International Journal of Cardiology 217 (2016) 161–166

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Coronary flow reserve as a link between exercise capacity, cardiac systolic and diastolic function☆

Juuso I. Blomster [a,b,c,1], Sara Svedlund [a,d,1], Helena U.Westergren [a], Li-Ming Gan [a,b,d,*]

[a] Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
[b] AstraZeneca R&D, Mölndal, Sweden
[c] Heart Centre, University of Turku, Turku, Finland
[d] Department of Clinical Physiology, Sahlgrenska University Hospital, Gothenburg, Sweden

ARTICLE INFO

Article history:
Received 19 February 2016
Received in revised form 25 April 2016
Accepted 30 April 2016
Available online 3 May 2016

Keywords:
Cardiac imaging
Systolic function
Diastolic function
Echocardiography
Coronary flow reserve

ABSTRACT

Background: Decreased coronary flow reserve (CFR) is associated with increased risk of adverse cardiovascular events. We sought to investigate how CFR from left anterior descending (LAD) coronary artery reflects clinical markers of cardiac function.

Methods: We enrolled 400 patients referred for myocardium perfusion scintigraphy due to chest pain at Sahlgrenska University Hospital in Gothenburg, Sweden. Transthoracic echocardiography including adenosine-assisted CFR in LAD was performed at a separate occasion.

Results: Median age was 62 years (range 32–83) and 47% were female. Prior myocardial infarction had occurred in 28% of the population. In adjusted multivariate models, CFR in LAD was associated with echocardiography left ventricle ejection fraction at rest ($\beta = 0.97$, $p = 0.033$) as well as under stress ($\beta = 1.52$, $p = 0.0056$) and maximum exercise capacity ($\beta = 6.27$, $p = 0.026$). CFR in LAD outweighed left ventricle ejection fraction as the determinant of maximum exercise capacity. Hyperaemic diastolic mitral annulus peak velocity measured by vector velocity imaging was inversely associated with LAD CFR ($\beta = -0.39$, $p = 0.0077$). In subgroup analyses these findings were associated with normal coronary perfusion in myocardium perfusion scintigraphy.

Conclusions: In patients with angina-like symptoms CFR measured in LAD reflects well both systolic and diastolic cardiac function emphasizing the essential role of myocardial microvascular circulation in cardiac physiology.

1. Introduction

The cardiac arterial bed can be divided into three compartments with distinct functions all complementing each other to ensure adequate blood supply to the myocardium. The largest arteries, epicardial coronaries (diameter >500 μm) function as capacitance vessels where symptomatic atherosclerosis, i.e. obstructive coronary artery disease (CAD), have traditionally been the focus of CAD treatment [1]. Prearterioles (diameter >100 μm) aim to maintain pressure irrespective of changes in coronary perfusion pressure and flow, whereas the third type of vessels consists of arterioles (diameter <100 μm) responsible for metabolic regulation of myocardial perfusion to match current demand. This vessel bed is often referred to as microcirculation and is influenced by a number of vasoactive factors, such as nitric oxide and adenosine [2]. Abnormalities in the circulation at the arteriolar level correspond to coronary microvascular dysfunction which may also impair myocardial perfusion and result in ischaemia [3]. In fact, this kind of microvascular CAD appears to be relatively common, as up to 25% of patients assigned to coronary angiography due to suspected acute coronary syndrome do not have obstructive CAD [4]. Moreover, from stable angina patients assessed by angiography, obstructive CAD seems to be present in only 1/3 of patients [5]. Much like obstructive CAD, this non-obstructive CAD, i.e. microvascular disease, is associated with adverse cardiovascular outcomes [6] and offers a plausible explanation why patients without obstructive CAD have a 2–4.5-fold greater risk for myocardial infarction [7].

Microvascular disease in arterioles can't be visualized by angiography due to their small size, but because of it's significance both invasive and noninvasive modalities have been developed to detect microvascular CAD. An indication of microvascular disease is achieved with coronary flow reserve (CFR; the ratio of induced hyperaemic blood flow to baseline) which is an integrated measure of flow through both large epicardial arteries and coronary microcirculation [8]. CFR of the left anterior descending (LAD) coronary artery during pharmacologic stress echocardiography has been found to provide effective prognostic information in patients with known or suspected CAD [9]. This seems evident across patient populations, such as those with diabetes [10],

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Dept of Molecular and Clinical Medicine, Sahlgrenska University Hospital, S: 413 45 Göteborg, Sweden.
E-mail address: li-ming.gan@gu.se (L.-M. Gan).

[1] Authors have contributed equally.

http://dx.doi.org/10.1016/j.ijcard.2016.04.179
0167-5273/

older age [11] or chronic kidney disease [12]. In particular, a CFR <2.0 has been associated with markedly increased cardiovascular (CV) risk in an unselected patient population [9]. The prognostic capability of CFR measured in LAD is concluded to reflect the extent of coronary microcirculatory dysfunction as CFR is not modulated by ongoing anti-ischemic therapy [13].

The inverse association of CFR in LAD coronary artery with adverse CV events is well documented. Two prior clinical studies suggest a possible link between CFR and diastolic function and exercise capacity in patients with heart failure with reduced ejection fraction [14] and prior CAD [15], but these studies have been small and haven't been able to control for known risk factors and confounders. Given the central role of microvascular function, also recently recognized in heart failure with preserved ejection fraction [16], we hypothesized that CFR as a composite marker for macro- and microvascular function could be a link between systolic and diastolic cardiac function and be reflected in maximum exercise capacity in patients with activity limiting angina pectoris symptoms.

2. Methods

From a consecutive series of 468 patients referred to myocardial perfusion scintigram (MPS) due to chest pain at Sahlgrenska University Hospital in Gothenburg, Sweden between 2006 and 2008 were assessed for participation to this trial. From these patients 400 were eligible for adenosine-induced hyperaemia examination and underwent CFR measurement in LAD coronary artery with transthoracic Doppler echocardiography. Echocardiography including CFR measurement was evaluated by predetermined protocols. Overnight fasting blood samples, demographic data including history of diabetes, CAD, hypertension, heart failure, smoking status and current cardiovascular medication were all collected while visiting hospital. All participants provided written informed consent as acceptance to participate. The study complies with the declaration of Helsinki and was approved by the Local Ethics Committee in Gothenburg, Sweden.

Hypertension and hyperlipidemia variables were created where each positive finding yielded one point. For hypertension (total score 0 − 2) assessed variables were antihypertensive medication and observed blood pressure above 140/90 mm Hg. For hyperlipidemia (total score 0 − 2) assessed variables were medication for hyperlipidemia and observed hyperlipidemia. Heart failure diagnosis was dichotomized (yes/no) based on previous heart failure diagnosis.

2.1. Myocardial perfusion scintigram and stress test

MPS was carried out by a standard clinical two-day protocol using two different dual-head SPECT cameras (Infinia or Millennium VG, GE Healthcare, Milwaukee, Wisconsin, USA) under ^{99m}Tc-sestamibi protocol. Stress tests were performed by symptom-limited maximal exercise capacity tests on ergometric bicycle or as a pharmacological challenge under adenosine infusion. Maximal exercise capacity level was measured in maximal work load reached in Watts from 190 patients who underwent symptom-limited exercise tests on ergometric bicycle. Reversible myocardial ischemia was observed automatically by the software ECT-tool box. The extent (1 = small <10%, 2 = medium 10–19%, 3 = large >19%) and severity (1 = mild, 2 = moderate, 3 = severe) of reversible myocardial perfusion abnormality were evaluated by experienced physicians. Normal MPS result was defined when both extent and severity of ischemia were scored 0 (none).

2.2. Echocardiography

A transthoracic echocardiogram was performed on all participants with a Sequoia C256 (Acuson Siemens Mountain View, CA) ultrasound system equipped with a 4 MHz probe. Left ventricular ejection fraction (EF) was determined by Simpson biplane method. The applied protocol has previously been described with excellent reproducibility [17].

2.3. Measurement of coronary flow reserve

The mid- to distal part of the LAD was visualized with 3.5 MHz color Doppler and pulsed Doppler was used to sample flow velocity signals at rest and during adenosine infusion (140 μg/min/kg) over 5 min. The measurement was performed under continuous blood pressure and ECG monitoring. CFR was determined by the ratio of mean diastolic flow velocity during peak hyperaemia and baseline from diastolic Doppler flow signals, Fig. 1.

2.4. Measurement of diastolic function

Vector velocity imaging with frame rate over 70 fps was used to assess diastolic mitral annulus peak velocity as a measure of diastolic function during both rest and adenosine-induced hyperaemia, Fig. 2. The measures were averaged from septal and lateral, as well as anterior and posterior mitral annulus in 4- and 2-chamber apical views, respectively. All obtained echocardiography data were digitally stored for off-line reviewing and measurements were performed using the ultrasound software Image Arena (Tomtec, Unterschlissheim, Germany).

2.5. Laboratory measurements

Commercial kits for biochemical analyses were used. Triglycerides, high density lipoprotein cholesterol and total cholesterol in serum were measured using reagent systems from Roche (Triglycerides/GB kit No; 12146029216, Cholesterol kit No; 2016630, Roche Diagnostics GMBH, Mannheim Germany), direct high density lipoprotein cholesterol (Horiba ABX, France) and HbA_{1c} by HPLC at the department of Clinical Chemistry, Sahlgrenska University Hospital, Gothenburg.

2.6. Statistical analysis

Data are presented as mean values with standard deviation (SD) in parentheses for continuous variables and as percent for categorical variables. Chi-square test was used for comparison of patient characteristics between the groups. Logistic regression was assessed with general linear model. The models with left ventricle EF and diastolic function were adjusted with age, sex, body mass index, hypertension, hyperlipidemia, LAD CFR and CAD in MPS. For the analyses of left ventricle EF, the multivariate model was added with diagnosis of heart failure. In the other models this was replaced with left ventricle EF. The final model of maximum exercise capacity included the variables above added with measure of diastolic function. To further assess associations with LAD CFR as a marker of microvascular function a subgroup of patients with and without CAD in MPS imaging were analyzed. Due to smaller number of individuals, in the subgroup analyses the models were adjusted with age, body mass index, LAD CFR and heart failure/ left ventricle EF respectively as described above. In multivariate models categorical variables (hypertension and hyperlipidemia) were analyzed by using the positive diagnosis as point of reference. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

3. Results

The mean age of the study participants was 62 years and 56% were men. The general characteristics of the study population are described in Table 1.

In multivariate models for systolic measures of left ventricle function, LAD CFR was associated with left ventricle EF at rest and under stress test induced hyperaemia (Table 2). In the assessments of diastolic function LAD CFR was associated with diastolic mitral annulus peak