Physiological Mechanisms for Calcium-Induced Changes in Systemic Arterial Pressure in Stable Dialysis Patients

Susan K. Fellner, Roberto M. Lang, Alex Neumann, Kirk T. Spencer, David A. Bushinsky, and Kenneth M. Borow

The mechanisms by which variations in blood ionized calcium (Ca\(^{2+}\)) influence systemic arterial pressures independent of changes in extracellular fluid volume, pH, and electrolytes are unknown. To study this issue, we dialyzed eight stable hemodialysis patients on three separate occasions during 1 week with dialysates differing only in calcium concentration. Ultrafiltration was adjusted to achieve the patient’s estimated dry weight. Postdialysis Ca\(^{2+}\) was measured, as were arterial blood gases, electrolytes, magnesium, blood urea nitrogen, creatinine, and hematocrit. Blood pressures and two-dimensional, targeted M-mode echocardiograms were recorded with the patient in the supine position after 15 minutes of rest. Postdialysis, three different levels of Ca\(^{2+}\) were achieved. Other measured biochemical variables and body weight did not differ among the three study periods. Changes in Ca\(^{2+}\) correlated directly with changes in systolic, diastolic, and mean blood pressures, left ventricular stroke volume, and cardiac output. In contrast, heart rate, left ventricular end-diastolic dimension, and total systemic vascular resistance were not altered significantly by changes in Ca\(^{2+}\). Thus, alterations in Ca\(^{2+}\) within the physiological range affect systemic blood pressure primarily through changes in left ventricular output rather than in peripheral vascular tone in stable dialysis patients. (Hypertension 1989;13:213–218)

Systemic arterial pressure is determined by the interaction between blood flow and resistance within the arterial tree. Changes in serum calcium concentration can theoretically alter either one or both of these hemodynamic variables. Prior clinical studies have suggested that hypercalcemia can cause a rise\(^1\)-\(^7\) or no change\(^8\)-\(^9\) in systemic arterial pressure, whereas hypocalcemia is reported to reduce blood pressure.\(^10\)-\(^12\) Studies in patients undergoing hemodialysis have suggested that raising dialysate calcium concentration diminishes the typical fall in blood pressure that occurs during ultrafiltration and hemodialysis.\(^13\),\(^14\) However, the major methodological problem encountered in these prior investigations has been the difficulty in varying arterial blood ionized calcium (Ca\(^{2+}\)) within the physiological range in a stable and reproducible manner. Furthermore, interpretation of these results has been hampered by simultaneous changes in pH, plasma volume, and other electrolytes that may obscure the unique actions of calcium on the cardiovascular system.

In the present study, systemic arterial blood pressures were measured in unanesthetized, stable hemodialysis patients immediately after dialysis on three separate occasions; dialysates differed only in calcium concentration. In this manner, the hemodynamic effects due to changes in Ca\(^{2+}\) could be separated from those due to alterations in plasma volume, pH, magnesium, potassium, hematocrit, urea, and other nitrogenous compounds.

Patients and Methods

The study population consisted of eight patients (four women and four men; mean age, 45±5 years; range 32–80 years) with stable chronic renal failure who had been undergoing regular hemodialysis for 34±18 months (range 5–135 months). The cause of renal failure was focal glomerulosclerosis in two patients; nephrosclerosis in two patients; and diabetic nephropathy, lupus erythematosus, ureteral obstruction, and unknown etiology in one patient.
each. None of the study patients had a clinical history suggestive of ischemic heart disease, chronic congestive heart failure, or abnormal cardiac rhythm, nor were left ventricular regional wall motion abnormalities detected by two-dimensional echocardiographic imaging. None of the patients was receiving antihypertensive medications, nitrates, \( \beta \)-blockers, digitalis, or calcitriol. Written informed consent was obtained in accordance with a protocol approved by the Clinical Investigation Committee of the University of Chicago Medical Center.

Each patient underwent hemodialysis three times within a single week with dialysate containing 0.5 mmol/l (low), 1.75 mmol/l (medium), or 2.5 mmol/l (high) calcium chosen in random order. The other constituents of the dialysate were otherwise identical (mmol/l): sodium 140, potassium 2.5, magnesium 0.75, chloride 111.5, acetate 36, and glucose 138.7. Dialysis was performed with a Travonel hollow fiber cuprophane dialyzer (Baxter Travenol Laboratories, Deerfield, Illinois) for 3.5 to 4 hours on a Gambro AK 10 machine (Gambro Lundia, Lund, Sweden) with ultrafiltration adjusted to achieve the patient’s estimated dry weight. The study was blinded, and only the dialysis technician knew the calcium concentration of the dialysate.

Immediately on completion of each hemodialytic procedure, blood was obtained from the arterial dialysis needle for determination of Ca\(^{2+}\), arterial blood gases, total calcium, electrolytes, creatinine, blood urea nitrogen (BUN), magnesium, and hematocrit. Ca\(^{2+}\) concentration was measured with an ion-specific electrode (Nova II, Nova Biomedical Company, Newton, Massachusetts). Micromolecule portion of parathyroid hormone was measured with a radioimmunoassay kit (Incstar, Stillwater, Minnesota) before the institution of the study. All other blood measurements were made by the blood chemistry laboratory or the pulmonary function laboratory of the University of Chicago Medical Center.

After removal of the dialysis needles, patients were weighed. They then rested in a recumbent position for 15 minutes, at which point systolic, diastolic, and mean blood pressures were measured in the upper arm by the oscillometric method (Dinamap 1846 SXP vital signs monitor, Critikon, Tampa, Florida). The oscillometric method has been shown previously to give reproducible measurements of systemic arterial pressures independent of cardiac index, systemic vascular resistance, left ventricular ejection fraction, and body surface area.\(^{15,16}\) A minimum of 10 blood pressure readings were recorded during the next 15 to 45 minutes.

Cardiac ultrasound imaging (Hewlett-Packard, Andover, Massachusetts) was performed with either a 3.5 or a 5 MHz transducer with the ultrasound beam directed just off the tip of the anterior leaflet of the mitral valve. Simultaneous two-dimensional as well as targeted M-mode echocardiograms of the left ventricle were recorded in conjunction with phonocardiograms, electrocardiograms, and systolic, diastolic, and mean blood pressure measurements. All tracings were obtained at end-expiration. Left ventricular end-systolic and end-diastolic dimensions were measured from the targeted M-mode echocardiographic recordings as described previously.\(^{17,18}\) Left ventricular end-systolic and end-diastolic volumes were estimated from echocardiographic dimensions by the method of Teichholz et al.\(^{18}\) This assumes that the visualized portion of the left ventricle is representative of global left ventricular performance, an assumption shown to be valid in normally shaped hearts in the absence of left ventricular asynergy. Cardiac output was calculated as left ventricular stroke volume times heart rate.\(^{19}\) Total systemic resistance was calculated as the Dinamap-determined mean arterial pressure divided by the echocardiographically measured cardiac output, multiplied by 80 to convert to dynes \( \cdot \) sec \( \cdot \) cm\(^{-5}\).\(^{20}\) After completion of these measurements, six of the eight study subjects underwent further investigation to determine the effect of Ca\(^{2+}\) on myocardial contractility. These data are reported elsewhere.\(^{21}\)

**Statistical Considerations**

Comparisons of the postdialysis hemodynamic and biochemical data obtained with the low, medium, and high calcium bath were performed by repeated-measures analysis of variance. Isolated differences between treatment groups were identified with the Bonferroni \( t \) test. A \( p \) value of \(<0.05\) was considered to be statistically significant.

**Results**

**Biochemical Changes**

When patients were dialyzed with baths differing only in calcium concentration, three significantly different levels of Ca\(^{2+}\) were achieved (Table 1). Arterial Ca\(^{2+}\) concentration was 1.04±0.04 mmol/l after dialysis with 0.5 mmol/l (low) calcium bath, 1.40±0.03 mmol/l after 1.75 mmol/l (medium) calcium bath, and 1.68±0.08 mmol/l after 2.5 mmol/l (high) calcium bath (Table 1). In six of eight patients, Ca\(^{2+}\) was measured again approximately 2 hours after completion of each of the dialysis runs; there were no significant differences between the values obtained immediately after dialysis and those measured 2 hours later.\(^{21}\) Arterial blood gases, electrolytes, creatinine, BUN, magnesium, and hematocrit, as well as body weight and heart rate did not differ among the three studies in each patient. Parathyroid hormone levels were markedly elevated in all but one patient (10.9±3.2 ng/ml, range 1.1–27.5 ng/ml; normal, <1.2 ng/ml).

**Hemodynamic Changes**

Table 2 summarizes the hemodynamic data obtained at each level of Ca\(^{2+}\). Heart rate did not differ among the studies. Systolic and diastolic blood pressures increased with higher levels of Ca\(^{2+}\) (Figure 1). The correlation coefficients for systolic
TABLE 1. Summary of Biochemical Measurements and Weights

<table>
<thead>
<tr>
<th>Variables</th>
<th>Dialysate calcium (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (0.5)</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>1.04±0.04</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>8.1±0.6</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>136±1</td>
</tr>
<tr>
<td>Chloride (mmol/l)</td>
<td>4.0±0.2</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>100±1</td>
</tr>
<tr>
<td>Dialysate calcium (mmol/l)</td>
<td>27±2</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>699±177</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/l urea)</td>
<td>12.7±1.8</td>
</tr>
<tr>
<td>Magnesium (mmol/l)</td>
<td>1.16±0.05</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>27±2</td>
</tr>
<tr>
<td>pH</td>
<td>7.44±0.02</td>
</tr>
<tr>
<td>Postdialysis weight (kg)</td>
<td>67±7</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*p<0.01 vs. low dialysis calcium.
†p<0.01 vs. medium dialysis calcium.

and diastolic pressures versus Ca\(^{2+}\) were 0.74 (p<0.001) and 0.46 (p<0.02), respectively. The relation between Ca\(^{2+}\) and systolic and diastolic pressures in individual study subjects is depicted in Figure 2. Higher levels of Ca\(^{2+}\) resulted in augmented left ventricular stroke volume and cardiac output (Table 2). In contrast, total vascular resistance (a measure of peripheral arteriolar tone) and left ventricular end-diastolic dimension (a commonly used measure of ventricular preload) did not change at the higher levels of Ca\(^{2+}\) (Table 2).

**Discussion**

We have shown that changes in systemic arterial pressure that occur with variations in Ca\(^{2+}\) are largely a function of alterations in left ventricular output rather than peripheral arteriolar tone in stable dialysis patients. Evidence for a role of Ca\(^{2+}\) in the modulation of systemic arterial pressure in humans and experimental animals has been examined by a number of previous investigators.\(^1\)–\(^7\),\(^10\)–\(^14\) However, our model is the first performed in conscious human subjects that permits assessment of the effects of variations in Ca\(^{2+}\) within the physiological range on systemic arterial blood pressure at a time that concomitant changes in blood volume, urine output, electrolytes, magnesium, pH, BUN or other nitrogenous molecules, and osmolality are eliminated as confounding variables. This was achieved by dialyzing stable hemodialysis patients three times within the same week with dialysate differing only in calcium concentration and by adjusting ultrafiltration to achieve the same target weight with each treatment.

The specific hemodynamic mechanisms by which changes in Ca\(^{2+}\) alter systemic arterial pressure have

### Table 2. Summary of Hemodynamic Data Obtained at Three Levels of Blood Ionized Calcium

<table>
<thead>
<tr>
<th>Variables</th>
<th>Dialysate calcium (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (0.5)</td>
</tr>
<tr>
<td>Ca(^{2+}) (mmol/l)</td>
<td>1.04±0.04</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>81±4</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>113±6</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>72±5</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>86±5</td>
</tr>
<tr>
<td>End-diastolic dimension (cm)</td>
<td>4.52±0.19</td>
</tr>
<tr>
<td>End-systolic dimension (cm)</td>
<td>3.29±0.22</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>49±5</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>3.9±0.3</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>1814±147</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*p<0.05 vs. low dialysis calcium.
†p<0.05 vs. medium dialysis calcium.
been controversial. Depending on the experimental model employed, previous investigators have found a reduction, no change, or an increase in systemic vascular resistance with hypercalcemia. However, interpretation of many of these studies has been difficult because \( \text{Ca}^{2+} \) was not measured, pharmacological rather than physiological doses of calcium were used, or various anesthetic agents altered cardiovascular hemodynamics. In addition, hypercalcemia causes an immediate diuresis and natriuresis that leads to a reduction of plasma volume, a decrease in venous return to the heart, and subsequently, an adrenergically mediated rise in systemic vascular resistance. These renal-induced alterations were not an issue in the current study because all patients were functionally anephric.

The rise in systemic arterial pressures noted with increasing \( \text{Ca}^{2+} \) in our patients was due to increases in left ventricular stroke volume (\( \Delta = 10\% \), low vs. medium; \( \Delta = 27\% \), low vs. high) without associated changes in heart rate, ventricular preload (as measured by end-diastolic dimension), or total vascular resistance. However, the expected response to an isolated increase in left ventricular output is arterial baroreceptor stimulation, possibly accompanied by activation of the smooth muscle stress-relaxation phenomenon leading to peripheral vasodilation and a fall in vascular resistance. The fact that our patients did not respond in this way may be explained by several factors. First, raising \( \text{Ca}^{2+} \) could have resulted in peripheral vasoconstriction, which masked the normal vasodilator response. This would be in accordance with the previously reported smooth muscle constrictor effect of hypercalcemia seen in isolated myofibrils and rat femoral arteries. Second is the possibility that our patients with chronic renal failure had abnormalities in arterial baroreceptor function (afferent limb) or autonomic nervous system dysfunction (effector limb). The presence of either of these abnormalities would lead to the conclusion that increases in \( \text{Ca}^{2+} \) had little direct effect on vascular smooth
muscle tone. Finally, it is possible that the peripheral vasculature in our patients was intrinsically abnormal and thus unable to undergo vasodilation in response to increased pressure and flow. Since total vascular resistance was at most only mildly elevated in our study population, and since we have previously shown that peripheral vasodilation can be easily obtained with nitroprusside in these patients, this explanation seems unlikely.

Several methodological issues should be addressed regarding the current study. First, serum catecholamines were not measured. However, Marone et al have previously shown that raising serum calcium does not change norepinephrine levels, although small increases in epinephrine do occur that nonetheless remain within the normal range. Whether the changes in Ca\(^{2+}\) in the current study influenced the release or action of other vasoactive hormones or autacoids is unknown. Second, parathyroid hormone was substantially elevated in all but one of our patients. Although infusion of parathyroid hormone in experimental animals has been shown to produce vasodilation, it is unlikely that the relatively small variations in parathyroid hormone that might occur in response to changes in Ca\(^{2+}\) during hemodialysis in patients with pre-existing secondary hyperparathyroidism (and parathyroid levels 10 times normal) could account for the magnitude of the changes in blood pressure observed in this study. Finally, use of total systemic resistance neglects the contribution of mean right atrial pressure to the resistance calculation. Since each patient was ultrafiltered to his or her estimated dry body weight with each dialysis, it was assumed that no significant interstudy differences in ventricular and atrial filling characteristics occurred. This was corroborated by the consistent measurements obtained for left ventricular end-diastolic dimension.

In summary, our findings demonstrate that the changes in blood pressure associated with controlled alterations in Ca\(^{2+}\) concentrations occur primarily from preload-independent variations in aortic blood flow rather than from changes in peripheral arteriolar tone in dialysis patients. This is particularly interesting when considering recent work from our institution that was performed with use of load-independent indexes of left ventricular contractility, which confirmed the hypothesis that myocardial contractility in humans varies directly with Ca\(^{2+}\). Thus, changes in systemic arterial pressures that occur with variations in Ca\(^{2+}\) within the physiological range are largely the consequence of alterations in left ventricular output in these patients.

Acknowledgments

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References


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**KEY WORDS** • systemic arterial pressure • blood pressure • calcium
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