized. They received 5 $ml \cdot kg^{-1} \cdot h^{-1}$ of a 5% glucose solution during the experiments.

### Sample Analysis

Blood samples were taken from the aortic catheter. Samples for ionized calcium concentrations analysis were drawn anaerobically into preheparinized syringes using a special heparin with calcium added equal to the binding of calcium by heparin (S4500 Heparin for Ionized Calcium Analyses, Radiometer A/S, Copenhagen, Denmark).[14]

### Data Analysis

A factorial analysis of variance with repeated measures design was used with the Bonferroni modification of the two-tailed paired *t* test to compare individual means when significant. Alpha was set at a level of 0.05 before modification. Data are presented as ± SEM. The protocol was approved by the Animal Care Committee of the University of Texas Medical School at Houston.

## Results

$pH_a$ did not change more than 0.04 from control values (awake 7.43 ± 0.01, enflurane 7.42 ± 0.01, halothane 7.43 ± 0.01, isoflurane 7.44 ± 0.01) during the experiments.

The results in conscious dogs are presented in table 1, during enflurane anesthesia (2.53 ± 0.01% end-tidal) in table 2, during halothane anesthesia (1.21 ± 0.00% end-tidal) in table 3, and during isoflurane anesthesia (1.61 ± 0.00% end-tidal) in table 4.

### Anesthetic Effects

The effects of the low anesthetizing concentrations of enflurane, halothane, and isoflurane were essentially the same as reported previously.[11,12] All of the anesthetics decreased MAP, SV, and LV dP/dt; enflurane and halothane also decreased CO; although the heart rate was increased with all three anesthetics, the changes were not statistically significant for any.

### Effects of Low $[Ca^{2+}]$ (compared with normocalcemia)

Heart rate increased awake and during anesthesia, but only during isoflurane anesthesia was the change greater

Table 1. Conscious Dogs

| | N | Control 1.40 ± 0.01 mM $[Ca^{2+}]$ | Low 1.05 ± 0.01 mM $[Ca^{2+}]$ | High 1.77 ± 0.02 mM $[Ca^{2+}]$ |
|---|---|---|---|---|
| HR (beats/min) | 7 | 78 ± 4 | 97 ± 5* | 87 ± 5 |
| MAP (mmHg) | 7 | 105 ± 4 | 112 ± 5* | 115 ± 3* |
| LAP (mmHg) | 6 | 6.3 ± 0.7 | 7.2 ± 1.3 | 8.3 ± 1.0 |
| CO (l/min) | 6 | 1.78 ± 0.13 | 1.92 ± 0.14 | 2.03 ± 0.10 |
| LV $dP/dt_{max}$ (mmHg/s) | 6 | 2827 ± 329 | 2492 ± 333* | 3784 ± 648* |
| SV (ml) | 6 | 23.2 ± 1.5 | 20.3 ± 1.2* | 24.3 ± 2.0 |
| SVR ($mmHg \cdot l^{-1} \cdot min^{-1}$) | 6 | 61.5 ± 3.6 | 60.7 ± 3.0 | 57.4 ± 2.3 |

N represents the number of dogs with the instrumentation necessary to make this particular measurement.
* $P < 0.05$ *versus* control.

TABLE 2. During 2.5% End-Tidal Enflurane

| | Control 1.37 ± 0.01 mM [$Ca^{2+}$] | Low 1.02 ± 0.01 mM [$Ca^{2+}$] | High 1.72 ± 0.02 mM [$Ca^{2+}$] |
|---|---|---|---|
| HR (beats/min) | 98 ± 1* | 108 ± 3† | 82 ± 4† |
| MAP (mmHg) | 70 ± 3* | 61 ± 3*† | 74 ± 2* |
| LAP (mmHg) | 4.7 ± 1.1 | 6.2 ± 0.9† | 6.0 ± 1.2 |
| CO (l/min) | 1.43 ± 0.06* | 1.36 ± 0.06* | 1.56 ± 0.12* |
| LV $dP/dt_{max}$ (mmHg/s) | 1365 ± 71* | 1018 ± 53*† | 1754 ± 104† |
| SV (ml) | 14.7 ± 0.5* | 12.9 ± 0.8*† | 19.2 ± 1.0*† |
| SVR ($mmHg \cdot l^{-1} \cdot min^{-1}$) | 49.8 ± 3.7* | 45.8 ± 4.4 | 48.6 ± 3.3 |

* $P < 0.05$ *versus* conscious.
† $P < 0.05$ *versus* control.

TABLE 4. During 1.6% End-Tidal Isoflurane

| | Control 1.40 ± 0.01 mM [$Ca^{2+}$] | Low 1.02 ± 0.01*† mM [$Ca^{2+}$] | High 1.74 ± 0.02 mM [$Ca^{2+}$] |
|---|---|---|---|
| HR (beats/min) | 108 ± 7* | 126 ± 5*†† | 90 ± 7† |
| MAP (mmHg) | 74 ± 4* | 75 ± 3* | 79 ± 3* |
| LAP (mmHg) | 3.8 ± 1.4* | 6.5 ± 1.5† | 5.0 ± 1.3 |
| CO (l/min) | 1.63 ± 0.15 | 1.94 ± 0.13† | 1.77 ± 0.18† |
| LV $dP/dt_{max}$ (mmHg/s) | 1599 ± 152* | 1508 ± 144* | 2250 ± 229*† |
| SV (ml) | 15.4 ± 1.4* | 15.8 ± 1.2* | 20.3 ± 1.5† |
| SVR ($mmHg \cdot l^{-1} \cdot min^{-1}$) | 48.0 ± 4.3* | 39.6 ± 3.2*† | 45.8 ± 3.9 |

* $P < 0.05$ *versus* conscious.
† $P < 0.05$ *versus* control.

than in the awake animals. Mean aortic pressure increased awake and decreased during enflurane anesthesia but did not change with halothane and isoflurane. Left atrial pressure increased during enflurane and isoflurane anesthesia, but the values were not different from awake. Cardiac output increased during halothane and isoflurane anesthesia, did not change during enflurane, and was less than in the awake animals during halothane and enflurane anesthesia. Stroke volume decreased awake and during enflurane anesthesia. The values during the three anesthetics were lower than awake. Systemic vascular resistance decreased during halothane and isoflurane anesthesia and were lower than awake. Left ventricular $dP/dt_{max}$ decreased awake, during enflurane and halothane anesthesia, and was less than awake with the two anesthetics.

### EFFECTS OF HIGH [$CA^{2+}$] (COMPARED WITH NORMOCALCEMIA)

Increasing [$Ca^{2+}$] from low to high values always improved hemodynamic conditions to normocalcemic values or above (tables 1–4). The main differences between the conscious and anesthetized animals were those due to the effect of the anesthetics themselves. Consequently, only mean arterial pressure and LV $dP/dt_{max}$ were lower during isoflurane anesthesia than in the awake animals. During both enflurane and halothane anesthesia, mean arterial pressure, cardiac output, and left ventricular $dP/dt_{max}$ were lower than during the comparable awake condition. In addition, stroke volume was also lower during halothane anesthesia.

TABLE 3. During 1.2% End-Tidal Halothane

| | Control 1.41 ± 0.01 mM [$Ca^{2+}$] | Low 1.05 ± 0.01 mM [$Ca^{2+}$] | High 1.74 ± 0.02 mM [$Ca^{2+}$] |
|---|---|---|---|
| HR (beats/min) | 86 ± 7 | 112 ± 7† | 80 ± 7 |
| MAP (mmHg) | 74 ± 4* | 75 ± 5* | 82 ± 3* |
| LAP (mmHg) | 7.5 ± 0.08* | 8.2 ± 1.3 | 8.3 ± 1.5 |
| CO (l/min) | 1.37 ± 0.07* | 1.64 ± 0.07*† | 1.50 ± 0.09*† |
| LV $dP/dt_{max}$ (mmHg/s) | 1415 ± 112* | 1223 ± 77*† | 1776 ± 98*† |
| SV (ml) | 15.9 ± 1.2* | 14.8 ± 0.9* | 19.3 ± 1.4*† |
| SVR ($mmHg \cdot l^{-1} \cdot min^{-1}$) | 56.2 ± 3.8 | 47.0 ± 2.4*† | 55.4 ± 2.8 |

* $P < 0.05$ *versus* conscious.
† $P < 0.05$ *versus* control.

## Discussion

### CRITIQUE OF METHODS

The control ($Ca^{2+}$) of 1.40 mM is normal for healthy dogs using the described technique. Adult reference values in humans for this electrode are 1.5–1.30 mM.

This protocol attempted to simulate clinical [$Ca^{2+}$] changes. In patients a decrease in [$Ca^{2+}$] is most frequently induced by infusing blood products containing citrate. $CaCl_2$ or Ca-gluconate are then often infused to counteract this decrease in [$Ca^{2+}$]. A change in [$Ca^{2+}$] of ± 0.35 mM (±25%) is within the range experienced in clinical practice.[15] Even though calcium most often is given as bolus injections, we chose to establish a stable increased [$Ca^{2+}$] using continuous infusion of $CaCl_2$ to avoid fluctuations in [$Ca^{2+}$]. The return of [$Ca^{2+}$] to normal after stopping $CaCl_2$ infusion was prolonged so that the order of testing could not be randomized.

Citrate also binds extracellular $Mg^{2+}$ ([$Mg^{2+}$]). The dissociation constant for $MgCit^-$ is identical to that of $CaCit^-$.[16] Infusion of citrate will therefore induce a decrease in [$Mg^{2+}$]. [$Mg^{2+}$] has been shown to block $Ca^{2+}$ entry in vascular smooth muscle and, hence, exaggerate the effect of low [$Ca^{2+}$].[17] Bristow *et al.* showed a small shift of the [$Ca^{2+}$]/LV dP/dt curve to the left (greater dP/dt at lower [$Ca^{2+}$]) when infusing citrate.[18] They showed that this difference disappeared using EGTA, which has a 100,000-fold greater affinity for complexing with $Ca^{2+}$ than $Mg^{2+}$ compared with citrate.[19] Thus, the

effect of citrate-induced low [$Ca^{2+}$] is buffered by a simultaneous decrease in [$Mg^{2+}$]. Because accurate measurement of [$Mg^{2+}$] in blood is not possible at present, we purposely did not assess the effects of citrate on [$Mg^{2+}$]. When [$Ca^{2+}$] has been adjusted to the normal range, citrate infusion is reported not to have any hemodynamic effects, but the method and results are not given.[5,9] Low [$Ca^{2+}$] in this study always refers to low [$Ca^{2+}$] induced by citrate. Even though the measurement at high [$Ca^{2+}$] is done at steady state, it may have been influenced by the preceding citrate infusion, but this is frequently the situation in patients.

## Hemodynamic Effects

Low [$Ca^{2+}$] decreased heart rate and high [$Ca^{2+}$] increased heart rate in the isolated canine heart.[20,21] Enflurane, halothane, and isoflurane also have negative chronotropic effects *in vitro* that may be counteracted by increasing [$Ca^{2+}$].[22] However, in intact chronically instrumented animals the three inhalation anesthetics usually increase heart rate,[11,12] probably through baroreflex mechanisms.

Low [$Ca^{2+}$] increased both heart rate and mean aortic pressure awake. During halothane and isoflurane anesthesia low [$Ca^{2+}$] increased heart rate without changing mean aortic pressure. During enflurane anesthesia low [$Ca^{2+}$] increased heart rate and decreased mean aortic pressure. Although all three anesthetics have been shown to depress baroreflexes with isoflurane having less effect than enflurane and halothane,[23] it does not seem that baroreflex mechanisms can explain the heart rate changes seen at low [$Ca^{2+}$].

Sialer *et al.*[24] demonstrated a decrease in cardiac rate and an increase in stroke volume induced by $CaCl_2$ infusion to dogs during urethane anesthesia. The heart rate effect was mediated through the vagus nerve.[24] Baroreceptor induced cardiac slowing in conscious dogs, with a high parasympathetic tone (low heart rate), is also shown to be primarily mediated through the vagus nerve, but during anesthesia with a high sympathetic tone and high heart rate (urethane), it is mainly mediated through withdrawal of sympathetic stimulation.[25]

Without marked changes in heart rate, preload or afterload, LV $dP/dt_{max}$ reflects contractile force reasonably well.[26] During low [$Ca^{2+}$] awake and during halothane and enflurane anesthesia, LV dP/dt was significantly decreased accompanied by an increase in heart rate. Awake there was also an increase in mean aortic pressure (afterload) and unchanged left atrial pressure (preload) indicating that contractile force was decreased. Likewise during halothane, unchanged mean aortic pressure and increased left atrial pressure accompanying the decrease in LV dP/dt strongly suggests a decrease in contractile force. Although mean aortic pressure was decreased by low [$Ca^{2+}$] and enflurane anesthesia, the increase in heart rate and left atrial pressure again made a decrease in contractile force seem a likely contributor to the decrease in LV dP/dt. Only during isoflurane and low [$Ca^{2+}$] was LV dP/dt unchanged. The more dramatic increase in heart rate accompanied by increased left atrial pressure appeared to modify the direct negative inotropic effect of low [$Ca^{2+}$] during isoflurane anesthesia.

During high [$Ca^{2+}$] awake, the increased LV dP/dt observed compared with the normal calcemic state may have been related to both inotropic stimulation and the increase in mean aortic pressure. However, during halothane, enflurane, and isoflurane anesthesia, it seems likely that the predominant effect of high [$Ca^{2+}$] was an increase in contractile force because cardiac output (halothane and isoflurane) and stroke volume were also increased without changes in mean aortic pressure, left atrial pressure, or heart rate (halothane) or a decreased heart rate with isoflurane and enflurane. These effects are consistent with previous observations that increased extracellular calcium ion partially antagonizes the negative inotropic effect of the potent inhalation anesthetics.[3,4]

In contrast to LV dP/dt, which reflects contractile force, the pumping function of the heart was estimated in our study by measurement of cardiac output and stroke volume. The determinants of cardiac output and stroke volume are similar to those of LV dP/dt.[27] The major difference is that afterload is inversely related to cardiac output and stroke volume, and, for this purpose, systemic vascular resistance is the best index of afterload. In addition, heart rate is also inversely related to stroke volume. In general, the effects of [$Ca^{2+}$] on the pumping function of the heart in these experiments were similar to those on LV dP/dt. Low [$Ca^{2+}$] decreased stroke volume awake and during enflurane anesthesia, although the increased heart rate could have played a role in the effect because cardiac output was unchanged. However, despite the tachycardia during low [$Ca^{2+}$] and halothane and isoflurane anesthesia, stroke volume was unchanged and cardiac output actually increased. A decrease in systemic vascular resistance (afterload) was probably responsible for this difference in the effect of low calcium on contractile force and the pumping function of the heart during halothane and isoflurane anesthesia.

As mentioned above, high [$Ca^{2+}$] in the conscious animals probably produced a mixed positive inotropic and peripheral vascular effect. This resulted in no change in either cardiac output or stroke volume. However, with all three anesthetics, high [$Ca^{2+}$] resulted in increased stroke volume, although cardiac output was increased only during halothane and isoflurane. The decrease in heart rate seen with enflurane may have been at least partly responsible for the lack of increase in cardiac output, but

a similar decrease in heart rate was also seen with isoflurane and cardiac output still increased.

The latter observation highlights the major difference between the interaction of $[Ca^{2+}]$ and the three anesthetics. During enflurane anesthesia low $[Ca^{2+}]$ produced more depression and high $[Ca^{2+}]$ resulted in less stimulation of cardiac function than occurred with halothane or isoflurane. Compared with the conscious state, all three anesthetics produced more cardiac depression at both normal and low $[Ca^{2+}]$. However, the pumping indices (stroke volume and cardiac output) were statistically the same as in the awake animals during isoflurane anesthesia and high $[Ca^{2+}]$. Thus, as in previous investigations of the effect of the three anesthetics on cardiac function in the chronically instrumented dog, isoflurane produced the least and enflurane the most depression.[11,12] However, the effect of changing $[Ca^{2+}]$ on cardiac function was different during all three anesthetics compared with the same animals awake. Thus, experiments performed with animals (or humans) anesthetized with halothane, enflurane, or isoflurane where changing $[Ca^{2+}]$ is investigated may not be extrapolated to the unanesthetized state.

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