Hemodynamic Interaction of Aspirin With Enalapril

To the Editor:

I am writing regarding the report by Spaulding et al that appeared in Circulation.1 These authors investigated the acute systemic and pulmonary hemodynamic response to 10 mg of enalapril in 20 patients with congestive heart failure; the patients were randomly assigned to receive either aspirin or ticlopidine. Enalapril, given after 1 week of such treatment, caused a significant reduction in systemic vascular resistance and mean systemic arterial pressure only in patients receiving ticlopidine; total pulmonary resistance and wedge pulmonary pressure (PWP) decreased significantly in both groups. The authors concluded that “a negative aspirin–enalapril interaction on prostaglandin synthesis presumably alters vasodilatation in systemic vessels, whereas prostaglandin-independent actions of ACE inhibition such as pulmonary arterial vasodilatation are maintained.”

One concern is the small number of patients in the study and the imbalance that existed between the groups: there were 33% fewer patients in the aspirin group than in the ticlopidine group. Another concern is the obvious importance of blood pressure in the calculation of systemic vascular resistance; a slight change in the reading may importantly alter calculated resistance and the significance of changes with enalapril. Blood pressure was taken with the cuff method, apparently without a random zero method, and no information was provided concerning variability.

Regarding the results, 2 points are difficult to interpret. First, according to the conclusive statement, the pulmonary circulation seems to be a selective target of the angiotensin II–mediated vasoconstriction. This argues, without any supporting evidence, against the systemic angiotensinergic vasodilator activity of ACE inhibitors.2,3 Second, studies that address the issue of a possible counteraction of cyclooxygenase inhibitors against the pulmonary hemodynamic effect of enalapril have provided results discordant with those reported by the authors.

Hall et al.,4 who studied similar patients who were given similar doses of aspirin and enalapril, did not observe any significant reduction of PWP and total pulmonary resistance 4 hours after administering those agents. Dzau et al.5 documented a significant increase in PWP when indomethacin was given to patients with advanced congestive heart failure, which suggests that vasodilator prostaglandins may play a substantial role in preserving the pulmonary circulatory homeostasis.

These observations suggest using caution when interpreting the findings from Spaulding et al’s study. Because of the limited number of patients receiving aspirin and the lack of a placebo control phase or a crossover design, the possibility of spontaneous variability in the pulmonary hemodynamics determined in this study cannot be ruled out. Moreover, definitive conclusions on the subtle interplay between pulmonary vessel reactivity to vasodilator prostaglandins and their blockade are probably not warranted.

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Response

We thank Dr Guazzi for his comments. The number of patients studied was based on the results observed in a previous study on the interaction between aspirin and enalapril.3 The imbalance between groups was mainly due to the exclusion of patients with baseline pulmonary capillary wedge pressures <15 mm Hg. Nevertheless, baseline characteristics and hemodynamics were similar in both groups.

Although the noninvasive monitoring of blood pressure by a cuff and mercury column sphygmomanometer is an old and simple method, it remains validated and extensively used in studies on the effects of drugs on systemic vascular resistance.1 Three consecutive measures were performed at each point, and the mean value was used for data collection. Because the study was double-blinded, the random zero method was considered unnecessary.

Dr Guazzi misinterprets both the results of our trial and previous studies. We clearly demonstrated that enalapril reduces systemic vascular resistance more effectively when given in combination with ticlopidine than with aspirin. Hall et al.1 and even Guazzi himself,2 also demonstrated a negative aspirin–enalapril interaction on mean arterial pressure decrease. These similar reductions in total pulmonary resistance when enalapril is administered in combination with aspirin or ticlopidine suggests that ACE inhibitors reduce pulmonary artery pressure by prostaglandin-independent mechanisms, such as a decrease in angiotensin II or norepinephrine3 or a bradykinin-induced increase in endothelin-derived nitric oxide.4 Indeed, Hall et al.1 also noted a reduction, although nonsignificant, in pulmonary mean artery pressure when enalapril was given with or after aspirin; this reduction was attributed to a lack of interaction between aspirin and enalapril in the pulmonary vessels.1

A large-scale study seemed difficult to devise and perform because hemodynamic measurements with continuous right heart catheterization during 4 hours were required. No placebo group or crossover design was planned because the purpose of our study was not to duplicate established findings on ACE inhibitors and aspirin interaction1–2 but to compare aspirin and ticlopidine when given with ACE inhibitors. Our sample size was chosen to study hemodynamic interactions. We clearly demonstrated that ticlopidine has no interaction with enalapril, in contrast to aspirin, which attenuates the systemic vasodilator effect of enalapril. However, definite conclusions on the clinical implications of our study would require a large, multicenter, clinical trial.

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