The Impact of Chronic Repetitive Leg Ischemia on Left Ventricular Function and Severity of Coronary Atherosclerosis in Patients with Acute Coronary Syndrome

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Significance of the Study

- In this study, the coexistence of peripheral arterial disease (PAD) and coronary artery disease (CAD) was associated with preserved left ventricular (LV) function at the early stage of the diagnosis of acute coronary syndrome, and was also associated with a more extensive coronary atherosclerosis and renal dysfunction. The protective effect of remote ischemic preconditioning (RIPC) triggered by intermittent claudication secondary to PAD might have a protective effect on LV function in patients with CAD. Hence, patients with CAD could benefit from RIPC.

Keywords

Peripheral arterial disease · Coronary artery disease · Ventricular dysfunction · Remote ischemic preconditioning

Abstract

Objective: The purpose of this study was to assess the impact of the presence of peripheral arterial disease (PAD) on left ventricular (LV) function in patients with coronary artery disease (CAD) presenting with acute coronary syndrome (ACS). **Subjects and Methods:** The medical records of the patients who were referred to Ankara Bayindir Hospital, Ankara, Turkey, due to a first episode of ACS were reviewed. Patients with concomitant PAD and CAD (group 1) were compared with those who had CAD only (group 2). The Mann-Whitney U and χ^2 tests were used to compare continuous and categorical variables, respectively. **Results:**

Baseline demographic data of 53 patients with PAD + CAD (42 men and 11 women; mean age 62.5 ± 9.5 years) and a group of 60 patients with CAD only (41 men and 19 women; mean age 59.9 ± 9.8 years) were similar, except for the serum creatinine level which was higher in group 1 than in group 2 (1.32 ± 0.34 vs. 1.03 ± 0.22 mg/dL, $p < 0.001$). Patients with CAD + PAD had significantly higher Gensini scores (62.6 ± 19.7 vs. 41.4 ± 26.8 , $p = 0.004$) and more 3-vessel disease than patients with CAD alone (62.2 vs. 31.6% , $p < 0.045$). There was a significant difference between the 2 groups regarding the LV ejection fraction at the time of the diagnosis ($52.0 \pm 8.2\%$ in the CAD + PAD group and $43.7 \pm 13.3\%$ in the CAD-alone group; $p = 0.017$). **Conclusion:** CAD concomitant with PAD was associated with preserved LV function at early stages of diagnosis in patients with ACS.

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Introduction

Atherosclerosis is a diffuse process that may affect different vascular beds, and coronary artery disease (CAD) and peripheral arterial disease (PAD) overlap considerably. Because both diabetes mellitus and PAD are accepted as CAD equivalents [1], the coexistence of PAD and CAD is associated with more extensive atherosclerosis and poor long-term survival than CAD only [2, 3]. However, in some reports, short-term cardiovascular outcomes in patients with PAD have been similar to in CAD patients without PAD, particularly in the early postoperative period [4, 5]. In numerous studies [6–9], it has been suggested that transient brief episodes of intermittent ischemia of the leg, experimentally and clinically known as remote ischemic preconditioning (RIPC), can provide potent myocardial protection. In this study, we hypothesized that RIPC triggered by intermittent claudication secondary to PAD might show a protective effect on left ventricular (LV) function in patients with CAD at the early stage of the diagnosis. Therefore, our aim was to evaluate the impact of chronic repetitive leg ischemia on LV function and the severity of CAD in patients with acute coronary syndrome (ACS).

Subjects and Methods

The medical records of the patients who were referred to Ankara Bayindir Hospital, Ankara, Turkey for a first episode of ACS from January 2002 to May 2015 were reviewed. Those who had concomitant CAD + PAD (group 1; 53 patients) were compared to those with CAD alone as the control (group 2; 60 patients). All patients in group 1 had a history of intermittent claudication, digital subtraction angiographic evidence of stenosis in the leg arteries below the aortic bifurcation or the abdominal aorta, and concomitant coronary angiographic evidence of CAD. The demographic variables, medical history, clinical features, and angiographic data were obtained from the medical and angiographic records. Serum levels of total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, and creatinine levels were also obtained from the medical records. The LV ejection fraction (LVEF) was analyzed by echocardiogram. To estimate the extent of the CAD, 2 experienced observers (E.Y. and M.G.), blinded to the patient's clinical data, visually analyzed the coronary angiograms of all patients from angiographic recordings in a random sequence. The CAD was defined as a 50% reduction in the internal diameter of the left anterior descending artery, right or circumflex coronary artery, or their primary branches. The CAD extension was classified according to the standard method into 1-, 2-, or 3-vessel disease and the Gensini score was calculated for each patient [10]. The Gensini score was computed by assigning a severity score to each coronary stenosis based on the degree of luminal narrowing and its geographic importance. The study was conducted in accordance with the Declaration of Helsinki and the local ethics committee approved the study protocol.

Statistical Analyses

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) v16 (SPSS Inc., Chicago, IL, USA) software. Continuous variables were expressed as mean $\pm$ standard deviation and categorical variables as numbers and percentages. The Mann-Whitney U test results were used for the comparison of continuous variables. The χ^2 test was used for the comparison of categorical variables. Differences were considered statistically significant when the p value was <0.05 .

Results

Baseline demographic data were similar in the 2 groups, except for the serum creatinine level which was higher in group 1 than in group 2 (1.32 ± 0.34 vs. 1.03 ± 0.22 mg/dL, $p < 0.001$) (Table 1). Patients with concomitant CAD + PAD had significantly higher Gensini score (62.6 ± 19.7 vs. 41.4 ± 26.8 , $p = 0.004$) and more 3-vessel disease (62.2 vs. 31.6% , $p < 0.045$) than patients with CAD alone. Group 1 also had significantly higher LVEF than group 2 (52.0 ± 8.2 vs. 43.7 ± 13.3 , $p = 0.017$). In the follow-up records of May 2015, 4 patients in group 1 (2 from chronic renal failure, 1 with ACS, and 1 with progressive LV dysfunction), and 1 in group 2 (from ACS) had died.

Discussion

In this small retrospective study, the coexistence of PAD and CAD was associated with preserved LV function at the early stage of the diagnosis of ACS, but it was associated with more extensive coronary atherosclerosis and renal dysfunction than in patients with CAD alone. These findings could be due to silent or atypical myocardial ischemia/infarction, believed to be the major cause of morbidity among people suffering from diabetes, due to a condition called diabetic neuropathy which can cause difficulties and a delay regarding a true cardiac diagnosis. Whereas the intermittent claudication limiting ambulation might have been an early symptom in seeking early medical attention and the patients therefore received medical treatment early, diabetic patients who did not undergo could have a delayed presentation due to silent myocardial ischemia/infarction, which leads to worse initial LV function than in patients with intermittent claudication [8, 9].

RIPC could have a protective effect on LV ventricular function. Numerous studies have shown that brief transient episodes of intermittent ischemia of the arm or leg

Table 1. Baseline demographic features and results

	Group 1 (<i>n</i> = 53)	Group 2 (<i>n</i> = 60)	<i>p</i> value
Age, years	62.5±9.5	59.9±9.8	0.360
Male	42 (79.2)	41 (68.3)	0.508
Female	11 (20.7)	19 (31.6)	
History of anterior myocardial infarction	22 (41.5)	25 (41.6)	1.00
Hypertension	33 (62.2)	30 (50.0)	0.552
Diabetes mellitus	20 (37.7)	28 (46.6)	0.765
Smoking	35 (66.0)	32 (53.3)	0.547
Total cholesterol, mg/dL	213.6±59.4	216.3±37.5	0.856
LDL-cholesterol, mg/dL	138.6±57.3	130.2±31.1	0.536
HDL-cholesterol, mg/dL	37.4±10.4	42.5±10.9	0.115
Triglyceride, mg/dL	219.3±100.7	205.9±105.7	0.661
Creatinine, mg/dL	1.32±0.34	1.03±0.22	0.001
1-vessel disease	11 (20.7)	16 (26.6)	0.734
2-vessel disease	9 (16.9)	25 (41.6)	0.103
3-vessel disease	33 (62.2)	19 (31.6)	0.045
Gensini score	62.6±19.7	41.4±26.8	0.004
LVEF, %	52.0±8.2	43.7±13.3	0.017

Values are expressed as *n* (%) or means ± SD. LVEF, left ventricular ejection fraction; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

could provide potent myocardial protection experimentally and clinically. It has been reported that PAD is an independent risk factor for late mortality only after coronary artery bypass grafting [4, 5]. All these studies revealed that RIPC might play an important role in cardioprotection in patients with PAD. Patients with chronic intermittent claudication due to PAD experience aching muscles during walking secondary to ischemia, and this ischemia may be responsible for the protective effect on LV function by triggering RIPC mechanisms. Kharbanda et al. [11] suggested that transient limb ischemia releases some neurogenic and circulating factors that induce protection against myocardial ischemia and reperfusion injury across species. In order to improve the long-term outcome for PAD patients, we need aggressive therapy for atherosclerosis. Regular physical activity/walking is recommended in patients with PAD. It has been shown that regular exercise has an important beneficial impact on functional capacity and the prevention of PAD and CAD, particularly through the beneficial effects on endothelial function, antioxidant systems, heat-shock protein expression, and vascular remodeling [12, 13]. Supervised physical training, besides being the most effective means to increase walking ability, also proved to have a benefit on LV contractility. It is probable that

moderate hemodynamic stress reduces the levels of inflammatory markers and increases flow-mediated vasodilation by ischemic preconditioning. In patients with CAD, it has been shown that increased walking ability is associated with improved LVEF [14, 15]. The recently published study of Bøtker et al. [16] has provided a promising result, showing that RIPC before hospital admission in the setting of ACS protects LV function. In previous studies demonstrating that RIPC has a protective effect on LV function, the RIPC was mostly provided artificially. However, our study showed that, most probably by a similar mechanism, RIPC triggered by intermittent claudication secondary to PAD can have a protective effect on LV function in patients with CAD. Consistent with the previous studies, our study supports that patients with CAD may benefit from RIPC. Although the precise mechanisms are not fully defined, RIPC can be a very important clinical tool in the management of CAD. However, the widespread adoption of RIPC will require demonstration of effect in large, unselected, cohort studies.

The limitations of this study included its retrospective and single-center design, its relatively small sample size, and the interval to balloon time and onset of the infarct were not evaluated.

Conclusion

In this study, at the early stages of diagnosis in patients with ACS, the coexistence of PAD with CAD was associated with preserved LV function when compared to the

patients with CAD alone. The RIPC triggered by chronic repetitive claudication may have a protective effect on LV function. However, further prospective trials evaluating the clinical importance of RIPC are needed to confirm this hypothesis.

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