Changes in Plasma Factor VIII Complex and Serum Lipid Profile during Atherogenesis in Cynomolgus Monkeys
Beverly W. Baron, Ross T. Lyon, Christopher K. Zarins, Seymour Glagov, and Joseph M. Baron

If endothelial injury plays a prominent role in early atherogenesis, the plasma levels of von Willebrand factor (VWF), which is made within and normally released from endothelial cells, might be expected to rise as a marker of the cellular damage. To evaluate this hypothesis, we measured plasma VWF (as VIIIIR:Ag), factor VIII:C, and serum lipids serially up to 37 weeks in 29 adult male cynomolgus monkeys on an atherogenic diet. Factor VIII:C peaked at 113% above baseline by week 10 (p<0.0001), then fell and remained 53% below baseline (p<0.04) during weeks 20 to 37. However, the overall rise in VWF was not significant. In contrast, serum cholesterol continued to rise after week 21. Serum phospholipids (PL), triglycerides (TG), and free fatty acids (FFA) showed a temporal pattern similar to VIII:C. Significant positive correlations with VIII:C were noted for PL (r=0.59, p=0.0001) and TG (r=0.36, p=0.0096). At autopsy, small to moderately advanced atherosclerotic lesions were distributed throughout the aortas of the majority of the animals. We conclude that changes in plasma VIIIIR:Ag do not correlate with atherogenesis in this model. However, the similar course of VIII:C, TG, and PL suggests that these substances may be involved and perhaps interrelated early in atherogenesis. (Arteriosclerosis 10:1074-1081, November/December 1990)

The sequence of changes and interactions among the multiple factors involved in early atherogenesis remains unclear. Other researchers have made observations that suggest that endothelial injury may play a prominent role in the pathogenesis of this process. However, we have not been able to document damage to endothelial cells in ultrastructural analyses of diet-induced atherosclerotic lesions. If endothelial injury and consequent release of intracellular components are indeed prominent features of early atherogenesis, one might expect that plasma levels of von Willebrand factor (VWF), which is manufactured in the Weibel-Palade bodies of vascular endothelial cells, would rise as lipid accumulates in arterial walls. Therefore, to evaluate this hypothesis further, we performed serial determinations of plasma VWF levels (measured as VIIIIR:Ag) and plasma VIII:C, which is noncovalently bound to circulating VWF, and we correlated these with the serum lipid profiles in groups of cynomolgus monkeys participating in an ongoing study of diet-induced atherogenesis.

Methods
Study Rationale and Outline
Twenty-nine adult male cynomolgus monkeys (Macaca fascicularis) that weighed 5 to 6 kg and were participating in another ongoing study in our laboratory were divided into two groups (Figure 1). In 19 animals, a high-grade stenosis was created by coarctation in the mid thoracic aorta; the coarctation was reversed 3 months later (coarctation reversal group). Five monkeys died within 2 to 4 weeks after coarctation. The surviving 14 animals were maintained on a control diet (Purina Monkey Chow) for 3 months (86 to 92 days). One week before coarctation reversal, an atherogenic diet (Purina Monkey Chow supplemented with 2% cholesterol and 25% peanut oil by weight) was begun. Five monkeys died within 2 to 4 weeks after coarctation. The surviving 14 animals were maintained on a control diet (Purina Monkey Chow) for 3 months (86 to 92 days). One week before coarctation reversal, an atherogenic diet (Purina Monkey Chow supplemented with 2% cholesterol and 25% peanut oil by weight) was begun. One monkey died at the coarctation reversal. The remaining 13 animals were sacrificed at intervals throughout the subsequent 37 weeks on the diet.

The sham group (10 animals) were fed the control diet for 3 months without surgical intervention until 1 week after starting the atherogenic diet, when a sham aortic coarctation reversal was carried out. These animals were sacrificed at intervals until the 14th week on the supplemented diet.

Periodic blood samples for coagulation assays and lipid profile were obtained at baseline and throughout the course of the study. Histologic evaluation of the degree of atherosclerotic change at predetermined levels of the thoracic and abdominal aorta was performed after death.
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Figure 1. Study outline: The effect of aortic coarctation reversal on atherogenesis in cynomolgus monkeys.

**Animal Handling and Surgical Procedure**

The monkeys were handled and cared for according to National Institutes of Health guidelines for laboratory animals and in accordance with the institutional guidelines of the University of Chicago. All animals were housed in individual cages and were allowed to eat and drink water ad libitum. Before the surgical procedures, each animal received parenteral antibiotics (250 mg cefazolin sodium intravenously). All operative procedures used sterile surgical techniques. The anesthesia for surgical procedures was by intramuscular injections of ketamine hydrochloride and intravenous administration of sodium thiopental (Surital) to obtain a surgical level of anesthesia. Blood was obtained under anesthesia with ketamine hydrochloride (15 mg/kg) given by intramuscular injection. All samples were venous except those done on a day of surgery or at sacrifice, when arterial specimens were collected. Coarctations were created by tightening a 3 mm wide polyethylene band placed circumferentially around the midthoracic aorta to create a localized high-grade stenosis resulting in a mean aortic pressure gradient equal to or greater than 45 mm Hg.

During reversal of coarctations, the polyethylene band was removed from around the aorta, and the coarcted segment of the aorta was dilated with a 2 cm long, 7 mm diameter angioplasty balloon advanced from a right femoral arteriotomy site. Two inflation-deflation cycles of 30 seconds' duration were performed in 3 to 5 atmospheres of pressure before removal of the balloon in its undistended state.

Sham animals were not subjected to vessel stenosis. Instead of reversal, they received a sham operation consisting of thoracotomy, rib resection, and transfemoral balloon dilatation of the midthoracic aorta.

At the time of sacrifice, the animals were exsanguinated under anesthesia after the final blood samples were obtained. The sections for histology were placed in 3% glutaraldehyde. The slides for light microscopy were made from paraffin-embedded histologic samples and were stained with hematoxylin and eosin, Weigert-Van Gieson, and Gomori trichrome aldehyde fuchsin.

**Coagulation Assays**

**Sample Handling**

All blood samples were anticoagulated in citrated Vacutainer tubes (one part 3.8% sodium citrate to nine parts blood), which were immediately refrigerated and processed within 2 hours (plasma was spun off and frozen at −70°C).

**Factor VIII:Ag Assay**

Factor VIII:Ag levels in monkey plasma were determined with a commercially available Rocket Electrommunoassay Method (Helena Laboratories, Beaumont, TX) for human factor VIII:Ag levels. The standard curves for normal human and baseline monkey plasma were parallel, but the monkey curve was consistently displaced to the right when plotted on two-cycle semilogarithmic paper (i.e., greater rocket height for each concentration of VIII:Ag in monkey plasma as compared with human plasma). Dilutions of monkey plasma were made to obtain values that fell on the monkey standard curve. The values are expressed as percents (100% equals one unit per milliliter of plasma).

**Factor VIII:C Assay**

Factor VIII:C levels in monkey plasma were determined against factor VIII-deficient human plasma (Dade Diagnostics, Inc., Miami, FL). A straight assay line without interference was obtained regularly for monkey plasma when the data were plotted on two-cycle log-log graph paper. For normal monkey plasma, this line was parallel to and above the line for human pooled normal
plasma (apparently indicating fewer units of factor VIII:C per milliliter of monkey plasma as compared to human plasma when assayed by this method). Dilutions of monkey plasma were made to obtain values that fell on the monkey standard curve. Values are expressed as percents (100% equals one unit per milliliter of plasma).

**Serum Lipid Determinations**

Serial values for total cholesterol, triglycerides, phospholipids, and free fatty acids were determined with standard biochemical techniques.

**Statistical Methods**

The results of the VIII:C, VIIIR:Ag, and serum lipid determinations were analyzed by group (coarcted, sham) and by time course and were expressed as the mean values±standard deviations. Differences between the groups and the time points were assessed by the Wilcoxon nonparametric test. Pearson correlation coefficients were used to test the relationships of the several parameters under study.

**Results**

**Morphologic Evaluation of Aortas**

Atherosclerotic lesions were present in the thoracic and abdominal aortas of the coarcted as well as the sham-operated animals sacrificed as early as 3 months. There was a spectrum of histologic changes ranging from early lesions with predominantly lipid-laden foam cells to plaques consisting of a variable quantity of elastin and collagen matrix admixed with lipid-laden cells. Although the majority of the animals had small to moderate plaques, in three of the monkeys the atherosclerotic process consisted of more extensive lesions; two of these animals were in the coarctation reversal group, and one was in the sham group. A detailed morphologic study of the aortic lesions in the two experimental groups in relation to the coarctation procedure will be the subject of another report.

**Coagulation Assays**

Levels of plasma VIIIIR:Ag and VIII:C in the coarctation reversal group before coarctation at weeks -11 to -13 (Figure 1) were not different from those obtained after coarctation at weeks 2 to 5 before the start of the atherogenic diet. This was based on eight animals that survived coarctation and that had paired values [VIII:C: 168.0%±27.2% (precoarctation) vs. 162.5%±40.7% (post-coarctation) p>0.5; VIIIR:Ag: 80.6%±37.1% (precoarctation) vs. 111.5%±57.8% (postcoarctation) 0.1<p<0.2]. Factor VIIIR:Ag and VIII:C levels did not differ significantly between the coarctation reversal and sham-operated group at comparable time points during the first 14 weeks on the atherogenic diet. Therefore, the data from the two groups were pooled during that period. Data beyond 14 weeks are from only the remaining coarctation reversal animals.

**Factor VIIIR:Ag**

An initial trough (p=0.19 relative to baseline) at week 1 was followed by a peak at week 4 (p=0.03 relative to week 1, but p=0.15 relative to baseline). Subsequently, there was insignificant oscillation about the baseline level until a major rise was seen at week 22 (p=0.01 vs. baseline). Levels then declined to baseline again by week 25 (p=0.08 relative to week 22 peak). Overall, there was a slight rise in VIIIR:Ag between baseline and week 37, but this was not a significant difference (p=0.36) (Table 1, Figure 3).

**Factor VIII:C**

Factor VIII:C levels were significantly depressed (p=0.0004 relative to baseline) at week 1 on the atherogenic diet, but subsequently rose to levels ranging between 45% (week 4, p=0.01 relative to baseline) to 113% (week 10, p=0.0001) above baseline. Peak levels were sustained until after week 18, when a sharp fall to a trough level of 53% below baseline occurred at week 20 (p=0.04 relative to baseline). The trough levels were sustained throughout the remainder of the study until week 37. A single elevated value at week 36 was not significantly different from the values for weeks 20 to 25 (p values=0.37 to 0.48) or week 37 (p=0.54). Overall, there was a significant rise in VIII:C levels until week 18, then a significant fall below baseline until week 37 (p=0.04) (Table 1, Figure 3).
Table 1. Factor VIII:C and VIII:R:Ag Changes during Atherogenic Diet

<table>
<thead>
<tr>
<th>Week</th>
<th>VIII:C (%)</th>
<th>VIII:R:Ag (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Baseline)</td>
<td>173.4±23.5 (16)</td>
<td>99.2±46.7 (16)</td>
</tr>
<tr>
<td>1</td>
<td>121.6±39.9 (16)</td>
<td>77.2±39.6 (16)</td>
</tr>
<tr>
<td>4</td>
<td>219.3±33.0 (6)</td>
<td>146.0±77.3 (6)</td>
</tr>
<tr>
<td>7</td>
<td>214.3±47.2 (7)</td>
<td>68.1±19.3 (7)</td>
</tr>
<tr>
<td>10</td>
<td>286.3±65.9 (15)</td>
<td>104.7±65.1 (15)</td>
</tr>
<tr>
<td>14</td>
<td>227.1±51.5 (21)</td>
<td>113.2±79.4 (21)</td>
</tr>
<tr>
<td>16</td>
<td>280.0 (2)</td>
<td>110.0±28.3 (2)</td>
</tr>
<tr>
<td>18</td>
<td>280.0 (3)</td>
<td>90.0 (3)</td>
</tr>
<tr>
<td>20</td>
<td>120.0 (2)</td>
<td>160.0±56.6 (2)</td>
</tr>
<tr>
<td>22</td>
<td>106.7±20.8 (3)</td>
<td>200.0±34.6 (3)</td>
</tr>
<tr>
<td>23</td>
<td>130.0±42.4 (2)</td>
<td>123.5±33.2 (2)</td>
</tr>
<tr>
<td>25</td>
<td>103.3±15.3 (3)</td>
<td>113.0±24.3 (3)</td>
</tr>
<tr>
<td>27</td>
<td>128.0 (1)</td>
<td>105.0 (1)</td>
</tr>
<tr>
<td>36</td>
<td>220.0 (1)</td>
<td>115.0 (1)</td>
</tr>
<tr>
<td>37</td>
<td>119.0±12.7 (2)</td>
<td>127.5±10.6 (2)</td>
</tr>
</tbody>
</table>

The values are the mean percents±SD (100%=1 unit/ml). The numbers of monkeys are shown in parentheses.

Relationship between Changes in VIII:R:Ag and VIII:C Levels

Although VIII:R:Ag levels were not significantly correlated overall with VIII:C levels, the respective patterns of change of these substances are of interest (Figure 3). After an initial fall in each at week 1, the VIII:R:Ag and VIII:C values rose at 4 weeks and then appeared to oscillate reciprocally between weeks 4 and 24. The values at weeks 36 and 37 suggest a second rise and fall of VIII:C, but the small number of animals tested at these times precludes any definitive interpretation.

Serum Lipid Levels

Five serum lipid components were assayed. There were no significant differences between the coarcted and sham groups during the first 14 weeks of the study. Therefore, the data were pooled during that period. Data beyond 14 weeks are for only the remaining coarctation reversal animals (Table 2, Figure 4).

The level of total cholesterol rose progressively to an initial peak of 7.18 times baseline at week 12. After a trough to 5.48 times baseline at week 21, the serum level rose again to a peak of 7.55 times baseline at week 25.

Serum triglyceride, free fatty acid, and phospholipid concentrations all reached peak levels at 2.02, 1.90, and 3.20 times baseline, respectively, at week 12 and declined thereafter. Triglyceride and free fatty acid levels reached nadirs at approximately one-half the starting levels at 21 and 17 weeks, respectively, whereas phospholipid concentration reached a plateau between weeks 21 and 30 at approximately 1.75 times baseline.

HDL cholesterol level fell by 4 weeks to approximately one-half the baseline concentration and later declined to levels of 0.28 to 0.38 times baseline between weeks 17 and 30.

Temporal Relationship of Serum Lipid Changes to Plasma VIII:C and VIII:R:Ag

Plasma VIII:R:Ag levels did not correlate significantly overall with any of the lipids studied. In contrast, VIII:C levels were positively correlated overall with the changes in total cholesterol (r=0.58160, p=0.0001). However, despite the overall correlation, there was a difference in pattern after week 21 when VIII:C levels remained below baseline and total cholesterol levels rose secondarily (Figure 4).

VIII:C levels were inversely correlated with HDL cholesterol concentrations (r=−0.35725, p=0.0055). Serum triglyceride, free fatty acids, and phospholipid levels showed a sequential pattern of change with an overall similarity to VIII:C. Triglyceride and phospholipid changes showed significant positive correlations with each other and with VIII:C (r=0.36202, p=0.0096; r=0.58539, p=0.0001, respectively), but free fatty acid level changes did not reach significant positive correlation levels with VIII:C (r=0.17098, p=0.1699).

Discussion

VIII:R:Ag Changes

Several observations by others1-5 had suggested to us that increases in local endothelial/subendothelial and, perhaps, plasma levels of VIII:R:Ag might be important indicators of the initiation and progression of atherosclerosis. Although we did not address the local role of VWF, its release and microenvironmental concentrations at the endothelial and subendothelial sites, or the relative concentration of very high molecular weight VWF multimers in plasma in this study, our data fail to indicate that plasma levels of VWF measured as VIII:R:Ag correlate with atherogenesis even in the earliest stages of initiation in this cynomolgus monkey model.

Why might there be no correlation of plasma VIII:R:Ag levels with atherogenesis despite the evidence of important involvement of VWF in local events at sites of vessel injury? Several considerations may apply: 1) Major dilution of released VIII:R:Ag in the plasma volume may obscure the correlation, assuming, of course, that VWF release is, in fact, a part of the initial events in atherogenesis. 2) The pace and focal nature of the atherogenic...
The two peaks of VIII:Ag (Figure 3) at weeks 4 and 22 that deserve comment are 1) the prominent, sustained rise in level during the first 4 months on the atherogenic diet followed by the sharp decline thereafter and 2) the lack of the expected synchronous change in VIII:C and VIII:Ag levels.

Although VIII:C is an acute-phase reactant, it seems unlikely that elevated levels following, and attributable only to, the surgery at week 1 would be sustained for several months and then fall to sub-basal levels. Also, no similar rise in VIII:C by weeks -2 to -5 was seen in the group of animals that had undergone coarctation at week -12 and had been maintained on the control diet. Furthermore, the lack of difference in VIII:C levels between the coarcted and the (as-yet-unoperated) sham group at week 0 (both groups on the control diet, but only the coarcted animals having had surgery 12 weeks earlier) suggests that the nonspecific effect of surgery is not an adequate explanation for the subsequent VIII:C changes.

Fatty infiltration of the liver on the atherogenic diet (as consistently seen in the monkeys in this study) might predispose to elevation of the circulating factor VIII complex, but, judging from human data, plasma VIII:Ag levels are often higher than VIII:C in parenchymal liver disease, and one would then expect to see a progressive or sustained VIII:C elevation rather than a decline with continued atherogenic diet. The relative contributions of liver parenchymal and vascular endothelial abnormalities to the VIII:C changes in this study are unknown.

The two major phases of VIII:C change seen in this study (an initial high plateau and a subsequent decline to...
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D—O VIII: C
O—& VIIIR:Ag
- • Total Cholesterol (TC)
- •—• Triglycerides (TG)
- •—• Phospholipids (PH)
- • Free Fatty Acids (FFA)
- —• High Density Lipoprotein Cholesterol (HDL)

Figure 4. Changes in plasma factors VIII:C, VIIIR:Ag, and serum lipid levels in cynomolgus monkeys during the course of an atherogenic diet (coarcted and sham groups combined).

decreased levels) suggest that, if these changes are causally related to atherogenesis, there may be sequential different steps (which arbitrarily might be called initiation and progression) in which VIII:C may be involved in different ways or be a marker for different processes. A biphasic pattern of prostacyclin (PGL2) changes in plasma during early atherogenesis in rabbits fed a cholesterol-rich diet is reminiscent of the VIII:C pattern noted here, although the time intervals were shorter (a peak after 2 weeks and a significant decrease after 6 weeks).

According to current concepts, VIIIR:Ag acts as a stabilizing carrier for VIII:C in the plasma. These two parts of the factor VIII complex are linked in noncovalent fashion, and their levels usually rise and fall synchronously, for example, after infusion of desmopressin. However, in selected circumstances, such as after exercise, there may be a disproportionate elevation of VIII:C without explanation. Also, plasma infusion in patients with von Willebrand's disease is followed by more prolonged VIII:C elevation than VIIIR:Ag change. Conversely, in parenchymal liver disease, VIIIR:Ag levels tend to be higher than VIII:C values. Our results suggest not only some dissociation of VIII:C from VWF levels, but also that there may be a sequential cycling of VWF first and VIII:C levels later. It is of interest in this regard that hepatic perfusion studies in animals have suggested that VIIIR:Ag may be needed for VIII:C release.

The examples of dissociated VIIIR:Ag and VIII:C levels cited above suggest there may be mechanisms of VIII:C stabilization in plasma in addition to the linkage with VWF. We speculate that one of the lipid fractions that has a similar time course to VIII:C might affect the VIII:C levels, for example, phospholipid, free fatty acids, or triglycerides. Of these, phospholipid in the form of liposomes is known to interact closely with VIII:C in its coagulation functions and has been shown in vitro to induce a two- to threefold increase in apparent VIII:C activity.

Serum Lipid Changes and Their Relation to VIII:C Levels

As expected, total cholesterol and its free and esterified fractions rose progressively and remained at or near peak levels at the end of the study, and the HDL cholesterol level fell early (4 weeks) and remained low thereafter. In contrast, the phospholipid and triglyceride levels showed a similarity in their time course and positive correlation with the VIII:C levels. We are especially interested in the phospholipid data because of current research on phospholipid-VIII:C complex formation.

Certain phospholipids in liposomal form, especially phosphatidyl serine, have the ability to dissociate VIII:C antigen from VIIIR:Ag and form a complex with it. It has also been shown that VIII:C Ag-phospholipid complexes are detectable in normal plasma, cryoprecipitate, factor VIII concentrates, and "activated" prothrombin concentrates. The time course of the phospholipid and VIII:C data in the present study coupled with the apparently enhanced VIII:C activity dissociated from VIIIR:Ag levels suggest that such complexes may have formed. Thus, although the elevated VIII:C levels noted in this study are likely to be too small and of themselves to be of clinicopathological significance, we postulate that they may be an indirect marker for the formation of VIII:C Ag-phospholipid complexes that may play a role in enhancing early localization of both components of the complex at sites of atherogenesis.

Recent studies of factor VII-phospholipid complex formation in human plasma, its correlation with triglyceride levels, and possible relation to cardiovascular disease risk suggest that there may be several important interactions between serum lipids and clotting factors related to atherogenesis.

Conclusions

We find that changes in plasma VIIIR:Ag levels failed to correlate with the atherogenic process even in the earliest stages in this cynomolgus monkey model. However, for reasons discussed earlier, we cannot use this lack of
correlation to conclude definitively whether or not endo-
thelial injury with accompanying VIIIIR : Ag release is a part
of this process. The dissociation between VIIIIR : Ag and
VIII : C levels observed in our study may reflect VIII : C
stabilization in plasma by mechanisms other than linkage
to VWF, for example, phospholipid complex formation.
The apparent temporal relationship between changes in
VIII : C, triglycerides and phospholipid levels further sug-
gests that these substances may be involved, and perh-
perts interrelated, early in atherogenesis.

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