Dose-Related Effects of Adenosine and Bradykinin on Microvascular Permeability to Macromolecules in the Hamster Cheek Pouch

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SUMMARY. The hamster cheek pouch preparation was used to assess microvascular permeability responses to three vasodilating agents: bradykinin, adenosine, and papaverine. Fluorescein isothiocyanate-dextran 150 was injected intravenously as a macromolecular tracer. To quantify changes in permeability, we calculated fluorochrome clearance values from the ratio of suffusate to plasma fluorescein isothiocyanate-dextran 150 concentration. The microcirculation was recorded on videotape, using epifluorescence and bright-field light microscopy. Topical application of bradykinin elicited dose-dependent increases in macromolecular permeability. Adenosine also augmented permeability in a dose-dependent fashion. The increases in tracer clearance, relative to control, were 9.4 nl/min for 10^-5 M adenosine and 39.4 nl/min for 10^-4 M adenosine. The standard error for these doses was 1.5 nl/min. Adenosine, 10^-6 M, did not alter permeability. The increment in clearance induced by 10^-4 M was comparable to that of bradykinin, 8 X 10^-7 M. Pretreatment with phenidone had no effect on the permeability response mediated by 10^-5 M adenosine. Topical application of papaverine enhanced the transvascular exchange of macromolecules in one-half of the preparations examined. Comparable doses of adenosine were approximately three times as effective. This study indicated that adenosine, like bradykinin, is capable of modifying microvascular permeability responses in the hamster cheek pouch. This modulatory effect appears to be due to a direct action on the postcapillary microvascular membrane. (Circ Res 58: 348-355, 1986)

Adenosine (ADO) is a potent vasodilating metabolite which modifies local blood flow in accordance with parenchymal oxygen requirements. This purine nucleoside has been proposed as the link between tissue metabolism and oxygen supply in heart (Berne, 1963; Olsson et al., 1978), skeletal muscle (Dobson et al., 1971; Bockman et al., 1976), intestine (Granger and Norris, 1980), and brain (Rubio et al., 1975). Although much attention has been directed to the role of ADO as a flow regulator, few investigations have addressed the question of ADO-mediated permeability responses.

Granger et al. (1978) examined the effects of ADO on intestinal hemodynamics and capillary fluid exchange in cat ileum. These investigators reported a decline in vascular resistance with no change in lymph flow and lymph oncotic pressure. Similarly, Williams and Peck (1977) reported the inability of ADO to promote exudation, upon intradermal injection in the rabbit. In contrast, Sugio and Daly (1983) observed that intradermal injections of ADO induced marked increases in plasma exudation in the rat. The inability of ADO to augment capillary permeability in cat intestine does not preclude such activity in other species. For example, serotonin increases permeability in the rat cremaster (Majno and Palade, 1961), but fails to do so in canine forelimb (Raymond et al., 1980). In fact, serotonin actually protects the forelimb from edema formation by antagonizing the action of bradykinin (BK). In view of the limited and contradicting observations of the potential of ADO as an edemogenic agent, more investigations are needed to clarify the influence of ADO on microvascular permeability.

The ability to diminish both arteriolar resistance and blood-lymph selectivity is characteristic of many inflammatory mediators. Since vasoactive agents such as histamine and bradykinin possess the dual capacity to regulate microvascular flow and transport, it seemed plausible that other vasodilators might also modulate the transvascular exchange of macromolecules.

The present investigation examined the influence of adenosine, papaverine (PAP), and bradykinin on the microvascular permeability to macromolecules in the hamster cheek pouch. Tracer extravasation induced by ADO and PAP was quantified on a dose-response basis and compared to that of BK, a known vasodilator and inflammatory agent. Our findings demonstrate that adenosine, and to some extent papaverine, promotes extravasation of macromolecules across postcapillary venules in the hamster cheek pouch.

Methods

All experiments were performed on the microcirculation of the hamster cheek pouch. Male Syrian hamsters (Me-
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These included a Nikon B exciter filter cassette comprised 50-W mercury lamp source in conjunction with the leakage. Individual fields of 0.033 mm² (32x) were also epiillumination for the evaluation of FITC-dextran 150 of a dichroic mirror DM505, a 490-nm excitation filter, with 10X occulars.

Fluorescein isothiocyanate dextran 150 (FITC-dx 150) was used as the fluorescent macromolecular tracer (Phar-...
TABLE 1

<table>
<thead>
<tr>
<th>Hamster</th>
<th>CI $\times 10^{-6}$ (mean ± SD)</th>
<th>Time (min)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.98 ± 3.48</td>
<td>95</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>2.12 ± 1.47</td>
<td>120</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>1.86 ± 1.56</td>
<td>120</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>2.91 ± 1.59</td>
<td>120</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>2.10 ± 1.58</td>
<td>120</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>1.09 ± 0.25</td>
<td>104</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>3.66 ± 0.87</td>
<td>120</td>
<td>22</td>
</tr>
</tbody>
</table>

Note: n refers to the number of 5-minute samples taken.

macromolecular selectivity resulting from the topical application of BK at concentrations of $1.6 \times 10^{-7}$, $3.2 \times 10^{-7}$, and $8.0 \times 10^{-7}$ M. Topical application of even the highest dose of BK did not alter systemic arterial pressure. All doses tested elicited increases in macromolecular transport, as determined by the formation of discrete sites of tracer exudation from postcapillary segments and fluorometric assessment of suffusate effluent. Leakage was visually detected within 2–4 minutes, and appeared to reach peak values in 6–10 minutes of BK application.

Suffusate FITC-dx 150 concentration increased within the first 5 minutes after BK application. Peak CI occurred 10–20 minutes after exposure to BK (1.6 $\times 10^{-7}$ M) and remained elevated for approximately 45 minutes in the four preparations examined. With BK (2.3 $\times 10^{-7}$ M), peak CI was obtained at 10–30 minutes after application and lasted for 45–65 minutes, slightly longer than the previous dose. The response to BK (8.0 $\times 10^{-7}$ M) was much more variable than that of the lower doses. Peak CI occurred at 5, 15, 20, and 85 minutes in four preparations. The duration of the clearance increment at this dose was approximately 90 minutes.

Figure 1 displays the clearance of FITC-dx 150 as a function of bradykinin concentration. Bradykinin, over the narrow range of $10^{-7}$ to $10^{-6}$ M, increased microvascular permeability in a dose-dependent manner. We did not intend to achieve a saturation of the effect of BK on permeability in this study.

Arteriolar diameters were measured in each preparation to confirm the vasodilator action of BK. Vasodilation occurred in all pouches examined. Bradykinin (1.6 $\times 10^{-7}$ M) increased the diameter of arterioles ranging from 20 to 50 $\mu$m by 53 ± 12%.

TABLE 2

<table>
<thead>
<tr>
<th>Hamster</th>
<th>Reduction</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.35</td>
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</tr>
<tr>
<td>2</td>
<td>2.50</td>
<td>1.72</td>
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<td>3</td>
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<tr>
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<td>2.02</td>
<td>1.50</td>
</tr>
<tr>
<td>5</td>
<td>2.04</td>
<td>1.89</td>
</tr>
</tbody>
</table>

Figure 1. FITC-dx 150 clearance as a function of bradykinin concentration. A dose-response relationship is shown. The data are expressed as means ± SD. When two groups were compared, Student’s nonpaired t-test was used. In all cases, P was less than 0.05. The number in parentheses refers to the number of pouches examined at each dose.

BK (3.2 $\times 10^{-7}$ M) by 67 ± 15%, and BK (8 $\times 10^{-7}$ M) by 111 ± 39%.

Papaverine

In a series of experiments, PAP of varying doses was applied to the splayed pouch to ascertain the concentration necessary to elicit vasodilation comparable to that of adenosine (10$^{-4}$ M), which increased mean arteriolar diameter 107.8 ± 60.1% ($n = 13$). PAP (4.3 $\times 10^{-5}$ M) promoted an increment in diameter of 105.5 ± 55.6% ($n = 12$), and therefore, was chosen as the test dose.

Topical application of PAP (4.3 $\times 10^{-5}$ M) had no effect on FITC-dx 150 permeability in six of the 11 preparations examined. Increased permeability in the five remaining pouches was evidenced by the presence of tracer in the interstitial space. In two of these preparations, PAP induced both discrete sites of tracer leakage.

Figure 2. Increment in FITC-dx 150 clearance following papaverine application. Clearance of FITC-dx 150 (mean ± se) was measured over the first 30 minutes following papaverine application. Approximately one-half of the preparations showed a leakage response. P, as determined by two-way ANOVA, is less than 0.0001. The number in parenthesis refers to the number of pouches examined.
of macromolecular leakage and diffuse leakage along the venules.

A comparison of the average clearance values recorded for the first 30 minutes subsequent to PAP administration is illustrated in Figure 2. The two-way ANOVA indicated two separate populations (P < 0.0001); the se for this analysis was 0.61 nl/min.

**Adenosine**

A series of 28 hamster cheek pouch preparations was used to assess the ability of ADO to modulate microvascular permeability to macromolecules. Topical application of ADO (10^{-4} M) elicited extravasation of tracer and the formation of discrete sites of fluorescent leakage (Fig. 3). As with BK, leakage was visually detected within 2–4 minutes, and peak leakage response seemed to occur at 6–10 minutes after exposure to ADO. Increased permeability to FITC-dx 150 was fluorometrically evident in the first 5-minute sample following ADO application. Peak Cl of fluorochrome resulted 20–35 minutes after exposure to ADO in eight of 12 preparations, and within the first 20 minutes in the remaining four pouches.

**FIGURE 3.** Effect of adenosine stimulation on microvascular permeability. Panel A: control state of the cheek pouch microcirculation following intravenous injection of FITC-dx 150. Panel B: same area after topical application of adenosine (10^{-4} M). Vessels showing leakage of fluorochrome are postcapillary venules 20-25 μm in diameter.

Topical application of ADO (10^{-5} M) also increased permeability to macromolecules in a time sequence similar to that of ADO (10^{-4} M) and BK. Peak Cl occurred 20–35 minutes after exposure to ADO in four of eight experiments. In the remaining preparations, peak Cl resulted in the first 20 minutes, and in one preparation at 55 minutes. As expected, the duration of the response to ADO (10^{-5} M) was less than that for ADO (10^{-4} M). Increase in suffusate fluorescence was detected up to a maximum of 70 minutes.

Adenosine (10^{-6} M) did not increase macromolecular permeability. No discrete leakage sites were elicited, and no increase in interstitial fluorescence could be detected visually. Analysis of suffusate samples confirmed these findings.

**Adenosine increased clearance in a dose-dependent manner.** Figure 4 displays the average clearance values obtained during the first 40 minutes after ADO application. In relation to control clearance, adenosine (10^{-6} M) increased Cl by 39.4 nl/min. That for ADO (10^{-5} M) was 9.4 nl/min. Since ADO (10^{-4} M) demonstrated no increase in permeability, the Cl value should approximate zero, once controls are subtracted. This is shown by a Cl value of 0.1 nl/min. The P value for the two-way ANOVA was 0.0001, and the se was 1.5 nl/min. Scheffe’s test verified that Cl of FITC-dx 150 was significantly different for all doses tested (P < 0.05), except 10^{-6} M.

A scanning of the microcirculation during the leakage period revealed that increases in permeability to fluorochrome were confined to the venous side of the circulation. Neither arterioles nor true capillaries exhibited permeability changes as determined by leakage site production. Therefore ADO, like BK, augmented visually detected FITC-dx 150 extravasation exclusively in venous segments. Diameters were measured to confirm the dilator activity of ADO in arterioles ranging from 20 to 50 μm. Adenosine 10^{-6} M increased arteriolar diameter by 54 ± 28%; ADO (10^{-5} M) increased diameter by 75 ± 30%, and (ADO 10^{-4} M) increased by 101 ± 47%.

**Blockade of Lipoxygenase and Cyclooxygenase Enzymes**

We used two hamsters as controls to assess whether phenidone itself had the capacity to modify microvascular permeability to FITC-dx 150, in addition to its inhibitor action on arachidonate metabolism. The intravenous injection of phenidone did not promote any visible leakage of fluorochrome. Pouches were examined for 1 hour. Analysis of suffusate fluorescence verified these observations.

A series of five hamsters were pretreated with phenidone. No changes in macromolecular permeability were apparent in the 20-minute interval between phenidone injection and topical application of ADO to the cheek pouch microvasculature. Adenosine (10^{-5} M) induced the formation of discrete sites
FIGURE 4. Increment in FITC-dx 150 clearance after adenosine application. Dose-response relationship is shown for the clearance (mean ± SD) of tracer over the first 40 minutes after adenosine application. Adenosine (10⁻⁵ M) had no effect on permeability. P, as determined by a two-way ANOVA, was less than 0.0001.

of fluorochrome leakage from microvessels. Pretreatment with phenidone neither blocked the permeability-altering effects of ADO nor altered the time course of the leakage response.

The permeability-enhancing effects of ADO were compared in animals with and without phenidone pretreatment. Clearance values were calculated for the first 40 minutes of the leakage response. Adenosine alone augmented the CL of FITC-dx 150 above control levels by 9.4 nl/min (Fig. 5), while in those pretreated with phenidone, adenosine increased CL by 12.2 nl/min. The P value for the two-way ANOVA was 0.44, and SE was 1.8 nl/min. Therefore, phenidone treatment had no effect on the ability of ADO to modify macromolecular exchange in the microcirculation of the hamster cheek pouch.

Discussion

Our results are the first to document a dose-response relationship between adenosine concentration and microvascular permeability to macromolecules in the hamster cheek pouch. To establish a baseline for comparison, we also studied the effects of bradykinin, a nonspecific inflammatory agent, and papaverine, a widely used vasodilator. The different data will be discussed first as separate phenomena, and then their interrelations as vasodilators and permeability modulators will be considered.

Technical Aspects

Due to the difficulties associated with quantification of fluorochrome exudation when using fluorescent intravital microscopic techniques, changes in macromolecular permeability have been evaluated primarily from a qualitative standpoint, that is, the visual detection of extravascular fluorescence. Quantitative measures such as the enumeration of leakage sites are rendered ineffective by diffuse-type leakage as well as the investigator's subjectivity in counting. In addition, the term "leakage site" is ambiguous in that the actual number of open junctions contributing to the production of one leaky site remains unknown. Conceivably, more junctions could open at higher doses with the elicitation of fewer leakage sites due to leakage overlap from junctions in close proximity. Although such information furnishes a general account of the potential of the cheek pouch vasculature to respond to vasoactive drugs, no conclusions may be drawn with respect to the actual quantity of material transported.

The chamber technique enables measurement of solute efflux with time (Mayhan and Joyner, 1984), thereby providing a more precise appraisal of macromolecular transport, both diffuse as well as discrete leakage. We chose to use this system to investigate the influence of vasodilating agents on macromolecular transport.

Bradykinin

In all 12 preparations in this series, BK reduced arteriolar resistance and augmented venular permeability to macromolecules. Arfors et al. (1979), Svensjö et al. (1979), and Gawlowski et al. (1982) suggested a dose-response based upon the number of fluorescent venular leakages. Our data are in agreement with their observations. By determining the clearance of FITC-dx 150 by spectrofluorometry, we have established the dose-response relationship for bradykinin on a firmer, stronger, quantitative basis. Graded concentrations of BK promoted a progressive elevation in the number of leakage sites induced, an increment in the quantity of tracer transported, and an increase in the duration of the altered permeability response.

Papaverine

Our data show that PAP augmented permeability to macromolecules in five of 11 preparations, as determined by an increase in the CL of FITC-dx 150. The fact that half of the preparations responded with increased permeability to FITC-dx 150 cannot be attributed to cytotoxicity, since Acosta et al. 

FIGURE 5. Influence of phenidone pretreatment on adenosine-mediated permeability responses. The data are expressed as mean ± SD. P, as determined by a two-way ANOVA, was 0.44.
Adenosine

Topical application of ADO, $10^{-5}$ M and $10^{-4}$ M, augmented the transvascular efflux of macromolecules as determined by the elicitation of discrete sites of FITC-dx 150 leakages and by an analysis of fluorochrome Cl values. Adenosine ($10^{-4}$ M) did not facilitate macromolecular exudation. Therefore, in the hamster cheek pouch, the threshold for ADO-mediated increases in permeability lies between $10^{-6}$ M and $10^{-5}$ M.

Clearance increased in a dose-related fashion. Fluorochrome exudation resulting from ADO application was similar to that produced by BK. Increases in permeability to fluorescent were confined only to the venous side of the circulation, particularly to postcapillary venules less than 20 μm in diameter. Because of the similarities between the target vascular segment and time course of the responses to ADO and BK, it is tempting to suggest that the operative mechanism of ADO-induced leakage is similar to that for histamine-type mediators. However, morphological correlates of endothelial contraction in preparations showing ADO-mediated leakage are needed to clarify this issue.

As vascular endothelium appears to play a dynamic role in the regulation of flow and transport, it is not surprising that these cells are believed to possess a number of receptors to a variety of hormone and vasoactive agents (Buonassisi and Venter, 1976; Awbry et al., 1979; Marceau et al., 1981; Heltianu et al., 1982; Pearson et al., 1983a, 1983b). The presence of an ADO receptor on vascular endothelium is a requisite for ADO-mediated gap formation, as these events would be predicated upon an endothelial purinoreceptor linked to contractile machinery. Further investigations are needed to explore possible receptor-effector coupling. These would be especially important since several subtypes of ADO receptors have been identified (Londos et al., 1980), and the existence of dual receptors, i.e., H1 and H2, on venous endothelium has been previously reported (Heltianu et al., 1982).

The finding that ADO modulates permeability to macromolecules in the hamster cheek pouch is of particular interest, since this nucleoside and well-known flow regulator also modulates inflammatory cell functions. ADO receptors are localized to the external cell surface of human lymphocytes (Marone et al., 1978), human basophils (Marone et al., 1979), human platelets (Haslam and Rosson, 1975), human neutrophils (Cronstein et al., 1983), and rat mast cells (Marquardt et al., 1978). The preponderant action of ADO on human blood cell types appears to be to suppress inflammatory activity. Adenosine inhibited antigen-mediated histamine release from human basophils (Marone et al., 1979), prevented platelet aggregation (Born and Cross, 1963), depressed immune activity in lymphocytes (Hirschhorn et al., 1970; Carson and Seegmiller, 1976), and antagonized the generation of superoxide anion by stimulated neutrophils (Cronstein et al., 1983). Furthermore, the inability to metabolize ADO properly has been clinically associated with severe combined immunodeficiency, a disorder characterized by a depression of both cellular and humoral immunity (Van der Weyden and Kelley, 1976).

Adenosine responses in the rat are similar to those in the hamster, as ADO exhibited pro-inflammatory activity. Adenosine potentiated IgE-mediated histamine release from rat mast cells (Marquardt et al., 1978), facilitated serotonin release from tail artery (Brown and Collis, 1981), and induced plasma exudation (Sugio and Daly, 1983). Adenosine exerts its physiological controls through the mediation of intracellular cyclic adenosine monophosphate (cAMP). Adenosine stimulates, inhibits, or has a biphasic effect on adenylyl cyclase levels (Londos et al., 1980), depending upon the species, the tissue, and the concentration applied (Haslam and Lynham, 1972).

Blockade of Lipoxygenase and Cyclooxygenase Enzymes

We pretreated hamsters with phenidone to determine whether ADO-mediated permeability changes in the cheek pouch ensued as a consequence of arachidonate metabolism. In the concentrations used, phenidone blocks both prostaglandin and leukotriene production (Blackwell and Flower, 1978; Burka and Paterson, 1980). Pretreatment with phenidone failed to prevent the augmentation in CI of FITC-dx 150 induced by ADO. Neither the permeability response nor its time course was altered. These results suggest that ADO-induced macromolecular permeability is mediated neither through the production of prostaglandins nor through the formation of leukotrienes. Adenosine has been reported to potentiate histamine release induced by anti-IgE, concanavalin A, and 48/80 from rat mast cells, but fails to alter the rate of spontaneous histamine release (Marquardt et al., 1978). Therefore, the augmentation in permeability subsequent to ADO exposure appears not to be due to mast cell stimulation. Our data suggest that these actions may result from a direct action of adenosine on the microvascular membrane.

Vasodilation and Permeability

Interestingly, adenosine ($10^{-6}$ M) increased arteriolar diameter by 54%, but failed to produce any change in microvascular permeability. The dilation
promoted by adenosine (10^{-6} M) was comparable to that of BK (1.6 \times 10^{-7} M). A BK dose that increased FITC-dx 150 in our experiments. These results suggest that vasodilation per se is an insufficient stimulus for the augmentation of macromolecular transport. Potent vasodilating agents such as isoproterenol fail to alter protein efflux (Raymond et al., 1980; Miller et al., 1982). Isoproterenol actually protects the microvasculature from the permeability-enhancing effects of BK (Svensjö et al., 1979). Under these conditions, vascular resistance is reduced without any accompanying change in permeability. The separation of permeability-enhancing effects from those on vascular resistance suggests that the augmentation in permeability is independent of changes in blood flow, microvascular pressure, and perfused surface area. The ability of a vasodilator to alter microvascular permeability may be elicited either through pressure-dependent mechanisms or through a direct action on the microvascular membrane.

A vasodilator may or may not elevate capillary hydrostatic pressure, depending on the ensuing modifications in pre- and postcapillary resistances (Fronke and Zweifach, 1975). Elevations in venous hydrostatic pressure beyond a critical level have been shown to increase both protein transport and lymph flow (Grega et al., 1979). Davis et al. (1986) reported that topical application of ADO (10^{-4} M) to the cheek pouch microcirculation elevates small vein pressures (less than 50 \mu m) by 3-4 mmHg. Vessels referred to as fifth-order venules (less than 10 \mu m) are subjected to an identical pressure rise. In our preparations, vessels with dimensions less than 10 \mu m exhibited no fluorescent leakage sites, suggesting that this modest but significant pressure increment is unable to mediate the observed changes in permeability. A comparable elevation of small vein pressures in the canine forelimb has also failed to enhance macromolecular exchange (Dobkins et al., 1981). Thus, a direct action on the microvascular wall may be implicated.

Joyner et al. (1979) failed to observe any correlation between changes in the number of leaky sites and increased volume flow for any dose of PGE_2 tested. As terbutaline produced similar increases in blood flow without eliciting leakage, intravascular pressure may not be a mechanism mediating gap formation. Elevations in venous pressure augment protein transport to a much lesser degree than as a permeability regulator. Wahl and Kuschnisky (1976) observed ADO-elicted vasodilation in cat pial arteries with doses as low as 10^{-7} M. Arteriolar dilation in the absence of venous permeability changes suggests a difference in the sensitivities of arterioles and venules to ADO stimulation.

In summary, we have determined in a quantitative manner the dose-effect relationship between adenosine concentration and microvascular permeability in the hamster cheek pouch. We have also related the potency of the adenosine effects to those produced by bradykinin in this microvascular bed. In addition, our results support the concept that vasodilating agents may directly modulate microvascular permeability.

We appreciate the expert advice from Dr. Stanley von Hagen on the statistical analysis of the data. We thank Drs. Patricia Dillon, Mauricio Boríl, and Arthur Ritter for invaluable constructive criticisms and suggestions in all phases of this work.

This research was supported in part by Grant HL 25032 from the USPHS NIH National Heart, Lung, and Blood Institute, a grant-in-aid from the American Heart Association (with contributions from the AHA—New Jersey Affiliate), and a grant from the Foundation of the UMDNJ.

Dr. W. Durán is an Established Investigator of the American Heart Association.

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Received February 14, 1985; accepted for publication November 27, 1985.

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Bergen Street, Newark, New Jersey 07103.

Received February 14, 1985; accepted for publication November 27, 1985.

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Circ Res. 1986;58:348-355
doi: 10.1161/01.RES.58.3.348

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