In Vivo Assessment in Sheep of Thromboresistant Materials by Determination of Platelet Survival

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SUMMARY The thromboresistance of 13 potentially blood-compatible polymers was assessed in sheep by determining survival of $^{51}$Cr-labeled platelets. Polymer tubing (120-150 cm x 2.0-2.3 mm i.d.) coiled around the neck was incorporated into the circulation through silicone rubber connectors as a carotid artery-external jugular vein shunt. The mean platelet half-life in control animals ("shunt control") was $78.2 \pm 2.8$ (SEM) hours. Eleven of the 13 polymers tested significantly shortened platelet half-life. Polyvinyl chloride ($T_{1/2} = 45.4 \pm 3.0$ hours), polyperfluoro ethylene ($T_{1/2} = 47.0 \pm 1.6$ hours), and a polymethyl acrylate (PMA)/acrilonitrile copolymer ($T_{1/2} = 50.7 \pm 7.0$ hours) produced the greatest shortening. Only silica-free polydimethyl siloxane ($T_{1/2} = 74.7 \pm 4.9$ hours) and PMA ($T_{1/2} = 81.5 \pm 3.4$ hours) were indistinguishable from shunt controls. Pretreatment of PMA tubing with autologous plasma in a paired trial significantly increased platelet half-life ($P < 0.05$ vs. untreated PMA). This system offers an economical, reproducible, sensitive, and biologically relevant method for assessment of the reactivity of artificial surfaces with platelets. Circ Res 46: 84-90, 1980

CONSUMPTION of platelets induced by contact of the blood with thrombus-promoting artificial materials complicates the use of prosthetic devices, such as vascular grafts (Harker et al., 1977a), artificial heart valves (Harker and Slichter, 1970; Weily and Genton, 1970), pump oxygenators (Bick, 1976), and apparatus for hemodialysis (Lindsay et al., 1977).

Thrombocytopenia or, in less severe cases, accelerated platelet destruction compensated by increased production is a characteristic feature of any clinical setting in which blood comes in contact with an artificial surface. The subject has been reviewed extensively (Berger and Salzman, 1974; Salzman, 1971a; Mason and Shinoda, 1975; Forbes and Prentice, 1978; Brash et al., 1976; Baier, 1975) and was the topic of a recent major conference (Vroman and Leonard, 1977).

Among the obstacles to development of improved thromboresistant artificial materials is the lack of a satisfactory system for assessing the reactivity of blood with surfaces. The properties of an ideal in vivo method would include the following: (1) sensitivity—the ability to discriminate among materials, especially those relatively compatible with blood and too nearly bland to produce gross thrombosis; (2) reproducibility—the capability of repetition with minimal experimental error; (3) economy—the ability to provide enough data points for statistical analysis at a reasonable cost with readily available laboratory animals; (4) versatility—applicability to a variety of test materials with different properties; (5) simplicity—no demand for complex surgical procedures or fabrication of complicated hardware; and (6) realism—reflection of events occurring continuously over a sustained period of time in a situation analogous to real life in man.

Determination of the life-span of $^{51}$Cr-labeled platelets in sheep bearing carotid artery to jugular vein shunts made of test materials satisfies most of these requirements.

Methods

Adult sheep of either sex were used. Under general anesthesia (sodium thiopental, 18 mg/kg, iv, supplemented by 1% halothane), a carotid artery to external jugular vein shunt was inserted, employing medical grade Silastic silicone rubber (Extracorporeal Medical Specialties, Inc., S-300 Saf-t-shunt) with etched Teflon vessel tips (Extracorporeal T-410). The arterial and venous limbs of the shunt were joined by an Extracorporeal etched Teflon connector, two of which also were used when lengths of the material to be tested were interposed. The total length of the basic shunt was 7 cm. Shunts remained patent up to 9 months and were replaced by reoperation if necessary. Blood sampling was by venipuncture in unoperated sheep—otherwise from...
the arterial limb of the shunt—and was conducted without anesthesia.

Materials were tested by interposing tubing 120-150 cm long and 2.0-2.3 mm i.d. (total surface area 75-108 cm²) between ends of the basic shunt. The tubing was filled with sterile 0.154 M NaCl before connection to the circulation; care was taken to avoid an air-blood interface. The test materials were inserted into the circuit at the time of collection of the blood sample 2 hours after platelet labeling (see below). The tubing, coiled around the neck and covered with a dry towel, was well tolerated by the sheep without restraint. Test materials were prepared specially or, if from commercial sources, were well-characterized polymers extruded as tubing or coated by deposition from solution under clean conditions (Nyilas and Kupski, 1970) on the inner surface of preformed tubes. When glassy polymers were studied, the coated tubing was encased in a rigid collar to prevent bending of the tubing and cracking of the plastic coatings.

A list of the materials tested is given in Table 1. Polyurethane tubing was extruded by Electronized Chemical Corp. using B51 polyester polyurethane (Hooker Chemical Co.). Silicone rubber tubing, medical grade, was from Dow Corning Corp. Plasticized polyvinyl chloride tubing (Tygon) was obtained from U.S. Stoneware (Div. of Norton Co.). Polyperfluoro ethylene tubing (Teflon) was supplied by Dow Corning Corp.

Tube coatings were prepared as follows: Methyl methacrylate, propyl methacrylate, ethyl methacrylate, hexafluoro isopropyl methacrylate, methyl acrylate, acrilonitrile, and styrene monomers were obtained from Polysciences, Inc., and were redis-tilled prior to polymerization. Polymethyl methacrylate (PMMA), polypropyl methacrylate (PPMA), polyethylene methacrylate (PEMA), polyhexafluoro isopropyl methacrylate (PHIMA), and polystyrene (PS) were prepared from these monomers by solution polymerization in dioxane. Polymethyl acrylate (PMA) was solution polymerized in methyl ethyl ketone and polymethyl acrylate/acrilonitrile co-polymer (PAN) (75% methyl acrylate, 25% acrilonitrile) was solution polymerized in dimethyl formamide. Polymerization was initiated with 2,2′-azo-bis-isobutyronitrile. Each polymer was precipitated with methanol and redissolved in chloroform prior to deposition from solution. Polydimethyl siloxane (PDMS) (Stauffer Chemical Co., SWS Silicones Div.), grade 472 with 0.1% vinyl content and free of any filler or heat-curing agents, was dissolved in toluene. Polyvinyl acetate (PVA) was obtained in the form of beads from Air Products and Chemicals, Inc., and was dissolved in ethyl alcohol.

Platelets were labeled with 51Cr in a closed system by the method of Abrahamsen (1968). Blood, 250 ml, was collected in a Fenwal bag containing 67.5 ml of acid-citrate-dextrose (ACD, USP Formu-la A), and the platelets were isolated by differential centrifugation. Platelet-rich plasma (PRP) was prepared by centrifugation at 400 g for 20 minutes at 22°C. Platelet-poor plasma (PPP) and a platelet button were prepared by centrifugation of PRP at 1600 g for 20 minutes. The platelet button was resuspended in Ringer’s-citrate-dextrose [70% vol/vol Ringer’s Inj., USP; 20% vol/vol trisodium citrate (3.12 g/dl); 10% vol/vol dextrose (5 g/dl)] and incubated with 1 mCi Na251CrO4 (New England Nuclear) for 45 minutes at 22°C. Unbound radioactivity was removed by resuspending the labeled platelets in PPP, sedimenting at 1600 g for 20 minutes, and removing the PPP by decanting. The washed labeled platelets were resuspended in 30-40 ml of plasma and reinfused through the venous end of the shunt in sheep which had been operated on—otherwise by venipuncture.

Blood samples were taken at 2, 20, 25, 46, 70, and 90 hours after infusion of the labeled platelets. Platelets were separated from red cells at room temperature by centrifuging at 1600 g for 10 minutes, decanting the PRP, resuspending the red cells in 4 ml of saline, centrifuging again at 1600 g for 5 minutes, and decanting the saline supernatant which was mixed with the PRP. The platelets then were washed by centrifuging at 2400 g for 10 minutes and resuspending in 1% ammonium oxalate and counted for ß-emission. Recovery of platelets in the blood sample was 80 ± 5%, determined by platelet counting of whole blood and PRP by the method of Brecher and Cronkite (1950). It proved to be essential to count radioactivity in the separated platelets rather than in whole blood, since, in sheep which had been used for repeated experiments, labeling of red cells contaminating the platelet sample was a significant source of error. The number of labeled platelets remaining in the circulation at the time of sampling was expressed as a percentage of those infused (percent yield). Recovery at 2 hours was in all cases greater than 40%.

Platelet half-lives were determined from computer-derived least squares fits of the best straight lines through linear and semi-log plots of percent yield vs. time. Half-lives determined from each fit

<table>
<thead>
<tr>
<th>Sample</th>
<th>Abbreviation</th>
</tr>
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<tbody>
<tr>
<td>No shunt</td>
<td>NS</td>
</tr>
<tr>
<td>Shunt control</td>
<td>SH</td>
</tr>
<tr>
<td>Polymethyl acrylate</td>
<td>PMA</td>
</tr>
<tr>
<td>Polydimethyl siloxane</td>
<td>PDMS</td>
</tr>
<tr>
<td>Polymethyl methacrylate</td>
<td>PMMA</td>
</tr>
<tr>
<td>Polypropyl methacrylate</td>
<td>PPMA</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>PU</td>
</tr>
<tr>
<td>Polyvinyl acetate</td>
<td>PVA</td>
</tr>
<tr>
<td>Polyhexafluoro isopropyl methacrylate</td>
<td>PHIMA</td>
</tr>
<tr>
<td>Polystyrene</td>
<td>PS</td>
</tr>
<tr>
<td>Silicone rubber (Silastic)</td>
<td>Sil</td>
</tr>
<tr>
<td>Polyethyl methacrylate</td>
<td>PEMA</td>
</tr>
<tr>
<td>Polymethyl acrylate/acrilonitrile co-polymer</td>
<td>PAN</td>
</tr>
<tr>
<td>Polytetrafluoro ethylene copolymer</td>
<td>Tef</td>
</tr>
<tr>
<td>Polyvinyl chloride</td>
<td>PVC</td>
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</table>
were weighted and averaged using computer-derived sums of squares of the deviations of the data points from the fitted curves according to the following formula: $M_w = (AS_B + BS_A)/(S_A + S_B)$, where $M_w =$ weighted mean half-life; $A =$ half-life determined from linear fit; $B =$ half-life determined from semilog fit; $S_A =$ sum of squares from linear fit; and $S_B =$ sum of squares from semilog fit. This is one of the methods recommended by the Panel on Diagnostic Application of Radioisotopes in Hematology (1977). Analysis of platelet survival by fitting linear or exponential curves alone or by fitting a $\gamma$ function provided results not statistically significantly different. However, experimental variation (expressed as the standard error of the mean) was greater when the data were analyzed by each of the latter methods than when the method of analysis described above was used.

Statistical analyses of differences among materials and data organization were performed on the PROPHET system, a national computer resource sponsored by the Chemical/Biological Information Handling Program, National Institutes of Health.

Experiments in which thrombosis of the shunt occurred were not included in the analysis because of our inability to distinguish between occlusion of the tubing due to kinking or other mechanical causes and failure due to highly reactive surfaces. There proved to be no correlation between the frequency of occlusion of tubing made of a given material and platelet survival.

**Results**

We performed 191 experiments with 36 sheep. Platelet half-life was a function of the surface area of tubing material to which the blood was exposed. However, platelet survival in unoperated sheep $[T_{1/2} = 61.9 \pm 2.5 (SEM) \text{ hours}, n = 22]$ was shorter than in sheep with the basic shunt $[T_{1/2} = 78.2 \pm 2.8 \text{ hours}, n = 17; P < 0.001]$, probably because it was necessary to draw blood for $^{51}$Cr labeling by venipuncture in the unoperated sheep, rather than through the arterial limb of the shunt. The latter route provided a more rapid flow of the blood collected for $^{51}$Cr labeling and may have been associated with less platelet activation and, therefore, with less artificial shortening of platelet life-span. In the subsequent comparisons of materials, the standard for comparison is the basic shunt ("shunt control"). When longer segments of silicone rubber tubing (polydimethyl siloxane with 35% silica filler) were added to the basic silicone rubber shunt, platelet survival was shortened $[T_{1/2} = 64.0 \pm 2.8 (SEM) \text{ hours at 50 cm}, P \text{ (vs. shunt control)} < 0.001; T_{1/2} = 61.8 \pm 2.0 \text{ hours at 150 cm}, P \text{ (vs. shunt control)} < 0.001].$

Figure 1 illustrates the results of comparison of 13 materials, shunt controls, and unoperated controls. Materials (and controls) are listed in order of increasing reactivity as indicated by decreasing mean weighted platelet half-lives. In addition, the number of trials ($n$) and the standard error of the mean for each material and control are shown. $F$ values were determined using Dunnett's test for comparison of multiple normally distributed samples vs. control (Dunnett, 1964). The test was applied using a one-tailed analysis at $P$ levels of 0.05 and 0.01. Data also were analyzed using the non-parametric Kruskal-Wallis and Wilcoxon rank sum tests (Hollander and Wolfe, 1973) which do not require that the data be distributed normally.

A number of important features of Figure 1 should be noted. Of the 13 materials examined seven (PS, Sil, PEMA, PAN, PVC, and Tef) produced statistically significant shortening of the platelet half-life ($P < 0.05$). Four materials (PMMA, PPMA, PVA, and PHIMA), which were not significantly different from the shunt controls at $P < 0.05$ had six or fewer trials. To test for a developing trend with these materials, Dunnett's test was reapplied assuming an $n$ (number of trials) of 5 time: the actual $n$. This resulted, for each of these four materials, in a significant difference vs. the shunt controls ($P < 0.05$). Only PMA and PDMS showed...
no statistically significant difference or even a trend toward significant difference vs. shunt controls. Analysis of the data in Figure 1 by the Kruskal-Wallis and Wilcoxon tests produced results equivalent to those obtained with the Dunnett's analysis. One-tailed nonparametric comparisons of the four borderline materials described above with the shunt controls yielded P values ranging from 0.07 to 0.10.

Comparison of PDMS (pure silicone rubber with no silica filler, T_{1/2} = 74.7 ± 4.9, SEM) with "medical-grade" silicone rubber tubing (T_{1/2} = 61.8 ± 2.0) using Student's t-test (Snedecor and Cochran, 1967) indicated a significant shortening of platelet survival with "medical grade" tubing (P < 0.05). Scanning electron micrographs of silicone rubber tubing (shown in Fig. 2 compared with PDMS-coated tubing) indicate that the silica filler is exposed at the surface, possibly available for direct contact with blood.

A direct comparison of PMA and the three polymeric methacrylates tested indicates a rank order of platelet half-lives as follows: PMA > PMMA > PPMA > PEMA. Although the number of trials with the acrylates was small, the median platelet half-life for PMA was greater than for PMMA (P < 0.08), PMMA (P < 0.09), and PEMA (P < 0.02). Median platelet half-lives for each of the methacrylates were not significantly different from one another.

As shown above, statistically significant differences between many materials and controls were obtained even though the number of trials for many materials was small and the variability associated with platelet half-life determinations was large. By way of illustration, Figure 3 shows computer-derived survival curves from four trials using one sheep and four different materials with weighted half-lives ranging from 58.7 hours to 83.2 hours. In Table 2, 15 trials are shown in which three determinations were performed with silicone rubber in each of five different sheep. Analysis of variance indicated that sheep-to-sheep variation was not a significant source of error relative to experimental error from other causes.

In vitro studies (Salzman et al., 1977) have shown that the reactivity of some surfaces with platelets can be influenced by preliminary exposure to cell-free plasma. This phenomenon was investigated in vivo by determining platelet life-span in sheep bearing treated and untreated polymethyl acrylate shunts (150 cm long). The following data were obtained in separate trials not included in the comparison of materials presented above. Platelet survival was determined twice in each of seven sheep, once with untreated PMA shunts and once with PMA shunts pretreated with citrated platelet-free plasma from the same sheep for 2 minutes before insertion of the tubing into the test circuit. Two weeks separated the two determinations. The sequence of tests was random. Care was taken to avoid an air-plasma interface at the surface of the tubing. The results of this comparison are shown in Figure 2.

**Figure 2** Scanning electron micrographs of the inner surface of (1) medical-grade silicone rubber tubing and (2) polyurethane tubing coated with PDMS (a. 890X; b. 8900X).
Fig. 3. Computer-derived survival curves obtained with one sheep and four materials: (1) shunt control, T_{1/2} = 83.2 hours; (2) PS, T_{ir} = 58.7 hours; (3) PMMA, T_{1/2} = 66.4 hours; (4) PMA, T_{1/2} = 75.5 hours.

Fig. 4. Analysis by paired t-test showed significant prolongation of platelet survival as a result of plasma pretreatment.

Discussion

Determination of platelet life-span in sheep bearing arteriovenous shunts of a test material is an economical, sensitive, realistic, reproducible test of the reactivity of the material with platelets. Although the technique has a substantial experimental error, one can demonstrate statistically significant differences among test materials with a reasonably small number of experiments. The error of the method probably could be reduced by taking replicate samples at each time point, by determining platelet recovery in each blood sample, and by sampling at additional intermediate times. The method is suitable for assessment of thrombore- sistant materials, whose subtle but important influences on blood elements may escape recognition by in vitro tests, especially those that employ anticoagulated blood. The large surface area possible in the form of tubing makes it feasible to test materials that are relatively but not perfectly unreactive. For materials which in 150-cm lengths do not shorten platelet survival compared to the basic 7-cm medical grade silicone rubber shunt, a logical next step would be the fabrication of a basic shunt from the test material. Provided the fluid mechanical re-

Table 2  Replicate Half-Life Determination using Silicone Rubber Tubing (Medical Grade Silastic)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sheep 1</th>
<th>Sheep 2</th>
<th>Sheep 3</th>
<th>Sheep 4</th>
<th>Sheep 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58.7</td>
<td>61.0</td>
<td>55.2</td>
<td>57.8</td>
<td>64.7</td>
</tr>
<tr>
<td>2</td>
<td>61.3</td>
<td>60.8</td>
<td>78.6</td>
<td>62.2</td>
<td>57.4</td>
</tr>
<tr>
<td>3</td>
<td>69.0</td>
<td>48.0</td>
<td>66.2</td>
<td>56.2</td>
<td>58.1</td>
</tr>
</tbody>
</table>

Fig. 4. Effect of plasma pretreatment of PMA-coated tubing on platelet survival.

There is evidence that an early event upon exposure of blood to a foreign surface is deposition of a layer of adsorbed plasma constituents, chiefly protein, on the surface (Baier and Dutton, 1969; Scarborough et al., 1969; Salzman, 1971b). The nature of the adsorbed layer is believed to play a decisive role in the changes in blood elements induced by contact with the surface. Fibrinogen appears to predominate among the protein species that constitute the initial adsorbed layer (Vroman and Adams, 1969). In vitro studies (Zucker and
Vroman, 1969; Packham et al., 1969; Salzman et al., 1969) have indicated that the reactivity of platelets with glass or polymer surfaces can be altered by preincubation of the surface with purified fibrinogen or albumin solutions. Fibrinogen increases reactivity, and, for many surfaces, albumin has the opposite effect. It has also been shown in vitro that PMA, more notably than other polymers studied, is made less reactive by preincubation with platelet-free plasma (Salzman et al., 1977). It is presumed that this effect results from selective adsorption of a coating layer of relatively bland plasma components, presumably proteins. We now report on the basis of these in vivo studies that preincubation of PMA with platelet-free autologous plasma resulted in virtual passivation of the test surface, presumably because of adsorption of a plasma component, probably protein, on the test surface. Such a result would not be expected a priori, since adsorption of plasma proteins is thought to precede reaction of platelets with artificial surfaces even when whole blood is presented to the surface. Preincubation for at least 1.5–2.5 minutes was required for passivation of PMA beads by plasma in vitro (unpublished data). When PMA tubing was preincubated for 2 minutes with citrated autologous platelet-poor sheep plasma, there was significant prolongation of platelet survival compared with the same sheep bearing a standard untreated PMA arteriovenous shunt. Since the determination of platelet survival in sheep requires 4–5 days, these results indicate that precoating of a polymer surface with plasma constituents before its contact with the blood can have lasting effects on the reactivity of the surface. Furthermore, it appears that events occupying the first few moments after initial contact of blood with an artificial surface may have a decisive effect on the long-term reactivity of the surface. Although these experiments dealt only with PMA, they may have broader implications for other materials in contact with the blood.

The acrylate derivative studied (PMA) has a glass transition temperature below 37°C, whereas all three methacrylates (PMMA, PEMA, and PPMA) are glassy at body temperature (Van Kreveldon, 1972). All the methacrylates were more reactive than PMA in their effect on platelet life-span. These results are consistent with the suggestion (Merrill, 1977) that the chain mobility of polymers may have a determinant effect on their reactivity with blood.

Of the materials studied, noncrosslinked filler-free PDMS and PMA were least reactive. The first of these previously has been found superior to conventional silicone rubber with silica filler under experimental conditions (Weathersby et al., 1975; Zapol et al., 1975) simulating clinical application and is now receiving clinical assessment in patients. Such an experience provides support for the relevance of determination of platelet survival in experimental animals in assessment of materials designed for contact with the blood.

Acknowledgments

We express our appreciation to Drs. Bernard J. Ransil and Arthur Dempster for their help with the statistical analysis of the data and to Noel Caragian for his technical assistance.

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Effects of Rapid Stimulation on the Transmembrane Action Potentials of Rabbit Sinus Node Pacemaker Cells

ITSUO KODAMA, JUNKI GOTO, SHIGEYUKI ANDO, JUNJI TOYAMA, AND KAZUO YAMADA

SUMMARY We studied the mechanism of post-overdrive suppression in superfused rabbit sinus node pacemaker cells. Small specimens of sinus node tissue isolated from rabbit hearts were driven at a fast rate (overdrive) for 10-120 seconds using single sucrose gap methods. During the control perfusion (35 °C Tyrode's solution), overdrive caused a progressive decrease in maximum diastolic potential (MDP), overshoot (OS), and maximum rate of depolarization at phase 0 [(dV/dt) max]. After cessation of the overdrive, the rate of diastolic depolarization decreased, and the spontaneous activity was suppressed temporarily (post-overdrive suppression). MDP, OS, [(dV/dt) max], and the spontaneous activity returned within a few seconds to the level observed before overdrive. Atropine (2 × 10^{-7} g/ml) did not influence the effects of overdrive. After ouabain administration (3 × 10^{-7} g/ml) or in low temperature perfusate (25 °C), the effects of overdrive were accentuated, and a marked suppression of spontaneous activity with a long pause of over several seconds was seen following the overdrive. These results suggest that the post-overdrive suppression of sinus node is attributable, at least in part, to ionic shifts following overdrive, and may be potentiated by metabolic dysfunction of pacemaker cells.


“Overdrive suppression tests” through the use of rapid atrial pacing have been employed extensively in the evaluation of patients with sinus node dysfunction (Mandel et al., 1972; Narula et al., 1972; Ferrer, 1973; Gupta et al., 1974; Strauss et al., 1976; Breithardt et al., 1977; Jordan et al., 1978). However, in spite of many in situ and in vitro studies, much remains to be clarified as to the underlying mechanism of sinus node post-overdrive suppression (Vassalle, 1977). West and collaborators (West, 1961; Amory and West, 1962; Vincenzi and West, 1963) reported that repetitive electrical stimulation of isolated rabbit sinus node tissue was followed by a period of suppression of spontaneous activity accompanied by membrane hyperpolarization. Since both the suppression and the hyperpolarization were potentiated by physostigmine and abolished by atropine, they attributed the negative chronotropic effect of the repetitive electrical stimuli to the release of endogenous acetylcholine from the sinus node tissue. Lu et al. (1965) obtained similar results in their experiments using isolated cat sinus node preparations. However, the finding that atropine did not abolish completely the post-overdrive suppression led them to the conclusion that, although acetylcholine release from the cardiac tissue plays an important role in sinus node post-overdrive suppression, other factors are involved in this phenomenon. These factors could include conduction failure within the sinus node or ionic shifts, e.g., those resulting from augmented K⁺ efflux and/or Na⁺ or Ca²⁺ influx. This hypothesis was supported by the in situ studies of Lange (1965).
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Circ Res. 1980;46:84-90
doi: 10.1161/01.RES.46.1.84
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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