Alterations in Calcium Levels of Coronary Sinus Blood During Coronary Arteriography in the Dog

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SUMMARY  Intracoronary administration of contrast materials causes myocardial depression which is related to several physiochemical properties of the contrast solution. The role of variations in ambient calcium ions (Ca\(^{2+}\)) in mediating this effect was evaluated in 19 anesthetized dogs. Sodium meglumine diatrizoate caused decreases in left ventricular peak systolic pressure (LVSP), \(-12.6 \pm 3.2\%\), and dp/dt at a left ventricular pressure (LVP) of 40 mm Hg, \(-14.3 \pm 4.1\%\). The total calcium (Ca) decreased from 10.2 \pm 0.2 to 6.5 \pm 0.2 mg\%/dL, while Ca\(^{2+}\) decreased from 4.6 \pm 0.1 mg\%/dL to 2.3 \pm 0.7 mg\%/dL. In the presence of systemic hypocalcemia the myocardial depressant actions of this contrast material were accentuated.

Intracoronary administration of contrast material with added Ca\(^{2+}\), calcium sodium meglumine metrizoate, caused no myocardial depression. Total calcium decreased only slightly (10.2 \pm 0.2 to 9.1 \pm 0.2 mg\%/dL), while Ca\(^{2+}\) increased (4.8 \pm 0.1 to 5.1 \pm 0.2 mg\%/dL). During systemic hypocalcemia, the calcium metrizate compound induced increases in LVSP and dp/dt/LVSP.

Thus, contrast materials caused myocardial depression which, at least in part, was related to reductions of ambient calcium through a dilutional and binding action. The addition of Ca\(^{2+}\) to monomeric contrast materials reversed the myocardial depressant action and produced a transient rise in ambient Ca\(^{2+}\).

ACUTE LEFT VENTRICULAR power failure and electromechanical dissociation are rare but disastrous complications of coronary arteriography. Currently-utilized ionic contrast materials have a direct depressing action on the ventricular myocardium which is related at least in part to the hyperosmolarity and high sodium ion content of the solution. This solution, which displaces blood during coronary arteriography, is also deficient in calcium ions (Ca\(^{2+}\)), which have a critical role in contraction of the sarcomere. Moreover, it has been suggested that the material most frequently used for coronary arteriography contains chelating properties which might further reduce ambient Ca\(^{2+}\) in the myocardium. It is well-established from early investigations that excitation-contraction coupling depends on the presence of free Ca\(^{2+}\), and electromechanical dissociation ensues upon lowering ambient Ca\(^{2+}\) in perfusate of isolated heart preparations. Recently, contrast material has been implicated as a causative factor in electromechanical dissociation occurring during coronary arteriography. The purpose of this study was: 1) to determine the extent of and the mechanism by which calcium is lowered in the coronary circulation during coronary arteriography; 2) to compare the severity and time sequence of depression in calcium levels in a “control state” and an induced acute heart failure state; 3) to assess the influence of preexisting systemic hypocalcemia on the myocardial depression induced by contrast materials; and 4) to compare the effects on calcium levels and myocardial contractility of a contrast material containing calcium ions with currently used non-calcium-containing contrast materials.

Methods

Nineteen mongrel dogs weighing 23–32 kg were anesthetized with pentobarbital sodium, 25 mg/kg, mechanically ventilated at 12 cycles/min, and right thoracotomies were performed. Teflon catheters were inserted into the left ventricle through an apical incision and positioned with the single end hole just below the aortic valve. The position was confirmed by fluoroscopic observation during the hand injection of a
few milliliters of contrast material into the catheter. A Teflon catheter was placed in the right common iliac artery. A Tygon catheter with a flanged tip was inserted into the coronary sinus and held in place by a pursestring suture. The incision in the coronary sinus was located approximately 2 cm proximal to its ostium. The position of the catheter in the coronary sinus was confirmed by contrast injections under fluoroscopic observation. The left coronary artery (LCA) was catheterized with a modified 7F Judkins catheter introduced through the left femoral artery.

During a 1-minute control period and during a 30-second period after the injection of contrast materials into the LCA, the following parameters were monitored: systolic (S), diastolic (D), mean (M) arterial pressures (AP); left ventricular peak systolic pressure (LVSP), and end-diastolic pressure (EDP); peak dp/dt and the quotient of dp/dt at a left ventricular pressure (LVP) of 40 mm Hg and a LVP of 40 mm Hg (dp/dt/LVP). Left ventricular dp/dt was derived by passing the LVP signal through a RC electronic circuit connected to function as a differentiator.

The LV response to the injection of 5 ml of contrast materials into the LCA was characterized by computing hemodynamic data at the following intervals: 1) the control period; 2) peak of the response during the first 10 seconds after injection; 3) peak of the response during the second 10-second period; 4) peak of the response during the third 10-second period. A stopwatch was used to time the peak opacification and clearance of contrast material from the coronary sinus after coronary arterial injection under fluoroscopic observation. The time of peak opacification (Tps) averaged 6.6 seconds, and the time of clearance of contrast from the sinus (Tc) averaged 13.9 seconds in the normal state. After myocardial depression, Tps averaged 10.7 seconds and Tc averaged 22.1 seconds.

Blood samples were withdrawn from the coronary sinus for the determination of total calcium (Ca.), Ca ++ and hematocrit (Hct). These samples were obtained at Tp, Tc, and 10 seconds after clearance (Tc + 10 sec), which had been determined in each dog in the normal state. All samples were immediately centrifuged after withdrawal. Samples were obtained at precisely the same times in the depressed state. It required approximately 3 seconds to withdraw the requisite 8 ml of blood from the coronary sinus. These sampling times corresponded approximately with the three hemodynamic observation periods.

Ca. was determined by the fluorometric methods (Corning Calcium Analyzer Model 940). The calcium-chelating agent used with this instrument was ethylene glycol bis, N, N' — tetraacetic acid (EGTA), which more selectively binds calcium than disodium ethylene diamine tetraacetate (EDTA). The fluorometric method determines essentially the total content of calcium in normal serum samples. Since it was considered that contrast materials in the serum samples might interfere with the accuracy of this method, calcium values of blood from the coronary sinus, determined by the fluorometric method, were compared with those determined by Atomic Absorption Spectroscopy in two dogs during the control period, and after intracoronary administration of sodium meglumine diatrizoate. The latter was recommended as the reference method. Values determined by the two methods were very similar and had a close linear relationship (fig. 1). Others have also noted that the fluorometric method measured total plasma or serum calcium and agrees closely with values obtained by Atomic Absorption Spectroscopy. As noted previously, there was a tendency for calcium values measured by Atomic Absorption Spectrophotometry to be slightly higher. This was particularly so at the lower levels of calcium observed after administration of contrast material and likely reflects the chelation of Ca ++ to substances as tightly as they are bound by EGTA. The mean value from quadruplicate measurements by the fluorometric method was obtained for each sample at specified time intervals during each intervention. Ca ++ was determined by the calcium ion selective flow through electrodes (Orion Instruments Model 5520). Measurements were made at 37°C. This electrode is unresponsive to chelates of calcium and measures only Ca ++. Commercially available calcium standards were used for calibrating each instrument before and after analysis of the serum samples.

Contrast materials evaluated in the current study were sodium meglumine diatrizoate (Renografin 76) and calcium sodium meglumine metrizoate (Isoaque 370). These materials are commercially prepared in buffered neutral solutions. The materials were evaluated in a control state (19 dogs), in the hypocalcemic state (nine dogs) and in acute heart failure state (10 dogs). Hypocalcemia was induced by the intravenous infusion of disodium EDTA at the
rate of 70 mg/kg/hr until pulsus alternans ensued. The infusion of an average of 102 mg/kg (range, 57–140 mg/kg) produced this effect and lowered the Ca₂⁺, from 9.3 to 5.6 mg%. Contrast materials were injected 2–3 minutes after this effect had been produced, at which time pulsus alternans had disappeared. Acute heart failure was induced by administering an additional depressing dose of pentobarbital Na, an added 15–20 mg/kg. Each dog was studied in the control state and again after either the induction of hypocalcemia (nine dogs) or acute heart failure (10 dogs).

The mean value and standard error of the mean (SEM) was determined for each hemodynamic variable, calcium value, and Hct during the control period and at the three observation periods after each perturbation. Significant differences between the means at the observation periods and in the control period were assessed by the paired t test.

**Results**

The animals were divided into two groups. The first group of 10 dogs was studied in the control state and after the production of acute heart failure. The second group was studied in the control state and after the induction of systemic hypocalcemia. The response during the control state did not differ in the two groups and, therefore, only the results in the first group (10 dogs) will be discussed in the next section. Results in the control state in the second group appear in figures 1 and 2.

**Alterations in LV Contractility and Coronary Sinus Calcium During Coronary Arteriography**

The injection of 5 ml of sodium meglumine diatrizoate (Renografin 76, Reno 76) into the LCA of dogs in the normal state produced a biphasic response consisting of initial decreases in AP, LVPSP, and dp/dt/LVPSP followed by slight increases in these parameters (fig. 3). The initial myocardial depression usually commenced by 3 seconds after the start of the injection and persisted for 1 or 2 seconds beyond the time of peak opacification of the coronary sinus (6–8 sec). The maximum decreases in LVPSP and dp/dt/LVPSP averaged –12.6 ± 3.2% and –14.3 ± 4.1%, respectively.

At the Tp of the coronary sinus, Ca₂⁺ declined from a control value of 10.2 ± 0.2 mg% to 6.5 ± 0.2 mg%, while Ca²⁺ dropped from 4.6 ± 0.1 mg% to 2.3 ± 0.7 mg% (fig. 2). The ratio of Ca²⁺ to Ca₄⁺ (Ca²⁺/Ca₄⁺) declined from 0.45 ± 0.01 to 0.35 ± 0.02. The Hct of coronary sinus blood decreased from 44.2 ± 0.6% to 23.4 ± 1.2%. There was no change in calcium values or Hct of systemic venous or arterial blood at this or later sampling periods.
EFFECT OF DIATRIZOATE ON LV HEMODYNAMICS

At Tc (11-15 sec), Ca\textsubscript{t} (9.7 ± 0.2 mg%), Ca\textsuperscript{++} (4.3 ± 0.1 mg%), and Ca\textsuperscript{++}/Ca\textsubscript{t} (0.45 ± 0.2) approximated control levels. The Hct averaged 43.2 ± 1.6%.

The contrast material containing Ca\textsuperscript{++}, sodium meglumine calcium metrizoate (Isopaque 370, ISO) caused a monophasic response, consisting of a rise in AP, LVPSP, and dp/dt/LVP\textsubscript{40} (fig. 4). The maximum increases in LVPSP and dp/dt/LVP\textsubscript{40} averaged 3.9 ± 0.8% and 12.3 ± 1.7%, respectively.

At Tp of the coronary sinus by Isopaque 370, Ca\textsubscript{t} declined slightly from 10.2 ± 0.2 to 9.1 ± 0.2 mg% while Ca\textsuperscript{++} increased from 4.8 ± 0.1 to 5.1 ± 0.2 mg% (fig. 5). The Ca\textsuperscript{++}/Ca\textsubscript{t} increased from 0.48 ± 0.02 to 0.55 ± 0.02. Hct of coronary sinus blood decreased from 43.9 ± 1.8% to 24.2 ± 1.7%. At Tc, Ca\textsubscript{t} (10.4 ± 0.2 mg%), Ca\textsuperscript{++} (4.9 ± 0.1 mg%), Ca\textsuperscript{++}/Ca\textsubscript{t} (0.48 ± 0.02) and Hct (43.5 ± 1.7%) approximated control levels.

Acute Heart Failure

The additive dose of pentobarbital induced hypotension and a substantial depression in parameters of LV contractile state in 10 dogs (fig. 3). Intracoronary administration of Reno 76 caused a monophasic response consisting of profound decreases in AP, LVSP, and dp/dt/LVP\textsubscript{40}. These persisted at 20 seconds after injection (fig. 3). The maximum decreases in LVPSP and dp/dt/LVP\textsubscript{40} averaged −15.7% and −28.7%, respectively.

At Tp of the coronary sinus, Ca\textsubscript{t}, Ca\textsuperscript{++}, Ca\textsuperscript{++}/Ca\textsubscript{t}, and Hct declined to an extent similar to those in the normal state (fig. 5). The depressions in these values were more persistent than in the normal state (fig. 2).

The response to Isopaque 370 was monophasic, consisting of increases in pressures, and dp/dt/LVP\textsubscript{40}, which persisted at 20 seconds after injection (fig. 4). These changes were not significantly different from those in the non-depressed state. Likewise, the changes in Ca\textsubscript{t}, Ca\textsuperscript{++}, Ca\textsuperscript{++}/Ca\textsubscript{t} were similar to those in the non-depressed state (fig. 5).

Induced Systemic Hypocalcemia

After the infusion of disodium EDTA in nine dogs, the peripheral venous Ca\textsubscript{t} declined to 5.6 ± 1.7 mg% and AP and LV contractile state were substantially depressed (figs. 3, 4). During hypocalcemia, Reno 76 provoked an even greater decrease in LVPSP (−33.3 ± 5.1%) and dp/dt/LVP\textsubscript{40} (−40.1 ± 3.9%) than in normocalcemic state (fig. 3). Instead of the
biphasic response noted during normocalcemia, the hypotensive and negative inotropic response persisted up to and beyond 20 seconds after the injection (fig. 3). In six of the nine animals, pulsus alternans recurred within 5 seconds after the injection of Reno 76. Both the early and late changes in AP, LVSP, and dp/dt/LVP40 were significantly greater than those in the hypocalcemic state (P < 0.01).

At Tp of the coronary sinus, Ca increments declined to 3.4 ± 0.9 mg% and remained below control, 4.7 ± 1.2 mg%, at 20 seconds after injection. The Hct also declined to a greater extent and remained below control at 20 seconds. Ca ++ was not measured in this group of animals.

The intracoronary administration of Isopaque 370 in the hypocalcemic state produced a monophasic response consisting of increases in AP, LVSP, and dp/dt/LVP40 (fig. 4). The initial increases in Tp were significantly greater (P < 0.01) than those which occurred in the normocalcemic state. During Tp of the coronary sinus (Ca = 5.9 mg%) and at the sampling period following opacification (Ca = 5.7 mg%), Ca ++ increased slightly above control values.

Discussion

This study indicates that the injection of currently used contrast material into the LCA caused a drastic, though transient, decline in total and ionized Ca ++ in the blood perfusing the myocardium. This decrease in total and ionized calcium (Ca ++ coincided temporally with the depression in LV contractile state. In addition to the decline in Ca, there was a relatively greater decrease in Ca ++.

The disproportionate decrease in ambient Ca ++ suggests that Ca ++ declines as a consequence of displacement of blood in the coronary circulation by contrast material and, additionally, by binding or chelating of Ca ++. The marked drop in Hct is consistent with displacement of the blood in the left coronary circulation by contrast material. The decline in Hct from 0.44 to 0.23 indicates that nearly half the blood in the coronary circulation was displaced transiently by the injectate. Another factor operative in this regard is shift of water into the coronary vascular bed due to the presence of the hyperosmolar contrast material. The disproportionate decline in Ca ++, reflected by the 22%
**Ca METRIZOATE**

![Graph](https://via.placeholder.com/500)

**FIGURE 5.** Time sequence of the alterations in coronary sinus calcium values and hematocrit (Hct) induced by the intracoronary arterial injection of calcium sodium meglumine metrizoate. Changes are shown in the same group of dogs in the normal and acute heart failure states. LV = left ventricular.

Decrease in Ca\(^{++}\)/Ca\(_t\) during Tp, is consistent with an acute alteration in the Ca\(^{++}\) binding capacity of the perfusate in the coronary circulation in the presence of ionic contrast material. In this regard, contrast material (Renografin 76) contains small quantities of sodium citrate (0.32%) and EDTA (0.04%); both of these substances chelate calcium. Caulfield et al.\(^{11}\) have shown that the addition of contrast material to blood in vitro produces a dose-related decline in Ca\(^{++}\) which is counteracted by addition of calcium chloride, implying that some component of the contrast solution does chelate Ca\(^{++}\).

It was considered that the presence of chelating agents in the contrast material might render calcium unavailable for binding with EGTA and render the total calcium values, as determined by the fluorometric method, artificially low. However, this effect would have actually tended to minimize the observed decrease in Ca\(^{++}\)/Ca\(_t\) in response to injection of the diatrizoate compound. The fluorometric method tends to slightly underestimate Ca\(_t\) in comparison to atomic absorption spectroscopy. This would cause a slight overestimation of the ratio of ionic to Ca\(_t\) in both the control state and after the injection of contrast material.

The actual mechanism by which non-calcium enriched ionic contrast material causes a disproportionate decline in Ca\(^{++}\) is not established in this study, but probably involves either chelation by substances in the contrast material or enhanced protein binding of the free Ca\(^{++}\). In addition to containing small quantities of chelating agents (citrate and EDTA),\(^{11}\) contrast material is known to bind and interact with serum proteins.\(^{15-17}\) An additional mechanism to con-
sider is the nonspecific effect that dilution of Ca\textsuperscript{2+} has on the proportion of Ca\textsuperscript{2+} in biological fluids.\textsuperscript{13} Dilution of biological fluids with ionic solution, such as sodium chloride, causes a decrease in the Ca\textsuperscript{2+}/Ca\textsubscript{L}.

The time at which the various calcium measurements were decreased coincided with the transient decline in LVSP and LV contractile state in response to the diatrizoate compound. In normal dogs these decreases lasted for less than 10 seconds and were followed by increases in the parameters of LV contractile state. Apparently, these later increases were adrenergically mediated, since in a previous study they were abolished by beta-adrenergic blockade.\textsuperscript{3} In the failure state, the persistently depressed calcium values coincided with the prolonged hypotension and depression in contractile state in response to the diatrizoate compound. On the other hand, the calcium-enriched contrast material induced an increase in Ca\textsuperscript{2+} which temporally coincided with a small increase in the parameters of the LV contractile state. The calcium metrizoate compound, as currently formulated, contains sufficient Ca\textsuperscript{2+} to raise the Ca\textsuperscript{2+} level in blood within the coronary circulation above that normally present.

Administration of diatrizoate compound in the hypocalcemic state produced more profound depressions in pressures and LV contractile than in the normal state, and these changes were protracted beyond Tp. In most animals with systemic hypocalcemia, contrast material provoked pulsus alternans. Pulsus alternans occurred routinely during the infusion of the calcium chelating agent, disodium EDTA, and served as a sign of severe hypocalcemia. The recurrence of pulsus alternans after administration of the diatrizoate compounds was a hemodynamic reflection of the reduction in calcium values produced by the contrast material. The most extreme effect of hypocalcemia, electromechanical dissociation, was not observed in the animals in the current study.

The concept that transient hypocalcemia contributes in part to the negative inotropic effect of ionic contrast materials is consistent with early experiments in isolated heart preparation, which showed that depression of ambient Ca\textsuperscript{2+} levels decreased the force of contraction and, if lowered sufficiently, induced electromechanical dissociation.\textsuperscript{6,9,10} Reduction of ambient Ca\textsuperscript{2+} to 1 mg\textsubscript{L} for 15–30 minutes has caused electromechanical dissociation.\textsuperscript{7} The lowest level of Ca\textsuperscript{2+} induced by contrast injection in previously normocalcemic animals in the current study averaged 2.09 mg\textsubscript{L}, well above the level at which electromechanical dissociation ensues. However, in an investigation in human subjects the average Ca\textsuperscript{2+} level in efflux from the coronary circulation during injection of contrast material into the LCA was below the critical level associated with electromechanical dissociation.\textsuperscript{11}

The variations in Ca\textsubscript{L} and Ca\textsuperscript{2+} levels across the coronary vascular bed in the current study are similar to those observed in Kutt et al.\textsuperscript{18} across the carotid vascular bed; the injection of a non-calcium enriched ionic contrast material into the carotid artery induced marked decreases in Ca\textsuperscript{2+} and, to a lesser degree, in Ca\textsubscript{L} of blood sampled from the jugular vein. The decline in Ca\textsuperscript{2+} in that study was sufficient to provoke regional tetany and this side effect could be alleviated by adding Ca\textsuperscript{2+} to the material. Thus, both the current study and the report by Kutt et al. support the notion that contrast material lowers Ca\textsuperscript{2+} by both a dilutional effect and by enhancement of Ca\textsuperscript{2+} binding or chelation, and important physiologic side effects can occur as a consequence. Furthermore, addition of contrast material to blood interferes with the clotting mechanism and this effect can be partially reversed by addition of Ca\textsuperscript{2+}.\textsuperscript{19}

The well-known negative inotropic effect of ionic contrast materials on the ventricular myocardium occurs as a consequence of several factors in addition to local hypocalcemia. Hyperosmolarity (approximately 1800 mOsm/l) and the high content of sodium ions (190 mEq/l) unbalanced by Ca\textsuperscript{2+} seems to have a major role in the transient myocardial depression, while the instantaneous deprivation of oxygen from the myocardium by the physical displacement of blood by contrast material seems to be of lesser importance.\textsuperscript{1-5, 20, 21} The addition of Ca\textsuperscript{2+} to contrast material ameliorates the negative inotropic effects of excess sodium ions.\textsuperscript{4} A competition by sodium and Ca\textsuperscript{2+} for transport across the myocardial membrane exists and is intrinsic to the intensity of the myocardial state.\textsuperscript{9} Thus, reduction in Ca\textsuperscript{2+} by ionic contrast material would be expected to exacerbate the negative inotropic influence of excess sodium ions.

The negative inotropic effects and hypocalcemia were prolonged in the presence of cardiac failure, suggesting that contact of contrast material with myocardial cells is prolonged in this state. Acute reduction in cardiac output and arterial hypotension likely caused a reduction in coronary blood flow and subsequently, a slower washing away of contrast material from the myocardium. An additional consideration in the prolonged negative inotropic effect is dysfunction of the baroreceptor reflex arc in the heart failure state.\textsuperscript{22, 23} The intracoronary administration of contrast material in the normal state induced a secondary inotropic effect which was abolished by beta-adrenergic blockade, suggesting that this may be a reflex effect.\textsuperscript{3} This secondary reflex effect in the normal state would be expected to cause elevations in cardiac output and coronary blood flow and to mask any persistent negative inotropic influence by contrast material which remains in contact with myocardial cells. The delayed positive inotropic effect of contrast material was not observed in the heart failure state. Attenuation of the baroreceptor reflex effect, such as occurs in the heart failure state, would be expected to allow any persistent negative influence to be manifested. Considered from the opposite point of view, prolonged contact of contrast material with the myocardium in the heart failure state might result in a sufficiently large residual negative inotropic influence to mask any reflex adrenergic influence.

In conclusion, coronary arterial administration of
currently-used ionic contrast materials devoid of Ca\(^{++}\) induced profound but transient reductions in Ca\(_i\) and, to an even greater extent, ionic calcium, which has a time sequence similar to the negative inotropic action. These effects were more profound and persisted for a longer time in the presence of heart failure. The effects of contrast material were also more severe in the presence of preexisting systemic hypocalcemia. Ionic contrast material with Ca\(^{++}\) minimized the reduction in Ca\(_i\), increased ionic calcium, and reversed the inotropic action. In this experimental model the properties of this contrast material had particularly salutary actions in the presence of heart failure and systemic hypocalcemia.

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