Platelet Function and Composition in Heart Transplant Recipients Compared With Nontransplanted Coronary Patients

Michel de Lorgeril, Georges Dureau, Pascale Boissonnat, Jeannine Guidollet, Irène Juhan-Vague, Charles Bizollon, and Serge Renaud

Accelerated coronary artery disease seems to be the main condition limiting long-term survival after heart transplantation. Ninety-one heart transplant recipients were compared with 94 nontransplanted coronary artery disease patients in an attempt to identify the factors responsible for the accelerated form of coronary artery disease occurring after heart transplantation. Among the parameters examined, heart transplant recipients exhibited a higher plasma level of insulin (8.5±0.5 versus 6.2±0.3 mIU/l, p=0.002), a lower plasma level of vitamin E (14.8±0.4 versus 16.9±0.7 mg/1, p=0.03), a higher platelet cholesterol-to-phospholipid ratio (8.9±0.3 versus 7.6±0.3, p=0.007), and an increased response to ADP-induced platelet aggregation (for the first wave, 29.1±0.9% of maximal aggregation versus 25.1±1.0%, p=0.002; for the second wave, 21.4±1.4% versus 15.9±1.1%, p=0.002, after adjustment for hematocrit), but no untoward changes in the level of fibrinogen, plasminogen activator inhibitor-1, antithrombin III, or lipoprotein(a). In addition, platelet aggregation in patients who required retransplantation as a result of severe coronary artery disease was similar before and after retransplantation. This suggests that severe coronary artery disease is not the cause of platelet hyperaggregability. In multiple-regression analysis, ADP-induced platelet aggregation in heart transplant recipients was significantly positively related to blood glucose (r=0.50, p<0.001) and inversely related to n-3 fatty acids from platelet phospholipids (r=0.40, p<0.01). These results are consistent with the view that a platelet disorder associated with or responsible for the increased thrombotic tendency could play a role in the pathogenesis of the disease. However, further studies are needed to investigate the mechanism of this platelet hyperaggregability, which is possibly related to a lipid peroxidation process (low plasma vitamin E) and/or to a diabetes-associated platelet lipid disorder (high insulin level). (Arteriosclerosis and Thrombosis 1992;12:222-230)
myocardial infarction, the incidence of major cardiac events is from 5% to 10% per year. In these events, the role of platelets is highly suspected, as it has recently been shown that spontaneous platelet aggregation predicts death and recurrences in such a group. The role of platelets in myocardial infarction is also documented by 1) the success of its prevention by aspirin, a drug that inhibits platelet aggregation and 2) the close relation between platelet aggregation induced by ADP and prevalent cases of myocardial infarction in the Caerphilly study.

The purpose of the comparison between HTR and CAD patients was to try to identify the factor associated with the acceleration of CAD in the HTR group. Our results indicate that after heart transplantation, there is a chronic platelet disorder characterized by a marked increase in ADP-induced platelet aggregation and a high platelet cholesterol-to-phospholipid ratio (an index of membrane fluidity). In addition, in the HTR group multivariate regression analysis has shown that ADP-induced platelet reactivity is positively associated with blood glucose and negatively associated with platelet phospholipid fatty acids of the n-3 series. These results suggest possible therapeutic applications.

**Methods**

**Patients**

Heart transplant recipient group. The HTR group consisted of 91 consecutive patients (83 men, eight women) recruited for an extensive biologic examination in our research unit (U.63). All the patients had undergone cardiac transplantation by the same surgical team at the nearby Cardiovascular Hospital. At the time of the biologic study, the age range of the patients was 21–65 years, and the posttransplantation survival time ranged from 6 to 113 months. All patients were treated by the standard triple-immunosuppressive treatment of cyclosporine, prednisone, and azathioprine. Exclusion criteria were heart failure (New York Heart Association [NYHA] class III or IV), malignant disease, or a recent acute rejection episode. None of them were taking antiplatelet or lipid-lowering drugs. Some of them were taking antihypertensive drugs, such as calcium channel–blocking agents (n=20), β-receptor–blocking agents (n=16), and angiotensin converting enzyme inhibitors (n=20). All patients had been advised by a dietician to adhere to a saturated-fat–restricted diet and to maintain ideal body weight. At the time of the study, all the patients were clinically stable and ambulatory.

Control group. Ninety-four consecutive nontransplanted CAD patients (82 men, 12 women), who were survivors of myocardial infarction, served as controls. The age range was 19–69 years. They were recruited during the same period as the HTR patients and within 3–6 months after a first documented myocardial infarction, for which they were also hospitalized at the Cardiovascular Hospital. Exclusion criteria were age (more than 70 years), heart failure (NYHA class III or IV), malignant disease, and intake of antiplatelet or lipid-lowering drugs. Some of them received a β-receptor–blocking agent (n=43) or a calcium channel–blocking agent (n=25) that was prescribed by their physician as a systematic postinfarctus prophylactic measure. All the patients were clinically stable and ambulatory and received counseling by a dietician to follow a saturated-fat–restricted diet.

**Clinical and Laboratory Data Collection**

All data were recorded during a visit to the clinic of the Research Unit, and all patients gave their informed consent. These studies were approved by the Ethics Committees of the Lyon Hospitals (Hospices Civils) and the INSERM organization.

**Arterial pressure and anthropometric measurements.** Arterial pressure was measured by an automatic sphygmomanometer between 8 and 10 AM while the subjects were in a fasting state and before venipuncture. Three measurements were made on the right arm after the subject has been sitting quietly for 5 minutes. Values recorded were the mean of the three measurements. Body mass index (BMI) (weight divided by height squared) was used as a measure of overall adiposity. The ratio of waist-to-hip circumference was determined to assess body fat distribution.

**Blood sample collection.** Blood samples were drawn without stasis from an antecubital vein, in the fasting state, through a 21-gauge butterfly needle. Thus, the blood of HTR patients was sampled at least 12 hours after the previous cyclosporine dose. For the platelet study, the blood was anticoagulated with 3.8% trisodium citrate (9:1, vol/vol). A 5-ml sample was collected in a tube containing EDTA for hematologic determinations (Coulter Counter Electronics, Hialeah, Fla.). Two 10-ml samples were taken without anticoagulant for biochemical and lipid determinations in serum.

**Biochemical and lipid determinations.** Creatinine, glucose, bilirubin, γ-glutamyl transferase, and alkaline phosphatase were automatically determined by a Chem 1 Bayer Diagnostic Analyzer (Domont, France), serum triglycerides and total cholesterol were measured with an enzymatic assay kit (Biomerieux, Lyon, France), and high density lipoprotein cholesterol (HDL-C) was measured with a dextran sulfate precipitation procedure. All measurements were standardized against reference materials (Pro Bio Qual) supplied by Biotrol Laboratories (Paris, France). Low density cholesterol–containing lipoprotein (LDL-C) was calculated with the following formula:

\[
LDL-C (\text{mmol/l}) = \frac{\text{total C (mmol/l)} - \text{HDL-C (mmol/l)} - \text{TG (mmol/l)}}{2.2}
\]

where TG is triglyceride.

Total serum apolipoprotein (apo) A-I and apo B were determined by immunonephelometry (Behring Laboratory, Marburg, FRG), and apo E was quantified by a simple radial immunodiffusion technique.
with a commercial kit (Daichi Pure Chemicals, Tokyo, Japan). The serum concentrations of lipoprotein(a) were measured by radial immunodiffusion by using a commercial kit (Immuno Diagnostika). The lower limit for this assay was 5 mg/dl lipoprotein(a). Plasma insulin was evaluated in citrated plasma with a commercial radioimmunoassay (CIS International, Saclay, France) and vitamin E by a colorimetric procedure.\textsuperscript{13} Antithrombin III activity was determined by the synthetic chromogenic substrate method (Diagnostica Stago, Paris, France). Plasminogen activator inhibitor (PAI) activity was evaluated with a commercially available kit obtained from Biopool (Umeå, Sweden).\textsuperscript{14} Results for PAI-1 activity were expressed in arbitrary units, with 1 unit corresponding to the amount that inhibited 1 IU tissue-type plasminogen activator (second international standard [86/670] from the National Institute for Biological Standards and Controls, London, UK). Whole-blood cyclosporine was measured by radioimmunoassay by using a specific monoclonal antibody (Baxter Laboratories; INCSTAR Corp., Stillwater, Minn.).

\textit{Plasma and platelet lipid analysis.} Plasma and platelet lipids were extracted by the method of Folch as in previous studies.\textsuperscript{15,16} The plasma lipid methyl esters were purified by thin-layer chromatography in one dimension, using aluminum sheets coated with 6OF\textsubscript{254} silica gel (Merck, Darmstadt, FRG) with petroleum ether/diethyl ether (90:30, vol/vol) as the solvent mixture. The total platelet phospholipids were separated from the other platelet lipids by thin-layer chromatography in one dimension, using aluminum sheets coated with 6OF\textsubscript{254} silica gel (Merck) with petroleum ether/diethyl ether (90:30, vol/vol). The plasma and platelet lipids were methylated by boron fluoride/methanol reagent (Merck) according to Morrisson and Smith.\textsuperscript{17} Fatty acids were analyzed by gas-liquid chromatography with a Carlo Erba HRGC 5160 Mega Series on SP-2340, with a fused-silica capillary column (30 m×0.32 mm i.d., 0.2-µm film; Supelco, Bellefonte, PA.), with the sample in 0.3 µl isooctane on the column and helium (19 cm/sec) as the carrier gas. Temperature was 90°C for the injection and 275°C for the flame ionization detector, with the column-temperature programming at 90°C for 1 minute, 5°C/min to 135°C, 2°C/min to 200°C, 3°C/min to 220°C, and left to stand for 15 minutes. The total platelet phospholipids were determined on the total lipid extract by a colorimetric method,\textsuperscript{18} and platelet cholesterol was determined by an enzymatic technique.\textsuperscript{19}

\textit{Platelet aggregation studies.} Blood samples were immediately centrifuged to obtain platelet-rich (PRP) and platelet-poor (PPP) plasmas. Platelet aggregation was performed on a recording aggregometer (Rubel-Renaud, Lyon, France) in PRP, with a platelet count adjusted to 300,000/µl by dilution with PPP as described.\textsuperscript{11,16,17} For the determinations, 500 µl PRP was warmed at 37°C for 2 minutes with stirring at 1,100 rpm. Then 100 µl of the aggregating agent diluted in complete Tyrode’s solution (pH 7.4) was added. These agents were thrombin (human lyophilized; Sigma Chemical Co., St. Louis, Mo.; final concentration in PRP, 0.08 National Institutes of Health units/ml), ADP (from equine muscle, Sigma; final concentration, 0.92×10\textsuperscript{-4} M), and collagen (soluble skin collagen, Worthington Biochemical Co., Freehold, N.J.; final concentration in PRP, 75 µg/ml).

The aggregometer was adjusted for each sample so that PRP gave no light transmittance and PPP gave 100% light transmittance. The extent of aggregation by each agent was evaluated as the percentage of maximum difference between PRP and PPP. The value retained was the mean of three measurements made with each agent. The delay between blood sampling and the platelet aggregation test was constant for each agent (between 70 and 90 minutes). The tracings obtained were analyzed by two independent observers.

During the study, it was observed that the hematocrit of the two groups was significantly different. In patients with a lower hematocrit, the resulting level of anticoagulant (sodium citrate) in plasma was lower than that in normal subjects, and a higher response to platelet aggregation could be expected. To solve that problem, platelet aggregation was determined twice in 23 patients, once as described above (the uncorrected percent aggregation) and a second time with a final citrate concentration adjusted according to the result of the hematocrit (the corrected percent aggregation). The adjustment of final citrate concentration was performed with the approach described by Kelton et al.\textsuperscript{20} For the three aggregating agents, the regression equations were computed with corrected percent aggregation as the dependent variable and hematocrit and the uncorrected percent aggregation as independent variables. For ADP, two regression equations were calculated for the primary and the secondary waves of aggregation. With these equations and hematocrit values, the adjusted platelet aggregation results were computed for each subject in both groups.

\textit{Statistical analysis.} All data are presented as mean±SEM. Discrete variables were compared by the Wilcoxon rank-sum test and continuous variables by Student's \textit{t} test. The relation between platelet aggregation and different parameters was evaluated by univariate and multivariate linear-regression analyses according to the \textit{STAT} 80 program (Statware Inc., Salt Lake City, Utah). The Wilcoxon paired \textit{t} test was used for the comparison of platelet aggregation before and after retransplantation. All statistical tests were two sided.

\textbf{Results}

\textit{Clinical, Biochemical, and Hematologic Results}

The HTR group was significantly (\textit{p}=0.007) younger than the CAD group. However, in both groups there was no correlation between platelet function tests and the age of the patients. In addition, there was no difference between groups in weight, BMI, and waist-
Lipemia

Hemostatic Parameters

No difference was observed between the two groups in fibrinogen and lipoprotein(a), whereas antithrombin III was higher (p=0.01) in the HTR group. PAI-1 was slightly lower in the HTR group, although this difference was not significant (Table 2).

Compared with the CAD group, there was a significant increase in platelet aggregability in the HTR group as assessed by platelet response to ADP. The first wave (36.2±0.9% versus 31.2±1.0%, p=0.001) as well as the second wave (31.8±2.2% versus 20±1.8%, p=0.0001) of platelet aggregation was higher, whereas platelet responses to collagen (43.7±2.5% versus 36.3±2.8%, p=0.056) were also increased but did not reach statistical significance. There was no difference between groups in platelet response to thrombin (data not shown). After adjustment for hemocrit, the significant differences in ADP-induced platelet aggregation persisted for both the first wave (29.1±0.9% versus 25.1±1%, p=0.002) and the second wave (21.4±1.4% versus 15.9±1.1%, p=0.002) (Figure 1).

Plasma and Platelet Phospholipid Fatty Acids

The fatty acid composition of the plasma total lipids is reported in Table 3 and of the platelet phospholipids in Table 4. In plasma, the significant changes observed in HTR patients were a decrease in stearic (18:0) and arachidonic (20:4[n-6]) acids and an increase in 20:3[n-6]. In platelets, there was a lower level of 18:0 in the HTR group, while that of n-9 and n-3 fatty acids were, in general, higher. The level of the n-6 fatty acids was similar. Also reported are the positive associations between platelet cholesterol to phospholipid ratio, an index of membrane fluidity. The HTR group had a significantly higher cholesterol-to-phospholipid ratio (p=0.002), and thus, reduced membrane fluidity. Of additional interest in this last group were the positive associations between platelet cholesterol and the level of blood cyclosporine (r=0.38, p=0.02) and between platelet 18:1(n-9) and plasma insulin (r=0.50, p<0.05).
Platelet Aggregation Relation to Other Clinical and Biologic Parameters

No relation was observed between platelet aggregation and age, either in HTR or in CAD patients. The increased platelet aggregability observed in HTR patients could be the consequence of progressive coronary disease and consequently should be related to survival (months after transplantation). In the present study, this survival was not related to platelet aggregation induced by thrombin, ADP, or collagen. In addition, in the six patients who required retransplantation as a result of severe CAD, platelet aggregation was measured at entry to the study and again 3 months after retransplantation. As shown in Table 5, the high platelet reactivity persisted after retransplantation. This indicates that increased platelet aggregation is not secondary to graft CAD because the severity of lesions in the transplanted heart did not modify the platelet reactivity.

Furthermore, platelet aggregation was not related to cyclosporine and prednisone posology, whole-blood cyclosporine level, blood pressure, BMI, or to the lipid parameters determined. Finally, the cause of the cardiomyopathy requiring transplantation (ischemic or nonischemic) and the occurrence of one or more major rejection episodes (defined as rejection requiring hospitalization and steroid treatment) were also not related to platelet aggregation. When multiple-regression analysis was used, blood glucose was strongly, independently, and positively correlated with ADP-induced platelet aggregation in the HTR group \( (r=0.50, \ p=0.0002) \) as well as in the two groups pooled together \( (r=0.25, \ p=0.01) \). Among the platelet phospholipid fatty acids, 20:5\( (n-3) \) and 22:5\( (n-3) \) were significantly and inversely correlated with ADP-induced platelet aggregation \( (r=-0.39 \) and \( r=-0.40, \ p=0.002) \).

### Table 4. Platelet Phospholipid Fatty Acids and Cholesterol

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>CAD</th>
<th>HTR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>18:0</td>
<td>6.95±0.08</td>
<td>6.31±0.30</td>
<td>0.006</td>
</tr>
<tr>
<td>18:1((n-9))</td>
<td>19.3±0.40</td>
<td>20.3±0.40</td>
<td>NS</td>
</tr>
<tr>
<td>20:1((n-9))</td>
<td>0.20±0.01</td>
<td>0.23±0.01</td>
<td>NS</td>
</tr>
<tr>
<td>20:3((n-9))</td>
<td>0.13±0.01</td>
<td>0.12±0.01</td>
<td>NS</td>
</tr>
<tr>
<td>18:3((n-3))</td>
<td>0.39±0.02</td>
<td>0.39±0.03</td>
<td>NS</td>
</tr>
<tr>
<td>20:5((n-3))</td>
<td>0.61±0.04</td>
<td>0.64±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>22:5((n-3))</td>
<td>1.69±0.08</td>
<td>1.73±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>22:6((n-3))</td>
<td>0.50±0.02</td>
<td>0.51±0.02</td>
<td>NS</td>
</tr>
<tr>
<td>18:2((n-6))</td>
<td>30.4±0.70</td>
<td>29.8±0.90</td>
<td>NS</td>
</tr>
<tr>
<td>20:3((n-6))</td>
<td>1.23±0.05</td>
<td>1.29±0.06</td>
<td>0.002</td>
</tr>
<tr>
<td>20:4((n-6))</td>
<td>6.91±0.02</td>
<td>6.08±0.03</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Results are mean±SEM. HTR, heart transplant recipients; CAD, nontransplanted survivors of myocardial infarction.
respective, p<0.01) in the HTR group, a correlation that persisted for 20:5(n-3) (r=-0.22, p<0.01) when the two groups were combined.

Discussion

The main finding of the present study seems to be that in HTRs, there is an increase in platelet aggregation, a result similar to that reported in animal and human kidney transplantation.3-5 In our HTRs, the platelet response to ADP was significantly enhanced compared with that of a control group composed of nontransplanted CAD patients who were survivors of a myocardial infarction, a condition known to be already associated with high platelet reactivity.9 Thus, the ADP-induced platelet aggregation observed in transplanted patients can be considered to be markedly elevated; it was associated with changes in platelet fatty acids and a high cholesterol-to-phospholipid ratio. The relative cholesterol enrichment observed in this study is known to be associated with decreased membrane fluidity23,24 and platelet hyperreactivity.25 These phenomena are known to occur in conditions like diabetes.26 Of interest in the present study is that ADP-induced platelet aggregation was lower in transplanted patients. In addition, the level of antithrombin III in the transplanted group presumably could be relatively protective. However, in two studies the presence of anti–B-cell or anti–human leukocyte antigen A antibodies was associated with the development of graft CAD.39,40 Thus, it seems that the investigations performed so far to unravel the risk factors involved in graft coronary disease have not been particularly rewarding.

In the early days of heart transplantation, platelet microthrombi initiated by immune injury to the endothelium and followed by intimal smooth muscle cell proliferation and lipid deposition were suspected to be the cause of the accelerated graft coronary disease.41,42 However, antiplatelet agents used in either experimental or clinical studies have not been very successful (except for two reports41,42) at preventing the disease. The hypothesis was therefore discarded. However, recent breakthroughs in our understanding of CAD in nontransplanted patients, together with our present results on platelet reactivity in transplanted patients, suggest a reevaluation of the platelet–thrombosis hypothesis in graft CAD.

One of the major recent finding emerging from clinical cardiology is the role of thrombosis in unstable angina and in rapidly progressive coronary disease. Angioscopic as well as pathological observations have shown that the only difference between stable and unstable coronary disease is the presence of a thrombus attached to endothelial ulceration, with or without an atheroma.43,44 In the absence of lysis, the thrombus is incorporated into the vessel wall and causes progression of the stenosis, as observed by angiography performed soon after the acute episode. Many authors now believe that endothelial disruption and thrombosis without clinical symptoms are the main causes of rapidly progressive forms of common CAD. Weeks or months after the acute episode, organized thrombi are indistinguish-

### Table 5. Platelet Aggregation Before and 3 Months After Retransplantation in Percent of Maximum Aggregation

<table>
<thead>
<tr>
<th></th>
<th>ADP, first wave</th>
<th>ADP, second wave</th>
<th>Collagen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>38.5±0.9</td>
<td>40.8±2.6</td>
<td>39.9±8.7</td>
</tr>
</tbody>
</table>

B, before; A, after.
able from typical atheroma. In the accelerated CAD of graft recipients, it is possible that a similar mechanism is involved. Recently, in a careful histological examination of transplanted hearts (M. de Lorgeril et al, unpublished observations), we have confirmed previous observations showing that multiple thrombi at various stages of organization are common findings in these hearts. Finally, in non-transplanted patients, spontaneous platelet aggregation was able to predict coronary events; a result concordant with a recent prospective study of more than 2,000 subjects in Wales. In this last study, patients with myocardial infarction presented a marked increase in the response of platelets to ADP, a pattern similar to that reported here for transplanted patients.

If platelets play an important role in graft coronary disease, it remains to be explained why antiplatelet treatment did not protect transplanted patients in previous studies. We have recently reported that the low-dose aspirin therapy (250 mg daily) that effectively reduces secondary aggregation to ADP in nontransplanted coronary patients did not decrease platelet aggregation at all in transplanted patients. Even 500 mg aspirin daily did not reduce secondary aggregation to ADP to the level observed in non-transplanted patients after only 250 mg. Further studies are needed to determine the mechanism of this aspirin resistance. However, it could explain the high frequency of thromboembolic events and the accelerated CAD that occurs in transplanted patients receiving aspirin. It should be noted that a similar pattern of platelet dysfunction associated with a high frequency of thromboembolic events has been already reported in kidney transplant recipients.

The sum of these data seems to support the hypothesis that a generalized platelet disorder occurs after transplantation, regardless of whichever organ is transplanted and the type of immunosuppression (with or without cyclosporine) used. Nevertheless, local factors (immunologic or even the sympathetic reinnervation recently reported) are probably responsible for the increased acceleration of CAD in grafted hearts compared with the arterial disease of the grafted kidney.

Concerning the mechanism involved in the platelet hyperactivity in transplanted patients, several possibilities that are suggested by the present results require further investigation. The plasma level of vitamin E, especially the vitamin E to non-HDL-C ratio, was significantly lower in transplanted patients, suggestive of peroxidative phenomena. As a matter of fact, we have recently reported increased in vivo lipid peroxidation in such patients compared with nontransplanted coronary patients. In that connection, our group has also recently shown that the hyperaggregability related to administration of hormonal contraceptives was a result of the formation of lipid peroxides in relation to a lowering of the plasma level of vitamin E. This phenomenon could be blocked by antioxidants in vitro and by vitamin E administration in vivo, suggesting that a similar study is certainly justified in transplanted patients.

A surprising result of the present study is the lower level, in both plasma and platelets, of stearic acid (18:0), a fatty acid that is the precursor of the n-9 family. By contrast, the level of its derivative, 18:1(n-9), is significantly higher, a result that indicates an increase in δ-9 desaturase activity. In severe insulin-dependent diabetes, an opposite result is observed, suggesting that the increase in δ-9 desaturase activity in transplanted patients could be related to their increased level of insulin. As a matter of fact, there is a significant positive correlation (r=0.50, p<0.05) in transplanted patients between the level of insulin and that of 18:1(n-9) in platelet phospholipids. In addition to 18:1, 20:1 and 20:3(n-9) (known to increase platelet reactivity) were significantly increased in platelet phospholipids. Considering the abnormal level of n-9 fatty acids as well as the cholesterol-to-phospholipid ratio in platelets, these findings suggest an abnormal lipid metabolism of platelets in transplanted patients and a possible link between these platelet disorders and the hormonal status of patients after transplantation. Finally, although the level of platelet n-3 fatty acids is slightly higher (even significantly higher for 22:5(n-3)) in the platelet phospholipids of transplanted patients, the n-3 fatty acids were significantly inversely correlated with platelet aggregation to ADP in these patients. It is well known that n-3 fatty acids decrease platelet aggregability in nontransplanted patients. Because fish oil supplementation has been shown to inhibit atherosclerosis in a cyclosporine-treated heart allograft model in the rat, the influence of n-3 fatty acids should be investigated further as potential agents to decrease the accelerated coronary disease of transplanted hearts.

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References


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