Blood Calcium Levels in the Presence of Arteriographic Contrast Material

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SUMMARY
One of the complications of coronary angiography is a sudden and persistent fall in blood pressure. This may be due to the presence of calcium chelating agents in the vehicle of the radio-opaque compounds. Depressed ambient calcium levels are associated with decreased myocardial contractility and when low enough cause electromechanical dissociation. Simultaneous measurements of radial artery and coronary sinus ionized calcium levels in nine patients during intracoronary injection of the contrast agent revealed a lowering of the level of ionized calcium in the coronary sinus to a point that can be expected to be associated with a decrease in myocardial contractility. This ionized calcium depression was more marked and prolonged in patients with arteriosclerosis, some reaching levels which, if persistent, could result in electromechanical dissociation.

Additional Indexing Words:
Angiographic contrast media
Coronary sinus
Depressed ionized calcium
Myocardial contractility

During the last four years a small number of deaths have occurred in association with coronary angiography at the Massachusetts General Hospital. Six of these cases have had a sufficiently similar course to suggest a common etiology. In each case the blood pressure fell to very low levels (20-40 mm Hg systolic) shortly after the intracoronary injection of the contrast agent (Renografin — 76 Squibb). During and for a period of minutes after the blood pressure fell, the electrocardiogram demonstrated sinus rhythm. At autopsy each of these cases had at least two severely stenotic epicardial arteries. There was no evidence of acute thrombosis or embolization. Further, each case presented with easily visible contrast agent in the intramyocardial veins (fig. 1). The clinical findings suggested an electromechanical dissociation. The presence of the contrast agent in the heart and the onset of electromechanical dissociation shortly after its introduction suggested a relationship. Electromechanical dissociation is brought about by lowering the ambient ionized calcium. The vehicle of the contrast agent used contains 0.32% sodium citrate and 0.04% disodium ethylene diamine tetraacetate, both calcium chelating agents. To test the hypothesis that the contrast agent used can lower ionized calcium levels two experiments were carried out. Increments of the contrast agent were added to dog plasma in vitro and the ionized calcium level determined. Secondly, ionized calcium levels of radial artery and coronary sinus plasma were determined before, during and following intracoronary injection of the contrast material in nine patients undergoing coronary angiography. The results substantiate the ability of the contrast agent to lower ionized calcium levels.

Materials and Methods
The effect of the contrast agent on calcium ion activity was evaluated in vitro. Thirty milliliters of blood from a heparinized dog were centrifuged and the plasma obtained. To one milliliter aliquots of the plasma 10, 20, 30, 40 or 50 λ of the contrast agent were added. After thorough mixing the calcium ion activity was determined with an ion specific electrode utilizing a flow-through configuration. Plasma from a second dog was obtained. Seven one milliliter aliquots were prepared and 40 λ of contrast agent was added to six of these samples. A calcium chloride solution containing 4 mEq of calcium/L and 140 mEq of sodium chloride/L was prepared and 0.1, 0.2, 0.3, 0.4 or 0.5 ml was added to 1 ml of the plasma containing contrast agent.

Nine patients undergoing selective coronary angiography by the Sones technique for the evaluation of chest pain were studied. Each patient was given 6000 IU of heparin. This obviated the need to use anticoagulants for the blood used in subsequent tests. A Zucker catheter was positioned in the

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proximal coronary sinus and a cannula placed in the radial artery percutaneously in order to sample systemic arterial and coronary sinus blood. Approximately 9 ml of contrast material was injected into the left coronary artery in this series. About 5 ml of blood was withdrawn from the coronary sinus catheter and the radial artery catheter immediately before, during, and 30, 60 and 120 sec after the intra-coronary injection of contrast agent. The blood was immediately centrifuged and the plasma used for sodium, potassium and ionized calcium determinations. The sodium and potassium levels were measured with a flame photometer and the ionized calcium levels with an ion specific electrode utilizing an ion exchange resin in a flow-through configuration. Commercially available standards were used for calibrating each instrument and these same standards were run before and after each determination. Statistical analysis was performed by a paired t-test where applicable and a $P < 0.05$ was considered statistically significant.

The pertinent contents of the contrast agent used are: 0.32% sodium citrate; 0.04% disodium ethylene diamine tetraacetate; sodium, 190 mEq/L; and virtually no potassium, less than 0.4 mEq/L by our measurements.

The determination of coronary artery disease was made in each of the nine patients on the basis of the coronary angiogram. Four cases were free of obstructive disease in both the left and the right coronary branches. The other five cases were all adjudged to have moderate to severe stenosis of either the left anterior descending or the left circumflex or both vessels (greater than 70% stenosis). Since all blood determinations were done in association with injection into the left main coronary artery, the state of the right coronary artery was not further considered.

**Results**

Figure 2 illustrates the fall in ionized calcium as increments of the contrast agent are added to normal dog plasma *in vitro*, as well as the rise in calcium ion activity associated with the addition of increasing portions of calcium to a fixed quantity of contrast agent in plasma.

Figure 3 summarizes the ionized calcium levels obtained from the coronary sinus and radial artery plasma. Clearly the injection of contrast agent results in substantial drops in levels of ionized calcium in patients with and without obstructive coronary disease. The patients with coronary occlusions return to preinjection levels more slowly than those free of coronary disease. Figure 4 indicates the change in sodium in the coronary sinus and radial artery plasma. Figure 5 indicates the change in potassium in the coronary sinus and radial artery plasma. The coronary sinus measurements indicate an average fall of sodium of 12.5% and of 15.5% for potassium during the injection of contrast media. The radial artery measurements of ionized calcium, sodium and potassium are not significantly different at any time during the procedure (figs. 3 and 4).

**Discussion**

Intra-arterial introduction of the arteriographic contrast medium under consideration results in a com-

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**Figure 1**

Sudan stain of left ventricle. The contrast material is sudanophilic and appears black in the photograph. The arrows delimit a vein containing the contrast material.

**Figure 2**

Effect of contrast material on calcium ion activity in vitro. In the left panel from 0 to 0.05 cc of contrast agent were added per cc of normal dog plasma and the calcium ion activity was measured. In the right panel the effect of adding ionised calcium to dog plasma containing contrast medium is depicted. Seven 1 cc aliquots of dog plasma were prepared. To six of these samples 0.04 cc of contrast agent (CM) were added. To five of the samples from 0.1 to 0.5 cc of a standard CaCl$_2$ solution containing 4 mEq/L of calcium were added. The calcium ion activity of each sample was measured.
plex of physiological changes as a result of the composition of the material. The material is hypertonic (about 900 mOsm/L), has about 190 mEq of sodium/L, contains two calcium binding agents and has a higher viscosity than blood. Hypertonic solutions generally lower vascular resistance, may have a positive or negative inotropic effect on the heart depending on concentration, and result in hemodilution. The elevated sodium concentration can result in depressed cardiac contractility. The calcium binding agents can lower the ionic calcium levels to those associated with depressed contractility (fig. 2). The mere presence of an agent in the capillary tree that displaces blood could depress cardiac action by lowering nutrient and oxygen supply. With this complicated situation in mind we have examined the calcium binding effects of the contrast agent and suggest that under certain circumstances they may be important.

The contrast agent used binds calcium in vitro (fig. 2). Addition of calcium chloride counteracts this binding. There is not a simple straight line relationship in these titrations. In normal plasma the ionic calcium is in equilibrium with albumin-bound calcium. Addition of the contrast agent provides two more binding agents, EDTA and sodium citrate. Thus the final mixture contains ionized calcium, calcium bound to albumin, calcium citrate and calcium bound to EDTA. This four pool system is unlikely to result in a simple titration curve.

The coronary sinus levels of ionized calcium are markedly depressed during the injection of contrast agent. This reduction is associated with an average 12.5% reduction in sodium and a 15.5% reduction in potassium. These figures preclude a simple dilution of the blood as the basis of the calcium reduction since the contrast medium contains 190 mEq/L of sodium and essentially no potassium or calcium. Simple dilu-

**Comparison of radial artery and coronary sinus calcium ion activity.** The upper panel contains data derived from the nonarteriosclerotic patients and the lower those with coronary artherosclerosis. The sample at C was obtained during the preinjection period, the second sample during injection and the remaining at 30, 60, 90 or 120 seconds after injection. The bars indicate the standard error of the mean. The only significant differences between the radial artery and coronary sinus values occurred during the injection period in both groups.

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**Comparison of radial artery and coronary sinus sodium content.** The upper panel compares total sodium values for radial artery and coronary sinus plasma in patients free of coronary artherosclerosis and the lower panel compares the same data in patients with artherosclerosis. The only significant P values occurred between the sodium levels during injection of the contrast agent. The P value refers to the difference between the coronary sinus sodium level and the radial artery sodium level. The bars indicate the standard error of the mean.

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Comparison of radial artery and coronary sinus potassium levels. The upper panel compares total potassium values of the radial artery and coronary sinus plasma in patients free of coronary arteriosclerosis and the lower panel compares similar data in patients with coronary arteriosclerosis. The only significant differences between coronary sinus and radial artery measurements occurred in the samples obtained during the period of injection. The bars indicate the standard error of the mean.

Diuresis should result in an elevation of sodium and an equivalent reduction in potassium and ionized calcium. The sodium and potassium changes may reflect marked fluid and ion shifts partially due to the fact that the contrast medium is hypertonic as is seen with systemic injections of contrast agents. Similar conclusions were reached by Kutt et al. using a different contrast agent, but one that was hypertonic and did contain calcium binding agents. In their studies the contrast agent was injected into the carotid artery and blood from the jugular vein was examined. They noted a marked fall in blood ionized calcium and magnesium; however total calcium and magnesium did not fall nearly as far, suggesting a binding of ionized calcium rather than simple dilution. Their data and ours strongly suggest that the fall in ionized calcium is due to the calcium binding agents in the contrast agent.

The relationship between rapid changes in blood ionized calcium and the ionized calcium levels of interstitial tissue have not been well investigated. Mucopolysaccharides, especially hyaluronic acid, bind calcium quite tightly. However some must be present in a labile form since hearts exposed to a calcium free medium cease contracting within a few minutes. Thus calcium necessary for cardiac contraction can be removed by perfusion with calcium free media suggesting that an important portion of the calcium is free to leave the interstitial space. Again Kutt et al. in their investigation of contrast media toxicity noted onset of localized tetanic contractions on the side of carotid injection. Tetany can be a symptom of depressed ionized calcium and in fact the tetanic contractions could be prevented by premixing the contrast agent with calcium gluconate.

Addition of contrast material with its attendant calcium chelating agents has a negative inotropic effect on isolated cat papillary muscle. When infused into the coronary arteries of man a similar negative inotropic effect is noted. When injected into the left ventricular cavity of dogs, depression of myocardial contractility occurs about 7 to 8 beats following injection, the time required to reach the cardiac capillary bed. The myocardial depression noted is nonspecific; it is seen with hypertonic agents as well as in the presence of reduced calcium.

Depression of ambient ionized calcium levels will decrease the force of contraction and if lowered sufficiently contraction will cease completely. By lowering the ambient ionized calcium level from 2.1 mEq/L to 0.54 mEq/L in isolated perfused hearts, electromechanical dissociation will occur in 15 to 30 minutes. If the perfusion medium is calcium free, dissociation will occur in 2 to 3 minutes. In the patients with coronary artery disease the coronary sinus ionized calcium levels attained values of 0.4-0.5 mEq/L, and took longer to return to normal values than in those patients with normal coronary arteries. At these ionized calcium levels no untoward fall in blood pressure occurred. Should the ionized calcium levels in the interstitial space of the myocardium drop to these levels or lower a serious drop in blood pressure would occur. In the presence of more severe coronary disease a greater drop in the cardiac ionized calcium could be expected, due to the slower progression of the contrast agent and thus more prolonged exposure of the myocardium to a low ionized calcium containing perfusion medium.

This study was prompted by the six cases in which, after careful evaluation of the heart and coronary arteries, no anatomic cause of death could be found. The presence of the contrast agent in the intramyocardial veins suggested a possible relationship and the clinical course was consistent with electromechanical dissociation. Without data from these cases this remains a suggestion. Lowering of ionized calcium activity in vivo and in vitro by the contrast agent used.
for selected coronary arteriography does occur and is a potentially dangerous situation, particularly in patients with extensive obstructive coronary disease.

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