Amlodipine Releases Nitric Oxide From Canine Coronary Microvessels: An Unexpected Mechanism of Action of a Calcium Channel–Blocking Agent
To the Editor:

In a recent interesting article, Zhang and Hintze stated that amlovidine but not nifedipine released nitric oxide from canine coronary microvessels and classified this as an unexpected mechanism of action. However, it should be noted that several years ago, the same phenomenon, ie, direct release of NO, was observed with nifedipine in small porcine coronary arteries, porcine arteria basilaris, and porcine arteria caudalis. Similarly, the vasodilating action of nitrendipine, nifedipine, nisoldipine, and nimodipine in guinea pig mesenteric vascular beds was found to be sensitive to L-NG-nitroarginine treatment. The latter was more pronounced in smaller arterioles (diameter <350 μm).

Regarding the mechanism of action underlying the release of NO, it was shown recently by use of the fura-2 technique that the calcium antagonist nitrendipine enhances the intracellular calcium concentration in suspensions of cultured endothelial cells. This effect was insensitive to thapsigargin but was sensitive to extracellular depletion of calcium, indicating that the observed increase in intracellular calcium concentration was mainly due to an influx of calcium rather than a calcium release from intracellular stores. The elevation of intracellular calcium by nitrendipine could be completely blocked by application of gadolinium, a trivalent lanthanide known to inhibit shear stress–activated cation-selective channels on endothelial cells. In addition, the authors showed that the increase in intracellular [Ca2+] by shear stress was further enhanced in the presence of nitrendipine.

In summary, the release of NO from vascular endothelium is not unique to amlovidine but seems to be a group phenomenon of 1,4-dihydropyridines. The NO release may be more or less prominent when various substances in various vessel types are compared. As shown, the NO dependence of vasodilation by 1,4-dihydropyridines may also be influenced by the position of the vessels within the vascular tree. In addition, this NO-releasing action is not restricted to vascular endothelium but can also be found in platelets, as shown for nifedipine, and contributes to its antiaggregatory effects.

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Different Cell Types Within the Sinoatrial Node
To the Editor:

In a recent article by Verheijck et al., 4 types of myocytes were reported within the rabbit sinoatrial node. The nodal cells presented spontaneous diastolic depolarization and could be classified in 3 types according to their shape and size after enzymatic dispersion of the sinoatrial node. Differently from working atrial myocytes, nodal cells reacted with the antineurofilament monoclonal antibody. The fourth type of myocyte was reported as “atrial cells.” They did not present neurofilament immunoreactivity, were quiescent, and presented a shape similar to working atrial myocytes. There was a gradual increase in the density of “atrial cells” from the central area of the sinoatrial node toward the crista terminals. The authors suggest that “atrial cells” of the sinoatrial node are identical to working atrial cells of the crista terminals.

The immunohistochemical search for atrial natriuretic peptide (ANP) may also help to distinguish between nodal cells and working atrial myocytes. Nodal cells are usually devoid of ANP, but this peptide is abundant within working atrial myocytes. The few cells that presented a low level of ANP immunoreactivity in the rat and human sinoatrial node probably correspond to the “atrial cells” described by Verheijck et al. These ANP-positive cells are principally found at the periphery of the sinoatrial node. Both their diameter and ultrastructural features are intermediate between typical nodal cells and working atrial myocytes. Additionally, the ANP-positive cells within the sinoatrial node are smaller and present weak ANP immunoreactivity compared with working atrial myocytes.

In conclusion, the “atrial cells” of the sinoatrial node reported by Verheijck et al.1 probably correspond to the ANP-positive transitional nodal cells described by other authors. They are not identical to working atrial myocytes, presenting an intermediate phenotype between typical nodal cells and working atrial myocytes.

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3. Benvenuti LA, Aiello VD, Higuchi ML, Palomino SAP. Immunohistochemical expression of atrial natriuretic peptide (ANP) in the conducting

Atrophy of Myocardium and Its Myocytes by Left Ventricular Assist Device

To the Editor:

Dipla and coworkers1 believe that their data support the notion that a temporary left ventricular assist device (LVAD) obviates the need for cardiac transplantation of the failing heart. Barry2 supports this notion.

The LVAD is a double-edged sword. The beneficial effects of this device are well known. Its action ensures sufficient nutrition to the peripheral tissues so that they can recover from starvation and also eliminates or decreases the harmful effects of the increased catabolic products produced by the starved tissues. Harmful effects of the LVAD are due to the rapid, profound decrease of cardiac work (contraction) that leads to atrophy of the myocardium and its myocytes.

An excellent description of the morphological changes that occur in myocardial atrophy is present in Bargmann and Doerr’s textbook.3 Modern textbooks of medicine and cardiology ignore this subject, with the exception of Braunwald’s,4 which devotes a single sentence published in fine print to it. This is as it should be. To quote Friedberg,5 “myocardial atrophy is a pathological entity and not a clinical disease.”

However, atrophy of the myocardium and its myocytes produced by LVAD tells a different story. It is sudden in onset and affects all the myocytes.

A photograph of the myocytes (not present in the text) taken from hearts that were on LVADs shows that these myocytes are smaller than normal, misshapen, occasionally broken, and separated from each other by wide open spaces. This is the picture of severe atrophy of the myocytes. The legend under Figure 2 states that the resting cell length of the myocytes that had been on the assist and had not been on the assist is similar. This is not true. The resting cell length of the myocytes from the heart failure patients was 175 μm, whereas that on the device was 169 μm.

If one considers the enormous number of myocytes that are in the heart and that they are 3-dimensional, not linear, one can anticipate that the mass of the heart and its size has diminished considerably when on the device. It is very likely that this shrinkage of the heart could have been recognized had a film of the chest and an echocardiogram been taken just before the assist was activated and immediately after it was inactivated.

Furthermore, the authors state that the myocytes on the device were able to maintain a higher percent shortening than the heart failure myocytes that were not on the device. The heart does not recognize percentages. The heart responds to the load imposed on it.

In a series of very elegant and beautiful experiments, Galinanes and coworkers6 used a novel heterotopic rat heart transplant preparation with the objective of investigating the effect of load on cardiac contractile function, mass, and high-energy phosphates over a 7-day period. In 1 group of rabbit hearts, conventional unloaded transplant preparation was used. In another group, novel loaded preparation was used in which the circulation of the blood was changed so as to divert distal venous blood to the left ventricle of the transplanted heart. In the first group, left ventricular developed pressure had fallen to 96 compared with 162 mm Hg in fresh controls. In group 2, left ventricular diastolic pressure and left ventricular volume were significantly higher than in group 1. The unloaded heart exhibited a significant loss of left ventricular weight. However, there was no significant weight loss in the loaded hearts. In conclusion, imposition of a load on the heterotopically transplanted heart prevented the loss of cardiac mass.

Kinoshita and coworkers7 studied the influence of prolonged ventricular assistance on the normal myocardium from the pathological viewpoint. They concluded that long-term ventricular assistance leads to myocardial atrophy. In addition, there is a possibility that compensatory hypertrophic changes in the residual intact myocardium can be limited.

There is, therefore, no likelihood that the assist can obviate the need for cardiac transplantation. Indeed, it is likely that the heart is weaker after the assist is inactivated than it was before the assist was activated, because the compensatory hypertrophy of the failing heart has diminished.

Finally, form and function look at the same object but with different lenses.

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*Dr Soloff died November 24, 1998.


Response

As a respected senior colleague, Dr Soloff offers a valuable perspective concerning the results of our recent studies. Although our findings demonstrate improved in vitro myocyte function after mechanical circulatory support, the ability of mechanical support to induce lasting myocardial recovery from chronic failure remains essentially unproven. Indeed, much of the work that we and others will be performing over the coming years will attempt to address the important issues raised in Dr Soloff’s timely and erudite letter. Better understanding of distinctions between atrophy and recovery, load-dependent versus load-independent responses, cell versus organ function, and transient versus lasting effects will ultimately be the fruits of our ongoing inquiry.

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Very-Low-Fat Diets

To the Editor:

I would like to respond to the recent Science Advisory from the American Heart Association Nutrition Committee on very low fat diets.1 The advisory ignored much of the published
scientific data supporting the value of a very-low-fat diet (VLFD) for the prevention and control of coronary heart disease (CAD). No mention was made of the vast amount of epidemiological data supporting the value of a VLFD. Numerous publications from the recent China project document that a society of millions existing on a VLFD has 1/25th the incidence of heart disease we have in the United States.

The statement cites 1 study by Ornish and 1 by myself from the Pritikin Center showing “impressive” results. The statement then goes on to criticize the VLFD studies for having a small number of subjects with limited follow-up. The writers ignored the previously published data on 4587 participants from the Pritikin program.2 They also ignored the follow-up data previously reported from the Pritikin program showing good long-term compliance and the avoidance of bypass surgery, as well as the control of diabetes and hypertension.3,4 They criticized the studies for not controlling for weight loss, which is a natural consequence of a VLFD. Because obesity is a major health problem in the United States, the American Heart Association should be supporting the VLFD, not criticizing it.

The statement criticizes the VLFD for causing a rise in triglycerides. The writers fail to recognize that a low-fat diet does not cause triglycerides to rise if the fat is replaced by unrefined, complex carbohydrates, naturally high in fiber, as reviewed by Anderson et al.5 Ornish et al6 reported regression of CAD on a 10% fat-calorie diet in spite of a rise in triglycerides.

The drop in HDL cholesterol on a VLFD is a natural consequence of the major drop in total and LDL cholesterol and does not confer the same risk as a low HDL cholesterol level on heart disease. Societies around the world existing on a VLFD, which by far exceeded 4.18 MJ/L, the physiological limit imposed by evolution.4 Additionally, the common habit of consuming fruit at the end of starchy meals, rather than separately, may heavily contribute to the hypertriglyceridemic effect that is currently ascribed to low-fat, high-carbohydrate diets per se.3 It is clear, therefore, that further work is needed before one concludes that those diets are unsafe.

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To the Editor:

Lichtenstein and Van Horn, for the American Heart Association’s Nutrition Committee, express concerns about long-term safety of very-low-fat diets.1 Such concerns, if regarded (as they should be) from an evolutionary viewpoint, soon emerge to be clearly groundless.2 Very-low-fat diets, in fact, can hardly be unsafe simply because they have genetically molded the lipid metabolism of both prehuman primates and human beings.2 For millions of years, oils, margarine, dairy products, and butter, all of which were nonexistent, did not increase unnaturally the human consumption of fat.2 Thus, for the most part of our evolution, the fat content of available diets barely exceeded 10% of energy because fat derived mainly from wild game, which is extremely lean.2 It is not surprising, therefore, that populations virtually free of both coronary atherosclerosis and diabetes invariably experience epidemics of those diseases after they switch from their traditional very-low-fat diets to the high-fat Western ones, for which human beings are genetically un-equipped and therefore can only be damaged by.2,3

Currently, as Lichtenstein and Van Horn extensively discuss,1 most concerns about safety of very-low-fat diets have to do with their reported unhealthy effects on triglyceridemia, which has been found to rise consistently in response to dietary replacement of fats with carbohydrates. So far, however, researchers unfortunately have not realized that the hypertriglyceridemic effect of low-fat, high-carbohydrate diets, rather than reflecting an inevitable shortcoming of abundantly consumed carbohydrates, may simply be due to the unnatural forms in which simple carbohydrates are usually ingested.4 For example, the authors of a study5 cited by Lichtenstein and Van Horn that found both tripled triglyceridemia and strongly stimulated fatty acid synthesis in response to a high-carbohydrate diet failed to realize that their findings, instead of showing the harmful effects of that diet in itself, are likely to mirror the unnaturally high energy density (5.23 MJ/L) of the liquid formula diet used,5 which by far exceeded 4.18 MJ/L, the physiological limit imposed by evolution.4

Additionally, the common habit of consuming fruit at the end of starchy meals, rather than separately, may heavily contribute to the hypertriglyceridemic effect that is currently ascribed to low-fat, high-carbohydrate diets per se.3 It is clear, therefore, that further work is needed before one concludes that those diets are unsafe.

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To the Editor:

I am concerned that the American Heart Association (AHA) Science Advisory on very-low-fat diets1 and the press release that were issued by the AHA have added more confusion to an already bewildered public and may discourage many people from making changes in diet that otherwise might have given them substantial benefits. When the AHA report was published, headlines proclaimed, “Very low fat diets are not beneficial and may be harmful,” yet a careful examination of the research data does not support this.

The advisory erroneously stated that LDL cholesterol (LDL-C) fell by 16% in the Lifestyle Heart Trial after 1 year. We reported that LDL-C decreased by 37.4% (from 151.4 to 94.8 mg/dL) in response to a very-low-fat, whole-food, vegetarian diet high in complex carbohydrates and low in simple sugars; walking; and stress management techniques—even though these patients already were following an AHA step 2 diet at baseline.2
In contrast, the step 2 diet has been shown to lower LDL-C by only 5% compared with high-fat diets. In a recent study, the step 2 diet failed to lower LDL-C at all in men or women unless combined with vigorous aerobic exercise. Thus, the authors’ statement that “[v]ery low fat diets in the short-term increase TG [triglyceride] levels and decrease HDL-C levels without yielding additional decreases in LDL-C levels” is inaccurate. Also, increases in triglycerides can be minimized or obviated by avoiding simple carbohydrates and increasing exercise. We recommend all patients to take 3 to 4 g/dl of flaxseed oil or fish oil to reduce triglycerides and sudden cardiac death.

HDL cholesterol (HDL-C) may decrease in those following a very-low-fat diet, but this may also occur on the AHA diet. Diet-induced lowering of HDL-C does not confer the same risk of coronary heart disease (CHD) as low HDL-C levels in Americans consuming a high-fat diet. Low HDL-C levels due to reduced fat intake are the result of a decreased transport rate rather than the increased catabolism that is responsible for most cases of low HDL-C levels in persons consuming a typical Western diet. Populations that consume low-fat, plant-based diets have low HDL-C and a much lower incidence of CHD than in the United States. When these countries begin consuming a Western high-fat diet, HDL-C levels increase along with the incidence of CHD.

In the Lifestyle Heart Trial, HDL-C levels decreased and triglycerides increased slightly in experimental group patients overall, although the ratio of LDL to HDL was improved. However, these patients showed a 91% reduction in the frequency of angina, regression of coronary atherosclerosis after only 1 year, and even more regression after 5 years. In contrast, control-group patients followed a step 2 diet and showed worsening of coronary atherosclerosis and increased angina after 1 year and even more progression of coronary atherosclerosis after 5 years. There were over twice as many cardiac events in the control group. In a recently completed multicenter demonstration project, we found high levels of adherence and similar clinical benefits in 333 CHD patients in 8 diverse hospitals.

Thus, it is very misleading to suggest that very-low-fat diets are harmful if HDL-C decreases when actual measures and outcomes of disease are examined rather than only risk factors, such as HDL-C. Other studies have confirmed our finding that the majority of patients with CHD who follow an AHA step 1 or step 2 diet show overall progression of coronary atherosclerosis when measured by serial arteriography. Therefore, a step 2 diet alone is inadequate for most people with documented CHD.

What about the general population? Patients with hypercholesterolemia may try a step 1 AHA diet; if that is sufficient to lower LDL below 90 mg/dl, that may be all they need to do. If not, go to a step 2 diet. Patients who do not respond adequately to a step 2 diet can then be given a choice: a “step 3” diet similar to one that we have studied that is much lower in dietary fat and cholesterol, or lipid-lowering drugs. Patients who do not respond to a step 3 diet can then add lipid-lowering drugs if needed.

We need to give patients the facts so that they can make informed and intelligent choices, not presume that it is too difficult for patients to reduce dietary fat below 30%. By analogy, most physicians do not tell patients who smoke to just cut back because it is too hard to quit; they say, “Yes, it may be difficult, but moderate changes in smoking will not do much.”

What about safety in the general population? The incidence of CHD and other chronic diseases is much lower in countries whose inhabitants have been eating very-low-fat, plant-based diets for tens of thousands of years. In contrast, the long-term safety of treating otherwise-healthy people with a lifetime of lipid-lowering drugs is unknown. Let’s work together to offer patients a full range of therapeutic options, including a very-low-fat, plant-based diet for those who are motivated to follow it.

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Response
The points brought up in the letters of Baschetti, Ornish, and Barnard challenging the wisdom of the American Heart Association (AHA) Nutrition Committee’s statement on very-low-fat diets are important and should be further discussed. Very-low-fat diets can take many forms. The apparent assumption of Baschetti, Ornish, and Barnard is that if the American public was encouraged to consume a very-low-fat diet, they would choose a diet comprising minimally processed plant-based foods. The proliferation of low-fat and fat-free foods that have appeared on the market in recent years strongly challenges this assumption. This phenomenon should not be blamed on the food industry, the consumer, or the recommendations of health organizations. It appears to be an unanticipated translation of the message in a way that has not qualitatively improved population-wide eating behavior to the extent that was intended. It is the message that needs clarification and modification.

Baschetti suggests that experience with very-low-fat diets exists from the Paleolithic period (estimated at ∼10% of calories) and that the apparently low rates of coronary heart disease (CHD) attest to its benefit. Presumably, the low rates of CHD during that period were also attributable to the relatively short life span of our prehistoric ancestors, when the major causes of death were likely to be accidents, infections, and complications of childbirth.

Ornish and Barnard fault the AHA for not putting more emphasis on the success of their own programs. Impressive as the reports are from the Pritikin Center and the Lifestyle Heart

Trial.\textsuperscript{5,6} 2 points need to be made. First, notwithstanding the recent report of Ornish et al\textsuperscript{6} on a small group of highly motivated subjects and without the benefit of a control group, we reaffirm our statement that long-term follow-up data remain unavailable. Neither the Ornish nor Barnard programs tested a very-low-fat diet as the sole intervention for achieving CHD risk reduction. Both used comprehensive lifestyle approaches that included not only the very-low-fat diet but also exercise, educational classes, cigarette smoking cessation, and social support, and additionally, in the Lifestyle Heart Trial, stress management. It is impossible to separate the effects of dietary modification alone from the potentially additive and/or synergistic effects of the other lifestyle modifications.

The AHA statement on very-low-fat diets\textsuperscript{1} was intended for the general population, not for individuals with established disease who are under medical care. It was clearly stated that “... a limited group of motivated, high-risk persons with elevated LDL-C levels and/or preexisting cardiovascular disease may benefit from very low fat diets but only with support, careful supervision, and regular follow-up by the healthcare provider.” In contrast to that stated by Barnard, the AHA does not recommend a 30\% fat-calorie diet. The AHA currently recommends $\leq 30$\% of calories as fat and either $<10$\% of calories as saturated fat (step 1) or $<7$\% of calories as saturated fat (step 2); 10\% to 15\% of calories as monounsaturated fat; up to 10\% of calories as polyunsaturated fat; and 300 mg of cholesterol per day (step 1) or 200 mg of cholesterol per day (step 2), coupled with habitual exercise.\textsuperscript{7} This plan allows for flexibility to accommodate individual preferences and social and cultural patterns, which is critical to long-term adherence to a diet that promotes reduced risk of CHD. This statement reflects the current status of the published data.

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Atrophy of Myocardium and Its Myocytes by Left Ventricular Assist Device
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