Normalization of coronary blood flow in the infarct-related artery after intracoronary progenitor cell therapy:
Intracoronary Doppler substudy of the TOPCARE-AMI trial

Summary Background Coronary microvascular dysfunction contributes to infarct extension and poor prognosis after an acute myocardial infarction (AMI). Recently, progenitor cell application has been demonstrated to improve neovascularization and myocardial function after experimental myocardial infarction. Therefore, we investigate coronary blood flow regulation in patients after AMI treated with intracoronary progenitor cell therapy. Methods and results In the TOPCARE-AMI trial, patients received either bone marrow-derived or circulating progenitor cells into the infarct-related artery 3–7 days after AMI. The present substudy investigates in 40 patients coronary blood flow regulation at the time of progenitor cell therapy and at 4-month follow-up by i.c. Doppler in the infarct artery as well as a reference vessel. At the initial measurement, coronary flow reserve (CFR) was reduced in the infarct artery compared to the reference vessel (median 2.5 vs. 3.4, p < 0.001). At 4-month follow-up, intracoronary progenitor cell therapy was associated with a normalization of CFR in the infarct artery (median 3.9 vs. reference vessel 3.8, p = 0.15). CFR also improved in the reference vessel, but mechanisms were different: reference vessel increase in CFR was secondary to an increased basal vascular resistance, probably due to reduced need for hypercontractility. In contrast, in the infarct artery, adenosine-induced minimal vascular resistance profoundly decreased, indicating an increased maximal coronary vascular conductance capacity. In addition, in a non-randomized matched control group (n = 8), minimal vascular resistance in the infarct artery was significantly elevated compared to progenitor cell treated patients 4 months after AMI (p = 0.012). Conclusions Intracoronary progenitor cell therapy after AMI is associated with complete restoration of coronary flow reserve due to a substantial improvement of maximal coronary vascular conductance capacity. The clinical importance of improved microcirculation by progenitor cell therapy in patients after AMI has to be established in further randomized trials.

Key words
Myocardial infarction – microcirculation – coronary disease – angiogenesis
Introduction

An acute myocardial infarction may lead to the development of heart failure, morphologically characterized by a left ventricular dilation [1]. This ventricular remodelling process starts early, in the first days after myocardial infarction due to loss of additional – still viable – myocardium, since the nutritional demand of hypertrophied cardiomyocytes in the infarct border zone may exceed the oxygen and nutrient supply provided by the reduced capillary network, leading to apoptotic myocyte cell death [2]. Therefore, restitution of the microvascular network within the infarcted tissue arises as an attractive novel therapeutic strategy after myocardial infarction [3–5].

In the clinical setting, an acute myocardial infarction is associated with coronary microvascular dysfunction [6], assessed for example, by coronary flow reserve [7], which is an important predictor of infarct expansion and recovery of contractility [8, 9]. Importantly, therapeutic strategies to improve coronary flow reserve after acute myocardial infarction are indeed associated with restoration of myocardial contractility [10].

In recent years, adult stem or progenitor cells were shown to contribute to the formation of new blood vessels (neovascularization), a process previously thought to be restricted to the embryonic developmental stage [11]. Experimental data indicate that application of adult bone-marrow-derived progenitor cells [2, 12, 13] as well as blood-derived progenitor cells with endothelial markers [14, 15] is capable of inducing neovascularization of ischemic tissue. Most importantly, therapeutic neovascularization using either bone marrow- or blood-derived progenitor cells prevented cardiomyocyte apoptosis and improved ventricular remodelling and contractility in animal models of acute myocardial infarction [2, 14].

Recently, the concept of stem cell therapy after an acute myocardial infarction has been transferred into the clinical setting, with studies also suggesting a beneficial effect on the post infarct ventricular function [16–18]. In the TOPCARE-AMI trial, we applied either bone-marrow-derived or circulating progenitor cells into the infarct artery during low pressure balloon insufflation to patients with an acute myocardial infarction within one week after successful initial revascularization by stent implantation [17, 19]. In order to get insights and generate hypothesis with respect to the potential neovascularization capacity of such therapy in patients with an acute myocardial infarction, we performed the present substudy of the TOPCARE-AMI trial, assessing the coronary blood flow by intracoronary Doppler measurements.

Methods

Study design

Patients with a first acute ST-elevation myocardial infarction which was treated by coronary stenting in the acute phase of myocardial infarction were included in the study as previously described in more detail [17]. The study was approved by the ethics committee of the Johann Wolfgang Goethe University of Frankfurt, Germany.

The study was designed as a pilot trial to assess the safety and feasibility of intracoronary progenitor cell therapy after myocardial infarction. In addition, parameters of myocardial and coronary vascular function were assessed in an exploratory fashion.

The interim angiographic, echocardiographic, PET, and coronary flow reserve data of the first 20 patients [19], detailed data obtained by magnetic resonance imaging [20], and the final clinical report of the TOPCARE-AMI trial [17] have been previously reported. The present paper is the final report of the Doppler substudy of the complete TOPCARE AMI trial, including not only all patients, but furthermore presenting the data in more detail allowing further insights into potential mechanisms. Thereby, coronary microvascular function was assessed in patients undergoing successful progenitor cell therapy without cardiac events or restenosis (>50% stenosis by quantitative coronary angiography) during follow-up (Fig. 1).

As previously reported [17], patients were randomly assigned to receive intracoronary infusion of either bone-marrow-derived or blood-derived progenitor cells 3–7 days after AMI. Collection, preparation and characterization of the progenitor cells have also been previously reported [17].

In the present substudy, we additionally investigated – as a non-randomized control group reflecting the natural course of coronary microvascular function – coronary hemodynamics in eight patients 4 months after acute myocardial infarction. These control patients were matched to the progenitor cell treated patients with respect to their clinical characteristics, including left ventricular ejection fraction, and treatment during the 4 months post acute myocardial infarction.

Catheterization procedure and Doppler measurements

Prior to coronary blood flow assessment, 0.2 mg i.c. nitroglycerin was injected in order to maximally dilate epicardial vessels without substantially affecting the microvasculature [21]. A Doppler wire (Flowire, Cardiometrics) was inserted in the infarct artery at the