Impairment of myocardial blood flow reserve in patients with asymptomatic left ventricular dysfunction: Effects of ACE-inhibition with perindopril

Ad F.M. van den Heuvel¹, Paul K. Blanksma¹, Hans-Marc J. Siebelink¹, Leen M. van Wijk¹, Frans Boomsma², Wim Vaalburg¹, Harry J.G.M. Crijns¹ & Dirk J. van Veldhuisen¹

¹Department of Cardiology/Thoraxcenter, University Hospital Groningen, Groningen; ²COEUR/Department of Internal Medicine, University Hospital Dijkzigt, Rotterdam, The Netherlands

Received 3 March 2001; accepted in revised form 7 May 2001

Key words: ACE inhibitors, coronary circulation, endothelial function, flow reserve, heart failure, myocardial blood flow

Abstract

Myocardial blood flow (MBF) reserve is impaired in patients with symptomatic chronic heart failure. Whether this is already present in asymptomatic left ventricular (LV) dysfunction, and whether it is affected by angiotensin converting enzyme (ACE) inhibition, is unknown. We examined MBF in 20 patients with asymptomatic LV dysfunction and compared them to healthy volunteers. MBF (reserve) was assessed with positron emission tomography (PET) and N-13 ammonia at rest, during dipyridamole stress test (DST) and during cold pressor test (CPT). Further, in the LV-dysfunction group, we studied the effects of 3 months treatment with ACE inhibition with a second PET study. Patients were randomized double-blind to perindopril 4 mg daily or placebo. MBF at rest was similar in controls and patients. DST-induced MBF reserve, however, was decreased in patients vs. controls (1.71 ± 0.2 vs. 2.62 ± 0.5, respectively p < 0.05). Also CPT-induced MBF was lower in patients (1.14 ± 0.06 vs. 1.23 ± 0.03, p < 0.05). After 3 months double-blind treatment, CPT-induced MBF decreased in the placebo group (from 1.12 ± 0.02 to 0.93 ± 0.06), but was preserved in the perindopril group (from 1.16 ± 0.08 to 1.14 ± 0.08 shifts from baseline: −0.19 ± 0.05 vs. −0.02 ± 0.07 respectively p = 0.07). This was compatible with a trend to a smaller increase in coronary vascular resistance during CPT (1.23 ± 0.08 vs. 1.03 ± 0.06, placebo vs. perindopril, p = 0.06). In patients with asymptomatic LV dysfunction, MBF, both after vasodilation and after CPT, is already impaired. ACE inhibition with perindopril during this short-term treatment had no significant effects.

Introduction

The most commonly reported abnormality of endothelial function in chronic heart failure has been impaired dilatation in response to infusion of acetylcholine, which is dependent on both an intact endothelium and normal smooth muscle function [1, 2]. In patients with symptomatic chronic heart failure, this has been shown to lead to impaired myocardial blood flow (MBF) reserve [1], but whether this is already impaired in patients with asymptomatic left ventricular (LV) dysfunction is unknown.

Angiotensin converting enzyme (ACE) inhibitors are established drugs in symptomatic heart failure, and may prevent disease progression in asymptomatic LV dysfunction [3]. Also, these agents may reduce ischemia [4], and recurrent ischemic events after myocardial infarction (MI) [5]. It has been suggested, that this favorable effect of
ACE inhibitors is associated with an improvement of endothelial function [6].

Positron emission tomography (PET) is currently the most sensitive method to detect and quantify myocardial viability [7, 8] and abnormalities in MBF. MBF (reserve) can be investigated with PET, at rest, during dipyridamole stress test (DST) (maximal vasodilatation) and after cold pressor test (CPT) (which is thought to represent partially endothelium mediated response of myocardial perfusion on autonomic stress) [9, 10]. CPT induces sympathetic release of norepinephrine and increases myocardial oxygen demand. The increase in myocardial metabolic demand has been shown to increase MBF and to dilate epicardial coronary arteries in patients with normal endothelial function, despite the α-adrenergic coronary constriction induced by sympathetic nervous system stimulation. In dysfunctional endothelium, MBF will decrease in response to CPT.

The aim of the present study was to examine MBF in patients with asymptomatic LV dysfunction, and to compare these findings with MBF in healthy volunteers. Also, we examined whether ACE inhibition (with perindopril) might have an effect on possible changes in the patients. Further, the relation between possible changes and plasma neurohormones (norepinephrine, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)), during CPT was studied.

**Methods**

**Study design**

The investigation conforms with the principles outlined in the Declaration of Helsinki. Approval was obtained from the ethics committee of the University Hospital, Groningen, before commencement of the study. Patients were included after written informed consent was obtained. This single center, exploratory study consisted of two parts: in the first, we compared patients with asymptomatic LV dysfunction with matched healthy volunteers, and the second part was a double-blind, randomized study of perindopril (4 mg) and placebo for 3 months duration. Inclusion criteria were: male or female patients, age >20 and <75 years, with mild LV dysfunction (ejection fraction (EF) 0.30–0.50), without overt symptoms of CHF or angina pectoris. Patients had to be >3 months post-MI, and were ACE-inhibitor naive. β-blockers, long-acting nitrates and/or calcium channel blockers were allowed as concomitant medication, but were stopped five half-life times before PET studies. Exclusion criteria were systemic hypertension (systolic blood pressure >180 mmHg, diastolic blood pressure >100 mmHg), hypotension (systolic blood pressure <100 mmHg), hemodynamically significant valvular disease, pacemaker treatment, serious other illnesses, diabetes mellitus, renal insufficiency (serum creatinine >150 micromol/l), electrolyte abnormalities (potassium >5.2 mmol/l, sodium <130 mmol/l), pregnant or lactating women, and women of childbearing potential not using adequate contraception.

Patients who met the inclusion/exclusion criteria were randomized to either perindopril or placebo, in a double-blind fashion. PET scanning was performed to investigate MBF (at rest, after DST, and after CPT). In the LV dysfunction group, PET imaging was again performed after 12 weeks double-blind treatment.

**PET imaging protocol**

All PET studies were performed after subjects had refrained from caffeinated beverages for a minimum of 12 h before the studies. Subjects were positioned in a 951 Siemens (ECAT) positron camera (Siemens AG, Knoxville, USA), which images 31 planes simultaneously over 10.8 cm. The in-plane spatial resolution of the camera is 6 mm FWHM. Data were automatically corrected for accidental coincidence and dead time. Subjects were positioned with the help of a rectilinear scan. Photon attenuation was measured using a rectilinear external ring source filled with 68Ge/68Ga. Continuous monitoring with 12 leads electrocardiography and blood pressure measurement was done (Dynamap, 10 min interval, continuously during provocation studies). MBF was studied using 13N-ammonia as tracer using the methods described by Hutchins et al. [11]. Dynamic rest