Assessment of myocardial matrix expansion with cardiac magnetic resonance: entering a new area of cardiac risk stratification in type 2 diabetes mellitus?

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This editorial refers to ‘Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission’, by T.C. Wong et al., on page 657

Type 2 diabetes mellitus (DM) may lead not only to early development of accelerated coronary artery disease (CAD) but also to cardiomyopathy (CMP), both of which confer an excess morbidity and mortality in these patients. As there is a continuous increase in the prevalence of DM in industrialized nations, it raises a considerable public health concern. Subclinical markers of early functional and structural vasculopathy such as an impairment of coronary circulatory function, increased carotid intima-media thickness (IMT), and coronary artery calcification have all been demonstrated independently to predict the initiation and/or progression of CAD and subsequent cardiovascular events. More recently, cardiovascular magnetic resonance (CMR) assessment of increased extracellular volume (ECV) fraction of the left ventricle, which can be assumed to probe features of adverse myocardial remodelling, predicted mortality and heart failure-related events in an independent fashion in a general cardiovascular risk cohort. It is important to consider that, despite the standard use of preventive antidiabetic medication, DM is still associated with a greater coronary atherosclerotic burden, accelerated CAD progression, and CMP manifestation than in those individuals with cardiovascular risk but without a hyperglycaemic state. This emphasizes the necessity for additional diagnostic and medical therapeutic strategies aiming to prevent or inhibit the progression of diabetes-induced vasculopathy and/or CMP and, thereby, to improve cardiovascular outcome.

Nowadays, CMR has evolved as a unique imaging tool to identify and characterize subclinical and clinically manifest alterations of the myocardial tissue. CMR in concert with intravenous use of gadolinium is commonly applied for determining myocardial perfusion with the first-pass technique as well as for the assessment of myocardial necrosis, oedema, fibrosis, and infiltrative processes with late gadolinium enhancement (LGE) image acquisition. Under normal circumstances, gadolinium is limited to the extracellular space. Alterations of myocardial tissue structure, however, due to myocardial infarction, oedema, fibrosis, and infiltrative disease leads to an expansion of the extracellular space. This causes a larger amount of gadolinium to diffuse and to accumulate in the altered myocardial tissue. The accumulation of gadolinium in concert with its slower wash-out rate as compared with normal myocardium manifests in a bright signal on delayed T1-weighted CMR images. Although LGE imaging with CMR excellently distinguishes abnormally altered from normal myocardial tissue, uniform diffuse processes such as the development of interstitial fibrosis in DM or hypertensive patients may remain undetected.

For this purpose, CMR contrast imaging with T1 mapping has been developed to assess more diffuse processes involving the extracellular or interstitial myocardial space, which goes beyond the scope of conventional LGE imaging (Figure 1). T1 mapping is performed by assessing the partition coefficient (λ) for gadolinium contrast from pre- and post-contrast images. The partition coefficient in concert with the blood haematocrit enables the ECV to be calculated.

\[ \lambda = \frac{\Delta R1 \text{ myocardium}}{\Delta R1 \text{ blood pool}} \]

pre- and post-gadolinium contrast.

ECV = (1 – haematocrit) × λ,

where R1 = 1/T1.
Quantification of ECV has been demonstrated to parallel closely histological markers of collagen volume fraction (representing diffuse fibrosis) \( (r = 0.69, P = 0.013) \) in an animal model.\(^{10}\) In addition, clinical validation of T1 mapping with CMR was performed in patients undergoing aortic valve replacement for aortic stenosis \( (n = 18) \) or myectomy in hypertrophic cardiomyopathy \( (n = 8) \).\(^{11}\) Also here, the ECV as determined with T1 mapping strongly correlated with histological fibrosis from biopsies \( (r = 0.89, P < 0.001) \). Conversely, it is important to be aware that expanded ECV determined from T1 mapping may not only represent diffuse interstitial fibrosis but it may also increase due to alterations of other components of the extracellular matrix such as non-collagenous proteins, fibroblasts, endothelial cells, vessels, oedema, and infiltrative diseases.\(^{12}\)

Wong and colleagues\(^{13}\) now provide three types of novel information. The authors demonstrate: (i) that DM is associated with increased ECV of the left ventricle; (ii) that ECV assessment identifies lower myocardial extracellular matrix expansion in DM individuals.
being treated with medication blocking the renin–angiotensin–
adosterone system (RAAS); and (iii) that increased ECV is associated
with mortality and/or incident hospitalization for heart failure in dia-
abetic individuals. This analysis included 1176 consecutive patients re-
ferred for CMR without amyloidosis and other forms of infiltrative
disease, hypertrophic cardiomyopathy, genetic disorders with dis-
tinct clinical characteristics, type 1 DM, and adult congenital heart
disease. In order to maximize generalizability, the authors also in-
cluded individuals with myocardial infarction. As myocardial infarc-
tion size can vary greatly, it was ascertained that ECV was measured
specifically in remote non-infarcted myocardium, avoiding even the
area at risk. It was found that DM patients (n = 231) had higher
median ECV than those with cardiovascular risks without diabetes
(n = 945): 30.2% vs. 28.1%, while a marked overlap was observed in
the individual measurements of ECV. In the cross-sectional com-
parison, RAAS blockade was independently associated with lower
ECV. Furthermore, over a median of 1.3 years, 38 diabetic individuals
had events (21 incident hospitalizations for heart failure; 24 deaths),
and, importantly, increased ECV was independently associated with
these events (hazard ratio 1.52, 95% confidence interval 1.21–
1.89). As in a previous investigation, ECV was calculated from pre-
and post-contrast T1 measurements applying an ECG-gated single-
shot modified look locker inversion recovery (MOLLI) technique.
This technique has been validated previously with a high reproduc-
bility of ECV measurements. ECV estimates were derived from
basal and mid ventricular short axis slices to yield the final value,
while apical slices of the left ventricle were excluded from analysis
to reduce error related to partial volume averaging.

This investigation constitutes the first report of an association
between measurements of ECV and clinical outcome, defined as
mortality and/or incident hospitalization for heart failure. It extends
previous observations in a non-specific cohort of 793 consecutive
patients with cardiovascular risk referred for CMR to a specific
population of DM patients. Notably, those DM individuals who
were on RAAS blockade had less ECV than those without. These
observations may indeed suggest that CMR assessment of ECV
may be a promising tool for an optimized identification and character-
ization of subclinical and clinically manifest diabetic CMP. The study
opens up a new avenue for assessment and monitoring of intensified
therapeutic responses in individual DM patients. Conversely, the
median follow-up period was only 1.3 years and the number of adverse
cardiac events limited to 21 incident hospitalizations for heart
failure, which can be seen as a relatively weak endpoint, in addi-
tion to 24 deaths in 231 DM patients. Compared with cardiovascular
risk patients without DM, DM patients were substantially older, had
more arterial hypertension, dyslipidaemia, suspicion for CAD, lower
left ventricular ejection fraction, and more advanced left ventricular
remodelling, as well as more frequent hospitalization. Overall, the
study may be relatively underpowered to adjust the multivariable
models fully in a high cardiovascular risk DM population. In addition,
risk adjustment may have been limited by unaccounted, potentially
unmeasured confounding factors. Larger studies with longer follow-
up, therefore, are desirable to investigate further the tightness of the
described association between CMR-determined increased ECV and
adverse cardiac events, in particular in subclinical DM patients with
normal cardiac function. Such comprehensive investigations are
clearly needed for a more precise assessment of the incremental
prognostic value of increased ECV and to define ECV thresholds to
optimize cardiac risk prediction in subclinical DM. Yet, defining
ECV thresholds to optimize cardiac risk prediction seems to
remain a challenge as there is a significant overlap in ECV between
DM and non-DM patients in the investigation of Wong et al., as
well as in cardiovascular risk individuals and healthy volunteers.
Another limitation of the current investigation may be seen in the
cross-sectional evaluation of the effects of RAAS blockade on ECV
in DM. Longitudinal follow-up studies evaluating the ECV before
and after RAAS blockade certainly are needed to provide more de-
finitive proof of causality and treatment success. Further, no informa-
tion about the mechanisms of death is provided. Thus, it remains
uncertain how many deaths were truly related to diabetes-
induced CMP or rather to no-cardiac but diabetes-related co-
morbidities. The current study therefore does not allow definite
conclusions to be draw on the association between ECV expansion
and specific cardiac causes of death. In addition, information on
other cardiac outcomes, such as myocardial infarction and coronary
revascularization, related to myocardial ECV expansion in DM would
be desirable.

Overall, the study of Wong et al. represents an important first
step in the identification and characterization of extracellular
matrix expansion with cardiac CMR and T1 mapping (Figure 1),
which carries important diagnostic and prognostic information in
DM. These observations stress the notion of a pathophysiological
link between increased ECV and adverse remodelling and, ultimately,
the transition to clinically manifest diabetic CMP. This CMR-guided
approach to identify increased ECV holds promise ultimately to
allow earlier and more precise identification and characterization
of diabetic CMP, and the assessment and monitoring of the thera-
peutic response in the individual DM patient. However, whether
such image-guided and personalized medical intervention striving
to prevent or delay the initiation and/or progression of left ventricu-
lar remodelling will ultimately manifest in improved clinical outcome
remains to be clinically evaluated.

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References
1. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease:
pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J;
2. Beckman JA, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease:
pathophysiology, clinical consequences, and medical therapy: part II. Eur Heart J;
3. Fromm AM, Scott CG, Chen HH. The development of heart failure in patients with
diabetes mellitus and pre-clinical diastolic dysfunction a population-based study.
Rasio O, Mach F, Golay A, Schindler TH. Improvement in coronary circulatory func-
tion in morbidly obese individuals after gastric bypass-induced weight loss: relation
to alterations in endocannabinoids and adipocytokines. Eur Heart J 2013;in press.
Common carotid artery intima-media thickness is as good as carotid intima-media
thickness of all carotid artery segments in improving prediction of coronary heart
disease risk in the Atherosclerosis Risk in Communities (ARIC) study. Eur Heart J;
2012;33:183–190.
imaging: subclinical atherosclerosis: the memory of lifetime risk factor exposure.
7. Wong TC, Pielker K, Meier CG, Testa SM, Klock AM, Aneizi AA, Shakespeare J,
Kellman P, Shroff SG, Schwartzman DS, Mulukutla SR, Simon MA, Schelbet EB.
A 64-year-old patient with heart failure and ‘chronic liver disease’: looking at the liver, the myocardium or the pericardium?

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A 64-year-old male, with type-2 diabetes and arterial hypertension, was referred to the cardiology outpatient clinic due to breathlessness on moderate exertion. He had been drinking ~40 g/day of alcohol for 20 years. Liver function tests were abnormal (increased AST: 51 U/L, ALT: 73 U/L, gamma GT: 305 U/L, and total bilirubin: 2.23 mg/dL) and the abdominal ultrasonography showed ‘chronic liver disease with mild ascites’. On physical examination, raised jugular venous pulse, wide splitting of S2 on cardiac auscultation, hepatomegaly and lower limb oedema were detected.

Echocardiography was performed showing a non-dilated left ventricle, with no hypertrophy and normal ejection fraction. The figure shows typical echocardiographic signs leading to the final diagnosis including the M-mode of the left ventricle (Panel A), the pulsed-wave Doppler at the level of mitral leaflet tips (Panel B), and the tissue-Doppler of the septal mitral annulus (Panel C). A cardiac CT scan (Panel D) and invasive haemodynamic evaluation (Panel E) were requested for additional diagnostic information.

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