Alteration in Prostacyclin and Prostaglandin E₂ Production
Correlation with Changes in Human Aortic Atherosclerotic Disease

Pierre H. Rolland, Rémy Jouve, Evelyne Pellegrin, Claude Mercier, and André Serradimigni

Prostacyclin (PGI₂) and prostaglandin E₂ (PGE₂) production was investigated in human aortas (five controls and 27 with atherosclerotic lesions). The specific activities of PGI₂ and PGE₂ synthetase were studied using radioimmunoassays of PGE₂ and 6-keto-PGF₁α of aortic microsomes incubated in the presence of additional substrate and cofactors. The atherosclerotic lesions were examined under the light microscope and were classified as Stage 1 when the disease was restricted to the intima and as Stages 2 and 3 when there were moderate or advanced lesions. Prostaglandin production for the control group (n = 5), Stage 1 (n = 7), Stage 2 (n = 10), and Stage 3 (n = 10) were as follows: 454 ± 15, 162 ± 81, 92 ± 90, and 65 ± 61 pmol 6-K-PGF₁α/50 mg protein/10 minutes; and 15 ± 12, 399 ± 406, 227 ± 174, and 366 ± 362 pmol PGE₂/50 mg protein/10 minutes (mean ± SD) respectively. We conclude that: 1) In normal aortas, PGE₂ production was low, while PGI₂ synthesis activity was elevated. The reverse situation was observed in aortas with atherosclerosis lesions (p < 0.05). 2) There was an inverse relationship between PGE₂ and PGI₂ production (p < 0.05). 3) There was a direct histologic relationship between lower PGI₂ production and atherosclerosis progression. A decided decline in 6-K-PGF₁α production was detected in aortas in the early stages (65% of control values). 4) By contrast, a progressive increase in PGE₂ production was found in Stage 2 and Stage 3 groups (p < 0.05). These results demonstrate that there are correlations between the changes in prostaglandin production and the morphological features of atherosclerosis development. Because of the pharmacologic properties of prostaglandins, these changes in prostaglandin production may promote the development of atherosclerosis.

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Vascular endothelium is thought to act as a barrier to the passage of blood constituents into the arterial wall. A loss of endothelial function would lead to the entrapment of blood constituents in the deep layer of the vascular walls and induce myogenic and lipogenic atherosclerotic mechanisms. There is abundant evidence that the endothelium also actively influences both plasma coagulation and platelet function, factors in the thrombogenic theory of atherosclerosis. Prostacyclin (PGI₂) is predominantly generated in arterial walls by the endothelial cells and can inhibit platelet aggregation and secretion in vitro and may also inhibit microthrombus formation in vivo, preventing the adhesions of platelets to the intimal lining of the blood vessels. It is conceivable that PGI₂ could be one specific factor accounting for the thrombogenic-resistant nature of endothelium. Atherosclerotic arteries produce less PGI₂ than normal vessels. Patients with ischemic heart disease have increased thromboxane A₂ (the proaggregatory prostanoid) plasma levels and decreased PGI₂ production. It was postulated that atherosclerosis could originate from a defect in PGI₂ production in the arterial wall and the resulting unbalanced equilibrium between thromboxane A₂ (TXA₂) and PGI₂ levels in plasma. We earlier reported that patients with peripheral atherosclerotic vascular disease ex-
hibited elevated TxB₂ plasma levels.¹⁷ Little is yet known concerning PGE₂ production by human arteries; however, PGE₂ may play a role in atherosclerosis since it induces platelet aggregation and can inhibit in vitro cholesterol ester hydrolyase activity, thus enhancing lipid deposition in arteries.⁵,⁶,¹⁸-²¹

The present study concerns the production of PGI₂ and PGE₂ in human aortas and the possible relationship of these substances to atherogenesis. Previous studies dealing with established lesions have failed to show a relationship to the type of atherosclerosis and PGI₂ production.¹¹⁻¹³ We have classified atherosclerotic lesions into three groups encompassing the very early stages of the development of atherosclerosis and here report the progressive, inverse PGI₂ and PGE₂ production changes in human aortas as atherosclerosis progresses histologically.

**Methods**

We studied 27 men (aged 58 ± 7 years) undergoing vascular surgery for aortobifemoral grafting due to atherosclerosis obliterans. No patient had received any drugs known to influence either metabolic values or arachidonic acid metabolism for at least 2 weeks before surgery. Our controls were five men (22 ± 3 years of age) undergoing cardiac surgery for valvular replacement. Informed consent was obtained from all subjects.

**Sample Collection**

We obtained aortas from the abdominal area of patients and from the controls. A single aortic specimen was collected from one patient. At the time of surgery, aortic samples were collected and processed for simultaneous histological and biochemical investigations as previously described for other tissues²²-²⁵ and modified as follows. During abdominal aortotomy, atheromatous areas were cut open longitudinally and a representative piece (10 mm x 3 mm) was removed from each edge of the entire arterial wall and was rinsed in saline. One piece was immediately immersed and stored in liquid nitrogen for later processing for biochemical examination. The other piece was fixed in glutaraldehyde for pathologic examination. Both types of analyses were performed separately in a blind manner.

**Pathologic Examinations**

Surgical examples were fixed in ice-cold, 3.7% glutaraldehyde in cacodylate buffer (0.1M, pH 7.4) for 2 hours, rinsed in ice-cold cacodylate buffer for 48 hours, postfixed for 1 hour in 2% osmium-tetroxyde in buffer and stained en bloc with uranyl acetate. After dehydration in graded acetone, samples were embedded in Epon 812. Semithin sections (1 to 2 µm) were stained with either methylene blue-azur II, Weigert’s stain, or Verhoeff’s stain as previously described.²²-²⁴ The classification of the lesions was based upon double-blind observations of slides under the light microscope.²⁶ Gross evidence of atherosclerosis such as fatty streaks or raised lesions did not influence the classification, which was a modification of a previously published lesion classification.²⁶-²⁹ We arbitrarily classified the lesions as early (Stage 1), moderate (Stage 2), and advanced (Stage 3) (see Figure 1).

**Stage 1**

Morphologic changes involved the aortic intima, defined as that area of the wall extending from the lumen to the internal elastic lamina.³¹ A Stage 1 lesion was characterized by edematous and hyperplastic change of the intima. There was a marked rise in the intimal amorphous ground substance (Figure 1 B) and the internal and external elastic lamina and endothelium were intact. As in the controls, the aortic media was an orderly arrangement of perivascular units (Figure 1 A), one unit consisting of two parallel elastin fibers with smooth muscle cells, elastin, and collagen fibers inserted between them.³⁰-³³

**Stage 2**

This intermediate stage had as its predominant histopathologic feature the intimal thickening of the aorta (Figure 1 C). Arrangement of medial lamellar units was progressively lost because of elastin fragmentation, smooth muscle and connective cells proliferation, and increasing fibrosis and ground substance content. When cholesterol ester crystals were present, we classified the aorta as Stage 3.

**Stage 3**

This stage was characterized by advanced, well-developed atherosclerotic lesions (Figure 1 D, E, F).³⁰-³³ The intima involved widespread proliferation and the endothelium was often completely absent. Internal elastic lamina was largely missing and other elastic lamina contained calcification. Extensive calcification, as well as cholesterol ester crystals and lipid deposits, were apparent.

**Prostaglandin Synthase Activity**

Prostaglandin synthesis activity was measured by specific radioimmunoassays (RIAs) of PGE₂ and 6-keto-PGF₁α production on a pellet of atherosclerotic lesions prepared as previously described and modified as follows. Specimens were stored in liquid nitrogen until processed in a cold room at 4°C. They were weighed frozen (about 0.5 g) and then were powdered in liquid nitrogen using a powder-hammer. Then the powder was transferred to ultracentrifugation tubes and homogenized in Hepes buffer (0.1 M Hepes, pH 7.4, containing 2mM CaCl₂, 1 mM MgCl₂, 2% glycerol, and 1 mM monothioglycerol) to a ratio of 1 gr/5 ml. With a P-10 Polytron apparatus, homogenization was achieved by two intermittent
bursts of 5 seconds interrupted by a cooling interval of 30 seconds. Homogenates were centrifuged for 15 minutes at 800 g to eliminate intact cells and debris. The supernatant was spun at 150,000 g for 45 minutes at 2° C and the pellet was suspended in the same volume of Hepes buffer and centrifuged again under the same conditions. The resulting pellet was suspended in a small volume of Hepes buffer and represented the high-speed pellet fraction (HSP). Incubations were carried out as previously described23 by incubating 0.2 ml of the HSP fraction diluted in Hepes-buffer to 1 mg protein/ml and containing 1 mM reduced glutathione and 1 mM epinephrine (final concentrations) with 10-5 M sodium arachidonate as substrate, for 10 minutes at 37° C. Incubations were terminated by the addition of 0.2 ml of citric acid (1 M), and radioactive PGE2 was added in trace amounts to evaluate any procedural losses. The organic extracts were dried under a nitrogen stream, lyophilized and then submitted to silicic acid chromatography as previously described17.23 and modified as follows: The dried extracts were dissolved in 2 μl acetic acid in 2 ml of a mixture of benzene/ethyl acetate (B/EA) (8:2, vol/vol). This was quantitatively transferred to the top of one column (5 ml disposable Corning glass pipettes fitted with silicone glass wool and silicone-treated by Siliclaid, Clay-Adams). Each column contained 0.5 g of activated silic acid (Malinnckrodt, 100 mesh) in B/EA (8:2). The flow rate was regulated by nitrogen pressure to about 1 drop every 3 seconds. To reduce the background, we eluted neutral lipids, cholesterol, and free fatty acids with 5 ml of B/EA (8:2). This eluate was discarded. PGAs were eluted from the column by 5 ml of B/EA (6:4), PGEs, TxB2, and 6-keto-PGF1α, as a combined peak by 7 ml of B/EA/methanol (6:4:0.3) and PGFs by 4 ml of B/EA/methanol (6:4:2). RIAs were performed on buffer-reconstituted residues from these fractions as previously described17,21. Finally, prostaglandin (PG) production was expressed as picomoles (pmol) of PG produced per 50 mg protein for 10 minutes at 37° C.

Statistical Methods

The results are reported as means ± standard deviation (SD). Inspecting our results concerning PG production, we noted an absence of a normal distribution. Therefore, we performed statistical examination of the results using the nonparametric Mann and Whitney rank correlation coefficient.

Results

This research studied 32 human aortas, five of which were aortic roots from controls. Atherosclerotic vessels (27 specimens) were classified as Stage 1 (7), Stage 2 (10), and Stage 3 (10), according to the pathologic classification defined in the Methods section. In the controls, the intimal part of the aorta was free of disease (Figure 1 A); in particular, there was no visible thickening of the intima. The aortic media of both the controls and the Stage 1 lesions was as described in each case studied; however, there were wide variations in texture, i.e., the number and thickness of lamellar units. Similar observations of texture variations have been previously reported30-35. The thoracic media has been described as showing more lamellar units with decreased thickness than abdominal aortic media.35 When comparing the controls to Stage 1 lesions in our series, we did not see this difference in texture. Thus, we could not be sure that smooth muscle cells were more abundant in the media of Stage 1 lesions (abdominal origin) than in the controls (thoracic origin). However, it should be noted that Stage 1 lesions showed more focal elastin fragmentation of elastin lamellae in the aortic media. This observation is presumably related to the difference in age between the controls and the patients.29,34 In Stage 2 and 3 lesions, both intimal and medial parts of the aorta were pathologically affected.

In control aortas, PGE2 production was found to be at a low level, while 6-keto-PGF1α synthesis activity was high (15 ± 12 and 454 ± 15 pmol/50 mg protein/10 minutes, respectively, n = 5). The finding of low PGE2 production confirms that our technique of assaying PG production avoids an artifactual conversion of arachidonate to PGs. The reverse situation in PG production was observed in atherosclerotic lesions. When we considered all lesions regardless of the stage, PGE2 production was markedly increased, while 6-keto-PGF1α was substantially reduced (312 ± 311 and 104 ± 86 pmol/50 mg protein/10 minutes, respectively, n = 27).

Individual results are presented in Figure 2. Both PGE2 and PGF1α production from lesion-bearing tissues were statistically different from controls (p < 0.05). These results demonstrate that the profile of PG production was dramatically changed in human atherosclerotic lesions as compared with normal aortas. It should be emphasized that PG production by controls was homogeneous with very low variance values for production of both PGs. By contrast,
PROSTANOID SYNTHESIS ACTIVITY AND ATHEROSCLEROSIS

A

B

C

D

E

F
Figure 2. Prostaglandin production by normal and atherosclerotic human aortas. Comparison of individual prostaglandin E2 and 6-keto-PGF$_{1\alpha}$ production by micrososomal fractions in five controls and 27 atherosclerotic patients.

Figure 3. Production of 6-keto-PGF$_{1\alpha}$ by normal and atherosclerotic human aortas. Comparison of individual 6-keto-PGF$_{1\alpha}$ production by microsomal fractions in five controls and 27 atherosclerotic patients classified according to the progressive stages of atherosclerosis.

Figure 4. Prostaglandin E2 production by normal and atherosclerotic human aortas. Comparison of individual PGE$_2$ production by microsomal fraction in five controls and 27 atherosclerotic patients classified according to the progressive stages of atherosclerosis.

lower 6-K-PGF$_{1\alpha}$ production (4.4-fold less than control value) and increased PGE$_2$ production (20-fold greater than control value) were heterogeneous activities, e.g., synthesis varied widely from sample to sample within groups.

Figure 3 compares PG productions in various disease stages for 6-keto-PGF$_{1\alpha}$; a similar comparison is shown in Figure 4 for PGE$_2$. Production of 6-keto-PGF$_{1\alpha}$ by controls, Stage 1, 2 and 3 groups were 454 ± 15, 162 ± 81, 92 ± 90 and 65 ± 61 pmol/50 mg protein/10 minutes, respectively. Statistical differences were noted between the controls and Stage 1 ($p < 0.005$) and between Stages 1 and 3 ($p < 0.05$), but there was no significant relationship in PG production between Stage 1 and 2 and between Stages 2 and 3. The decline in PG production was, therefore, between controls and Stage 1 lesions (Stage 1 value was 35% of controls) and between early and advanced stages (Stage 3 value was 40% of Stage 1 and 14% of control value). Finally, there was no statistical difference in 6-keto-PGF$_{1\alpha}$ in each consecutive step, although the averages were progressively lower.

Figure 4 shows PGE$_2$ production by controls, and Stages 1, 2, and 3 groups, which were 15 ± 12 (n = 5), 399 ± 406 (n = 7), 227 ± 174 (n = 10), and 366...
± 362 (n = 10) pmol PGE<sub>2</sub>/50 mg protein/10 minutes, respectively. The mean prostaglandin E<sub>2</sub> production within the various stages was in all patient groups significantly higher than in controls (p < 0.005). In contrast to 6-keto-PGF<sub>1α</sub>, PGE<sub>2</sub> production did not differ significantly between atherosclerotic stages; however, individual values showed abnormally large variances in PGE<sub>2</sub> production. This is particularly apparent in the Stage 1 group where four of seven cases showed a slight increase in PGE<sub>2</sub> production. By contrast, the other three cases produced large amounts of PGE<sub>2</sub> (higher than in Stage 3 lesions). A progressive increase in the mean PGE<sub>2</sub> values was detected between controls and Stage 2 and 3 cases, but this was only a statistical tendency (p < 0.1). These findings suggest that in the later stages, PGE<sub>2</sub> might parallel the progression of atherosclerosis. To confirm this possibility, we investigated the relationship between PGE<sub>2</sub> and 6-keto-PGF<sub>1α</sub> production, since the latter was inversely linked to atherosclerosis development.

As shown in Figure 5, an inverse relationship (p < 0.05) was noted between PG productions regardless of the lesion stage, thus providing indirect evidence that PGE<sub>2</sub> production increased when atherosclerosis extended through the arterial wall. Since the total PG production by arterial wall microsomes (PGE<sub>2</sub> + PGI<sub>2</sub>) was roughly equal in all groups (469 in controls and 431 in Stage 3 (pmol/50 mg protein), our results suggest that arachidonate metabolism may be diverted from PGI<sub>2</sub> synthesis to PGE<sub>2</sub> production. However, the relative proportion of the change contributed by the intimal or medial components of arterial wall remains to be determined.

**Discussion**

Loss of endothelial integrity has long been implicated as a factor in the development of atherosclerosis, and many investigators have demonstrated a direct relationship between the frequency, magnitude, and duration of endothelial damage and the subsequent development of atherosclerotic lesions. According to the thrombogenic theory of atherosclerosis, the prostacyclin-thromboxane balance implies that the lowering of PGI<sub>2</sub> production by arterial walls results in a parallel loss of endothelial thromboreistance. Prostaglandin E<sub>2</sub> enhances platelet aggregation and chemotaxis of white blood cells, increases vascular permeability, and inhibits cholesterol ester hydrolase. Therefore, a rise in PGE<sub>2</sub> production by the arterial wall could favor the development of atherosclerosis.

In this study, we attempted to answer the following questions: 1) is PGI<sub>2</sub> production similarly lowered in early, moderate, and advanced stages of vascular disease, and 2) what are the basic characteristics of PGE<sub>2</sub> production by atherosclerotic vessels? The production of 6-keto-PGF<sub>1α</sub> was assayed to reflect PGI<sub>2</sub> synthesis activity since prostacyclin is unstable and spontaneously converts to this stable metabolite. Although PGI<sub>2</sub> may be metabolized into substances other than 6-keto-PGF<sub>1α</sub> in vivo, our use of 6-keto-PGF<sub>1α</sub> should be valid since PG production was measured within a microsomal fraction and PG metabolizing activities are located within the cytosol. By definition, PG synthetase activity is the production of PG per unit weight of microsomes when the enzyme is incubated with a sufficient concentration of substrate and cofactors. Our results report the amount of enzyme present per unit weight of microsome, and provide additional data to that obtained in previous experiments based on arterial rings (intact cells).

Earlier observations showed that glutathione promotes the production of E-type PG rather than PGI<sub>2</sub> and that this effect is specific for GSH in comparison to the effects of other sulfur-containing molecules. The enzyme PG H-PG E<sub>2</sub> isomerase that catalyzes the isomerism of PGH<sub>2</sub> into PGE<sub>2</sub> requires glutathione as a cofactor. Glutathione and the enzyme responsible for its accumulation are widely distributed at high concentrations in most tissue. In our studies, controls showed high 6-keto-PGF<sub>1α</sub> production, while PGE<sub>2</sub> synthesis activity remained at a
very low level; thus in incubation conditions, there were few, if any, artifactual shifts of PGI₂ to PGE₂ formation.

We have observed that normal human aorta produces significant amounts of prostacyclin and very little PGE₂; however, in atherosclerotic vessels there is decreased PGI₁ production and a marked increase in PGE₂ synthesis. Thus, in the human aorta, prostaglandin production changes in parallel to the histological progression of atherosclerosis. Atherosclerosis is a progressive disease and there has been no general agreement about its pathologic staging. Our primary interest was to establish the basic characteristics of PG production according to the histological status of human aortas. For this purpose, we established an arbitrary classification restricted to the histological appearance under the light microscope. As controls, we used aortic roots from young adults instead of apparently disease-free aortic areas from the patients. Since age-matched controls were unavailable, our control group represents a compromise. We cannot completely rule out the possibility that there are significant differences in arterial wall arachidonic acid metabolism between the upper thoracic and the abdominal portion of the aorta. There are several stages of atherosclerosis which regularly coexist in the same individual and often in adjacent segment of the same artery. There is no evidence that the "normal adjacent segment" to an atherosclerotic lesion is effectively free of disease, but it has been shown that the "normal" coronary segment near a stenosis is seldom normal. Stage 1 lesions included the patterns of early intimal changes leading to the atherosclerotic processes, characteristic of the slowly developing or naturally occurring disease. However, these intimal changes do not inevitably lead to an advanced lesion, although they always precede moderate and advanced lesions as defined by Stage 2 and Stage 3.

Prostacyclin production declined according to the severity of the disease: PGI₁ production fell sharply in the early stages of the disease and, progressively decreased to very low values in advanced disease. The change observed in PGI₁ production at Stage 1 could have been due to age difference. However, this is unlikely since Stage 1 intima was disproportionately thicker than normal intimal thickening associated with aging. In Stage 2 and 3 lesions, prostacyclin decreased to very low levels as endothelial damage increased and the disease extended to involve the media. In these cases, the prostacyclin synthetase exhibited a lower specific activity. In addition, lower PGI₁ production might have resulted from a peroxylized lipid accumulation, since these molecules are potent inhibitors of PGI₁ generation by the arterial walls. Our results disagree with previous reports by Sinzinger et al. who failed to detect a relationship between reduced PGI₁ production and the stage of atherosclerosis. There are several possible explanations for these discrepancies. We used a sensitive and specific RIA instead of a bioassay and we presented PG production from microsomal fractions instead of from multiple samples of iliac and femoral arteries obtained from a small series of patients. Finally, the pathologic staging was quite different, particularly since our histologic classification included the early stage of the disease.

The marked depression of PGI₁ synthesis, noted in the early lesions, is biologically relevant and might be pathologically important. Yet, its role is unclear, since even though the lesions are widely distributed in atherosclerotic arteries, most will not develop into advanced stenosis. It is conceivable that a reduction in PGI₁ is one factor favoring arterogenesis in the early stages, although the progression of the disease depends upon factors other than PGI₁. Recent results from normal and virus-transformed endothelial cells in culture do not support the hypothesis that PGI₁ is responsible for the lack of platelet adherence to normal vascular endothelium, and bring into question the importance of PGI₁ in the thrombogenic theory of arterogenesis. Morphological features of Stage 1 intimal lesions are associated with changes in the endothelial cell morphology and in the glyocalyx, consequently vascular permeability is affected, leading to an increased entrapment of plasma fluids and components, as well as focal changes. The results of our study suggest that PGI₁ production serves as a marker of endothelial integrity at an early stage of atherosclerosis.

We also found that human atherosclerotic aortas produce significant amounts of PGE₂. Prostaglandin E₂, in contrast with PGI₁, showed no statistically significant relationship with PGE₂ production and the stages of the disease. However, individual values show that, on the average, PGE₂ production increases with the progression of atherosclerosis. The absence of a statistical relationship may be due to the large range of PGE₂ production within groups. Individual values of PGE₂ production at Stage 1 was only slightly higher than that in controls in four of seven cases, while the other three cases produced extremely high amounts of PGE₂. Smooth muscle cells (SMC) and fibroblasts from arteries have been reported to produce PGE₂. The role of SMC in this high PGE₂ production is unclear, since the media was disease-free in controls and Stage 1. By contrast, fibroblasts could participate in this process in Stage 1 lesions containing hyperplastic intimal connective tissue. In addition, inflammation or edema could account for the abnormally high PGE₂ since inflammatory cells can produce large amounts of PGE₂. The inverse relationship between PGE₂ and PGI₁ production argues for an increased PGE₂ production as the lesion progresses. Thus, there is a reciprocal relationship between decreasing PGI₁ production and increasing PGE₂ production in the aortic wall as atherosclerosis progresses.

In conclusion, there appears to be a relationship between the changes in prostaglandin E₂ and PGI₁ pro-
duction and the morphologic changes of progressive atherosclerotic development, although the biologic, pathologic, and pharmacologic significance of this relationship in vivo remains to be ascertained. This phenomenon may contribute to atherosclerosis development; in early stages, lower PGII may encourage thrombogenic events and their consequences. Thereafter, PGE2 may give fibroblastic cells a proliferative advantage while favoring lipid deposition within arterial walls. The therapeutic implications of these findings are still unclear since the significance of PG in atherosclerosis is still uncertain.

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Index Terms: human aorta • atherosclerosis histology • prostacyclin • prostaglandin E2 • prostanoid synthesis activity

Erratum
The Editors regret that during the typesetting of the abstract below, which appeared in the September/October 1983 issue of Arteriosclerosis (page 466a), the first two authors were omitted. The corrected abstract is reprinted in its entirety.

★Low Heart Rate Retards Coronary Atherosclerosis

P.A. Beere, C.K. Zarins, S. Glagov, Depts. of Pathology and Surgery, University of Chicago, IL

To assess the role of heart rate (HR) in coronary atherogenesis, we reduced HR by sinoatrial node ablation (SNA) in five adult male cynomolgus monkeys (148 ± 11 to 102 ± 22) and subjected 10 monkeys to sham operations. These procedures provided a postoperative range for all 15 animals of 73 to 156 beats/min. The 15 animals could then be divided into high HR (137 ± 13, N = 7) and low HR (97 ± 14, N = 8) groups (p < 0.001, Student's t test) with respect to the mean for all 15 (116 ± 24). All animals were fed an atherogenic diet for 6 months. HR, recorded by 24-hour telemetry at bimonthly intervals, remained stable for each group. Blood pressure (128/84; 120/80 mm Hg), serum cholesterol (660; 711 mg%), and body weights (5.5; 5.4 kg) did not differ significantly for the two groups. Coronary atherosclerosis (lesion area and percentage of occlusion) was measured at six standard sites after in situ pressure-fixation. The low HR group (LHR) had less disease than high HR group (HHR). Average lesion area for the LHR (0.06 ± 0.05 mm²) was only ¼ of that for HHR (0.21 ± 0.26 mm²; p < 0.01, Mann-Whitney test). Maximum percentage of occlusion was 23.5% ± 12.1% for LHR, and 37.0% ± 24.4% for HHR (p < 0.01, Mann-Whitney test). The proportion of sections with greater than 25% occlusion for LHR (15%) was only one-half of that for HHR (29%; x² = 1.67, p < 0.1). The protective effect of physical training and relatively low psychosocial stress on ischemic heart disease may be attributable in part to low HR.
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P H Rolland, R Jouve, E Pellegrin, C Mercier and A Serradimigni

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