

## Efficacy of Handgrip Stress Test for Evaluation of Cilazapril Treatment in Patients with Heart Failure

Dear Editor

The study by Tavlı et al (1) published in one of the recent issues of the Anatolian Journal of Cardiology was undertaken for the evaluation of cilazapril treatment in patients with heart failure using the handgrip test in 30 rather elderly patients. Further, this study was designed for focused on optimizing medical therapy with the goal of preventing the progress of heart failure. Their handgrip protocol was carried out by short duration, because all patients in the study were in severe congestive heart failure grading III and IV of NYHA classes and coronary artery disease was documented in most of the patients. Since they chose the class III and IV of NYHA, their physical activity was limited, because class III was the marked limitation of physical activity at rest and ordinary activity will lead to symptom, and class IV is an inability to carry on any physical activity without discomfort. Their symptom of congestive heart failure is presented even at rest.

In low output states, there is an activation of the renin-angiotensin system and thus adrenergic nervous system is also activated (2). Several tissues, including myocardium, vasculature, kidney and brain have the capacity to generate angiotensin II which may play an important role in the pathogenesis of congestive heart failure. The angiotensin II is a potent vasoconstrictor and it increases adrenergic activity secondary to elevation of systemic vascular resistance in patients with congestive heart failure (3, 4). Although the use of angiotensin converting enzyme inhibitor has been established therapy for the treatment of congestive heart failure, it might cause adverse effects due to hypotensive effects, development of renal insufficiency and hyperkalemia (5)

Cilazapril, a nonthiol angiotensin converting enzyme inhibitor, has been developed based on the high potency of cilazapril as compared to captopril and enalapril (6). Its once-a-day administration is particularly important for compliance in patients with congestive heart failure, the majority of whom tend to be elderly.

The results showed that the most significant findings in this study were the hypotensive effects both at rest and during exercise, the PAPd decreased from

$33 \pm 7$  mm Hg to  $28 \pm 5$  ( $p < 0.002$ ). However there was no adverse hypotensive effects in this study. From the standpoint of pre- and after-load reduction, cilazapril might increase exercise capacity such as duration of exercise tolerance if the authors could use the treadmill test. Although there were no significant change of serum creatinine level before and after cilazapril, the serum creatinine level should be monitored continuously, because it increased from  $1.1 \pm 0.3$  mg/dl to  $1.2 \pm 0.4$  mg/dl after only three days of medication.

This study has shown that cilazapril an angiotensin converting enzyme inhibitor was effective hemodynamically for the treatment of severe congestive heart failure both at rest and during exercise. However, the initiation and titration of the pharmacotherapy regimens used in the care of patients with severe congestive heart failure should be conducted carefully with monitoring of blood pressure and renal function. We are waiting the results of rather large-scale randomized trials of cilazapril in those heart failure patients particularly elderly especially in the Middle East.

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## Author's Reply

Dear Editor,

We appreciate the interest of Professor Akira Kurita and Professor Bonpei Takase to our study and would like to reply to their comments.

The aim of this study was to investigate the effects of handgrip stress test on changes of cardiovascular hemodynamic parameters before and after cilazapril treatment in patients with congestive heart failure. Handgrip protocol in our study was designed similar to previous studies (1-3). The handgrip exercise was chosen as the technique for increasing heart rate and afterload because it is a rapid, noninvasive method that can be applied easily bedside. All patients in the study were in congestive heart failure. Patients unable to comply with the test were excluded from the study.

As it is very well known, in moderately severe systolic heart failure, cardiac output and external ventricular performance at rest are within normal limits but are maintained at these levels only because the end-diastolic fiber length and the ventricular end-diastolic volume (ventricular preload) are elevated. The elevation of left ventricular diastolic pressure are associated with abnormally high levels of pulmonary capillary pressure in patients with heart failure, sometimes even at rest (4). Heart failure is characterized by generalized adrenergic activation and parasympathetic withdrawal (5). The renin-angiotensin and endothelin systems also contribute to the increased systemic vascular tone in heart failure. Angiotensin II may also play a direct role in modifying adrenergic activity and function of the myocardium.

In our study, the hypotensive effect was observed only during the handgrip exercise, not at rest. So I do not agree with the statement, which indicates the presence of hypotension at rest. A previous study (6) showed that cilazapril (5 mg/day) did not decrease mean arterial pressure significantly after three days of therapy in patients with congestive heart failure. PAPd was decreased from  $33\pm 7$  mmHg to  $28\pm 5$  mmHg ( $p<0.002$ ) during the handgrip test. But a similar effect was not present during the rest time. For this reason, all of the parameters were taken before and after 2.5 mg cilazapril therapy during the

handgrip stress test. No adverse effects including hypotension due to cilazapril were observed during the handgrip exercise. Biochemical markers including serum creatinine, sodium and potassium were monitored daily regarding renal functions after three days of treatment serum creatinine levels did not change significantly ( $1.1\pm 0.3$  mg/dl to  $1.2\pm 0.4$  mg/dl). Serum sodium levels also did not change significantly after three days of therapy ( $141\pm 4.9$  mEq/l to  $142.1\pm 4.9$  mEq/l). Patients were followed in the coronary care unit during the handgrip exercise.

This study showed beneficial effects of cilazapril on hemodynamics of congestive heart failure during the handgrip stress test.

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