Dietary Probucol Preserves Endothelium-dependent Relaxation of Arteriovenous Fistula in Hypercholesterolemic Rabbits

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Background: Shear stress caused by arteriovenous fistula (AVF) enhances endothelium-dependent relaxation (EDR) but oxidized low-density lipoprotein (ox- LDL) counteracts its effect. Probucol, a lipid soluble antioxidant, may preserve EDR of AVF by limiting oxidation of LDL.

Methods: Twenty New Zealand rabbits, fed with 2% cholesterol chow for 4 weeks, underwent AVF. They were then divided into two groups: continuing with 2% cholesterol chow alone (group I) and 2% cholesterol chow with 1% probucol supplement (group II). Another 10, fed regular chow, were assigned to the control (group III). The levels of cholesterol and LDL were measured. Segments of the AVF afferent arteries were harvested to check intimal thickness, and endothelium-dependent and independent relaxations, after 4 weeks dietary treatment had been completed.

Results: Both cholesterol and LDL levels were significantly elevated after 4 weeks of cholesterol feeding. These profiles reached higher levels at 8 weeks in group I and were less increased in group II. The intimal hyperplasia ratio was 48% in group I, 34% in group II and 24% in group III. Maximal EDR response to either acetylcholine or receptor-independent calcium ionophore A23187 in group II was greater than that in group I (66 $\pm$ 1.9% versus 38 $\pm$ 1.2%, p = 0.02; 76 $\pm$ 2.4% versus 30 $\pm$ 0.8%, p = 0.01) and not different from that in group III (74 $\pm$ 2.4%, 84 $\pm$ 3.7%). There was no similar difference of denuded arterial rings among the three groups (76 $\pm$ 3.2%, 78 $\pm$ 3.7%, 82 $\pm$ 4.1%).

Conclusion: Cholesterol can limit EDR of AVF and produce vulnerability to early occlusion and thrombosis. Probucol supplement under hyperlipidemia status preserves EDR and not endothelium-independent relaxation.

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Key words: endothelium-dependent relaxation, cholesterol, arteriovenous fistula, probucol.

Vascular access continues to be the principal problem in patients requiring long-term hemodialysis. A series from the Brigham and Women's Hospital in Boston reported a 1-year paten-

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cy rate for arteriovenous fistula (AVF) of 64% and a 2-year patency rate of 50%.[1] Excluding technical failures and premature venous intimal hyperplasia, most cases of early AVF failure are attributed to sudden thrombosis by low flow status due to hypotension or atherosclerotic vessels. In animal models of atherosclerosis and isolated human atherosclerotic coronary arteries, endothelium-dependent relaxation (EDR) is impaired, and platelet aggregation and its adhesion to endothelium are severely increased.[2] Loss of these protections predisposes the blood vessel to vasospasm and enhances thrombus formation. Uremic patients' need for AVF creations is generally associated with atherosclerotic vessels and this pathology may play critical roles in the pathogenesis of acute AVF occlusion. Oxidized low-density lipoproteins (ox-LDL) enhance oxidative stress and contribute to EDR factor (EDRF) abnormalities. Probucol, a lipid soluble antioxidant, can effectively alleviate LDL modification by endothelial cells,[3] preserve EDR[4] and prevent an increase in vascular superoxide generation.[5] These antioxidant protection studies achieved effective prevention of atherosclerosis in animal models, although most were limited in systemic aortic great vessels. Speculating whether antioxidants could also limit severity of atherosclerotic lesions and preserve EDR in peripheral small vessels is appealing. This study attempts to determine whether EDR, increased by AVF shearing forces and downregulated by hypercholesterolemia, could be regained by combined antioxidant protection.

METHODS

Twenty New Zealand rabbits, fed 2% cholesterol chow for 4 weeks prior to surgery to simulate the clinical scenario of hyperlipidemia with atherosclerotic vessels, underwent femoro-femoral AVFs. One surgeon performed all procedures to eliminate variation in technique. The rabbits were randomly assigned to two groups following AVF surgery. Group I rabbits were fed continuously with 2% cholesterol chow and group II rabbits were fed cholesterol chow supplemented with 1% probucol. Cholesterol chow was purchased from Purina Mills, Inc. (Richmond, Indiana, USA) and probucol from Sigma Chemical Co (St. Louis, Missouri, USA). The 1% probucol was prepared by dissolving pure probucol in 70% ethanol and spraying it over the 2% cholesterol chow. Blood samples for lipid profiles and probucol levels were collected at weeks 4 and 8 after dietary treatment. Plasma total cholesterol and LDL concentrations were measured by an enzymatic method (Boehringer Mannheim GmbH, Mannheim, Germany). Probucol levels were determined by analytical high performance liquid chromatography (HPLC), using a modification of the procedure described by Satonin and Coutant.[6] Four weeks following surgery, the afferent arteries of AVF were harvested and each prepared as a 5 mm ring for subsequent organ chamber experiments. The influence of atherosclerotic effect on intimal thickness of AVF was verified histopathologically. Care was taken to avoid any endothelial injury of the rings during manipulation. In some other arterial rings, forceps were inserted and gently rolled back and forth to purposely denude the endothelium. All animals received humane care in compliance with *the Guide for the Care and Use of Laboratory Animals* (National Institute of Health Publication, no. 85-23, revised 1985) and approval of the project protocol was obtained from the animal review committee of the hospital.

Histological examination

In preparation of histological readings of intimal thickness, junction areas of AVF from each specimen were embedded in paraffin and sectioned to 5 μm thicknesses for hematoxylin-eosin staining. Calculating the ratio between the diameter of the remaining patent lumen and the entire intimal layer derived the change of intimal thickness.

Organ chamber experiments

Arterial rings, with and without endothelium, from the experimental and control groups were analyzed in parallel in a multibath organ chamber system. The rings were suspended in individual organ baths filled with physiological solution (25 ml, 37°C, aerated with 95% oxygen and 5% carbon dioxide; PO_2 = 400 ± 20 mmHg; pH = 7.4). The optimal points in the length-tension relationship were measured by progressively stretching the ring with two clips connected to strain gauge force transducers (Statham UC2, Gould Inc., Cleveland, Ohio, USA). The response to prostaglandin $F_{2\alpha}$ (2×10^{-6} mol/L) imposed at each level of distension was assumed as

maximal. In all experiments, the presence or absence of endothelium was confirmed by response to acetylcholine (ACh) (10^{-6} mol/L) in rings contracted with potassium ions (20 mol/L). Once optimal tension was achieved, the rings were allowed to equilibrate for 45 minutes prior to administration of drugs. To compare the degree of EDR between the control and experimental groups, cumulative dose-dependent responses to ACh and calcium ionophore A23187 (10^{-9} to 10^{-4} mol/L) were measured in rings contracted with norepinephrine. Endothelium-independent relaxations were exposed to increasing concentrations of sodium nitroprusside (10^{-9} to 10^{-4} mol/L).

Drugs

ACh, calcium ionophore A23187, sodium nitroprusside and prostaglandin $F_{2\alpha}$ were obtained from Sigma Chemical Co. (St. Louis, Missouri, USA). All drugs were prepared daily with distilled water, except A23187, which was dissolved in dimethyl sulfoxide (Sigma Chemical Co., St. Louis, Missouri, USA). Drug concentrations are expressed as final molar (mol/L) concentrations in the organ chambers.

Data analysis

The data were expressed as means ± standard deviation of the mean. In all experiments, *n* represents the number of animals from which blood vessels were obtained. In rings contracted with prostaglandin $F_{2\alpha}$, responses are expressed as percent changes from contracted levels. The effective concentration of agonists causing 50% inhibition of the contraction (IC_{50}) to prostaglandin $F_{2\alpha}$ was calculated from each concentration response curve and the means of these values were presented as a negative logarithm of the molar concentrations. Comparison of data between groups was performed with analysis of variance (ANOVA) and the Turkey *t*-test was applied when ANOVA identified significant difference. A *p* value of < 0.05 was considered statistically significant.

RESULTS

Plasma lipid profiles

Table 1 shows animals' weights, total plasma cholesterol, LDL and probucol concentrations among the three groups. Animals in group III, fed with standard normal chow, had significantly lower plasma cholesterol and LDL levels compared with those in groups I and II after 4 weeks of cholesterol chow. These differences increased after a further 4 weeks cholesterol chow and the probucol supplementation did not lower the plasma cholesterol levels in group II significantly. The cholesterol level (mg/dL) was 359 ± 114 versus 274 ± 87, $p = 0.08$ and the LDL level was 235 ± 106 versus 154 ± 79, $p = 0.07$, in group I and II, respectively.

Table 1. Body Weights, Lipid Profiles and Probucol Concentrations of Three Groups of Rabbits after Four and Eight Weeks of Different Dietary Treatments

		Group I	Group II	Group III
4 weeks	Body weight (g)	3248±153	3241 ±114	3147 ±124
	Cholesterol (mg/dL)	276 ±94*	257 ±63*	65 ±4.3
	LDL (mg/dL)	196 ±83*	185 ±87*	14 ±0.3
	Probucol (ng/dL)	ND	1106±83	ND
8 weeks	Body weight (g)	3649±174	3764 ±147	3667 ±214
	Cholesterol (mg/dL)	359±114*†	274(87*	78 ±5.2
	LDL (mg/dL)	235 ±06*†	154±79*	18 ±1.2
	Probucol (ng/dL)	ND	1547 ±112	ND

Abbreviations: Group I: fed cholesterol for 8 weeks; Group II: fed cholesterol chow for the first 4 weeks, then concomitant probucol and cholesterol for the next 4 weeks after AVF creation; Group III: fed with normal chow for 8 weeks and reserved as the control. Number of animals studied in each group = 10. All values are expressed as mean ± standard deviation (SD). ND: not determined; LDL: low density lipoprotein.

* $p < 0.05$: Group I or II versus Group III

† $p < 0.05$: Group I versus Group II

Intimal hyperplasia of afferent arteries of AVF

There were 3 AVF early occlusions identified during sacrifice in group I, 1 in group II and 1 in group III. Intimal thickness of over 40% of AVF lumen occlusion was identified in another 4 rabbits in group I. The intimal hyperplasia ratios (diameter of intimal layer/intimal layer plus residual patent lumen) in group II were greater than those in group I (48% versus 34%), although the difference was not significant ($p = 0.07$) (Table 2). No animals in group III had an intimal hyperplasia ratio over 40%.

EDR

Fig. 1 and Table 3 show the effects of dietary cholesterol and probucol supplementation on ACh-induced vasodilatation. Though all arterial rings exhibited concentration-dependent relaxation to ACh in all groups (Fig. 1A), the probucol supplemented

Table 2. Intimal Hyperplasia of Afferent Arteries of Arteriovenous Fistula (AVF)

Intimal thickness ratio*	Group I (n = 7†)	Group II (n = 9)	Group III (n = 9)
Mild (< 25%)	1	6	8
Moderate (< 40%)	2	3	1
Severe (> 40%)	4	1	0
Average	48%	34%	24%

* intimal hyperplasia ratio = diameter of intimal layer/intimal layer plus residual patent lumen.

† There were 3 AVF total occlusions identified during sacrifice in group I, 1 in group II and 1 in group III. The affected animals were excluded from the intimal hyperplasia statistics.

group (group II) showed better EDR compared with the cholesterol fed only group (group I) (p = 0.02). In addition, this protective relaxation by probucol could achieve an equivalent response to that of the control group (group III). Calcium ionophore A23187 induced comparable concentration-dependent relaxation in all groups (Fig. 1B). Similar to ACh, use of supplemental probucol showed better EDR than cholesterol alone (p = 0.01). Both indicate that EDRs hindered by hyperlipidemia status could be ameliorated by probucol supplementation.

Endothelium-independent relaxation

Increasing concentrations of sodium nitroprusside (10^{-9} to 10^{-4} mol/L) induced similar concentration-dependent relaxation in arterial rings without endothelium in all three groups (Fig. 1C). In contrast to ACh and calcium ionophore A23187, supplemental probucol showed no difference in relaxation compared with group I. There was also no difference in the effective concentration causing 50% of the maximal relaxation to the agonists, either with or without probucol supplements (Table 3).

Table 3. Endothelium-Dependent and Independent Relaxation of Afferent Arteries of AVF

	IC_{50} (-log mol/L)*		
	Group I	Group II	Group III
With endothelium			
Acetylcholine	3.12±0.23‡	6.12±0.47	6.45±0.57
Calcium ionophore A23187	2.98±0.33‡	6.63±0.72	7.12±0.64
Without endothelium			
Sodium nitroprusside	5.82±0.26	5.76±0.31	6.03±0.34
Maximal relaxation (%)†			
With endothelium			
Acetylcholine	38±1.2	66±1.9	74±2.4
Calcium ionophore A23187	30±0.8	76±2.4	84±3.7
Without endothelium			
Sodium nitroprusside	76±3.2	78±3.7	82±4.1

Abbreviations: *: Values are given as mean ± standard error of the mean (SEM); -Log IC_{50}: negative logarithms of the concentration (mol/L) of agonist causing 50% inhibition of contractions (*i.e.* median effective dose) induced by prostaglandin $F_{2\alpha}$ ($2x10^{-6}$ mol/L).

† Values are given as mean ± SEM. Maximum relaxation (%) expressed as maximal inhibition of contraction induced by prostaglandin $F_{2\alpha}$ ($2x10^{-6}$ mol/L) with the agonists (10^{-4} mol/L).

‡ $p < 0.05$: Group I versus group II.

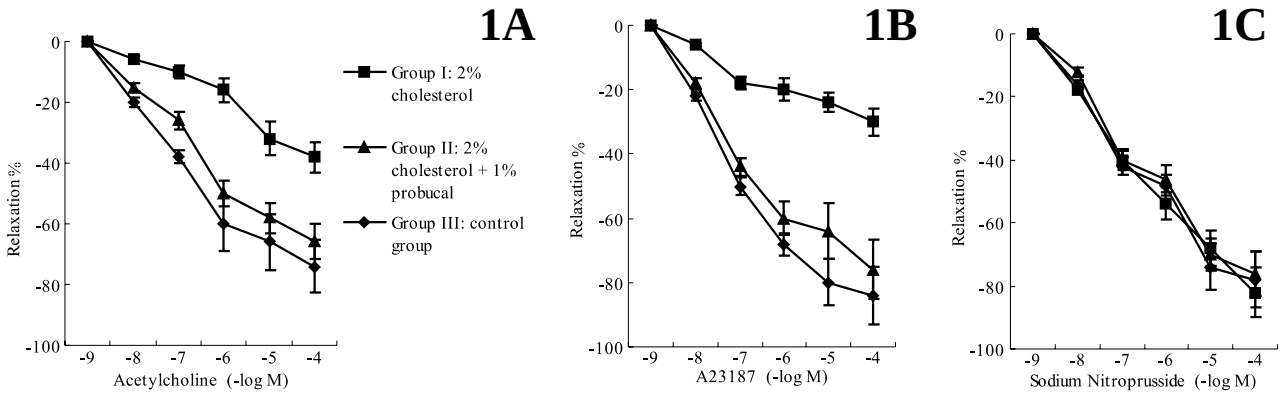

Fig. 1 Cumulative concentration response curves for acetylcholine. Calcium ionophore A23187 and sodium nitroprusside in afferent arteries of AVF were expressed after 8 weeks of dietary treatment. Values are expressed as means ± standard error of the mean (SEM) for the group fed cholesterol (Group I), the group fed concomitant cholesterol and probucol after AVF creation (Group II) and the control group (Group III).
*: statistically significant difference ($p < 0.05$) between the groups.

DISCUSSION

This study demonstrated that probucol maintains EDR of afferent arteries of AVF from cholesterol fed rabbits. The plasma lipid profile and intimal proliferation of AVF in probucol supplemented rabbits were improved but not significantly different than cholesterol fed only animals. This indicates that the protective effects of probucol are neither a simple cholesterol-lowering effect nor a counteraction of intimal morphological changes.

Vascular remodeling of AVF, oxidative stress and impairment of EDRF

Acute changes of blood flow by AVF induce compensatory adjustments in arterial diameters. These structural adaptations, so-called remodeling, normalize the vascular shear stress and minimize stretch-induced tension. Girerd et al. employed a high-resolution echo tracking system to measure radial artery remodeling in response to the increased shear stress in AVF. Results showed that the structural adaptation of the artery resulted in remodeling but no vascular hypertrophy.[7] This remodeling, recognized as endothelium-dependent, is produced by the release of EDRF. Researchers have proposed that EDRF may be nitric oxide (NO). As a potent vasodilator, NO has many biological functions, such as inhibition of monocyte and platelet adhesion to endothelial cells and smooth muscle cell proliferation, and is crucial in preventing blood flow obstruction and thrombus formation in blood vessels. However, NO shares with EDRF the property of being hypersensitive to destruction by superoxide anions and ischemic reperfusion injury.[8,9] Under the setting of atherosclerosis, superoxide production is elevated and is the principal source of oxidative stress in vivo.[5] The superoxide reacts destructively with NO, limiting the biological activity of EDRF or becoming hydroxyl radicals, which can be cytotoxic to endothelial cells through direct peroxidation of lipids or proteins.[10,11] A primary target of vascular oxidative stress is LDL. Healthy arteries exposed to substantial amounts of ox-LDL show impaired relaxation in response to the agonists of EDRF release.[12] Analytical findings in this study were coincident with other findings, which showed that animals fed cholesterol developed high LDL levels in plasma and abnormal EDR by ACh, a G_{Is} protein-dependent EDRF agonist. Relaxation responses to calcium ionophore A23187, a receptor-independent EDRF agonist, showed the same responses as ACh. Clinically, uremic patients with hypercholesterolemia and atherosclerotic vessels have high percentages of sudden AVF occlusion even without intimal hyperplasia. Impairment of EDRF in atherosclerosis, and failure to adequately respond to sudden pressure and flow changes during hypotension, contribute to platelet deposition and vasospasm, which lead to premature AVF occlusion.

Probucol and EDRF protection

Antioxidants, which limit the vascular oxidative stress of ox-LDL, can decrease atherogenesis and atherosclerosis. Strategies to prevent or reverse endothelial dysfunction induced by ox-LDL have the potential to ameliorate vascular damage. Probucol, a cholesterol-lowering antioxidant, is lipid soluble, and localized primarily in membranes where it limits lipid peroxidation damage and oxidative modification of LDL.[13] Probucol also mediates the vascular responses of platelet and leukocyte adhesion to endothelial cells,[14] monocyte transmigration[15] and direct cytotoxicity.[16] Carew and associates showed that probucol-treated animals had significantly less aortic atherosclerosis than the lovastatin treatment group but an equivalent reduction in plasma cholesterol;[17] these findings were confirmed in this study. Inhibition of luminal stenosis severity in the probucol group was also found but it was not sufficiently strong to account for the oxidative stress protection. Preservation of EDR may be crucial to improved outcome.

Study limitations

This study primarily observed morphological adaptations and functional changes in vascular relaxation. The mechanisms underlying the protective effects of probucol against oxidative stress remain unclear and their possible ultrastructural changes have not been investigated. Furthermore, the possible existence of interspecies response heterogeneity to probucol in humans and rabbits also requires elucidation before probucol supplementation therapy is applied clinically.

In conclusion, ox-LDL and reactive oxygen species impair EDRF action, inhibit vascular vaso-

motor tone and enhance platelet adhesion. Such abnormalities are critical to the pathophysiology of early AVF occlusion and thrombosis. The data presented here indicates that antioxidant treatment with probucol effectively increases EDRF in cholesterol fed rabbits. The preservation of EDR, rather than its cholesterol-lowering effect or intimal hyperplasia inhibition, accounted for the majority of beneficial actions. We propose that an improved understanding of oxidative stress, the vascular activities of AVF and probucol protection can play a significant role in therapy for uremic patients with associated atherosclerosis, in the near future.

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食用維他命 E (probucol) 可以保存高膽固醇兔子動靜脈廔管的血管內皮依附性舒張

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背景： 動靜脈廔管造成的剪力可以增強血管內皮依附性的舒張，但氧化性低密度的脂蛋白會拮抗它的作用。維他命 E (probucol)，脂溶性的抗氧化劑，可能因限制低密度脂蛋白的氧化而保存動靜脈廔管引起的血管舒張特性。

方法： 20 隻紐西蘭兔子在餵食 2% 膽固醇飼料 4 星期後接受動靜脈廔管手術，它們接下來因餵食的飼料分成兩組，第 1 組繼續 2% 膽固醇飼料，第 2 組除了膽固醇飼料再添加 1% 維他命 E (probucol)，第 3 組是 10 隻餵食正常飼料但也接受廔管手術作爲對照組。血液中的全膽固醇，低密度脂蛋白濃度定期監測，在手術後 4 星期摘取廔管傳入動脈端看血管內膜增生厚度與測量血管內皮依附性或獨立性的舒張反應。

結果： 在餵食膽固醇飼料 4 星期後，膽固醇和低密度脂蛋白的血液濃度有明顯上升，這些數值到 8 星期時，在第 1 組達到更高值，但第 2 組沒有明顯上升。血管內膜厚度增生比例 3 組依次爲 48%，34% 和 24%。最大血管內皮依附性舒張反應，不管是對乙醯膽鹼 (66%±19% 比 38%±1.2%，p = 0.02) 或受體獨立性的鈣紫酮 A23187 (76%±2.4% 比 30%±0.8%，p = 0.01)，第 2 組都比第 1 組反應強烈，但與第 3 組並無差別 (74%±2.4% 比 84%±3.7%)。至於對移除血管內皮後的血管舒張反應，在 3 組之間並沒有差別 (76%±3.2%，78%±3.7%，82%±4.1%)。

結論： 膽固醇可以因抑制廔管內皮依附性舒張反應而造成早期廔管阻塞或血栓。在高膽固醇狀態下，添加維他命 E (probucol) 可以保存血管內皮依附性血管舒張反應，但不會影響內皮獨立性的血管舒張。

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關鍵字： 血管內皮依附性血管舒張，膽固醇，動靜脈廔管，維他命 E (probucol)。

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