Intracellular Calcium and Sodium in Hypertensive Patients
RICHARD S. COOPER, NASREEN SHAMSI, AND SHERRY KATZ

SUMMARY Untreated subjects with mild to moderate hypertension were compared with normotensive controls recruited from the same ambulatory screening clinic. All subjects were black. Resting levels of cytosolic free calcium were estimated in washed platelets with the fluorescent intracellular probe fura 2, and sodium and potassium were measured in red blood cells. Calcium levels were 21% higher in the hypertensive subjects ($p = 0.02$), and a 9% increase in sodium was observed in an expanded sample ($p = 0.04$). Neither intracellular calcium nor intracellular sodium had a significant linear correlation with blood pressure when hypertensive subjects and controls were examined separately or when the two groups were combined. Potassium was slightly but not significantly increased in hypertensive subjects. Among the participants for whom both calcium and sodium measurements were available, a weak, nonsignificant correlation between these ions was noted ($r = 0.2; n = 48$). This correlation was significant among participants in the control group examined separately ($r = 0.3; n = 33; p = 0.05$). Although the measurements were performed in different cell lines, these findings demonstrate increases in both intracellular calcium and sodium in hypertensive humans.
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KEY WORDS • calcium • hypertension • fura 2 • sodium-calcium exchange

THE role of intracellular electrolytes in the pathogenesis of hypertension is a subject of considerable interest. Given the role of intracellular calcium, $[\text{Ca}^{2+}]_i$, in coupling excitation-contraction in vascular smooth muscle, it is important to know if hypertensive persons maintain higher levels of free $[\text{Ca}^{2+}]_i$. An increase in $[\text{Ca}^{2+}]_i$ must occur in vascular smooth muscle to maintain the elevated peripheral resistance of established hypertension, no matter what the inciting cause. If this phenomenon were generally observed in other tissues as well, it might suggest a systemic defect in the handling of cellular Ca. However, the multiple exchange and storage mechanisms that regulate cellular Ca metabolism are extremely complex and difficult to isolate for study. It is still unclear whether flux rates, cell stores, or resting levels of Ca are the key determinant of increased vascular smooth muscle tone. Because of its well-described role as a secondary messenger in controlling tension development and the recent development of improved measurement techniques, free $[\text{Ca}^{2+}]_i$ has been the subject of several recent studies. Intact vascular smooth muscle has never been isolated from hypertensive humans, and work to date has been performed on blood cells. In this study, $[\text{Ca}^{2+}]_i$ was estimated in platelets with a newly available fluorescent intracellular dye and intracellular sodium ($[\text{Na}^+]_i$) and potassium ($[\text{K}^+]_i$) were measured in red blood cells.

Subjects and Methods
Recruitment of Participants
Hypertensive subjects were identified by practitioners in the Ambulatory Screening Clinic of Cook County Hospital. Persons with a diastolic blood pressure between 90 and 115 mm Hg were given a return appointment for the hypertension clinic within 7 days. Subjects were included only if they had not taken antihypertensive or other prescription medications within the last 15 days and were free of other major medical illnesses. No additional investigations were performed to rule out secondary causes of hypertension, but all...
hypertensive subjects had mild to moderate increases in blood pressure (BP) and no signs or symptoms suggestive of secondary causes. On the return visit, subjects were interviewed and their height and weight were measured with shoes off on a balance scale. BP measurements were made with the subjects in a sitting position with the antecubital fossa at heart level. Two observers made all measurements using a standard mercury manometer. Three readings were taken, with the radial pulse counted between Readings 2 and 3. The mean of the last two readings was used for analysis. Subjects with mean diastolic BPs exceeding 90 mm Hg on the second visit were asked to participate in the study. Informed consent was obtained, and venous blood was drawn from the arm in acid-citrate-dextrose Vacutainer tubes. Blood was gently inverted and transported to the laboratory within 1 hour.

Normotensive participants were identified in the same screening facility. Persons seeking care for minor illness (e.g., skin rash, backache), who did not have notable pain, an elevated temperature, or other acute symptoms, and who were not taking prescription medication were invited to participate. The same evaluation procedure used in hypertensive subjects was performed at this visit, and subjects with a mean diastolic BP under 90 mm Hg were included. Complete descriptive data for the series are reported in Table 1.

The same recruitment procedures were used to obtain a larger number of participants to study for [Na\(^{+}\)], and [K\(^{+}\)]. Descriptive characteristics for this larger sample were very similar to those of the [Ca\(^{2+}\)] sample; mean diastolic BP was 100.2 mm Hg in hypertensive subjects and 75.8 mm Hg in controls. The group composition and sex were very similar to those of the [Ca\(^{2+}\)] sample.

### Intracellular Calcium Measurement

Free cytosolic Ca was estimated with the fluorescent dye fura 2 (Molecular Probes, Junction City, OR, USA). Like its predecessor quin 2, fura 2 is taken up by the cell in its membrane-permeant acetoxymethyl ester form and trapped intracellularly after removal of the esters. Calcium is chelated by the dye, and estimation of the relative amounts of the bound and unbound species make it possible to determine the concentration of free [Ca\(^{2+}\)].

Assays were performed with a slight modification of the methods described by Erne et al. and Grynkiewicz et al. Specimens were centrifuged at 140 g for 10 minutes at room temperature. The platelet-rich plasma was removed and incubated in a shaking water bath for 30 minutes at 37°C with a 3-μM concentration of fura 2/AM. The platelet-rich plasma was then placed on a 27 x 100-mm Sepharose 2B-CL column that had been washed with 150 ml of 4-(2-hydroxyethyl)-1-piperazine-ethane sulfonic acid (HEPES) buffer (pH 7.4; osmolality, 300). The elution medium contained 10 mM HEPES, 145 mM sodium chloride, 5 mM potassium chloride, 1 mM magnesium sulfate, 0.5 mM sodium phosphate, and 6 mM glucose; Ca was omitted to prevent platelet aggregation. The platelet fraction in the eluent was identified by the appearance of turbidity, collected in 1-ml vials, and pooled to obtain a total volume of 3.5 ml. The washed platelet preparation was then reincubated at 37°C for 30 minutes in a solution with Ca restored (1.5 mmol) at a platelet concentration of 2.0 to 4.0 x 10\(^{7}\)/ml. Fluorescence was read at an emission wavelength of 510 nm and sequential excitation wavelengths of 340, 360, and 380 nm on a Perkin-Elmer fluorometric spectrophotometer (Model 204; Norwalk, CT, USA). Specimens were then lysed with Triton X100, and the measurements were repeated before and after adding an excess of EGTA, with pH adjusted to 8.3. The ratio of the emission fluorescence at excitation wavelengths 340 and 380 nm was taken to be an estimate of levels of [Ca\(^{2+}\)].

Calibration was accomplished as described by Grynkiewicz et al. with the following equation:

\[
Ca = K_c \left( \frac{R - R_{\text{max}}}{R_{\text{max}} - R} \right) \left( \frac{S_n}{S_b} \right)
\]

where \(R\) is the ratio of fluorescence at 340 and 380 nm in the unlysed specimen, \(R_{\text{max}}\) is the ratio of the unbound species, \(R_{\text{max}}\) is the ratio of the bound species after lysis, and \(S_n\) and \(S_b\) are the fluorescence of the free and bound form, respectively, at 380 nm. A value

### Table 1. Descriptive Characteristics of Hypertensive and Normotensive Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n = 38)</th>
<th>Hypertensive (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37 ± 10</td>
<td>49 ± 9*</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>16:22</td>
<td>12:7</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>10.9 ± 2.3</td>
<td>10.7 ± 2.2</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>68</td>
<td>53</td>
</tr>
<tr>
<td>Consumes alcohol (%)</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td>Average number of</td>
<td>0.9 ± 0.8</td>
<td>1.1 ± 0.9</td>
</tr>
<tr>
<td>alcoholic drinks/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consumes &gt; 5 drinks/day</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>at least 1 day/week (%)</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Ever was a heavy drinker (%)</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Employment status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Unemployed</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td>Other (e.g., retired,</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>disabled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipids (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>191.7 ± 36.6</td>
<td>194.9 ± 31.7</td>
</tr>
<tr>
<td>High density lipoprotein</td>
<td>45.1 ± 14.5</td>
<td>46.4 ± 12.4</td>
</tr>
<tr>
<td>cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>88.7 ± 47.8</td>
<td>121.6 ± 63.1†</td>
</tr>
<tr>
<td>Room temperature (°C)</td>
<td>24.1 ± 4.8</td>
<td>24.9 ± 1.3</td>
</tr>
<tr>
<td>Time of blood sampling (%)</td>
<td>9000–1200</td>
<td></td>
</tr>
<tr>
<td>1200–1400</td>
<td>47</td>
<td>58</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>27.0±5.7</td>
<td>29.5±4.2†</td>
</tr>
</tbody>
</table>

*Most values are means ± SD.

\(^*p < 0.01, \ ^{†}p < 0.05\), compared with value in normotensive subjects.
of 224 was assumed for the $K_d$, based on published data. Monitoring the fluorescence signal at 360 nm made it possible to confirm the presence of adequate amounts of dye in the intact cells, since this value represents the peak of the fura 2 spectral curve. The intracellular concentration of fura 2 obtained by this loading procedure was estimated by linear extrapolation of the signal intensity from lysed specimens to a curve constructed from known concentrations of fura 2. Based on the assumption that 1 µL of water was the volume of dilution for 10⁶ platelets, the concentration of fura 2 ranged from 3 to 12 µM.

The technical error on blind duplicates performed on the same day was 7.7% over the course of the study, based on 37 pairs. (Technical error was estimated by the formula $\sqrt{\sum d^2}/2N$, where $d =$ the difference between pairs and $N =$ the number of pairs.) Values are expressed as a percentage of the sample mean. Intraindividual variation over time based on five pairs was 9%. On the basis of the statistical method of Liu et al., the intraindividual to interindividual ratio was 0.6, indicating that subjects had been well characterized by a single measurement.

Platelets occasionally are activated during the preparation phase and yield high levels of resting $[Ca^{2+}]$. Activation leads to a continued increase in the ratio of fluorescence at 340/380 nm over time and results in clumping. Such specimens were subsequently deleted from the analysis.

**Intracellular Sodium and Potassium Measurements**

$[Na^+]$, and $[K^+]$, were determined in red blood cells by a method previously described and are expressed as mmol/L of cells. In brief, cells were washed in a solution containing 112 mM magnesium chloride and lysed with distilled water. The sodium concentration was determined in the lysate with the flame photometer and corrected for initial hematocrit. Technical error for blind duplicates performed on the same day was 7.7% over the course of the study, the pooled sample. Furthermore, in a case-control study, the entry criteria should sharply separate the two groups, creating a truncated distribution of the variables in each group and making analysis of linear relationships difficult.

Data on $[Ca^{2+}]$, and $[Na^+]$, were available on 33 normotensive and 15 hypertensive participants. Significant differences in intracellular electrolytes were noted in these subgroups only for $[Ca^{2+}]$; however, this result probably was due to the limited sample size (hypertensive subjects: $[Ca^{2+}] = 119.0$ nmol/L, $[Na^+] = 8.4$ mmol/L, $[Ca^{2+}] = 96.2$ mmol/L, $[Na^+] = 8.2$ mmol/L). A significant correlation between $[Ca^{2+}]$, and $[Na^+]$, ($r = 0.3; p = 0.05$) was observed in hypertensive subjects, and neither age nor obesity was related to the end points of interest, $[Ca^{2+}]$, and $[Na^+]$, statistical procedures to adjust for these differences were not performed. All subjects were black and of relatively low social status. Smoking and alcohol habits did not differ systematically, and persons with recognized alcohol-related medical problems were excluded. Because serum lipids have been shown to influence flux rates of electrolytes across the cell membrane, they were included in the screening and evaluation; no important differences were noted. Room temperature, which influences BP, and time of day (to reduce the likelihood of circadian variations) were controlled and well matched.

A 25 mm Hg difference in diastolic BP was obtained between hypertensive subjects and controls (Table 2). $[Ca^{2+}]$, was increased in hypertensive subjects as compared with normotensive controls ($p = 0.02$). $[Na^+]$, recorded in an expanded series recruited in an identical manner, was significantly higher as well ($p = 0.04$).

In a correlation matrix including all the continuous variables, only the expected relationships among age, body mass index, and BP emerged. Neither $[Ca^{2+}]$, nor $[Na^+]$, was correlated significantly with BP among hypertensive subjects or controls examined separately as a single group. A weak correlation between $[Ca^{2+}]$, and systolic BP ($r = 0.12; t = 0.88$) was observed in the pooled sample. Furthermore, in a case-control study, the entry criteria should sharply separate the two groups, creating a truncated distribution of the variables in each group and making analysis of linear relationships difficult.

Results

The descriptive characteristics of the two groups are presented in Table 1. Significant differences in age and body mass index were observed. Since hypertensive subjects were anticipated to be more obese than normotensive subjects, and neither age nor obesity was related to the end points of interest, $[Ca^{2+}]$, and $[Na^+]$, statistical procedures to adjust for these differences were not performed. All subjects were black and of relatively low social status. Smoking and alcohol habits did not differ systematically, and persons with recognized alcohol-related medical problems were excluded. Because serum lipids have been shown to influence flux rates of electrolytes across the cell membrane, they were included in the screening and evaluation; no important differences were noted. Room temperature, which influences BP, and time of day (to reduce the likelihood of circadian variations) were controlled and well matched.

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the control group, but this relationship was not significant when the participants were analyzed as a group. These findings should be interpreted with caution, however, since the [Ca\(^{2+}\)] and [Na\(^{+}\)], assays were performed in separate cells. No relationships among serum lipids and intracellular electrolytes were noted. In stepwise linear regression with each electrolyte considered sequentially as the dependent variable, sex was the only variable to meet the significance level for entry in the equations for [Na\(^{+}\)], and [K\(^{+}\)], (p = 0.03).

**Discussion**

In recent years increasing attention has been focused on the possibility that the basic cellular abnormality in hypertension is an inability to maintain a normal transmembrane electrolyte gradient.\(^1\)\(^-\)\(^4\) It has been suggested that chronic excess Na intake leads to elaboration of a substance that inhibits Na\(^{+}\)-K\(^{+}\) pump activity, with a subsequent rise in [Na\(^{+}\)],.\(^1\)\(^7\)\(^-\)\(^2\)\(^4\) Since, in some tissues at least, Na\(^{+}\)-Ca\(^{2+}\) exchange helps maintain the nanomolar [Ca\(^{2+}\)], concentration of the cytosol, an increase in [Ca\(^{2+}\)], would result from higher [Na\(^{+}\)]. Although this hypothesis has gained wide currency, it has been subject to only limited direct tests. We sought to examine the resting levels of [Ca\(^{2+}\)], in platelets and [Na\(^{+}\)], in red blood cells of hypertensive subjects. Small (9–20%) but significant increases in intracellular concentration of both these electrolytes were observed. To our knowledge, this report represents the first demonstration of an increase in both of these ions in the same group of hypertensive subjects.

In contrast to previous reports on [Ca\(^{2+}\)], and hypertension, we used the intracellular probe fura 2. The advantages of fura 2 over quin 2 are a 30-fold greater quantum efficiency, a slightly higher \(K_a\), and a spectral shift with a change from the bound to the unbound species.\(^1\)\(^1\)\(^\)\(^1\)\(^1\)\(^1\)\(^1\)\(^1\) Although the cells are still lysed to calibrate final concentrations, some of the problems with quin 2 are eliminated. The essential measurement with fura 2 involves the ratio of the two excitation wavelengths, and a calibration formula provides estimates of [Ca\(^{2+}\)], levels. With quin 2, the maximal fluorescence with each specimen after lysis is a key variable in the calculation, and this cannot always be reliably determined. At the same time, background fluorescence and light scattering are more of a problem with quin 2; these factors contribute equally to the recorded signal at both excitation wavelengths and can be neglected when the ratio is calculated. Continuous measurements are also easier to make.

Our finding of a modest difference in [Ca\(^{2+}\)], contrasts to the 56% increase noted by Erne et al.,\(^6\) but is somewhat higher than that observed in three other studies (Table 3).\(^7\)\(^-\)\(^9\) Although the magnitude of the difference between normotensive and hypertensive subjects varied in each study, four of the five studies — including all those relying on platelets — showed a positive change. Given the limitations of sample size and inherent sample-to-sample variability, any single study may miss differences of 5 to 20%; a better estimate of the true relationship can be obtained by independent replication of the results in several comparable investigations. Based on pooled data from 20 studies that compared red blood cell [Na\(^{+}\)], in hypertensive (\(n = 965\)) and normotensive (\(n = 1857\)) subjects, Hilton\(^2\)\(^3\) calculated an average increase of 13% in the hypertensive subjects, a difference that is highly significant statistically (p<0.001). Published studies on [Ca\(^{2+}\)], in platelets include fewer participants (84 hypertensive and 101 normotensive subjects) and the results are more widely spread, so pooling of the data seems unwarranted; however, a clear trend toward higher values among hypertensive subjects is emerging. Thus, it would seem reasonable to conclude that the relationship is real, if quantitatively small. Whether this finding is restricted to the platelet deserves further study.

There is no a priori reason to assume that differences in [Ca\(^{2+}\)], must be large in hypertension. The sensitivity of the fluorescent dyes has likewise not been rigorously studied. Since the dyes chelate available Ca, they act as an intracellular sink and may remove sufficient [Ca\(^{2+}\)], to selectively lower the higher values. The findings of Erne et al.,\(^6\) demonstrating a 50% increase in [Ca\(^{2+}\)],, are somewhat difficult to interpret. The reported correlation of [Ca\(^{2+}\)], and BP in that study was 0.9. Given that BP varies from minute to minute and the usual correlation between BP on two visits rarely exceeds 0.7, this extremely high correlation with [Ca\(^{2+}\)], seems implausible.

It is of interest that the three positive studies reported to date have all used the platelet. The platelet does not

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**Table 3. Summary of Studies on Intracellular Calcium Concentration and Hypertension**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cell line</th>
<th>[Ca(^{2+})], (nmol)</th>
<th>Difference (%)</th>
<th>p value of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normotensive</td>
<td>Hypertensive</td>
<td></td>
</tr>
<tr>
<td>Erne et al.(^6)</td>
<td>Platelets</td>
<td>108 (38)</td>
<td>168 (45)</td>
<td>+56</td>
</tr>
<tr>
<td>Bruschi et al.(^7)</td>
<td>Platelets</td>
<td>127 (25)</td>
<td>145 (20)</td>
<td>+14</td>
</tr>
<tr>
<td></td>
<td>Lymphocytes</td>
<td>112</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Lew et al.(^8)</td>
<td>Neutrophils</td>
<td>142 (10)</td>
<td>139 (10)</td>
<td>-2</td>
</tr>
<tr>
<td>Shore et al.(^9)</td>
<td>Lymphocytes</td>
<td>120 (19)</td>
<td>131 (22)</td>
<td>+9</td>
</tr>
<tr>
<td>Present study</td>
<td>Platelets</td>
<td>98 (38)</td>
<td>119 (19)</td>
<td>+21</td>
</tr>
</tbody>
</table>

Number of subjects is shown in parentheses.
contain contractile proteins, but no obvious advantages are otherwise apparent and several limitations can be cited. \([\text{Ca}^{2+}]\), increases when platelets are activated, and the washing procedure occasionally will cause spontaneous aggregation. Furthermore, there is reason to be concerned that the hypertensive state might lead to a secondary alteration of platelets. Further work using several cell lines simultaneously will be required to answer these questions.

Several reports have appeared on the measurement of \([\text{Ca}^{2+}]\), with ion-selective electrodes and a freeze-thaw technique. The values for \([\text{Ca}^{2+}]\), reported with this method are in the micromolar range, compared with the nanomolar values obtained with fluorescent dyes, including quin/fura and aequorin. It seems highly likely that contamination with membrane-bound Ca or Ca in the extracellular fluid interferes with these measurements. Increases in \([\text{Ca}^{2+}]\), in hypertension have been reported with this method, as well as a decrease with treatment.

Jy and Haynes recently used a combination of two fluorescent probes, chlorotetracycline and quin 2, and found that resting cytosolic \([\text{Ca}^{2+}]\), in platelets determines the Ca level in the organelles and that both respond to changes in the external Ca. The finding of higher free \([\text{Ca}^{2+}]\), thus may actually reflect total stores. As they apply to hypertension, however, these observations are contradicted by work in neutrophils, in which Ca stores were assessed by measuring changes in free \([\text{Ca}^{2+}]\). If Na–Ca exchange is the major link between a humoral ouabainlike factor and increased vascular tone, it is further disconcerting that this exchange mechanism has been difficult to demonstrate in blood cells. Several investigators have been unable to show increases in \([\text{Ca}^{2+}]\), with quin 2 in experiments designed to raise \([\text{Na}^{+}]\). and we have likewise found no increase in \([\text{Ca}^{2+}]\), with fura 2 in ouabain-treated platelets (unpublished data, 1986). While Na–Ca exchange plays a prominent role in cardiac muscle, it appears to be less important in vascular smooth muscle and blood cells, and an actual reversal of the intracellular-extracellular Na gradient may be required before an effect is observed. Earlier work did indicate that platelets become hyperaggregable in a low extracellular Na medium, suggesting that the functional test may be more sensitive than the dyes. If, of course, platelets or other blood cells do not depend to any major degree on Na+–Ca2+ exchange to maintain \([\text{Ca}^{2+}]\), they cannot be used to test the so-called Blaustein hypothesis as currently formulated.

An increase in \([\text{Na}^{+}]\), was also noted in this study in an expanded example. On a percentage basis the increase in \([\text{Na}^{+}]\), was about half of that observed for \([\text{Ca}^{2+}]\), which is roughly consistent with the proposed 1:3 coupling of Na+–Ca2+ exchange. Although a significant correlation was noted between \([\text{Na}^{+}]\), and \([\text{Ca}^{2+}]\), in the control group, this relationship should be interpreted cautiously given the small size of the sample and the fact that \([\text{Ca}^{2+}]\), and \([\text{Na}^{+}]\), were measured in different cells. Unfortunately, \([\text{Ca}^{2+}]\), cannot be assayed in red blood cells with these dyes (because of the interference of heme), and the measurement of \([\text{Na}^{+}]\), in platelets is technically difficult. Whether higher \([\text{Na}^{+}]\), in red blood cells implies a similar increase in platelets is, of course, problematic. At stake, however, is an increase in multiple tissues, including primarily the vascular smooth muscle; therefore, if a generalized abnormality could be demonstrated, it would be of even more interest. An increase in \([\text{Na}^{+}]\), in white blood cells has been reported, although the findings are inconsistent.

All participants in this study were black. Red blood cell \([\text{Na}^{+}]\), consistently has been shown to be higher in blacks, suggesting a possible cellular basis for an increased susceptibility to hypertension. To our knowledge, no data have yet been published comparing \([\text{Ca}^{2+}]\), in blacks and whites. Based on the small numbers accumulated in our laboratory, if differences exist they must be small.

As with previous studies of Na flux in red blood cells, the usefulness of blood cells as models for the study of hypertension remains an important unresolved question. The nature of the measurements being made with the quin-fura class of intracellular probes also requires a great deal more evaluation. Different cellular pools may be available for fura 2 and other probes, such as aequorin. There is a further need to examine the relationship between free \([\text{Ca}^{2+}]\),, bound Ca, and flux parameters. Finally, only direct examination of intact vascular smooth muscle cells can be considered an adequate test of the hypothesis under consideration. The preliminary findings accumulated with blood cells appear encouraging, however, and the techniques to make the required observations are rapidly improving. If this line of research develops successfully, it may finally be possible to define important intermediate processes in the pathogenesis of hypertension and to move beyond descriptive variables such as obesity, age, and race.

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