

treatment ( $5.8 \pm 1.0 \times 10^9/l$  untreated,  $5.9 \pm 1.1 \times 10^9/l$  after 12 weeks pravastatin or cholestyramine), and unaltered in children with FH ( $6.4 \pm 1.5 \times 10^9/l$  in controls,  $6.7 \pm 1.8 \times 10^9/l$  in FH).

In a comparison of 21 insulin-dependent diabetic patients with persistent microalbuminuria versus nonmicroalbuminuric diabetic controls, no change was seen in plasma viscosity or fibrinogen, although adverse changes in lipoproteins were present.<sup>6</sup> However, in this case, white cell counts were significantly raised ( $6.3 \pm 1.6 \times 10^9/l$  in controls,  $7.4 \pm 1.4 \times 10^9/l$  with microalbuminuria,  $p < 0.05$ ). Taken together, these results suggest independent associations of plasma viscosity or white cell count with cardiovascular risk factors and are compatible with their independent contributions to the prediction of coronary events as demonstrated by Yarnell and coworkers.<sup>1</sup>

Other risk factors may have a more direct effect on rheology. For example, smoking cessation in healthy subjects results in significant falls in plasma viscosity and fibrinogen after only two weeks.<sup>9</sup> We therefore suggest that the strength of the predictive value of hemostatic/rheological variables for subsequent coronary heart disease is based on a number of interrelations. First, some cardiovascular risk factors such as smoking or microalbuminuria directly affect rheology or white cell count. Second, plasma fibrinogen, which is directly involved in atherogenesis and thrombosis, also strongly affects blood rheology. Third, rheological factors themselves influence blood flow patterns adjacent to the arterial wall and may thus affect blood cell-endothelial interactions, possibly enhancing the development of atheroma or thrombus. Finally, rheological parameters act as a marker of the severity of occult atherosclerosis.

Yarnell and coworkers found the predictive value of white cell count, and either plasma viscosity or fibrinogen remained after statistical correction for several risk factors and for preexisting arterial disease. However, given the long subclinical course of atherosclerosis before it becomes apparent electrocardiographically or symptomatically, it is likely that undetected arterial disease had a significant effect on rheological factors. This may have accounted for much of their remaining predictive value in the multivariate model.

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## Hyperinsulinemia, Sex, and Risk of Atherosclerotic Cardiovascular Disease

We read with interest the recent article (Modan et al,<sup>1</sup> *Circulation*, September 1991) and accompanying editorial addressing the role of excess fasting insulin, an indicator of insulin resistance, as an explanation for differences in cardiovascular risk between men and women. Although the findings are of great interest and fit with our hypothesis and views, it may not be sufficient to characterize women only by the presence or absence of hyperinsulinemia. That is, all women are not the same, whether it is in an endocrinological,<sup>2,3</sup> physical,<sup>2,4</sup> genetic, or metabolic sense.<sup>5,6</sup> The common problem of androgen excess in women (signaled by the frequently observed characteristic of hirsutism) is a biological experiment in nature allowing insights to be gained on the role of steroid hormones and cardiovascular disease risk.<sup>2,3</sup> Android obesity is prevalent among hirsute women.<sup>4</sup> These women have documented insulin resistance, higher blood pressures than their regularly menstruating, nonhirsute, nonhyperandrogenic peers, and they tend to have more than one cardiovascular risk factor (i.e., clusters).<sup>4</sup>

It is not clear whether this subset of our female population is included in the statement "... women are somehow protected from the clinical implications of atherosclerosis, which are the major causes of morbidity and premature mortality in men in industrialized countries..." The study by Modan et al did not address hirsutism as a signal for this subset of the female population and it did not with adequate power look at those female individuals with overt features of androgen excess (android obesity, hirsutism, temporal hair recession, oligoamenorrhea, or documented androgen excess).

We believe that whereas insulin resistance may be a significant reflector of pathophysiological risk, its role in relation to sex steroids<sup>5</sup> (both androgens and estrogen) merits much more investigation in women and in men as well.

Cardiovascular risk in the absence of carbohydrate intolerance, obesity, and hypertension needs to be assessed in other subgroups of hyperinsulinemic women, e.g., hyperandrogenic, android versus gynoid, active versus sedentary, etc., before the statement "... the low cardiovascular disease rates in all hyperinsulinemic women..." can be generally accepted.

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### Myocardial $\alpha_1$ -Adrenergic Receptor Stimulation

Regarding the recent article in *Circulation* by Landzberg et al,<sup>1</sup> in particular their reference to the nonresponsiveness of heart failure patients to the  $\alpha$ -adrenergic receptor stimulation by phenylephrine, it is noteworthy that the heart rate of patients in heart failure was significantly higher than that of normal subjects receiving the same dose of the  $\alpha$ -adrenergic agonist. It has been shown that increases in heart rate reduce the  $\alpha$ -adrenergic stimulation of contractility induced by  $\alpha$ -agonists in isolated myocardial preparations.<sup>2,3</sup> In our previous article on  $\alpha$ -adrenergic effects on contractility induced by methoxamine,<sup>4</sup> we showed the same effect in intact human subjects when heart rate was increased by atropine or pacing. It is surprising that the authors do not refer to the different heart rates in their heart failure patients as an explanation for their findings.

In the "Discussion" section of their article, Landzberg et al<sup>1</sup> commented that in our experiments<sup>4</sup> "phentolamine did not significantly diminish the effect of methoxamine on  $E_{max}$ , suggesting that  $\alpha$ -adrenergic receptor stimulation may not have been responsible for the observed effect" of this drug. In fact, we mentioned that although the average slope of the end-systolic pressure (ESP)/dimension (ESD) relation ( $m$ ) was not modified, the expected effect of phentolamine on  $m$  values was observed in three of the five subjects who received this drug. Moreover, in all subjects, the ESDs at each level of ESP attained during constant methoxamine infusion were larger after phentolamine, an observation clearly suggesting that phentolamine antagonized the inotropic effect of methoxamine.<sup>4</sup>

Landzberg et al<sup>1</sup> also state that we "failed to demonstrate an  $\alpha$ -adrenergic receptor-mediated positive inotropic response to systemic administration of phenylephrine," when, in fact, we did not use phenylephrine in our experiments. What we did provide evidence for was the existence of an  $\alpha$ -adrenergic receptor-mediated positive inotropic response to methoxamine, because the  $m$  values during methoxamine infusion were significantly higher than those obtained during the infusion of angiotensin II, and this effect was not blocked by propranolol and was, as mentioned above, reduced by phentolamine.<sup>4</sup> In addition, we clearly showed that this inotropic effect was attenuated or abolished with increases in heart rate induced by atropine or cardiac pacing. We feel that our previous communication did represent the first available evidence in favor of a positive inotropic effect mediated by  $\alpha_1$ -adrenergic receptors in the human heart and that the article by Landzberg et al provides valuable evidence in support of such a positive inotropic effect.

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### Reply

Drs. Curiel and Perez-Gonzalez have raised a salient point regarding the role of heart rate in determining the response to  $\alpha$ -adrenergic receptor stimulation. In vitro studies, it has often been noted that the contractile response to  $\alpha$ -adrenergic receptor stimulation is less at high (versus low) frequencies of stimulation.<sup>1</sup> For example, the contractile response to  $\alpha$ -adrenergic receptor stimulation in guinea pig ventricle is greater at a stimulation frequency of 1 Hz than at 2.5 Hz.<sup>2</sup> However, these frequencies of stimulation are far removed from the physiological range, and it is not known whether changes in heart rate within the physiological range affect the contractile response to  $\alpha$ -adrenergic receptor stimulation in vitro or in situ.

We agree that the observations in the study by Curiel et al<sup>3</sup> suggest that a positive inotropic effect may have occurred with systemic methoxamine administration. However, the critical test of this conclusion, the ability to block this effect with a specific  $\alpha$ -adrenergic receptor antagonist (phentolamine), was not statistically significant. Therefore, conclusions regarding the contractile effect of methoxamine were necessarily indirect and based on assumptions that cannot be validated. The role of heart rate in determining the response to methoxamine is likewise difficult to interpret. The substantial reflex-mediated decrease in heart rate that occurred during systemic methoxamine and angiotensin II infusions in the study of Curiel et al<sup>3</sup> reinforces a point we made in our article, namely, that the direct hemodynamic effects of infused agents such as methoxamine, as well as their secondary reflex-mediated effects on autonomic outflow to the cardiovascular system, complicate the interpretation of such studies. It is for this reason that we felt that infusion of phenylephrine directly into the coronary artery (thereby largely avoiding systemic hemodynamic effects) was necessary.

We regret that at one point in our article when referring to the study of Curiel et al, we inadvertently stated that they used phenylephrine. Please note that during the major discussion of that article, the use of methoxamine was correctly cited. We believe that the important observations of Curiel, Perez-Gonzalez, and colleagues are complementary to ours, and together, these studies support the conclusion that  $\alpha$ -adrenergic receptor stimulation has a direct inotropic effect in human hearts in situ.

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