establish the precise pathophysiology of the association between pulmonary hypertension and hyperthyroidism.

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Prognostic Value of von Willebrand Factor Concentrations in Pulmonary Hypertension

To the Editor:

We were very interested to read the article by Lopes and Maeda (November 1998).1 Our research group is also interested in the discovery of molecular, prognostic markers for primary pulmonary hypertension (PPH) by noninvasive methods; to that effect, we have also completed a research work to be published in Heart and Vessels. I would like to compare some aspects of both research findings.

Both Lopes and Maeda1 and our team tried to establish if the measurement of the plasmatic concentration of von Willebrand factor (vWF:Ag), a reliable marker of endothelial cell dysfunction, can be a prognostic factor in PPH. Like Lopes and Maeda1 say in their article, we agree that “endothelial cell injury and dysfunction have been well documented in pulmonary hypertension and the possibility exists that the magnitude of the endothelial dysfunction is related to the extent and severity of the microvascular damage in pulmonary hypertension.” Furthermore, Lopes and Maeda1 go on to establish a relationship between the concentration of vWF and the mortality rate in a group of 11 PPH patients, which, in our opinion, can be affected by other factors in addition to endothelial dysfunction.

In contrast, in our research, we relate, by a more direct way, the value of plasmatic vWF:Ag in a group of 18 PPH patients to the severity of the damage within the pulmonary vasculature endothelium. In order to do this, we used as an additional, indirect marker of pulmonary vasculature change, determining the plasma concentration of vWF in the radial artery (the behavior of which is similar to the aorta due to the rapid blood transit that exists between them) and in the antecubital vein, which has already been used before as an indicator of events that may occur in the pulmonary artery.2 We then calculated the relationship between both concentrations (antecubital vein/radial artery vWF ratio). According to Rich,2 endothelial cell function can be evaluated in PPH patients, depending on the response of the pulmonary circulation to endothelium-dependent and independent vasodilators; therefore, patients with more severe disease are unresponsive to either class of vasodilators. For this reason, we used the grade of response of the patients with PPH to an acute trial with both endothelium-dependent and independent vasodilators as indirect measure of endothelial dysfunction. This pharmacologic test was performed before the vWF was measured, and consisted of isosporernal, 3 to 5 μg infused into the pulmonary artery in 1 min; hydralazine, 0.33 mg/Kg infused into the pulmonary artery over 3 min; and nifedipine, 10 to 20 mg sublingually. Patients were considered as responders when they had the following: (1) a significant reduction in pulmonary artery pressure or indexed pulmonary vascular resistance > 20% from baseline, (2) a predominant pulmonary vasodilator response as assessed by the decrease in the ratio of pulmonary to systemic arterial resistance, and (3) absence of any deleterious effect in pulmonary gas exchange. Patients who did not comply with these criteria were considered nonresponders. According to the evidence that has already been mentioned, we can suppose that these patients will have a more damaged endothelium than the responder group. If some difference can be shown to exist between the behavior of vWF between both groups of patients, these can be related directly to the magnitude of the endothelial damage.

Both research articles showed a significant increase in vWF:Ag in patients with PPH compared to the control group. Lopes and Maeda1 found a mean concentration of 231.1 ± 89.1% of vWF:Ag in patients with PPH vs 87.0 ± 22.7% in control subjects, while the mean values found by our group in venous blood were 163.3 ± 44.0% in patients vs 103.6 ± 42.8% in control subjects, and in arterial blood values were 151.5 ± 47.3% vs 101.2 ± 28.2% in control subjects. The greater plasmatic concentration of vWF:Ag found by Lopes and Maeda1 with respect to our values could be due to the difference in the techniques used (electroimmunodiffusion in the case of Lopes and Maeda1 and enzyme-linked immunosorbent assay in our case) and that the patients studied by Lopes and Maeda1 had New York Heart Association class III or IV symptoms, while the patients studied by us presented New York Heart Association class I, II, or III symptoms.

However, we have already mentioned that differences exist in the analysis of other data obtained in both articles. Lopes and Maeda1 found a relationship between the increase of vWF:Ag and the reduction in the short-term survival of the patients with PPH, so that a vWF:Ag of > 240% was 54% sensitive for and 93% specific for identifying patients who were unlikely to survive 1 year, with an overall predictive value of 75%. However, we observed a relationship between the antecubital vein/radial artery vWF ratio and the severity of the disease according to the different vasodilating response of PPH patients. The mean antecubital vein/radial artery vWF ratio in nonresponder patients (7 of 18 patients), which, according to what we have already explained are considered as the patients with more severe disease and therefore with the most damaged endothelium, was 1.29, whereas the responders patients (11 of 18 patients) had a mean ratio of 0.99. Specifically, we observed that an antecubital vein/radial artery vWF ratio > 1.1 was 80% sensitive for and 87.5% specific for identifying nonresponder patients with an overall predictive value of 80%.

The antecubital vein/radial artery vWF ratio can be compared indirectly to the behavior of the mentioned molecule between the pulmonary artery and the aortic artery, these results suggest that in the more severely
affected patients there exists a net consumption of vWF at the level of the pulmonary vasculature, probably related to an increase in platelet adhesion and aggregation phenomena. On the other hand, Badimon et al. described an increase in platelet adhesion and aggregation in relation to progression of vascular injury associated with atherosclerosis, in which the histologic vascular alterations are similar to those found in PPH. This additional information together with the loss of response to both dependent and independent vasodilators in nonresponder patients suggests that the measurement of the antecubital vein/radial artery vWF ratio can be directly related with the level of endothelial dysfunction in patients with PPH.

In our opinion, if the severity of PPH can be directly related with the intensity of the endothelial cell damage, we feel that our results are more in accordance with this relationship. However, we believe that the results found by both research teams, despite their very different perspectives, can be considered complementary and equally valuable, since they show that plasmatic vWF determination can be used as a prognostic factor in PPH. Due to the low frequency of this disease, however, both studies had a small sample number of patients, so we feel that it would be valuable to carry out a larger study so that the prognostic value of plasmatic concentration of vWF in PPH can be established.

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To the Editor:

Prediction of prognosis is crucial in primary pulmonary hypertension (PPH), since therapeutic decision such as patient assignment to heart and lung transplantation depend on the identification of subjects who are unlikely to survive over the short term. In this way, several indexes have been proposed, including hemodynamic and histopathologic data as well as clinical characteristics and response to vasodilators.1 In our laboratory, we have been involved in the identification of biochemical indexes that may be obtained noninvasively. Quantitative and structural changes in circulating von Willebrand factor (vWF) appear to correlate with short-term survival. In particular, exceedingly high vWF plasma levels seem to be associated with worrisome short-term prognosis in primary and secondary precapillary pulmonary hypertension.2,3

High circulating levels of vWF in precapillary pulmonary hypertension have been reported by several authors.4,5 Such high levels were also observed by Collados and Borbolla. The authors also observed that the antecubital vein/radial artery vWF ratio was elevated in patients with severe PPH who did not respond to vasodilator stimuli. On the basis of this observation, they propose that vWF is “cleared” in the pulmonary circulation in these patients.

However, it would be important to look over the absolute levels of vWF for antecubital vein and radial artery. For the authors to conclude that there is consumption of vWF in pulmonary circulation in the nonresponders, the observed radial artery vWF level has to be lower than normal. If radial artery vWF is higher than normal in these patients (nonresponders), what would be the site of vWF overproduction? If radial artery vWF is high in the nonresponders and antecubital vein vWF is even higher, would the authors like to suggest that there is increased production of vWF in systemic microcirculation in their patients?

Although we agree with the authors in that some of their findings are complementary to ours, we think that future studies will be necessary to clarify some points regarding vWF behavior in pulmonary hypertension.

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Ciprofloxacin vs the Pneumococcus

To the Editor:

We read with interest the recent article by Harwell and Brown (February 2000),1 which reviewed drug resistance of Streptococcus pneumoniae. However, little attention was given to the efficacy of ciprofloxacin against the pneumococcus. The indications and usage of ciprofloxacin in the treatment of lower respiratory tract infections (LRTI) caused by streptococcal pneumonia have remained controversial.

We reviewed 18 large clinical studies, including our own,2–4 and we analyzed the results of ciprofloxacin in the treatment of LRTI. From these 18 studies, we derived a total cumulative number of streptococcal LRTI treated with ciprofloxacin, which numbered 204 patients. Based on analysis of the results in these documented patients,2 we conclude that >90% of the 204 patients with streptococcal pneumonia LRTI treated with ciprofloxacin were reported cured.

There were isolated reports of treatment failures in this group, particularly in a single study by Davies et al.2 In that study, of the 26 patients with pneumococcal acute exacerbation of chronic