Background: C-terminal prosaposin (copeptin) is a marker of hypersomolar-ity and endogenous stress and has demonstrated promising prognostic potential in heart failure (HF) and after acute myocardial infarction. Levels of copeptin are known to peak few hours after chest pain onset and then decline. Yet admission levels of copeptin have not been investigated in a large cohort of patients with ST-segment elevation myocardial infarction (STEMI).

Purpose: The aim of this study was to examine the associations of admission copeptin with long- and short-term all-cause mortality, and hospital admission for HF in STEMI patients.

Methods: This substudy was conducted as part of The Danish Study of Optimal Acute Treatment of Patients with STEMI (DANAMI-3). Blood samples for analyses of copeptin were obtained immediately upon arrival in the catheterization laboratory before primary percutaneous coronary intervention was performed. Admission levels of copeptin were divided into quartiles and the Kaplan Meier survival curves were compared across quartiles by the log-rank test. We assessed all the outcome events using Cox proportional hazard models adjusted for age, gender, time since onset of symptoms, heart rate, estimated glomerular filtration rate, angiographic thrombolysis in myocardial infarction flow, diabetes, hypertension and history of: myocardial infarction, congestive HF, stroke and smoking.

Results: In total 1119 patients were included. The median age was 62 years (25th to 75th percentiles; 53–70) and 76% were men. Blood samples were obtained with a median interval of 2.8 hours (25th to 75th percentiles; 2.1–4.4) after onset of symptoms. Levels of copeptin were significantly higher in the group of patients presenting within 0 to 3 hours after onset of symptoms (median 99.4 pmol/L, 25th to 75th percentiles; 32.0–208.1) compared with patients presenting in the interval of 3 to 6 hours (median 55.2 pmol/L, 25th to 75th percentiles; 16.3–159.1) and with patients presenting after 6 hours (median 25.2 pmol/L, 25th to 75th percentiles; 10.3–72.0; p<0.0001). During a median follow-up of 4.8 years, the 1st quartile of copeptin was associated with increased mortality (hazard ratio 1.10, 95% CI 1.03–1.17, p<0.01), whereas the 3rd quartile was associated with increased short and long-term mortality (hazard ratio 1.68, 95% CI 1.23–2.28, p<0.01). Moreover, a doubling of copeptin was, in adjusted models, associated with an increased risk of long-term mortality (hazard ratio 1.45, 95% CI 1.20–1.75, p<0.01). Copeptin was not significantly associated with increased short-term mortality. Additionally, compared with patients presenting in the 1st quartile, the 3rd and 4th quartiles of copeptin were associated with increased hospital admission for HF (hazard ratio 1.24, 95% CI 1.09–1.40, p<0.01, and hazard ratio 1.73, 95% CI 1.49–2.00, p<0.01, respectively).

Conclusions: Admission copeptin was associated with increased short and long-term mortality in STEMI patients.

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Copeptin - a marker of short- and long-term mortality in patients with ST-segment elevation myocardial infarction
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Oclusion of left anterior descending artery impairs microvascular function in the left circumflex and the right coronary artery area in adioprine
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Introduction: Oclusion of major coronary artery induces myocardial infarction (MI) leading to remodeling of the left ventricle (LV), which is reportedly caused by endothelial dysfunction (ED). We herein hypothesized that occlusion of the major coronary artery may induce microvascular dysfunction in the adjacent area which is perfused by the intact coronary arteries.

Methods: MI was induced by the placement of the ameredi constrictor ring around the left anterior descending artery (LAD) in adult Göttingen pigs 8 weeks before the assessment, while age-matched normal ones were used for the control (n=6 each). Regional wall motion, myocardial blood flow (MBF) and index of microvascular resistance (IMR) of the LV was studied by cardiac magnetic resonance (CMR), 13N-ammonia positron emission tomogram (PET) and fluorescency-guided pressure wire studies, respectively.

Results: The CMR study consistently showed akinetic anterior LV wall with an ejection fraction of 40±7% at 4 weeks and 40±8 at 8 weeks after the MI induction. Systolic regional wall motion in the adjacent area of the infarction was progressively worsened over the period, assessed by the CMR. In the PET study, MBF at hyperemia was significantly greater in the left circumflex (LCX; 1.5±0.2 ml/min/g) and the right coronary (RCA; 1.3±0.3 ml/min/g) than that in the LAD area (1.0±0.1 ml/min/g, P<0.05) at 4 weeks, and then in the LCX and the RCA areas significantly decreased (LCX: 1.0±0.1 ml/min/g, p<0.05; and RCA: 1.3±0.2 ml/min/g, p<0.05) at 8 weeks. Further, CFR of the LCX area (1.1±0.3) was significantly smaller than that of the control (2.2±1.0, P<0.01), while CFR of the RCA area was not different between them. Electron microscopy study showed swelling of the endothelium and disruption of the microvessels in the adjacent area. Therefore, we conclude that MI induces microvascular dysfunction in the adjacent area, associated with reduction of myocardial blood flow and regional wall motion.

Conclusions: C-type natriuretic peptide knockout mice
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Background: We previously reported that C-type natriuretic peptide (CNP) is secreted from vascular endothelial cells and proposed the possibility that endothelin-derived CNP is involved in the regulation of vascular tone, remodeling and regeneration.

Purpose: We assessed the functional significance of endothelium-derived CNP in the regulation of blood pressure in vivo.

Methods: We generated and analyzed vascular endothelial cell-specific CNP knockout (CNP ecKO) and vascular smooth muscle cell-specific CNP receptor, guanylyl cyclase-B (GC-B), knockout (GC-B smKO) mice. Results: Both CNP ecKO and GC-B smKO mice showed neither the skeletal arteriolar nor the early mortality observed in systemic CNP or GC-B knockout mice. Significantly elevated blood pressures and an enhanced acute hypertensive response to nitric oxide synthetase inhibition were observed in CNP ecKO mice. Acetylcholine (ACh)-induced, endothelium-dependent vasorelaxation was impaired in rings of mesenteric artery isolated from CNP ecKO mice. Furthermore, when we pretreated these arteries with the NOS inhibitor L-NAME and the cyclooxygenase (COX) inhibitor indomethacin, the impairment of ACh-induced vasorelaxation was enhanced in CNP ecKO arteries, suggesting that the impairment of endothelium-dependent vasorelaxation in CNP ecKO mice involves NO- and prostaglandin-independent pathways, possibly an endothelin-derived hyperpolarization factor (EDHF) system. We further found that endothelin-1 (ET-1) gene expression was enhanced in pulmonary vascular endothelial cells from CNP ecKO mice, which also showed significantly higher plasma ET-1 concentrations and a greater reduction in blood pressure in response to an endothelin receptor antagonist than their control littermates. By contrast, GC-B smKO mice showed blood pressures similar to control mice, and acetylcholine-induced vasorelaxation was preserved in their isolated mesenteric arteries. Nonetheless,