The Effects of Handgrip Stress Test on Hemodynamic Parameters Before and After Cilazapril Treatment in Patients with Heart Failure

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Objective: To assess the effect of cilazapril treatment on several hemodynamic parameters during handgrip maneuvers in patients with congestive heart failure. Cilazapril, an ACE inhibitor with high affinity, has been shown to be highly effective against a variety of vascular disorders. The effectiveness of isometric handgrip exercise on changes of cardiovascular hemodynamic parameters before and after cilazapril treatment in patients with congestive heart failure is unknown.
Methods: The study population included 30 patients (16 male, 14 female) with mean age of 65±18 years. The effects of handgrip maneuver on hemodynamic parameters were studied by right heart catheterization and Doppler echocardiography.
Results: Heart rate (HR) and mean arterial pressures (MAP) increased significantly after handgrip maneuver (from 95±6 beats/min to 101±12 beats/min; from 109±15 mm Hg to 118±19 mm Hg, $p<0.05$ respectively). Pulmonary capillary wedge pressure (PCWP), pulmonary artery systolic (s) and diastolic (d) pressures (PAP), cardiac index (CI), right ventricular systolic and diastolic pressures (RVPs and RVPd), left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF) did not change after handgrip maneuvers ($p>0.05$). On the other hand, PAPs and PAPd , RVPs and RVPd, MAP and HR ($p<0.05$) decreased significantly during handgrip maneuvers after cilazapril treatment. However PCWP and CI, LVEF, RVEF did not change after treatment ($p>0.05$).
Conclusion: Cardiovascular response to handgrip maneuver may be a marker of failure to respond to compensatory mechanisms. Cilazapril treatment was associated with significant improvement in hemodynamic parameters during handgrip stress test, the mechanisms of which are increased sympathetic and renin-angiotensin system activation, and altered vascular tonus. *(Anadolu Kardiyol Derg, 2003; 3: 38-42)*
Key Words: Handgrip maneuver, heart failure, hemodynamic parameters

Introduction

The effect of handgrip maneuvers on left ventricular (LV) function has been investigated extensively by various techniques (1, 2). Hemodynamic studies have been supplemented by data on dynamic changes in LV function (3). Both cardiac catheterization and Doppler echocardiography has permitted to quantify cardiac function accurately (4). Angiotensin-converting enzyme (ACE) inhibitors have been shown to be highly effective against a variety of vascular disorders (5). Angiotensin converting enzyme inhibitors are widely used in the treatment of congestive heart failure (CHF). Indeed, there is no doubt this class of drugs can increase both survival and quality of life in patients with CHF characterized by severe or moderate alterations in cardiac function (6). Previous studies have demonstrated that maneuvers such as postural changes, pharmacological interventions and isometric exercise alter noninvasive parameters of LV function in normal subjects (7).

The aim of this study was to investigate the effects of handgrip (HG) stress test on changes of cardiovascular hemodynamic parameters before and after cilazapril treatment in patients with congestive heart failure.

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Methods

Patients: The study population included 30 patients with a mean age of 62±12 years (age range 42 to 72 years). Sixteen of them were male and the remaining 14 were females with a diagnosis of coronary artery disease (CAD) documented with coronary angiography and congestive heart failure (New York Heart Association class III-IV). These patients had ongoing medical therapy with digitalis, diuretics and nitrates before the study. If patients had been administered an ACE inhibitor previously, two weeks of drug abstinence was introduced. They were given cilazapril 2.5 mg/day for three days. No adverse effects due to cilazapril were observed.

Exclusion criteria

Patients were excluded if any of the following was present: acute pulmonary edema within the previous 15 days, hemodynamically important aortic or mitral valve stenosis, myocardial infarction or open heart surgery within the previous three months, unstable angina, anticipated cardiac surgery, serum creatinine concentration >3 mg/dl, hypertrophic or restrictive cardiomyopathy or pericardial disease.

Informed consent was obtained from all patients. Baseline measurements were made while the subject was supine and in the left lateral decubitus position. After baseline recordings, the subject performed isometric HG exercise using a hand-held dynamometer at 40 % of maximal grip for at least 2 minutes (8). Handgrip test was done before and after 3 days of cilazapril administration.

Echocardiographic measurements

Echocardiographic examination was performed with a Hewlett-Packard viewpoint ultrasound system using 3.5 mHz transducer. All images were recorded on super VHS videotape for subsequent quantitative analysis and assessment of left ventricular and right ventricular ejection fractions.

Catheterization protocol

Heart catheterization via the right jugular approach was performed with a Swan-Ganz catheter and baseline resting hemodynamic data were obtained. Cardiac output was determined with the indicator dilution method. Repeat measurements of pressures: pulmonary capillary wedge pressure (PCWP), pulmonary artery systolic (PAPs) and diastolic (PAPd) pressures, right ventricular systolic (RVs) and diastolic (RVd) pressures were obtained.

Statistical analysis

For each subject, more than 3 measurements in each phase were obtained and averaged. All data are expressed as mean ± standard deviation of the mean. Data were analyzed using the student t-test to evaluate differences in measurements before and after treatment. A "p" value of less than 0.05 was considered as significant.

Results

Analysis of hemodynamic variables determined during the baseline and handgrip maneuvers (Table 1)

Table 1: Hemodynamic data during the baseline and handgrip maneuvers

Variable	Baseline (n:30)	Handgrip (n:30)	p value
Heart Rate (beats/min)	95±6	101±12	0.017
PCWP (mmHg)	31±14	37±17	0.141
PAPs (mmHg)	62±18	66±18	0.393
PAPd (mmHg)	22±10	27±11	0.07
RVPs (mmHg)	58±18	65±19	0.148
RVPd (mmHg)	14±7	18±10	0.078
MAP (mmHg)	109±15	118±19	0.046
CI (lt/dk/m^2)	2.4±0.7	2.7±0.9	0.155
LVEF (%)	36±9	38±10	0.419
RVEF (%)	35±7	36±7	0.582

Abbreviations: (PCWP: pulmonary capillary wedge pressure, PAPs: Pulmonary artery pressure systolic, PAPd: pulmonary artery pressure diastolic, RVP: right ventricular pressure, MAP: mean arterial pressure, CI: cardiac index).

showed that all of the pressures increased after handgrip exercise, however these changes did not reach statistical significance. Heart rate and mean arterial pressure increased significantly after handgrip maneuvers ($p<0.05$), while cardiac index did not increase significantly.

Table-2 shows the hemodynamic variables during handgrip before and after cilazapril treatment. Pulmonary arterial systolic and diastolic pressures, RV systolic and diastolic pressures decreased significantly after cilazapril treatment. Mean arterial pressure, heart rate also reduced markedly after cilazapril treatment ($p<0.05$), while PCWP and CI did not change significantly.

Biochemical parameters, including serum sodium, creatinine, bilirubin levels, and cardiothoracic ratio (Table 3) changed insignificantly after cilazapril treatment.

Discussion

Isometric handgrip exercise in the form of sustained HG produces centrally mediated increases in HR and systolic blood pressure (7). The circulatory response to HG exercise is complex and partly dependent on the severity of the HG stress. The general response to isometric HG exercise is similar to that of any type of exercise and consists of an increase in HR and blood pressure. The increases in cardiac index are thought to be primarily due to the increase in HR.

Twenty-five years ago, sustained isometric contraction of forearm flexor muscles was shown to induce a cardiovascular reflex consisting of increase in heart rate, arterial blood pressure and cardiac output (3). The precise nature of this reflex is not completely understood, but it appears to require afferent neural impulses from the exercising extremity and may be related to inhibition of vagal activity (9,10). Although the cardiac output response may be blunted, the anticipated responses in heart rate and blood pressure are not blocked by administration of propranolol, indicating that more is involved than a simple increase in beta-adrenergic stimulation (11). The hemodynamic response to isometric handgrip exercise has been studied in a series of normal subjects and heart disease (1-4). In normal adult subjects, heart rate, systemic arterial pressure, and cardiac output increase, whereas systemic vascular resistance shows no

Table 2: Hemodynamic data during handgrip maneuvers before and after cilazapril treatment

Variables	Before treatment(n.30)	After treatment(n:30)	p value
HR (beats/min)	101±12	92±10	0.003
PCWP (mmHg)	37±17	30±12	0.071
PAPs (mmHg)	66±18	58±12	0.04
PAPd (mmHg)	33±7	28±5	0.002
RVPs (mmHg)	65±19	56±16	0.05
RVPd (mmHg)	19±8	14±6	0.008
MAP (mmHg)	118±19	104±14	0.002
CI (lt/dk/m^2)	2.7±0.7	2.6±0.6	0.555
LVEF (%)	38±10	37±10	0.700
RVEF (%)	36±7	36±8	1.0

Abbreviations: (PCWP: pulmonary capillary wedge pressure, PAPs: Pulmonary artery pressure systolic, PAPd: pulmonary artery pressure diastolic, RVP: right ventricular pressure, MAP: mean arterial pressure, CI: cardiac index).

Tablo 3: Clinical data before and after cilazapril treatment.

Parameters	Bafore	After	p value
Serum sodium (mEq/liter)	141.1±4.9 (125-152)	142.1±4.9 (132-150)	NS
Creatinine (mg/dl)	1.1±0.3 (0.5-2.4)	1.2±0.4 (0.5-2.6)	NS
Bilirubin (mg/dl)	1.1±0.7 (0.4-4.9)	1.05±0.8 (0.3-5.2)	NS
Cardiothoracic ratio	0.61 (90% range 0.52-0.75)	0.60 (%90 range 0.50-0.74)	NS

Abbreviation: (NS: non significant)

change, indicating that the increase in systemic arterial pressure is caused by increased cardiac output rather than by a vasoconstrictor response. No significant or consistent change in left ventricular end-diastolic pressure or stroke volume occurs, whereas stroke work, a function of both arterial pressure and stroke volume, generally increases. The current study demonstrated that the cardiovascular responses to handgrip test in advanced (NYHA, class III-IV) heart failure are inadequate to increase filling pressure, cardiac output and ejection fraction. Contrast ventriculography studies in normal subjects have shown that handgrip exercise results in a decrease in left ventricular end-systolic and diastolic volumes and slight increase in ejection fraction. The augmentation of left ventricular performance during isometric exercise may be caused by both increased left ventricular myocardial contractility and the Frank-Starling mechanism. Studies of myocardial mechanics performed during isometric exercise revealed increases in Vmax, the theoretic maximal velocity of contractile element shortening at zero loads, and in left ventricular peak Dp/dt (3, 4). Patients with heart disease and decreased left ventricular function or inotropic reserve commonly show an abnormal hemodynamic and contractile response to isometric exercise. Although left ventricular peak dp/dt may increase in diseased hearts, changes are of less magnitude than in normal subjects. Left ventricular stroke work may increase, remain unchanged, or decrease in response to isometric exercise in pathologic states. This may itself be evidence of compromised left ventricular function. Significant increases in left ventricular end-diastolic pressure and PCWP are seen commonly in the abnormal response to isometric exercise and indicate decreased inotropic reserve and dependence on Frank-Starling mechanism in order to augment left ventricular performance. In decompensated hearts, stroke work may not increase and may actually fall despite increased left ventricular filling pressures (9). This is an abnormal response, indicating poor left ventricular performance, and may be accompanied by a decrease in cardiac output and an increase in systemic vascular resistance .

Angiotensin-converting enzyme inhibitors are now well-established drugs for the treatment of hypertension and congestive heart failure (5, 6). Cilazapril is rapidly absorbed and converted to cilazaprilat, which achieves peak plasma concentrations between 1.5 and 2 hours after single administration (12). Following single oral doses of cilazapril, ACE activity is nearly completely directly proportional to the circulating concentration of cilazaprilat. Cilazapril lowers blood pressure generally without causing a reflex heart rate acceleration, and spectral analysis of heart period variability during ACE inhibition with this compound suggest a reduction in vasomotor sympathetic control (13,14). Patients with chronic congestive heart failure respond to cilazapril with an increase in exercise capacity and fuınctional improvement (15, 16). The hemodynamic response is characterized by decrease in systemic blood pressure, systemic vascular resistance, and pulmonary capillary wedge pressure, whereas cardiac index increases at rest and during submaximal exercise (14). In heart failure, increase in preload can not augment systolic function, because the failing heart has reduced preload reserve (17). The mechanism of negative chronotropic effects of cilazapril in our study may be due to improvement of muscle perfusion and secondary to decrease in preload and afterload. In response to increase in afterload, the normal heart usually augments contractility to maintain cardiac output. The failing heart is less able to do so, and enhancement of afterload may compromise cardiac output (18,19). Therefore, the circulating renin-angiotensin system, which is activated in congestive heart failure in an attempt to maintain cardiac output, ultimately may precipitate worsening of myocardial function. In advanced heart failure, there is an increase in sympathetic tonus but the heart fails to respond to this compensatory mechanisms in early stages of heart failure. Cardiovascular response to handgrip may be a marker of failure to respond to compensatory mechanisms.

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