Platelet Calcium and Quenched-Flow Aggregation Kinetics in Essential Hypertension

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Abnormal platelet function may contribute to the complications of essential hypertension. We have studied the kinetics of platelet aggregation induced by adenosine diphosphate (ADP) or epinephrine, plasma β-thromboglobulin, and basal, cytosolic, and free calcium, as correlates of platelet function. Fifteen untreated patients with essential hypertension and without detectable atherosclerosis, 18–40 years old, were compared with 30 matched normotensive control subjects. Maximal rates of platelet aggregation (Vmax with ADP and epinephrine were significantly higher in patients than in control subjects (p<0.03), as assessed by quenched-flow aggregometry. However, significance was lost when Vmax was corrected for the platelet count. Paradoxically, the activation constants (Ka) for ADP were higher in patients than in control subjects (p<0.03). With ADP as the inducing agent, onset time (t) or lag period before aggregation begins was longer in patients than in control subjects (p<0.02). β-Thromboglobulin levels, an index of in vivo platelet activation, were not significantly different between the two groups (p=0.13). The mean platelet cytosolic free calcium concentration was higher in patients (213±19 nM) than in control subjects (172±14 nM), but this difference was not statistically significant (p=0.07). However, there was a close correlation between the free calcium level and systolic, diastolic, and mean blood pressure (p<0.003, p<0.04, p<0.004, respectively). No difference in platelet volume between the two groups was found. Our data suggest that platelets in the early stages of essential hypertension display an overall increased aggregation potential but a diminished sensitivity to ADP. The tendency toward elevated calcium suggests that in hypertensive patients the platelets circulate in an already activated state; this occurrence could contribute to acceleration of atherosclerosis. (Hypertension 1989;13:558–566)
humoral factor responsible for elevated intraplatelet free calcium concentration in essential hypertension was reported by Lindner et al. In contrast, other groups have concluded that platelet cytosolic free calcium levels are not increased in hypertension. Epidemiological factors such as sex, age, hypercholesterolemia, and diabetes mellitus are all suggested risk factors for atherosclerosis and have been found to affect platelet function.

Our study was designed to investigate the hypothesis that platelets in patients with essential hypertension behave differently from those in matched control subjects. Using the new technique of quenched-flow aggregometry coupled with resistance-particle counting, we studied platelet aggregation kinetics in platelet-rich plasma (PRP). Using adenosine diphosphate (ADP) and epinephrine as inducing agents, we followed reactions occurring within 5 seconds of cell stimulation. We also sought to establish possible correlations between aggregation kinetic parameters, blood pressure, platelet cytosolic free calcium, and plasma β-thromboglobulin levels. The new fluorescent dye Indo 1 was used to determine intraplatelet free calcium concentrations. These data have been reported in preliminary form.

Subjects and Methods

Subjects

Forty-five adults, none of whom took analgesics or any other medications for at least 2 weeks before the study, were enrolled. There were 30 normotensive control subjects and 15 patients with essential hypertension (seven men and eight women), aged 21–39 years. The control subjects were all medical center personnel with no history of hypertension among their first degree relatives. The patients had either been previously untreated or had not received treatment for at least 2 weeks before the start of the study. All had average, seated diastolic blood pressure readings above 94 mm Hg after at least three readings taken 2 minutes apart. These measurements were confirmed on at least two occasions 1 week apart. Diastolic pressure was recorded at the complete disappearance of arterial Korotkoff sounds. A history and general physical examination were performed on all subjects. Criteria for exclusion from the study were: a history or clinical evidence of diabetes mellitus, occlusive vascular disease, renal, hepatic or hematologic disorders; tobacco use, either habitual or less than 48 hours before the study; alcohol consumption, either habitual or less than 48 hours before the study; and total cholesterol values greater than the 75th percentile. All subjects remained on a free diet with no restriction of sodium intake.

Duplex Scans

In the patient group, noninvasive imaging of the carotid and femoral arteries was performed in the Neurovascular Laboratory at the University of Virginia Hospital. Real-time-B-mode ultrasound displays of vessel anatomy were obtained with the Carolina Medical DOPSCAN PLUS Model D1060 instrument. With the Model UTB B-mode transducer, machine performance included: operational depth, 3 cm; and focus, 1.35–1.5 cm at 10 MHz. Imaging of the carotid and femoral arteries and the bifurcations was done within technical limitations. The studies were interpreted by a single investigator who is a recognized expert in the field. All patients whose scans suggested the presence of either vascular intimal disruption or atherosclerotic plaque were excluded from the study.

Preparation of Platelet-Rich Plasma

PRP was prepared by differential centrifugation from venous forearm blood anticoagulated with acid-citrate-dextrose. Details of this procedure have been previously described. Blood samples were obtained after a 12-hour fast with the subject in a seated, resting position for 10 minutes. Large bore (19 gauge) needles were used with gentle aspiration of the blood into plastic syringes.

Quenched-Flow Methods

Quenched-flow aggregometry was developed by Gear at this institution, and the apparatus is described in detail elsewhere. The basic principle is to pump PRP and an inducing agent through narrow-bore Teflon tubing (0.2–0.3 mm i.d.) and quench the reaction at the outlet. The speed of quenching has been estimated at less than 0.2 seconds, and reaction times as low as 0.3 seconds have been routinely studied. Flow conditions are close to physiological, and shear rates (34 dynes/cm² for 0.25 mm i.d.) in the reaction tubing are not low enough to cause so-called spontaneous aggregation or high enough to cause platelet lysis or activation. The hydrodynamic conditions have been fully reported.

Platelet Aggregation by Single-Particle Counting

Reactions were quenched with 0.9% NaCl, and the inducing agents were ADP (0.5, 1.0, 1.33, 2.0, 2.86, 5, and 10 μmol/l) and epinephrine (10 μmol/l). Aggregation was defined as the percent of single platelets left in the system after various reaction times, with the control or preaggregation value serving as 100%. These percentages were plotted against time. The rate of aggregation Vₐ,vₐ was derived from the slope of the curve; values were normalized to a platelet count of 200,000/mm² in the reaction tubing. The onset time was calculated as the intersection of a tangent at the maximum rate of aggregation projected backwards and the 100% axis. This parameter reflects the time required before platelet activation begins. Rate of aggregation was then plotted against agonist concentration. From this curve, sensitivity (defined as an apparent Kᵦ) and maximal rate of change (defined as an apparent Vₐ,vₐ) were determined by a Michaelis-Menten analysis.

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Single-Particle Counting and Sizing

Platelets were counted and sized\(^3^3\) with a resistive particle counter (Particle-Data, Elmhurst, Illinois) calibrated with 2.02 μm latex particles. Before sizing, each sample was incubated at 37° C for 10 minutes.

Cytosolic Calcium

Cytosolic free calcium concentrations \([\text{Ca}^{2+}]\) were determined in washed platelets with the new, fluorescent dye Indo-1-AM (Molecular Probes, Eugene, Oregon). Dye loading and washed platelet preparation were carried out according to the method of Jones and Gear,\(^3^4\) but fibrinogen was excluded from the Eagle’s balanced salts solution. The loading procedure may be summarized as follows: Platelets were incubated with 2.5 μM Indo 1-AM in PRP for 30 minutes at 37° C in the presence of apyrase, prostacyclin, and indomethacin; the platelets were then washed in acid-citrate-dextrose that contained apyrase and albumin and were finally suspended in the Eagle’s balanced salts buffer containing bicarbonate, albumin, HEPES buffer, and hirudin to minimize any thrombin activation. Such preparations can aggregate readily to ADP if fibrinogen is added and can exhibit similar quenched-flow kinetics as platelets not loaded with Indo 1.\(^3^4\) They are therefore not refractory. The Indo 1–loaded samples were left to sit for at least 30 minutes at room temperature, protected from light, to allow full hydrolysis of the Indo 1-AM ester. Any residual ester was detected by an emission scan from 370 to 500 nm, with a shoulder at about 440 nm representing unhydrolysed ester.

Samples (2 ml) were placed in plastic cuvettes, and measurements were carried out using a Perkin-Elmer MPF-44A fluorescence spectrophotometer (Perkin-Elmer Corporation, Norwalk, Connecticut). The cuvettes were warmed at 37° C for 15 minutes to enable full shrinkage of the platelets to their discoid shape should any swelling have occurred.\(^3^5\) Excitation light (335 nm) was focused on the cuvette, and the fluorescence emission at both 395 nm and 480 nm was sequentially monitored at right angles. To compensate for dye leakage from platelets, blanks were prepared for each sample by centrifugation at 12,000 rpm for 6 minutes, just before the measurements were made. A standard curve, fit to an equation for one binding site, was prepared from the fluorescence ratio (395/480) of a series of \([\text{Ca}^{2+}]\)/EGTA [ethylene glycol 0,0'-bis(2-amino-ethyl)-N,N',N''-tetraacetic acid] buffer samples.\(^3^4,\(^3^6\) \([\text{Ca}^{2+}]\),] was calculated by interpolation of the 395/480 signal ratio with the standard curve.

\(\beta\)-Thromboglobulin

Plasma concentrations of \(\beta\)-thromboglobulin were determined with a commercially available radioimmunoassay kit (Amersham Corporation, Arlington Heights, Illinois). In all subjects, forearm venipuncture was performed with large bore (19 gauge) butterfly needles. Blood was gently withdrawn into plastic syringes and immediately placed into preservative-coated tubes accompanying the radioimmunoassay kit. The samples were frozen and assayed an average of 10 days after collection. The upper and lower limits of the assay were 218 and 5 ng/ml, respectively. Interassay variability was 10–15%.

Plasma Renin Activity

The GammaCoat radioimmunoassay kit (Baxter Travenol Diagnostics Inc., Cambridge, Massachusetts) was used for determination of plasma renin activity at pH 6.0. Performance characteristics of the assay included a sensitivity of 0.018 ng/tube and an interassay variability of 5–10%.

Statistical Analysis

Initial data analysis was performed with SAS, version 5.03 (Statistical Analysis Systems Institute, Cary, North Carolina). Calculation of all aggregation kinetic parameters was done with the BIOMEDICAL STATISTICAL SOLUTIONS program (Cantec Inc., Atlanta, Georgia). Student’s test for unpaired data was used to evaluate differences in the means between patients and control subjects for all observations. Correlation was determined by standard linear regression. The data are reported as the mean±SEM, unless otherwise stated.

Human Studies

Investigations were performed after approval by the University of Virginia Human Investigation Committee and in accord with assurance HHS 596 filed with and approved by the Department of Health and Human Services.

Results

This study examined platelet aggregation kinetics, intraplatelet free calcium and plasma \(\beta\)-thromboglobulin levels in 15 patients with uncomplicated mild-to-moderate essential hypertension and in 30 closely matched control subjects (Table 1). The age ranges were 21–38 and 21–39 years in control subjects and patients, respectively. Known essential hypertension had been present in the patient group for 1–18 years. Significant atherosclerosis

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<th>TABLE 1. Demographic Characteristics</th>
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<td>Characteristic</td>
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<tr>
<td>Age</td>
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<td>Hypertension duration (yr)</td>
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<td>Men</td>
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<td>Women</td>
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Values are mean±SEM where appropriate and are derived from 30 control subjects and 15 patients. Data in parentheses are percentages. None of the values were significantly different \((p>0.05)\).
was excluded in the control group by physical examination and determination of the plasma lipoprotein distribution profile. Noninvasive imaging of the carotid and femoral arteries was used as an additional screening technique in patients (Figure 1). Both groups compared favorably with respect to sex and race distributions. The clinical profiles of both patients and control subjects are shown in Table 2. Mean heart rates did not differ significantly, and mean systemic arterial pressures were, on the average, 8 mm Hg above the level required for the diagnosis of hypertension. Plasma total cholesterol levels tended to be higher and HDL cholesterol fraction lower in patients than in control subjects, but the difference did not achieve statistical significance \((p=0.13)\). However, the mean plasma triglyceride concentration in the patient group (Table 3) was almost twice that of the controls \((p=0.006)\). Values for plasma renin activity were evenly distributed over a range of 0.1–4.2 ng/ml/hr with no apparent clustering by race (not shown). Although the mean platelet count was lower in the patients than in control subjects, the values were not statistically different \((p=0.20)\). The mean platelet volume in the patient group equaled that in the control group (Table 4).

**Aggregation Kinetics**

Using quenched-flow aggregometry, we followed platelet aggregation reactions occurring within 5 seconds of cell stimulation with ADP or epinephrine. Maximal rates of platelet aggregation \((V_{max})\) with ADP (Figure 2) were significantly higher \((p<0.03)\) in patients than in control subjects \((30.1±2.9 \text{ vs. } 22.3±1.0\%/sec)\). However, when the \(V_{max}\) was corrected for the platelet count, statistical significance was lost \((\text{patients, } 33.8±1.5\%/sec; \text{control subjects, } 29.3±1.5\%/sec)\).

Paradoxically, the activation constants \((K_a)\) for ADP were significantly higher in patients versus control subjects \((2.86±0.69 \text{ vs. } 1.05±0.13 \mu M, p<0.03)\).

Aggregation characteristics with epinephrine were similar and are shown in Figure 3. The raw or uncorrected values for \(V_{max}\) were higher in patients than in control subjects \((12.1±1.0 \text{ vs. } 9.5±0.6\%/sec)\). Again, when the data were normalized for a platelet count of 200,000/mm\(^3\), no statistical difference was seen \((\text{patients, } 15.1±1.8\%/sec; \text{control subjects, } 12.6±1.0\%/sec)\).

A positive correlation between \(V_{max}\) with ADP and age was noted in both patients \((p<0.03, r=0.56)\) and control subjects \((p<0.04, r=0.41)\).
With ADP as the inducing agent, the onset time before aggregation begins in patients (Figure 4) was nearly double that observed in control subjects (0.7 ± 0.1 vs. 0.4 ± 0.1 seconds). No significant difference in the onset time to epinephrine was observed between the two groups. In patients, but not in control subjects, the mean onset time to ADP was longer in nonwhite patients (1.1 ± 0.2 seconds) than in white patients (0.6 ± 0.1 seconds) and was negatively correlated with the duration of hypertension (p = 0.05, r = 0.51). Although mean triglyceride levels in the patient group were significantly higher than in control subjects, no correlation with measured platelet kinetic aggregation parameters was noted.

β-Thromboglobulin

Plasma β-thromboglobulin concentrations were not significantly higher in patients than in control subjects (Figure 5). The mean value in the patient group was 34.3 ± 14.4 ng/ml whereas in control subjects was 28.3 ± 11.1 ng/ml (values are mean ± 1 SD). There was a large overlap between the two groups in the ranges of β-thromboglobulin values obtained. Significantly, no correlation was observed between β-thromboglobulin concentration and any of the platelet aggregation kinetic parameters described. Plasma β-thromboglobulin concentrations were independent of both systolic (p = 0.18, r = 0.36) and diastolic (p = 0.30, r = 0.29) blood pressure. No significant correlation with hypertension duration was noted (p = 0.44, r = 0.22).

Cytosolic Calcium

Resting intraplatelet free calcium concentrations determined by Indo 1 fluorescence are shown in Figure 6. The mean value in patients (213 ± 19 nM) was higher than that in control subjects (172 ± 14 nM), although this difference did not achieve statistical significance. In hypertensive individuals, but not in control subjects, a strong positive correlation (Figure 7) was noted between the cytosolic calcium concentration and systolic blood pressure (p < 0.003). A similar high degree of correlation with mean systemic arterial pressure (p < 0.004) and a smaller, but significant, positive correlation with diastolic blood pressure was also observed (p < 0.04). Platelet cytosolic calcium did not correlate with plasma renin activity. Interestingly, a negative correlation between onset time of aggregation with epinephrine and cytosolic calcium concentration was present in the patient group only (p < 0.05, r = 0.53). A weak, positive association was observed between the raw values for V_max with ADP and intraplatelet calcium concentration (r = 0.49, p = 0.06). Intraplatelet [Ca^{2+}], were not significantly correlated with plasma β-thromboglobulin levels in either patients or control subjects. It should also be noted that the mean volume of Indo 1–loaded platelets did not differ significantly (p > 0.3) between the starting PRP and final test suspension. Hence, the presence of Indo 1 does not appear to alter platelet morphology.

Discussion

During the last decade, attention has been increasingly focused on the description of platelet functional abnormalities in hypertension and on the concept that blood platelets may play a role in both

### Table 4. Hematological Characteristics

<table>
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<th>Characteristic</th>
<th>Controls</th>
<th>Patients</th>
<th>p value</th>
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<tr>
<td>Hematocrit (%)</td>
<td>42±1</td>
<td>42±1</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet count (10^9/mm³)</td>
<td>307±10</td>
<td>333±20</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet volume (fl)</td>
<td>6.1±0.1</td>
<td>6.1±0.2</td>
<td>NS</td>
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Values are mean±SEM from 30 controls and 15 patients. NS refers to p > 0.05.
the genesis and thrombotic complications of a chronic elevation in intra-arterial pressure.

The goal of our study was threefold: 1) to test whether platelets in patients with essential hypertension possess different aggregation kinetics compared with those from matched control subjects, 2) to establish possible correlations between platelet cytosolic free calcium, blood pressure, and platelet aggregation characteristics, and 3) to investigate the possibility that plasma β-thromboglobulin is elevated and correlates with the state of platelet activation as reflected in aggregation kinetic parameters.

Platelet Aggregability

We found that $V_{\text{max}}$ in essential hypertension was faster than in control subjects with either ADP or epinephrine as inducer (Figures 2 and 3). Therefore, there may be a greater aggregation tendency in such patients based on a combination of their platelet count and platelet reactivity. The difference between hypertensive patients and matched control subjects was not significant on a specific platelet basis.

Interestingly, more ADP (higher $K_a$) was required to induce platelet aggregation in the patients than in control subjects (Figure 2), and a significantly longer onset time or lag period before aggregation began was noted for the hypertensive group (Figure 4). These observations contrast with several reports in which platelet reactivity was significantly greater in hypertensive patients and with other reports in which no differences were found. This apparent discrepancy may be related to the fact that there are several in vivo and in vitro methods currently used for detection of hypersensitive platelets and that different phases of function may be monitored. For example, Poplawski et al found increased platelet adhesiveness in hypertensive patients. The major features of these methods have been reviewed. Also, different selection criteria for patients in each study may also result in heterogeneity on the basis of the hypertension and likely important epidemiological variables.

The relation between $V_{\text{max}}$ with ADP and age described in our study is consistent with a report that ADP-induced platelet aggregation tendency increased with age in 958 randomly selected subjects. Our data also suggest, but do not confirm, a slightly lower sensitivity to ADP in the platelets of black hypertensive individuals compared with white subjects that is reflected in the longer onset time; a similar relation has been reported previously.
Platelet Calcium and Blood Pressure

Platelet cytosolic calcium levels may serve as a sensitive index of cellular activation. Our data revealed a strong positive correlation between cytosolic calcium sensed by Indo 1 and systemic and systolic blood pressure in hypertensive individuals (p<0.004 and p<0.003, respectively; Figure 7). A positive correlation was also noted between cytosolic calcium and $V_{\text{max}}$. Therefore, we have evidence that platelet calcium homeostasis is disturbed in essential hypertension and that this may be related to increased platelet function. Elevated cytosolic calcium in hypertension has been observed by others with Quin 2 as fluorescent indicator. In two studies there was a close correlation between blood pressure and cytosolic calcium. However, in several animal models of hypertension, no change was found and a recent human study of 29 untreated patients showed no relation between calcium and blood pressure.

The question then arises as to the potential linkage between the increased cytosolic calcium and the changes in platelet reactivity we found with the quenched-flow approach. How is the prolonged lag time before ADP induces aggregation related to the overall increase in platelet aggregability? One rationale may involve the existence of partially activated platelets as a result of prior stimulation during in vivo circulation. It is known that platelets can become refractory such that a greater concentration of agonist is required to induce subsequent aggregation. The preactivated platelet may then aggregate more efficiently.

A second rationale may be developed from the possibility that there is a change in the heterogeneous character of the circulating platelet population in subjects with essential hypertension. Platelets are heterogeneous in functional ability as well as in physical properties such as size or density. We have used the quenched-flow approach to show that platelets that are most sensitive to ADP (low $K_a$) actually tend to aggregate less rapidly (low $V_{\text{max}}$). A similar trend was observed in platelets separated essentially according to size. Large platelets possess a low $V_{\text{max}}$ and $K_a$, whereas small platelets have a high $V_{\text{max}}$ and $K_a$ (Carty and Gear). These small cells contain the lowest specific content of glycogen, an observation consistent with increased resting levels of cytosolic calcium and a more active phosphorylase kinase.

In essential hypertension there may be a shift in the nature of the platelet population, perhaps as a result of an alteration at the precursor level, or an abnormal conditioning during circulation. We might have predicted an alteration in platelet size, but we found no difference (Table 4) between hypertensive and normotensive groups. This is in contrast to a recent report from Norway. The question of heterogeneity of platelet size and function has interested investigators for some time. Although there are clear differences in function and biochemical characteristics, it is generally agreed that platelet size does not correlate with platelet age.

A number of mechanisms, confirmed and presumptive, responsible for elevated platelet [Ca$^{2+}$]i in hypertension have been proposed. These include: a structural, platelet-membrane permeability defect, with alteration of the sodium-potassium adenosine triphosphatase (Na$^+$,K$^+$-ATPase) membrane pump mechanism; decreased platelet calmodulin concentration leading to altered activity of the Ca$^{2+}$-ATPase pump system; and an imbalance between vasoconstrictor hormones (angiotensin II) and vasodilators such as atrial natriuretic factor. Lindner et al recently suggested that plasma from patients with essential hypertension contains a substance that raises the intracellular free calcium in normal platelets. Interestingly, although a tight correlation between blood pressure and platelet cytosolic free calcium existed in our patient group, no such relation existed in the normotensive group. This observation does not argue against a putative humoral factor. According to Lindner et al, this factor may affect transmembrane calcium flux through calcium channels, increase release from cellular stores, or inhibit the Ca$^{2+}$-ATPase pump.

Recently, a significant positive correlation between platelet [Ca$^{2+}$]i and plasma renin activity was reported in 18 untreated patients with essential hypertension and 17 normotensive control subjects. Although the distribution of plasma renin activity values in the latter study closely approximated those that we report, we were unable to document any association between plasma renin activity and intraplatelet calcium concentration.

$\beta$-Thromboglobulin, Blood Pressure, and Platelet Activation

We also found that venous plasma $\beta$-thromboglobulin levels were not significantly different in the group of hypertensive patients than in matched control subjects. Moreover, there was a large overlap between the two groups in the ranges of $\beta$-thromboglobulin values as determined by the same radioimmunoassay method. In addition, no correlation between the state of platelet activation and plasma $\beta$-thromboglobulin levels was observed. These findings differ from two previous reports in which plasma $\beta$-thromboglobulin concentration and ADP-induced platelet aggregation were significantly higher in patients with uncomplicated essential hypertension compared with respective control subjects. In both studies the plasma $\beta$-thromboglobulin levels and the platelet functional defect were reversed after drug therapy for hypertension. Conversely, Catalano et al in a study of patients with severe hypertension and associated peripheral vascular disease, reported no difference in plasma $\beta$-thromboglobulin concentrations within the range of normal values. Other investigators have con-
tended that venous β-thromboglobulin levels in patients with World Health Organization (WHO) Class I disease do not differ significantly from those in age- and sex-matched controls, but these levels are significantly increased in the more advanced stages of hypertension (WHO Classes II-III). However, even this finding was not confirmed by others.19 Our study, in addition, showed that the plasma β-thromboglobulin concentration was independent of the level of blood pressure elevation and the duration of hypertension.

The discordance in the β-thromboglobulin data that was reported by various groups is difficult to reconcile. One problem is the fact that the conditions of sample procurement and processing may directly influence the subsequent plasma level of this release marker.24,25

Final Comments

Three limitations of this study are obvious. First, only a single subgroup of patients with essential hypertension was studied. Second, we did not investigate plasma or urinary catecholamine concentrations, which may affect platelet activation24,25 and cytosolic calcium.20 Third, the effect, if any, of antihypertensive therapy on the observed platelet function abnormalities was not studied.

In conclusion, our work suggests that several platelet functional abnormalities are detectable in the early stages of hypertension, before clinically detectable atherosclerosis develops. The platelets may undergo certain biochemical changes that decrease their affinity for the vascular endothelium but enhance their aggregation potential once they are sufficiently stimulated. These modifications in the platelet kinetic profile may result from overproduction of an abnormal platelet subpopulation, altered conditioning of mature platelets, or the effect of a humoral factor on calcium-regulated intraplatelet events.

Acknowledgments

We thank Barbara Weaver, Marcia Lehman, and John Spears for their help with the chemical assays; Donald Kaiser, PhD, for help with the statistical analyses; and Anne Shipe for assistance with preparation of the manuscript.

References


**Key Words**: β-thromboglobulin • adenosine diphosphate • platelets • calcium • epinephrine
Platelet calcium and quenched-flow aggregation kinetics in essential hypertension.
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_Hypertension_. 1989;13:558-566
doi: 10.1161/01.HYP.13.6.558

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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