Imaging of coronary artery function and morphology in living mice - applications in atherosclerosis research

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssalen Arvid Carlsson, Academicum, Medicinargatan 3, Göteborg, fredagen den 25 maj 2007, klockan 09.00

av

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Avhandlingen baseras på följande delarbeten:

I. **Non-invasive imaging of coronary arteries in living mice using high-resolution echocardiography**, Li-ming Gan, Johannes Wikström, Göran Bergström and Birger Wandt, *Scandinavian Cardiovascular Journal* 2004;38:121-6

II. **Functional and morphological imaging of coronary atherosclerosis in living mice using high-resolution color Doppler echocardiography and ultrasound biomicroscopy**, Johannes Wikström, Julia Grönros, Göran Bergström, Li-ming Gan, *Journal of the American College of Cardiology* Vol. 46, No. 4, 2005:720-7

III. **5-lipoxygenase gene deficient mice show preserved in vivo coronary function following lipopolysaccharide challenge**, Johannes Wikström, Julia Grönros, William McPheat, Carl Whatling, Ulla Brandt-Eliasson, Daniel Karlsson, Regina Fritsche-Danielson, Li-ming Gan, *Submitted*

IV. **Relationship between in vivo coronary flow velocity reserve and atherosclerotic lesion characteristics in mouse**, Johannes Wikström, Julia Grönros, Li-ming Gan, *In manuscript*

V. **Adenosine induces dilation of epicardial coronary arteries in mice - relationship between coronary flow velocity reserve and coronary flow reserve in vivo using transthoracic echocardiography**, Johannes Wikström, Julia Grönros, Li-ming Gan, *Submitted*

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Abstract

Atherosclerosis in the coronary arteries is the major reason for myocardial infarction and cardiovascular death. In the clinic, several imaging systems make it possible to study coronary artery function and morphology non-invasively, such as transthoracic Doppler echocardiography (TTDE). Coronary flow velocity reserve (CFVR), as assessed using TTDE, can be applied to detect early as well as late pathological changes in atherosclerotic disease. However, no imaging method has been capable of addressing coronary artery morphology and function in mouse, the most widely used experimental animal in cardiovascular disease. In this context, we set out to develop an ultrasound-based methodological platform to study coronary artery function and morphology and to explore how it could be used to confirm pathological cardiovascular changes in mouse. We showed that detection and measurements of left coronary artery (LCA) flow velocity in the proximal and more distal segments is feasible using TTDE. In order to measure coronary function, we introduced a CFVR protocol where coronary hyperemia was induced either by mild hypoxia or with adenosine. For the first time, we applied a novel ultrasound biomicroscopy (UBM) technique to morphologically measure atherosclerosis-related narrowing of coronary arteries and to detect adenosine-induced hyperemic dilatation of the LCA. Using a combination of TTDE and UBM, we were able to calculate a coronary flow index and thereby compare flow velocity-based CFVR and flow-based CFR in mouse. Using TTDE and UBM, we have been able to measure atherosclerosis-related changes measured as minimal lumen diameter (MLD) in the proximal LCA. In the absence of coronary stenosis, we showed that endotoxin reduced CFVR, and that some of the deleterious effects are mediated through the 5-lipoxygenase pathway. In another study, CFVR was found to co-vary with different inflammatory cytokines and atherosclerotic lesion characteristics at different time-points. In summary, we have developed a unique imaging platform to study mouse coronary artery function and morphology, and found that the established imaging read-outs appear to reflect important pathophysiological features of atherosclerosis.

Key words: atherosclerosis, coronary artery, coronary flow velocity reserve, imaging, mouse, transthoracic Doppler echocardiography, ultrasound biomicroscopy

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