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Release and Clearance Mechanisms of Cardiac Troponin

Akademisk avhandling

Som för avläggande av Karin Starnbergs medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, den 20 maj 2020, klockan 13.00.

av Karin Starnberg

Fakultetsopponent:

Alma Mingels PhD

Maastricht University Medical Center, Holland

Avhandlingen baseras på följande delarbeten

I. **Starnberg K**, Jeppsson A, Lindahl B, Hammarsten O. Revision of the Troponin T Release Mechanism from Damaged Human Myocardium. Clinical Chemistry, 2014;60,8: 1098-1104.

II. Fridén V, **Starnberg K**, Muslimovic A, Ricksten SE, Bjurman C, Forsgard N, Wickman A, Hammarsten O. Clearance of cardiac troponin T with and without kidney function. Clinical biochemistry, 2017; 50, 9: 468-474.

III. **Starnberg K**, Fridén V, Muslimovic A, Ricksten SE, Nystrom S, Forsgard N, Lindahl B, Vukusic K, Sandstedt J, Dellgren G, Hammarsten O. A Possible Mechanism behind Faster Clearance and Higher Peak Concentrations of Cardiac Troponin I Compared with Troponin T in Acute Myocardial Infarction. Clinical Chemistry, 2020;66,2: 333-341.

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Abstract

Myocardial infarction (MI) is often suspected when a patient presents with chest pain. MI is defined as cardiac necrosis due to ischemia, most often mediated through impaired coronary perfusion. Cardiac necrosis results in the release of myoglobin, creatine kinase and cardiac troponin (cTn) to the circulation. According to current guidelines, the MI diagnosis is, to a large extent, based on the patient's levels of cTn. This thesis examines the mechanisms of cTn release and subsequent clearance from the circulation. The trimeric cardiac troponins, troponin T (cTnT), troponin I (cTnI) troponin C (cTnC), bind to each other and via cTnT to insoluble filaments in the cardiomyocyte. Contrary to the prevailing opinion we found that a large fraction of cTnT could be released in 37°C plasma from necrotic human cardiac tissue without degradation of insoluble filaments. In contrast to myoglobin, which lacks affinity for cardiac tissue, the release of cTnT was highly plasma volume-dependent, which could explain the delayed clearance of cTnT observed in patients with MI. We then examined the clearance of cTnT from the circulation by injecting cardiac extracts containing both myoglobin and cTnT in rats. We also examined the renal extraction of circulating cTnT by comparing the cTnT concentration in blood samples from the renal vein and an artery in heart failure patients. We found high renal extraction of cTnT and that correction for renal clearance makes the cTnT analysis slightly better at finding patients with an MI in the emergency ward. We next examined the difference in release and clearance of cTnT and cTnI using the currently most frequently used clinical assays. We found that most cTnT and cTnI released from human cardiac tissue were degradation products produced by tissue-resident proteases. We also found that cTnI was degraded and released much faster than cTnT, whereas their subsequent clearance, once they reached the circulation, did not differ between cTnT and cTnI in either rats or humans. Our data potentially explain why cTnI reaches higher levels and disappears faster than cTnT in patients with MI.

Keywords: Cardiac Troponin T, Cardiac Troponin I, Biomarkers, Human, Myocardium, Animals, Kidney-dependent Clearance, Myocardial infarction

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