Effects of Intravenous Prostacyclin in Variant Angina

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SUMMARY A lack in prostacyclin (PGI2) production due to atherosclerosis may play a role in the pathophysiology of some of the clinical manifestations of ischemic heart disease and, in particular, of coronary vasospasm. We therefore evaluated the effects of i.v. PGI2 in nine patients with variant angina and six normal volunteers.

In normal subjects, PGI2 (2.5, 5, 10 and 20 μg/kg/min) had significant antiplatelet effects, caused a dose-dependent decrease in both systolic and diastolic arterial pressure and a decrease in pulmonary resistance. Heart rate increased in a dose-dependent manner, but no consistent effects on myocardial contractility (evaluated by ultrasound) were observed. Side effects were negligible and readily reversible.

Although producing obvious antiplatelet and vasodilatory effects, PGI2 did not affect the number, severity and duration of spontaneous ischemic episodes due to coronary vasospasm in five patients and ergonovine-induced spasm in three. However, the number of ischemic episodes was consistently reduced in one patient during four consecutive periods of PGI2 infusion alternated with placebo. A severe, prolonged ischemic episode with ST elevation and pain was consistently observed in this patient every time PGI2 was discontinued.

In the appropriate environment, PGI2 can be administered safely to patients with ischemic heart disease. Occasionally, PGI2 may result in a complete disappearance of ischemic episodes due to coronary vasospasm, but usually it is ineffective. These conflicting results could be related to different etiologies of coronary spasm.

PROSTACYCLIN (PGI2), an arachidonic acid metabolite produced by the vascular endothelial cells and by the lungs,1-4 exerts powerful vasodilating and antiplatelet effects in vitro5-8 and in vivo.9-12 These effects may avoid intravascular thrombosis, maintain endothelial integrity and, possibly, control vascular smooth muscle tone. Decreased PGI2 production by the atherosclerotic arterial wall might play a role in some of the clinical manifestations of ischemic heart disease.13-20 Masére et al.21 suggested that coronary vasospasm could result from an increased vascular sensitivity to vasoconstrictor stimuli, secondary to a reduction in local PGI2 production at the site of atherosclerotic lesions. Moreover, the hypothesis that transient coronary vasospasm might be precipitated by thromboxane A2 locally released by aggregating platelets,22 in the presence of endothelial lesions has recently gained attention.23-26 Finally, cyclical transient reduction in coronary flow, occurring in experimentally narrowed coronary arteries,27-28 has been prevented by the administration of PGI2.29

In a preliminary study, we investigated the hemodynamic, antiplatelet and possible side effects of PGI2 in six healthy volunteers. In a second study, we evaluated the effects of PGI2 infusion in nine patients with variant angina, traditionally considered a clinical landmark of transient coronary vasospasm.29-34

Material and Methods

Study I

Subjects

Five healthy male subjects, all coauthors of the present report (SC, GC, GAC, AM and CP), ages from 32-50 years (mean age 38 years) volunteered for the study. One male patient (NV), age 34 years, submitted to routine coronary angiography and coronary sinus catheterization because of atypical precordial pain. He gave informed consent to the infusion of the drug after the completion of the diagnostic study, which had failed to demonstrate coronary lesions or hemodynamic or myocardial metabolic abnormality.

PGI2 Preparation and Mode of Administration

The sodium salt of PGI2 (Wellcome Laboratories) was dissolved in glycine buffer (pH 10) and injected, by a constant-flow Harvard pump, into a right ante-
cubital vein at rates of 2.5, 5, 10 and 20 ng/kg/min (0.025, 0.05, 0.1 and 0.2 ml/min, respectively), for consecutive periods of 30 minutes each. During the infusion, the PGI₂ temperature was kept constant at 2°C. The biologic activity of PGI₂, assessed by its effects on ADP-induced platelet aggregation was checked before and at the end of each experiment by incubating 0.01 ml of the solution (containing 10 ng of PGI₂) with 1 ml of platelet-rich plasma.

Protocol

In four subjects, a 16G polyethylene catheter was positioned in the mid-right atrium under fluoroscopic control. In AM and NV, pulmonary arterial pressure (PAP) and right atrial pressures (RAP) were continuously monitored through a Swan-Ganz thermodilution catheter (Edwards Laboratories). In NV, continuous measurements of left ventricular (LV) pressure and dP/dt were obtained by a pigtail catheter. The catheters were connected to Statham P23Db pressure transducers adjusted to equal sensitivity and continuously perfused with normal saline. The pressure signals and one ECG lead were continuously recorded on analog magnetic tape and played back on photographic paper for subsequent analysis. Arterial pressure was measured by a cuff manometer every 3–5 minutes. In AM and NV, the cardiac output (CO) was measured by the thermodilution technique. In each instance, at least five consecutive CO measurements were obtained by an Edwards 9520 instrument; CO was calculated as the mean of the last three consistent measurements. Transcutaneous aortic flow velocity (TAV) was measured in five subjects by a Doppler technique, according to the method of Light and Cross. The measurements derived from the TAV recordings were the time-averaged (mean) flow velocity and the area of each TAV complex, which have been shown to reflect directional changes in CO and stroke volume (SV), respectively. Standard M-mode echocardiographic tracings were obtained using an Echo-Cardio-Visor 03 instrument (Organon Teknika) to calculate LV and atrial dimensions and LV percent fractional shortening. Citrated blood samples were obtained under basal conditions, at the end of the 2.5- and 20-ng infusions and 60 minutes after the end of the infusion. In vitro aggregation of platelet-rich plasma was assessed in a standard Born aggregometer using incremental doses of ADP. In three subjects, hemodynamic and platelet aggregability were also measured during a 30-minute infusion of the vehicle alone (TRIS buffer) at the highest rate (0.2 ml/min).

Study 2

Patients

We studied nine patients (eight males and one female), ages 49-64 years (mean 54 years), admitted to our department for frequent anginal attacks that occurred mainly at rest without any identifiable cause. Five of them also reported a limited tolerance to physical activity. Each patient gave informed written consent.

Bicycle ergometer exercise testing was performed in all patients with progressive increases in work load every 2 minutes, up to a submaximal heart rate or to development of symptoms or ECG changes. The test was positive in six. Twelve-lead ECG tracings obtained in all patients during at least one spontaneous anginal episode revealed transient ST-segment elevation in all.

Coronary arteriography, performed in seven patients by the Judkins technique, revealed three-vessel disease in three patients, two-vessel disease in two and one-vessel disease in two. A transient episode of coronary vasospasm accompanied by ECG changes similar to those recorded in the coronary care unit (CCU) was documented in five (spontaneous in two, induced by ergonovine maleate in three). Patients PE and FF did not give consent to coronary arteriography.

Before the study, all patients underwent continuous ECG monitoring in the CCU for at least 3 days to assess objectively the frequency and the temporal distribution of the ischemic episodes, with or without anginal pain.

The ECG lead showing the most evident ST-T changes during the episodes was selected for this purpose. Six patients showed more than 10 episodes per day and were selected for the continuous infusion of PGI₂. The other three patients had a low daily frequency of ischemic episodes and a positive response to ergonovine, and we studied the effects of PGI₂ on ergonovine-induced coronary vasospasm in these patients. The clinical, ECG and angiographic data are listed in table 1.

Protocol

PGI₂ was prepared as described for study 1 and infused intravenously with a constant-flow Harvard pump through a polyethylene catheter introduced percutaneously and advanced in the superior vena cava. The biologic activity of the drug was checked, as described for study 1, at the beginning and at the end of each infusion period.

In each patient, the rate of infusion was increased progressively by 4 ng/kg/min every 5 minutes (with a maximum of 20 ng). The maximal dose tolerated without unpleasant side effects was then continued. Doses ranged from 8–20 ng/kg/min.

PGI₂ Infusion in Spontaneous Angina

In each patient, the drug was administered during the time of day when the greatest number of episodes had been documented during continuous ECG monitoring. PGI₂ or the vehicle alone were alternately infused for four consecutive periods of 3 hours each. In patient PE, the infusion was repeated on 2 successive days. The ECG lead showing the most obvious changes during the ischemic episodes was continuously monitored on the CCU central station and simultaneously analyzed in real time by a computer program with beat-by-beat display of heart rate and ST-T positive and negative areas. The data were also simultaneously recorded on an analog magnetic tape. Arterial pressure (cuff) was measured every 5 minutes in the first 30 minutes of each infusion period and then every 30 minutes. Citrated blood samples
were obtained during control and every hour during PGI₂ infusion to measure in vitro platelet aggregation by ADP. All antianginal treatment was discontinued 24 hours before the onset of the study. Only nitrroglycerin or i.v. nitrates were given when required. Episodes of transient acute ischemia were assessed on the basis of transient ST-segment positive or negative displacement (≥ 0.15 mV) or pseudonormalization or peaking of T waves that lasted at least 30 seconds.33, 34

PGI₂ Infusion in Ergonovine-induced Angina

In the three patients in whom a transient ischemic episode with ST-segment elevation could be induced by i.v. injection of ergonovine maleate (doses of 0.025–0.2 mg, administered in scalar doses), the test was repeated 30 minutes after a PGI₂ infusion had been started according to the protocol for infusion during spontaneous angina. The ECG was continuously monitored; arterial pressure measurements (cuff) and a 12-lead ECG tracing were obtained every minute.

Results

The biologic activity of PGI₂ did not change significantly between the beginning and the end of each infusion period. The percent inhibition of ADP-induced in vitro platelet aggregation at the beginning and at the end of the infusions was 87 ± 9% and 82 ± 5%, respectively.

In all subjects and patients, PGI₂ infusion produced skin flushing, especially marked on the face and the palms, accompanied by a sensation of warmth in the same areas. Two subjects complained of headache and three of restlessness. Three patients experienced nausea and one vomited. Side effects disappeared a few minutes after the infusion was stopped or the rate was reduced.

Study 1

Hemodynamic Effects

The hemodynamic findings during control and PGI₂ are summarized in table 2. PGI₂ infusion resulted in a significant dose-dependent drop in both systolic (10 ± 3%, mean ± sd) and diastolic (19 ± 5%) arterial pressure (p < 0.05 and 0.01, respectively) at doses of 20 and 10 ng/kg/min. Heart rate increased progressively during the infusion and reached a maximum during the 20-ng stage (21 ± 5%, p < 0.01). No consistent changes in right atrial pressure occurred at any of the infusion rates. All subjects showed a progressive increase in transcutaneous mean aortic flow velocity, with a maximum (47 ± 27%, p < 0.01) at the end of the 20-ng infusion stage without significant changes in the TAV index of SV. None of the echocardiographic variables measured changed significantly during the infusion. In subject AM, both systolic and diastolic PAP decreased (20% and 35%, respectively) but remained unchanged in NV.

CO increased progressively in both subjects AM and NV, reaching a maximum (average of 32%) at the end of the 20-ng infusion stage, but SV was practically unchanged. LV end-diastolic pressure decreased 3 mm Hg in NV, without any appreciable changes in LV
TABLE 2. Hemodynamic Findings During Control and PGI₂ Infusion

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>SAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>EDD (cm)</th>
<th>ESD (cm)</th>
<th>FS%</th>
<th>TAV-M (cm/sec)</th>
<th>TAV-SV (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>61 ± 7</td>
<td>131 ± 8</td>
<td>88 ± 8</td>
<td>101 ± 7</td>
<td>6.0 ± 0.7</td>
<td>4.1 ± 0.4</td>
<td>41.7 ± 3.2</td>
<td>28.6 ± 1.8</td>
<td>25.0 ± 3.3</td>
</tr>
<tr>
<td>2.5</td>
<td>67 ± 11</td>
<td>125 ± 9</td>
<td>84 ± 10</td>
<td>97 ± 9</td>
<td>5.85 ± 0.3</td>
<td>3.9 ± 0.2</td>
<td>41.2 ± 2.5</td>
<td>30.8 ± 7.4</td>
<td>28.0 ± 4.6</td>
</tr>
<tr>
<td>5</td>
<td>66 ± 9</td>
<td>124 ± 9</td>
<td>82 ± 8</td>
<td>96 ± 8</td>
<td>6.1 ± 0.2</td>
<td>4.1 ± 0.2</td>
<td>42.2 ± 0.5</td>
<td>29.8 ± 5.4</td>
<td>27.4 ± 3.4</td>
</tr>
<tr>
<td>10</td>
<td>68 ± 10*</td>
<td>126 ± 11</td>
<td>79 ± 10*</td>
<td>94 ± 11</td>
<td>6.1 ± 0.2</td>
<td>4.2 ± 0.3</td>
<td>41.7 ± 2.6</td>
<td>33 ± 7.3*</td>
<td>29.6 ± 4.8</td>
</tr>
<tr>
<td>20</td>
<td>73 ± 5*</td>
<td>122 ± 13*</td>
<td>73 ± 10†</td>
<td>89 ± 10</td>
<td>6.2 ± 0.2</td>
<td>4.2 ± 0.4</td>
<td>42.7 ± 3.3</td>
<td>39 ± 7.3†</td>
<td>32.0 ± 7.0</td>
</tr>
<tr>
<td>R</td>
<td>60 ± 6</td>
<td>132 ± 7</td>
<td>92 ± 7</td>
<td>105 ± 8</td>
<td>5.8 ± 0.3</td>
<td>4.0 ± 0.2</td>
<td>40.0 ± 2.3</td>
<td>26.2 ± 2.4</td>
<td>26.2 ± 4.5</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
*p < 0.05.
†p < 0.01.

Abbreviations: HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; EDD = end-diastolic diameter (echo); ESD = end-systolic diameter (echo); FS% = percent fractional shortening; TAV-M = transaortic flow mean velocity; TAV-SV = transaortic flow velocity index of stroke volume; C = control; R = recovery.

dP/dt max or min. All hemodynamic measurements returned to the control levels within 15 minutes after the end of the infusion.

Effects of Platelet Aggregability

ADP-induced platelet aggregation was reduced in all subjects at the dose of 20 ng/kg/min (64 ± 8%). In GC, an antiaggregatory effect (47%) was already evident at the dose of 2.5 ng/kg/min. The platelet aggregability returned to the control level within 1 hour after the end of the infusion in subjects SC, CP, and AM, but it was still 32 ± 5% lower than control in GC, GAC and NV. No changes in hemodynamics or in vitro platelet aggregation were observed in three subjects in whom the vehicle alone was infused, at the highest rate, for 30 minutes.

Study 2

Effects on Platelet Aggregation and Hemodynamics

The results of ADP-induced platelet aggregation during control and PGI₂ infusion in the individual patients are summarized in figure 1. PGI₂ reduced both primary and secondary platelet aggregation induced by ADP (54 ± 35% and 46 ± 24%, respectively). Mean arterial pressure decreased from 107 ± 12 to 93 ± 12 mm Hg (p < 0.01) and heart rate increased from 72 ± 8 to 87 ± 10 beats/min in the first 30 minutes of PGI₂ infusion (p < 0.05). Arterial pressure returned to the control levels within 1 hour after the onset of the infusion in three patients and remained slightly reduced in the other three. Heart rate remained elevated in all patients throughout the infusion. During PGI₂ administration, three patients showed marked bradycardia accompanied by severe hypotension, nausea and diffuse diaphoresis, which promptly disappeared when the infusion rate was reduced.

Effects on Spontaneous Ischemic Episodes

During the study we recorded 90 ischemic episodes, 54 of which were characterized by ST-segment elevation and 36 by pseudonormalization or peaking of T wave. Only 21 were accompanied by angina.

PGI₂ did not affect the number, severity and duration of episodes of acute myocardial ischemia in five patients; the total number of ischemic episodes during the two placebo and PGI₂ periods were 17, 16, 33 and 24 respectively; the differences were not statistically significant (fig. 2). Accordingly, no significant difference was found between the number of ischemic

![Figure 1](http://circ.ahajournals.org/doi/fig/10.1161/01.CIR.78.6.473)
episodes recorded during the two PGI₂ infusion periods and the corresponding periods of the days before and after the study (fig. 3).

However, patient PE appeared to respond consistently to PGI₂ infusion. The number of ischemic episodes was reduced from six during placebo to two during PGI₂ when the drug was infused at a rate of 10 ng/kg/min, and no ischemic episodes were observed during three periods of PGI₂ given at a rate of 20 ng/kg/min, while in the three corresponding placebo periods, four, three and five ischemic episodes were observed. Furthermore, a prolonged and severe episode accompanied by pain consistently occurred every time PGI₂ infusion was stopped (fig. 4).

Effects on Ergonovine-induced Coronary Vasospasm

Under control conditions, ergonovine maleate produced a complete focal spasm of the left anterior descending coronary artery in two patients and severe diffuse caliber reduction with delay in filling of the circumflex in one. The spasm was superimposed on a critical lesion in two patients and occurred in an angiographically normal vessel in one. It was accompanied by ST-segment elevation in the anterior leads in the first two patients and ST-segment depression in the anterolateral precordial leads in the third one. No apparent differences in severity and duration of ECG ischemic changes were noted in two patients when the same dose of ergonovine maleate was given during PGI₂ infusion. The patient who showed ST-segment depression and incomplete spasm during the control test had ST-segment elevation in the same leads during PGI₂.

Discussion

Continuous infusion of PGI₂ in normal subjects produced antiplatelet effects similar to those described previously and a dose-dependent drop in arterial pressure, accompanied by an increase in heart rate and CO. PAP also fell during PGI₂ in one subject and remained unchanged in the other. Therefore, in man, as in several other animal species, PGI₂ decreases both systemic and pulmonary resistance. Since no changes in RA pressure or in left atrial and LV dimensions suggestive of venous pooling became evident during the infusion, the drug seems to affect primarily arterioles rather than capacitance vessels, in accordance with previous findings.

The increase in heart rate during the infusion may be consequent to a baroreceptor reflex or produced by a direct effect of the drug on sinus node automaticity.

The absence of significant effects on SV, echocardiographic indexes of myocardial contractility and LV dP/dt rules out a primary inotropic effect of the drug. The marked increase of the TAV index of SV in subject CP, who showed the largest drop in systolic and diastolic arterial pressure, was probably due to reduced ventricular afterload.

Therefore, PGI₂ in man produces obvious vaso- dilatory and antiplatelet effects and may be useful in the management of patients with acute ischemic syndromes, especially if ischemia is produced by coronary vasospasm.

A localized decrease in arterial PGI₂ could facilitate
transient acute coronary vasoconstriction or platelet aggregation. In turn, vasoactive substances released by aggregating platelets could precipitate or aggravate coronary vasospasm and initiate a vicious circle, leading to coronary thrombosis and myocardial infarction. Theoretically, PG12 should therefore be ideal for these patients also because the hemodynamic changes and the side effects observed in normal subjects were negligible and readily reversible when the drug was discontinued. Furthermore, the increase in heart rate produced by the drug should not significantly affect the myocardial oxygen consumption, because arterial pressure is decreased.

However, our results only partially support this hypothesis. Although the typical hemodynamic and antiplatelet effects of PG12 were documented in all patients, in eight the drug had no effect on the number, duration and severity of episodes of transient acute myocardial ischemia either occurring spontaneously or induced by ergonovine maleate.

However, patient PE consistently showed a dramatic reduction in the number of ischemic episodes. The attacks were significantly reduced when PG12 was infused at a rate of 10 ng/kg/min and completely abolished during three consecutive infusions of 20 ng/kg/min, suggesting a dose-dependent effect of the drug. The prolonged ischemic episodes consistently observed after each PG12 infusion suggests a rebound in coronary vasoconstriction due to the acute withdrawal of the drug. We could not find any clinical feature to account for his different response to the drug, except for a low platelet count (60,000/ml) consequent to hepatic cirrhosis and hypersplenism. The favorable response to PG12 in this patient could also be related to the fact that his variant angina was not caused by vasospasm. However, the positive response to ergonovine makes this hypothesis unlikely.

Several factors may account for the conflicting results. Coronary vasospasm is likely to result from different stimuli affecting the vascular tone; their relative role in the individual patient will condition the therapeutic effect of a specific agent. However, no information is available on the actual physiologic levels of circulating PG12, its role in the regulation of coronary tone, or the relative importance of circulating and local vascular PG12. Furthermore, the action of exogenous PG12 on the human coronary circulation is not clear. In vitro incubation of PG12 with isolated human coronaries produces a paradoxical increase in vascular tone when high concentrations are used. Finally, the fate of exogeneous i.v. PG12 is unknown. Prolonged incubation of PG12 with human plasma leads to the formation of a new unidentified compound which, although retaining the antiplatelet effects, contracts instead of relaxes isolated bovine coronary strips.

Szczeklik et al. described the results of a long-term (72-hour) i.v. infusion of PG12 in seven patients with angina at rest who apparently did not respond to conventional treatment with oral nitrates. Symptoms completely disappeared in five patients and improved in two. The authors suggested that PG12 prevented ischemic episodes by avoiding the formation of platelet microaggregates releasing the vasoconstrictor thromboxane A2 in the coronary circulation. However, in a recent study in patients with variant angina, we could not find significant difference in the number of ischemic episodes recorded during control and after complete blockade of platelet thromboxane A2 with low-dose aspirin. The significance of the finding reported by Szczeklik et al. is difficult to assess because no information is provided on the number of attacks in the run-in period or on the associated antianginal treatment; the occurrence of transient acute myocardial ischemia was not evaluated objectively, and the effects of PG12 were not compared with those of placebo.

In conclusion, our study demonstrates that in man, PG12 has antiplatelet and vasodilatory effects similar to those observed in several other animal species. Its use appears safe in the appropriate environment in patients with ischemic heart disease. The side effects promptly disappear when the infusion rate of the drug is reduced. Occasionally, the acute administration of PG12 may result in the complete disappearance of episodes of acute myocardial ischemia due to coronary vasospasm, suggesting that a generalized or local reduction in PG12 production could contribute,
at least in some cases, to its occurrence. The lack of any apparent effect observed in the majority of patients could be related either to the prevalence of other etiologic factors in the genesis of coronary vasospasm or to the transformation of exogenous PGF2 in unknown metabolites with different biologic activities.

More basic and clinical studies are required for a better understanding of the actual role of PGF2 in the regulation of coronary vascular tone in physiologic and pathologic conditions.

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Changes in Plasma Lipid and Lipoprotein Levels in Men and Women After a Program of Moderate Exercise

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SUMMARY Levels of high-density lipoprotein (HDL) cholesterol and other lipids and lipoproteins of 24 men and 37 women were measured before and after a 10-week exercise program. The program involved three sessions of aerobic exercise each week, with 15–20 minutes of activity at 70% of maximal heart rate. Men and women had significantly different lipid patterns in response to exercise, despite equivalent increases in maximal oxygen uptake. Men showed a 5.1% increase in HDL cholesterol, a 6% decrease in low-density lipoprotein (LDL) cholesterol, and a 12.4% increase in the HDL/LDL ratio. In contrast, women showed a 1% decrease in HDL cholesterol, a 4.3% decrease in LDL cholesterol, and no significant change in the HDL/LDL ratio. The number of sessions attended correlated positively with HDL/LDL changes in men and correlated negatively with HDL/LDL changes in women. These findings suggest that moderate exercise may have different effects on men and women.

REGULAR PHYSICAL ACTIVITY is associated with decreased incidence of coronary heart disease (CHD), and persons with CHD may benefit from physical training. Exercise may reduce coronary risk by altering plasma lipid and lipoprotein levels. Two of the major lipoproteins that transport cholesterol in plasma are low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol. High levels of LDL cholesterol are related to increased risk of CHD and high levels of HDL cholesterol may protect against CHD. There has been increased interest in HDL cholesterol because its negative relationship with CHD is stronger than the positive relationship between CHD and either total cholesterol or LDL cholesterol.

Highly trained athletes have lower levels of cholesterol and LDL cholesterol, and higher levels of HDL cholesterol than sedentary persons of the same age and sex; this is true of runners, skiers, and swimmers. Hartung et al. found that marathon runners have higher HDL cholesterol levels than joggers, who in turn have higher levels than sedentary persons. Findings like these underscore the need for prospective studies to determine whether increases in physical activity produce beneficial changes in plasma lipid and lipoprotein levels.

Prospective studies on exercise and lipid changes have yielded conflicting results. Studies of men have shown consistent increases in HDL cholesterol during...
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