NONINVASIVE ASSESSMENT OF CARDIOMYOCYTE BREADTH FROM EXTRACELLULAR VOLUME FRACTION WITH MRI

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Purpose: Changes in cardiomyocyte size are involved in the adaptive response to various environmenal stimulation. Noninvasive cardiomyocyte size estimation *in vivo* is helpful for early detecting and monitoring myocardial remodeling. As the myocardial extracellular volume fraction (ECV) is a reflection of the relative volume of the extracellular space and cells in myocardium, we infer that the size of the cardiomyocytes affects ECV and in the other hand could be reflected by ECV. In this study, we are intended to determin whether there is correlation between ECV and histological cardiomyocyte breadth (CMyB)**.**

Methods: The present animal study complies with the Declaration of Helsinki and was approved by the ethics committee of our institute. Eleven domestic pigs (8 male, 3 female) weighing 20–26 kg (mean 24 kg) were anesthetized with an intravenous infusion of sodium pentobarbital at 0.1 mg/kg per minute after premedication of intramuscular diazepam. Endotracheal intubation and mechanical ventilation were performed for maintaining the intake of oxygen and controlling breath during MR scanning. The animals received 0.2 to 0.25 mmol/kg body weight of Gd-DTPA (Magnevist, Bayer Shering Pharma AG, Berlin, Germany) which was infused manually at a rate of about 0.5 ml/sec, followed by 5 ml saline at the same rate. A mid-ventricular short axis plane was selected for T1 mapping using a Modified Look-Locker Inversion Recovery sequence [1] before the contrast injection and repetitively during the 5 - 60 minutes period after contrast injection at different intervals of 0.5 to 5 minutes. Regions of interest(ROIs) were selected from the interventricular septum for ECV calculation in each pig, as ECV = $\lambda \cdot$ (1 - hematocrit), where λ is the myocardial contrast partition coefficient [2], and was calculated by relating change in longitudinal relaxation rate (R1 = 1/T1) of myocardium ($R1_m$) versus that of left ventricular blood pool ($R1_b$). Intravenous blood samples were collected before euthanasia for hematocrit measurement. Two random tissue samples were excised from each isolated heart after carefully positioning into the corresponding ROI in the MR image and were formalin fixed for 2–4 days before paraffin-embedding. One section perpendicular to the mid layer myocardial fibers was sectioned from each paraffin-embedded sample at 4 μm and stained with hematoxylin and eosin. Myocyte breadth in cross section were evaluated by imposing an ellipse on each profile and measuring the minor axis of the idealized outline [3]. Measurements were taken from four field of view (FOV, 356 μm × 266μm) per section and 80-120 cross-sectioned profiles per FOV. Thus, the mean value of the minor axis length was calculated based on data from 8 FOVs in each heart.

Results: The mean (± SD) ECV value of the 11 pigs were 0.264 ± 0.041, and the mean (± SD) CMyB was 9.98 ± 0.77 μm. ECV exhibited negative correlation with the CMyB ($r = 0.781$, $p = 0.005$).

Discussion: The negative correlation between ECV and CMyB revealed in this study implies larger myocyte size does not indicate proportionally increased extracellular space, generating a smaller ECV. Both genetic and environmental factors may affect the myocyte size during growth and development of heart, which results in the extensive range of ECV even though under physiological conditions. Theoretically, asymmetric changes in myocyte size and the extracellular space should lead to change in ECV thus are able to be detected. However, whether change in myocyte breadth in response to the abnormal conditions, such as pressure overload, metabolic disorders of energy, insufficient oxygen supply as well as excessive cardiac work, has a definite linear relationship with ECV is still to be determined in future studies.

Conclusion: ECV correlates negatively with CMyB under physiological conditions, and might be a potential biomarker for cardiomyocyte size estimation *in vivo*.

References:

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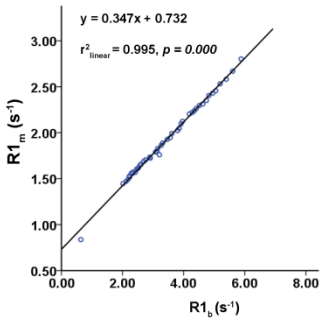

Figure 1. An example of the linear relationship between $R1_m$ versus $R1_b$. The myocardial contrast partition coefficient (λ) was calculated as the slope of the regression line.

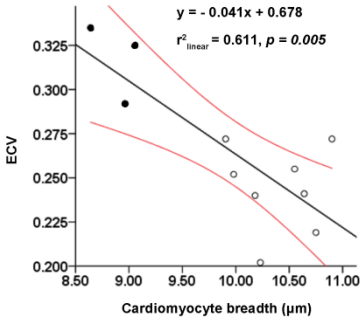

Figure 2. Relationship between CMyB and the ECV. Note that the three female animals (dots) have the smallest CMyBs but the largest ECV values.