Comparison of carvedilol and metoprolol in patients with acute myocardial infarction undergoing primary coronary intervention – The PASSAT Study

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Summary Background The value of early therapy with beta-blocking agents in acute myocardial infarction (AMI) undergoing reperfusion is not yet well established. Newer beta-blocking agents such as carvedilol offer potential advantages in the setting of ischemia and reperfusion injury. Methods We randomized 100 patients with acute ST-elevation myocardial infarction (STEMI) to receive either 12.5 mg carvedilol or 50 mg metoprolol tartrate orally already before percutaneous coronary intervention (PCI) of the infarct-related artery, uptitrating to a daily target dose of 50 mg carvedilol or 150 mg metoprolol during the first week. Pts. were subjected to left ventricular (LV) angiography just before reperfusion and after 14 days to compare ejection fraction (EF) and regional wall motion abnormalities by quantitative LV analysis. Furthermore, kinetics of cardiac troponin T (cTnT), NT-proANP, NT-proBNP, endothelin, arginine vasopressin, epinephrine and norepinephrine were assessed during the first 12 hours and again at 2 weeks. In addition, reperfusion-induced rhythm abnormalities like VT, triplets, couplets, and bradycardic events were assessed continuously during the first 12 hours starting at reperfusion by Holter analysis. Results Both groups did not differ with respect to onset of pain, target vessel, extent of coronary heart disease, age, gender, rate of stenting or use of a GP IIb/IIIa inhibitor, pre- and postinterventional TIMI flow grade, time course of heart rate or blood pressure. There were neither significant differences in the cardiac and neurohumoral markers nor in the occurrence of arrhythmias between both treatment groups. Within 14 days, EF improved by 5.8 ± 2.0% (mean ± SEM) in the metoprolol group and by 5.2 ± 2.1% in the carvedilol group (n.s.). Area of infarction was reduced by 6.1 ± 2.9% in the metoprolol group and by 12.8 ± 3.6% of total LV outline in the carvedilol group (n.s.). Maximum hypokinesia in the central infarcted region was diminished by 0.40 ± 0.11 standard deviation (SD) in the metoprolol group and by 0.34 ± 0.13 SD in the carvedilol group (n.s.). Conclusion In the setting of direct PCI in acute STEMI, administration of carvedilol before reperfusion appears not to be superior to metoprolol with respect to myocardial injury and improvement of global and regional LV function. The study documents equivalent improvement of LV function and similar kinetics of cardiac and neurohumoral markers in pts. with acute STEMI undergoing direct PCI if the pts. were immediately treated with either carvedilol or metoprolol. Thus, superiority of carvedilol in experimental studies did not translate into a clinical benefit. Key words Catecholamines – ischemia – myocardial infarction – receptors, adrenergic, alpha – receptors, adrenergic, beta – reperfusion – neurohumoral factors – ventricular function
Introduction

It is well accepted that early treatment with beta-blockers in acute myocardial infarction (AMI) reduces mortality and ischemic events (Class I Recommendation AHA/ACC guidelines). Trials with intravenous beta-blockers have shown reduction of early mortality by 13% when used within 24 hours after onset of chest pain [1, 2]. These studies were conducted before the widespread use of aspirin and reperfusion therapy; thus, the value of early beta-blocker therapy is less well established in the context of current treatment standards [3, 4]. Moreover, there is debate whether the nonselective beta- and alpha-adrenoceptor blocker carvedilol offers advantages over beta1-selective agents particularly in ischemia/reperfusion injury. It has been shown that reperfusion injury is associated with an increase in the number of ventricular alpha1-adrenoceptors, enhanced alpha1-adrenoceptor mediated electrophysiological responsiveness and increased intracellular calcium accumulation secondary to alpha1-adrenoceptor activation [5]. Elevated levels of norepinephrine are associated with impaired angiographic reperfusion and increased myocardial damage after mechanical recanalization [6]. In addition, it has been shown that alpha-adrenergic stimulation increases coronary vascular resistance and thereby contributes to the so-called phenomenon of no-reflow or slow-flow commonly observed after thrombolysis and/or mechanical reopening of an infarct-related artery [7].

Taken together, there is considerable clinical and experimental evidence that the simultaneous blockade of alpha- and beta-adrenoreceptors reduces the extent of myocardial injury in ischemia/reperfusion more effectively than selective beta1-receptor antagonism.

There are, however, also arguments in favor of selective beta1-adrenoceptor blockade in acute myocardial infarction. One is derived from a meta-analysis of beta-blocker trials in AMI showing that the beneficial effects of beta-blockers were mainly related to the degree of heart rate reduction which was achieved. It is plausible that reduction of heart rate can be more easily accomplished with beta1-selective blockade than with comprehensive adrenoceptor blockade, which results in peripheral vasodilatation. Superiority of beta1-selective antagonism is also suggested by the observation of opposing effects of beta1- and beta2-adrenergic receptors on cardiac myocyte apoptosis. Beta2-receptor stimulation increases apoptosis, while beta2-receptor stimulation inhibits apoptosis [8].

Actually there are several experimental studies comparing carvedilol and traditional beta-blockers in experimental myocardial infarction, but there is virtually no clinical trial which has addressed this question, so far. Regarding the experimental studies all investigators used in vivo ischemia/reperfusion models. Carvedilol was compared with propranolol, metoprolol, and bisoprolol, respectively [9–12]. These studies concurrently documented a 30% decrease of infarct size with carvedilol over propranolol, metoprolol or bisoprolol and all concluded that the superior cardioprotection of carvedilol was not the consequence of hemodynamic variances [9–12]. Very recently, the COMET study was published, which is the first comparison of different beta-blocking drugs on long-term mortality and morbidity in patients with chronic heart failure. COMET reported a significant survival benefit with carvedilol over metoprolol, which further underscores the need for a head-to-head comparison of carvedilol and metoprolol in acute myocardial infarction [13].

We therefore conducted a prospective, randomized, clinical study comparing early treatment with metoprolol or carvedilol in patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). The study was powered to document potential differences in infarct size of absolute 10% and in ejection fraction (EF) of absolute 6% between both treatment arms. In order to quantify infarct size we used sensitive angiographic tools according to Sheehan [14, 15].

The present study is unique in several respects. It is the first study comparing two beta-blockers in patients with STEMI which are subjected to mechanical reperfusion routinely using coronary stents and GP IIb/IIIa antagonists, thus, representing the currently accepted optimal reperfusion strategy in STEMI.

Furthermore, as long-term outcome is related to neurohumoral activation in AMI and because beta-blockers interfere with several neuro-hormonal axes, we performed serial measurements of circulating hormones during this study.

Methods

Patient selection

Patients referred to the hospital within 8 hours after the onset of an acute myocardial infarction and eligible for PCI were considered for the study. Patients were excluded if pretreated with an alpha- or beta-receptor blocker, in case of acute congestive heart failure (killip-class III–IV), severe bradycardia <55 bpm, hypotension <100 mmHg systolic, AV-block °II–III, left bundle branch block, or known incompatibilities against carvedilol or metoprolol. Patients who had a history of bronchospasm and/or