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Lipid Lowering: An Important Factor in Preventing Adriamycin-Induced Heart Failure

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The contribution of lipid lowering in protection against adriamycin cardiomyopathy achieved by probucol, an antioxidant and a lipid-lowering drug, was assessed by comparing its beneficial effects with that of lovastatin, another lipid-lowering drug with no known antioxidant properties. Adriamycin (cumulative dose, 15 mg/kg body weight) was given to rats in 6 equal injections (intraperitoneally) over a period of 2 weeks. Probucol (cumulative dose, 120 mg/kg body weight) or lovastatin (cumulative dose, 48 mg/kg body weight) was given in 12 equal injections (intraperitoneally) before and concurrent with adriamycin. After 3 weeks of post-treatment with adriamycin, congestive heart failure, ascites, congested liver, and depressed cardiac function were seen. Adriamycin treatment decreased glutathione peroxidase activity and increased lipid peroxidation. Adriamycin increased plasma triglycerides, total cholesterol, and high- and low-density lipoproteins. Myocardial triglycerides and total cholesterol were also increased. Probucol completely prevented the development of congestive heart failure and normalized myocardial and plasma triglycerides and total cholesterol, and significantly decreased plasma high- and low-density lipoproteins. Lovastatin significantly attenuated but did not completely prevent cardiomyopathic changes due to adriamycin. Lovastatin decreased plasma total cholesterol and low-density lipoproteins as well as myocardial triglycerides and total cholesterol. Plasma triglycerides and high-density lipoproteins were still high in the adriamycin plus lovastatin group. Probucol improved glutathione peroxidase activity and reduced lipid peroxidation whereas lovastatin had no effect on these adriamycin-induced changes. These data suggest that adriamycin cardiomyopathy is associated with an antioxidant deficit as well as increased myocardial and plasma lipids. Complete protection by probucol against adriamycin-induced congestive heart failure may be due to the unique combination of its antioxidant and lipid-lowering properties. (Am J Pathol 1997, 150:727–734)

Adriamycin (generic name doxorubicin) is a very potent anti-tumor antibiotic. Unfortunately, its usefulness is seriously limited by the development of cardiomyopathy and congestive heart failure. Cardiotoxicity is dose dependent and is usually expressed if the total cumulative dose of the drug given is over 550 mg/m^2 body surface area.[1] However, in different conditions when cardiac workload is increased, even a smaller cumulative dose can lead to cardiomyopathy and congestive heart failure.[2] Cases of adriamycin-induced cardiomyopathy have been described even 4 to 20 years after the treatment has been completed.[3] Thus, considerable research has focused on understanding the mechanisms of adriamycin-induced cardiomyopathy as well as on finding ways to prevent the development of cardiomyopathy.[4,5] It appears that adriamycin cardiotoxicity is multifactorial.[6–14] However, a careful analysis of the published data suggests oxygen-radical-induced injury to be a common factor in most of the studies.[4,14–17]

Probucol, an antioxidant as well as lipid-lowering drug, has been reported to completely prevent the

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adriamycin-induced cardiomyopathy without interfering with its anti-tumor effect.[18] As adriamycin depressed myocardial antioxidants and probucol countered this effect, observed protection was suggested to be due to the enhancement of endogenous antioxidants.[16] However, the role of the lipid-lowering property of probucol was not examined and could not be ruled out. In the present study, we examined the contribution of lipid lowering in the probucol protection by comparing its effects with another lipid-lowering drug with no known antioxidant properties. Thus, using an already established animal model of adriamycin-induced cardiomyopathy,[16,19] effects of lovastatin were compared with that of probucol with respect to adriamycin-induced changes in plasma and myocardial lipids as well as myocardial glutathione peroxidase, lipid peroxidation, and hemodynamics.

Materials and Methods

Animal Model

Male Sprague-Dawley rats (body weight, 250 ± 10 g) were maintained on normal rat chow. Rats were divided into six groups: control (CONT), adriamycin treated (ADR), probucol treated (PROB), probucol plus adriamycin treated (PROB+ADR), lovastatin treated (LOV), and lovastatin plus adriamycin treated (LOV+ADR). Adriamycin (doxorubicin hydrochloride) was administered intraperitoneally in 6 equal injections (2.5 mg/kg ADR each) to animals in the ADR, PROB+ADR, and LOV+ADR groups over a period of 2 weeks for a cumulative dose of 15 mg/kg body weight as described previously.[16,18] Probucol was given to animals in the PROB and PROB+ADR groups, following the same schedule as described for lovastatin, in a cumulative dose of 120 mg/kg body weight, divided into 12 equal intraperitoneal injections, as described before.[18] In an earlier study, it has been reported that a probucol dosage of less than 120 mg/kg offered only a partial protection.[16] Lovastatin was also given intraperitoneally to the LOV and LOV+ADR groups in 12 equal injections (each injection containing 4 mg/kg of lovastatin, total cumulative dose of 48 mg/kg), over a period of 4 weeks, 2 weeks before adriamycin administration and 2 weeks alternating with adriamycin injections. For determining the appropriate dose of lovastatin, in a pilot study, three different concentrations (4, 8, and 12 mg/kg) of lovastatin were tested with respect to their lipid-lowering effect. A maximal lipid-lowering response was achieved at the dose of 4 mg/kg, and therefore this dosage was used. CONT animals were injected with the vehicle alone (lactose, 75 mg/kg in saline) following the same regimen as ADR.

All animals were observed for as long as 3 weeks after the last injection for general appearance, behavior, and mortality. At the end of the 3-week post-treatment period, animals were assessed hemodynamically and sacrificed by decapitation, and blood was collected in heparinized tubes. The latter was immediately centrifuged at 1500 × *g* for 10 minutes, separating plasma for the assessment of plasma lipids. Atria and other connective tissue from hearts were dissected away, and ventricles were used to assess myocardial lipids, glutathione peroxidase activity, and lipid peroxidation.

Hemodynamic Studies

Animals were anesthetized with sodium pentobarbital (50 mg/kg intraperitoneally). A miniature pressure transducer (Millar Micro-Tip) was inserted into the left ventricle *via* the right carotid artery. Left ventricle systolic, left ventricle end diastolic, aortic systolic, and aortic diastolic pressures were recorded.

Glutathione Peroxidase Assay

Glutathione peroxidase activity was expressed as nanomoles of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidized to nicotinamide adenine dinucleotide phosphate (NADP) per minute per milligram of protein, with a molar extinction coefficient for NADPH at 340 nm of 6.22×10^6.[20] The ventricles were homogenized (10% w/v) in 0.05 mol/L potassium phosphate buffer (pH 7.4). Cytosolic glutathione peroxidase was assayed in a 3-ml cuvette containing 2.0 ml of 75 mmol/L phosphate buffer, pH 7.0. The following solutions were then added: 50 μl of 60 mmol/L glutathione, 100 μl of glutathione reductase solution (30 U/ml), 50 μl of 0.12 mol/L NaN_3, 100 μl of 15 mmol/L Na_2 EDTA, 100 μl of 3.0 mmol/L NADPH, and 100 μl of cytosolic fraction obtained after centrifugation at 20,000 × *g* for 25 minutes. Water was added to make a total volume of 2.9 ml. The reaction was started by the addition of 100 μl of 7.5 mmol/L H_2O_2, and the conversion of NADPH to NADP was monitored by a continuous recording of the change of absorbance at 340 nm at 1-minute intervals for 5 minutes.

Thiobarbituric-Acid-Reactive Substances

Myocardial lipid peroxidation was assessed by determining thiobarbituric-acid-reactive substances

Table 1. *Effects of Probucol and Lovastatin on Adriamycin-Induced Changes in Heart Weight, Body Weight, Mortality Rate, and Ascites*

Animal group	Heart weight (g)	Heart weight/ body weight ratio $\times 10^3$	Mortality (%)	Ascites (ml)
CONT	1.63 ± 0.08	2.93 ± 0.07	0	0
ADR	1.10 ± 0.05*	2.34 ± 0.03†	45	110.12 ± 15.6†
PROB	1.52 ± 0.03	2.78 ± 0.09	0	0
PROB+ADR	1.46 ± 0.06	2.66 ± 0.12	0	1.25 ± 1.25
LOV	1.66 ± 0.09	2.89 ± 0.11	0	0
LOV+ADR	1.14 ± 0.02*	2.68 ± 0.05	20	34.28 ± 18.2*

Data are mean ± SEM of 6 to 8 animals for all studies except for mortality. For determining mortality, 20 animals were used in each of the CONT, PROB, PROB+ADR, and LOV groups, and 40 animals each in the ADR and LOV+ADR groups.
*Significantly different from CONT, PROB, PROB+ADR, and LOV; $P < 0.05$.
†Significantly different from CONT, PROB, PROB+ADR, LOV, and LOV+ADR; $P < 0.05$.

using a modified thiobarbituric acid method.[21] Hearts were quickly excised and washed. The ventricles were homogenized (10% w/v) in buffered 0.9% KCl (pH 7.4). The homogenate was incubated for 1 hour at 37°C in a water bath. A 2-ml aliquot was withdrawn from the incubation mixture and pipetted into an 8-ml Pyrex tube. A 1-ml volume of 40% trichloroacetic acid and 1 ml of 0.2% thiobarbituric acid were promptly added. To minimize peroxidation during the subsequent assay procedure, 2% butylated hydroxytoluene was added to the thiobarbituric acid reagent mixture.[22] Tube contents were vortexed briefly, boiled for 15 minutes, and cooled in a bucket of ice for 5 minutes. A 2-ml volume of 70% trichloroacetic acid was then added to all tubes and contents were again vortexed briefly. The tubes were allowed to stand for 20 minutes. This was followed by a centrifugation of the tubes for 20 minutes at 3500 rpm. The color was read at 532 nm on a Zeiss spectrophotometer and compared with a known malondialdehyde standard.

Lipid Analysis

Plasma triglycerides, total cholesterol, high-density lipoproteins, and low-density lipoproteins were determined enzymatically using kits obtained from Sigma Diagnostics (352, 352-3, and 336, Sigma Chemical Co., St. Louis, MO) and expressed as milligrams per deciliter of plasma. For cardiac lipids, ventricles (1 g) were homogenized in 10 ml of 0.05 mol/L potassium phosphate buffer (pH 7.4) and centrifuged at 40,000 × *g* for 30 minutes. Supernatants were assayed using the same Sigma kits and expressed as milligrams per gram of tissue.

Proteins and Statistical Analysis

Proteins were determined by the method of Lowry and associates.[23] Data are expressed as the mean ± SEM. For a statistical analysis of the data, group means were compared by one-way analysis of variance, and Bonferroni's test was used to identify differences between groups. Statistical significance was acceptable to a level of $P < 0.05$.

Results

General Observations and Mortality

Within 1 week after the last adriamycin injection, animals in the ADR and LOV+ADR groups developed scruffy, yellowish fur and red exudate around the eyes. However, animals in the ADR group appeared sicker and more lethargic compared with the LOV+ADR group. Animals in the PROB+ADR group did not show any of these changes. At 3 weeks after treatment, both the ADR and LOV+ADR groups of animals had enlarged abdomens and ascites, and the amounts of fluid in the ADR group were approximately three times higher than that of the LOV+ADR group (Table 1). In the PROB+ADR group, only 1 animal of 8 had a slightly distended abdomen with approximately 10 ml of fluid (Table 1). The mortality rate was significantly higher in the ADR than in the LOV+ADR group. All animals in the CONT, PROB, PROB+ADR, and LOV groups survived. The liver was congested and enlarged in all animals in the ADR group. Heart weight was significantly less in the ADR and LOV+ADR groups as compared with the CONT, PROB, PROB+ADR, and LOV groups (Table 1). However, heart weight/body weight ratio was significantly lower only in the ADR group compared with all other groups.

Hemodynamic Studies

Aortic systolic, aortic diastolic, left ventricular peak systolic, and left ventricular end diastolic pressures were recorded in all groups, and these data are

Table 2. *Effects of Probucol and Lovastatin on Adriamycin-Induced Hemodynamic Changes*

Animal group	LVPSP	LVEDP	ASP	ADP
CONT	121.62 ± 2.34	5.23 ± 0.54	110.28 ± 2.88	73.39 ± 1.72
ADR	85.67 ± 1.91†	30.00 ± 2.41†	82.33 ± 2.18*	60.78 ± 0.92*
PROB	115.42 ± 1.9	6.88 ± 3.01	105.12 ± 5.30	70.82 ± 2.12
PROB+ADR	119.16 ± 4.28	8.74 ± 1.9	99.38 ± 6.2	67.22 ± 3.26
LOV	121.68 ± 3.64	5.49 ± 0.92	114.23 ± 4.53	75.38 ± 2.67
LOV+ADR	108.40 ± 5.29	20.08 ± 2.91*	91.31 ± 4.12*	65.86 ± 3.48

LVPSP, left ventricular peak systolic pressure; LVEDP, left ventricular end diastolic pressure; ASP, aortic systolic pressure; ADP, aortic diastolic pressure. Values are mm Hg, mean ± SEM of five to seven experiments.
*Significantly different from CONT, PROB, PROB+ADR, and LOV groups ($P < 0.05$).
†Significantly different from CONT, PROB, PROB+ADR, LOV, and LOV+ADR groups ($P < 0.05$).

shown in Table 2. The ADR group showed a significant decrease in aortic systolic, aortic diastolic, and left ventricular peak systolic pressures and a significant elevation in the left ventricular end diastolic pressure. All of these values in animals in the PROB and PROB+ADR groups were no different from the CONT group (Table 2). Lovastatin treatment had some beneficial effects on adriamycin-induced hemodynamic changes, such that aortic diastolic and left ventricular peak systolic pressures were normalized (Table 2) in the LOV+ADR group. Although there was some improvement in the aortic systolic and left ventricular end diastolic pressures compared with the ADR group, these values were still significantly different compared with the CONT group.

Myocardial Glutathione Peroxidase and Lipid Peroxidation

Glutathione peroxidase activity was reduced in the ADR and LOV+ADR groups by approximately 40% compared with the CONT group (Figure 1). Lovastatin treatment itself did not have any effect on glutathione peroxidase activity (Figure 1). The enzyme activity in the PROB and PROB+ADR groups was no different from the CONT group. Lipid peroxidation was evaluated by the measurement of thiobarbituric-acid-reactive substances, and these data are shown in Figure 2. Thiobarbituric-acid-reactive substance levels were approximately 70% higher in the ADR group. The PROB and PROB+ADR groups did not show any change in the thiobarbituric-acid-reactive substances. In the LOV+ADR group, there was a significant increase in the thiobarbituric-acid-reactive substances as compared with the CONT and LOV groups.

Plasma and Cardiac Lipids

Plasma triglycerides, total cholesterol, high-density lipoproteins, and low-density lipoproteins as well as cardiac triglycerides and total cholesterol levels were analyzed in all groups (Tables 3 and 4). Adriamycin treatment caused significant increase in the plasma triglycerides, total cholesterol, high-density lipoproteins, and low density lipoproteins as well as in the cardiac triglycerides and total cholesterol. Although there was a trend toward a decrease in all lipids in the PROB group, the change was significant only in the case of the plasma high-density lipoproteins and cardiac total cholesterol as compared with

Table 3. *Effects of Probucol and Lovastatin on Adriamycin-Induced Changes in Plasma Lipids*

	Triglycerides (mg/dl)	Total cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
CONT	188.00 ± 16.79	88.91 ± 15.18	26.42 ± 5.70	34.68 ± 4.56
ADR	646.23 ± 86.56*	325.29 ± 35.8†	46.05 ± 5.84‖	134.58 ± 17.63†
PROB	146.12 ± 13.72	64.78 ± 4.99‡	12.42 ± 0.66¶	27.88 ± 3.28
PROB+ADR	231.52 ± 24.52	114.50 ± 11.22	16.85 ± 2.10¶	70.48 ± 6.68**
LOV	204.97 ± 58.8	78.33 ± 5.43‡	43.61 ± 5.32#	31.27 ± 2.51
LOV+ADR	588.60 ± 42.76*	170.57 ± 18.32§	54.32 ± 8.12#	72.17 ± 13.82**

Data are mean ± SEM of six to eight animals. HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*Significantly different from CONT, PROB, PROB+ADR, and LOV ($P < 0.05$).
†Significantly different from CONT, PROB, PROB+ADR, LOV, and LOV+ADR ($P < 0.05$).
‡Significantly different from ADR and LOV+ADR ($P < 0.05$.
§Significantly different from CONT, ADR, PROB, and LOV ($P < 0.05$).
‖Significantly different from CONT, PROB, and PROB+ADR ($P < 0.05$).
¶Significantly different from CONT, ADR, LOV, and LOV+ADR, and LOV ($P < 0.05$).
#Significantly different from CONT, PROB, and PROB+ADR ($P < 0.05$).
**Significantly different from CONT, ADR, PROB, and LOV ($P < 0.05$).

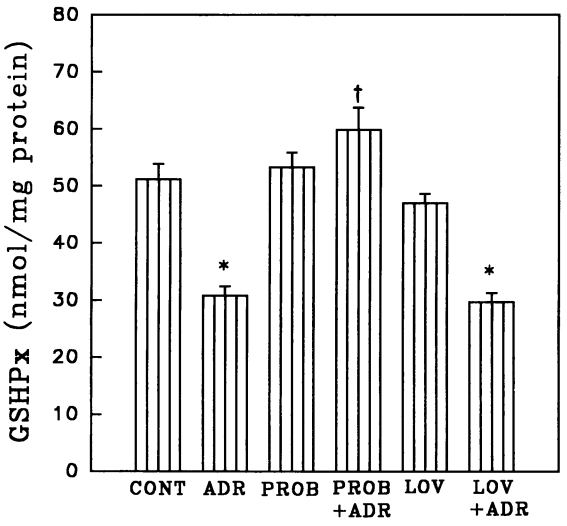

Figure 1. *Effects of probucol (PROB) and lovastatin (LOV) on adriamycin (ADR)-induced changes in myocardial glutathione peroxidase (GSHPx) activity. *Significantly different from the CONT, PROB, PROB+ADR and LOV groups (P < 0.05). †Significantly different from the CONT, ADR, LOV, and LOV+ADR groups (P < 0.05).*

the CONT group. In the PROB+ADR group, plasma triglycerides and total cholesterol as well as cardiac total cholesterol were normalized toward CONT values. In these animals, plasma high-density lipoproteins were significantly lower compared with the CONT and ADR groups. In the PROB+ADR group, plasma low-density lipoproteins were decreased and were significantly less as compared with the ADR group but still higher than the CONT, PROB, and LOV groups (Table 2).

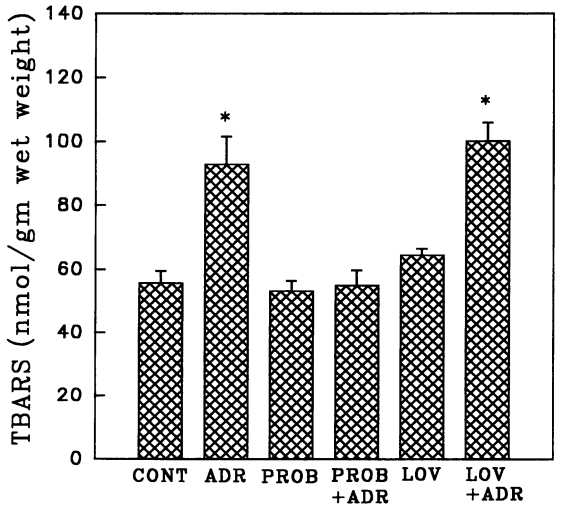

Figure 2. *Effects of probucol (PROB) and lovastatin (LOV) on adriamycin (ADR)-induced changes in lipid peroxidation assessed by thiobarbituric-acid-reactive substances (TBARS). *Significantly different from the CONT, PROB, PROB+ADR, and LOV groups (P < 0.05).*

Table 4. *Effects of Probucol and Lovastatin Treatment on Adriamycin-Induced Changes in Cardiac Lipids*

	Triglycerides (mg/g tissue)	Total cholesterol (mg/g tissue)
CONT	27.52 ± 2.09	13.72 ± 1.38
ADR	45.50 ± 3.05*	20.30 ± 1.39*
PROB	24.79 ± 0.99	8.05 ± 0.67†
PROB+ADR	27.86 ± 2.19	11.20 ± 0.92
LOV	28.4 ± 1.59	7.98 ± 0.02†
LOV+ADR	23.9 ± 2.06	10.41 ± 0.01

Data are mean ± SEM of five to seven hearts.
*Significantly different from all other groups ($P < 0.05$).
†Significantly different from CONT ($P < 0.05$).

Lovastatin did not influence plasma and cardiac triglycerides or plasma low-density lipoproteins. However, cardiac total cholesterol was significantly decreased and plasma high-density lipoproteins were increased in the LOV group as compared with the CONT group. In the LOV+ADR group, plasma triglycerides were significantly higher than in the CONT and LOV groups but was comparable to the ADR group. Plasma total cholesterol in this group was significantly less than the ADR group, and plasma high-density lipoproteins and low-density lipoproteins were also higher than the CONT group. Cardiac triglycerides and total cholesterol levels in the LOV+ADR group were comparable to the CONT group.

Discussion

Rat as a Model for Adriamycin Cardiomyopathy

The occurrence of adriamycin-induced congestive heart failure in patients[1,2] and its reproduction in different animal models is now a well established phenomenon.[4] Characteristic hemodynamic as well as myocardial cell structural changes associated with adriamycin-induced cardiomyopathy have been documented in humans,[1,6,24,25] and have also been reproduced in a variety of animals including rats.[26,27] Some of the features noted in common in patients and different animal models include refractory heart failure as well as loss of myofibrils and cytoplasmic vacuolization in the cardiac myocytes.[1,28,29] As the rat seems to mimic many structural and functional features of adriamycin-induced cardiomyopathy in humans, its use as an animal model has been frequent as well as reliable.[4,16,19,28,30–32] The model used in our study is highly reproducible.[19,28] In the present study, the presence of congestive heart failure in the adriamy-

cin group was indicated by an increase in the end diastolic pressure, depressed cardiac function, formation of ascites, congested liver, and dyspnea in these animals.

Probucol, a lipid-lowering drug, an antioxidant, and a promoter of endogenous antioxidants,[16,18] completely prevented these adriamycin-induced changes as well as mortality seen up to 3 weeks. Similar findings using probucol have been reported before.[18] A delayed protection by probucol against adriamycin-induced cardiotoxicity remains to be established. The present study shows for the first time that lovastatin, a lipid-lowering drug without any known antioxidant property, also has a significant beneficial effect. However, this protection with lovastatin with respect to the hemodynamics, ascites, and mortality was only partial, which may have to do with the lack of any co-existing antioxidant effect. Although three different doses (4, 8, and 12 mg/kg) of lovastatin were used by us in a pilot study, with respect to the different lipids analyzed here, a maximal lipid-lowering effect was seen at 4 mg/kg lovastatin. Thus, increasing the concentration of lovastatin could not have offered any better cardiac protection.

Adriamycin and Hyperlipidemia

The adriamycin-induced hyperlipidemia seen in this study has also been reported by others.[33–35] In this regard, rats injected twice with a relatively low dose of adriamycin (2 mg/kg each injection) at a 20-day interval developed marked hyperlipidemia indicated by an approximately fivefold increase in total cholesterol and up to a ninefold increase in plasma triglycerides.[35] An increase in total serum cholesterol, triglycerides, and phospholipid levels was also seen in rats injected with a cumulative dose of 24 mg/kg of adriamycin, and this increase was accentuated when rats were fed a high-cholesterol diet.[33] We also observed a threefold increase in plasma triglycerides and approximately a fourfold increase in total cholesterol and low-density lipoproteins in the adriamycin group. Adriamycin is reported to cause the development of chronic glomerulonephritis leading to progressive glomerulosclerosis associated with the nephrotic syndrome.[35] Typically, nephrotic syndrome is characterized by the presence of persistent proteinuria, hypoalbuminemia, hyperlipidemia, and lipiduria.[34,35] Thus, it is likely that the hyperlipidemia observed due to adriamycin treatment is basically the result of adriamycin-induced nephrotic syndrome.[33,35]

Hyperlipidemia and Heart Failure

Probucol and lovastatin, lipid-lowering drugs used in this study, had overall beneficial effects on adriamycin-induced lipid changes in the plasma as well as the heart. Probucol decreased triglycerides to a much greater extent than lovastatin. The effects of the two drugs on total cholesterol and low-density lipoprotein levels were similar whereas high-density lipoproteins were decreased due to probucol and increased due to lovastatin treatment. Comparable effects of probucol and lovastatin on total cholesterol have been described in rats with bilateral ureteral obstruction, whereas both drugs had a very limited effect on triglyceride levels.[36] Probucol improved renal function in rats with bilateral ureteral obstruction and lovastatin did not.[36] Since lipid lowering with probucol as well as lovastatin had a modulatory effect on adriamycin-induced cardiomyopathic changes, it is suggested that hyperlipidemia is deleterious for heart function and appears to contribute to the adriamycin-induced heart failure.

Adverse effects of high concentration of free fatty acids on cardiac contractility have been described before.[37] Perfusion of isolated rat hearts with solutions containing different free fatty acids/albumin ratios showed that not only high concentrations of free fatty acids have deleterious effects on cardiac contractility but the study also suggested that an increase in the free fatty acids/albumin ratio was an important factor.[37] A reported decrease in carnitine levels in the heart due to adriamycin[38] may also promote the formation of free fatty acids. In this regard, carnitine plays a central role in the transfer of long-chain fatty acids into the mitochondrial matrix where β-oxidation takes place.[39] Not only does the adriamycin-induced hyperlipidemia described in our study as well as by others[33,35] increase free fatty acids concentration, but it is also accompanied by hypoalbuminemia.[34,40] Thus, adriamycin treatment increases the free fatty acids/albumin ratio by affecting both components adversely. We suggest that a modulation of the hyperlipidemia both by probucol and lovastatin improves the free fatty acids/albumin ratio, which may have a favorable effect on the cardiac function.

Oxidative Stress and Heart Failure

It is now well established that adriamycin promotes production of free oxygen radicals[14,17,41] and causes lipid peroxidation.[16,18] Free radical species are a known cause of myocardial dysfunction.[5] In this study, we confirmed a decrease in the antioxi-

dant enzyme glutathione peroxidase and an increase in lipid peroxidation due to adriamycin. The mechanism of the adriamycin-induced decrease in glutathione peroxidase activity is not clear, but it may involve oxidative-stress-induced changes at the gene and/or at the protein levels. Although probucol administration prevented this lipid peroxidation and antioxidant changes, treatment with lovastatin did not correct the adriamycin-induced depletion of glutathione peroxidase activity and increase in lipid peroxidation. In a study comparing the beneficial effects of probucol and lovastatin on kidney function in bilateral ureteral obstruction, probucol was found to improve glutathione levels as well as kidney function, whereas lovastatin did not influence any of these parameters. The study emphasized the role of antioxidants in probucol protection of the kidney function.[36] Clearly, a complete prevention of adriamycin-induced cardiomyopathy with probucol depends on the antioxidant increase as well as lipid-lowering effects of the drug.

In the absence of any information about the precise role of each of the different lipid fractions, it is tentatively suggested that a reduction in the combined hyperlipidemia may have a salutary effect against cardiomyopathic changes. A better protection against adriamycin-induced changes can be achieved if the lipid-lowering effect is complemented by the promotion of endogenous antioxidants as is the case with probucol.

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