Healthy ageing in females is associated with altered cardiac energetics related to both systolic and diastolic function: a comparison of MRS, cardiac tagging and cine imaging

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Introduction: Cardiac contraction and relaxation requires use of ATP. While it is well-established in normal ageing there is a decline in diastolic function [1], it is unclear whether the ratio of PCr/ATP declines with age [2,3], and we do not know if there is a direct relationship between these two essential components of myocardial function. A direct relationship would imply that the mechanism of age-related cardiac dysfunction is at least in part related to energy consuming processes in the heart. In this preliminary work, we bring together cardiac ^{31}P spectroscopy, cardiac tagging and diastolic function to examine healthy ageing.

Methods: 25 healthy females with normal 12-lead ECG and no previous history of cardiac disease were recruited, covering the age ranges 18-40, 40-60 and over 60 years of age: all subjects were normotensive (< 150 mmHg systolic and < 90 mmHg diastolic). For all subjects, using a Philips 3T Intera Achieva (Best, NL), we acquired (i) cine-MRI to assess morphological parameters, (ii) cardiac tagging to evaluate cardiac strain and torsion and (iii) ^{31}P-MRS to assess myocardial energetics.

MR protocol: (1) Cardiac tagging: Using a 6-channel Philips cardiac array to receive signal, tagged images of the myocardium in the short axis were obtained throughout the cardiac cycle. A multishot turbo-field echo sequence with TFE factor 9 was used (TR/TE/FA/NEX = 4.9/3.1/10°/1, SENSE factor 2, FOV 350x350mm, voxel size 1.37x 1.37mm with an orthogonal grid with tag spacing of 7mm). Two adjacent slices of 10mm thickness were acquired at mid-ventricle with a 2mm gap. *(2) Cardiac morphology:* High resolution, short axis cine-MRI was available for all subjects using methods reported previously [5] to provide measurements of LV mass, blood pool volumes and diastolic parameters. *(3) Cardiac ^{31}P spectroscopy:* a 10cm diameter ^{31}P surface coil (Pulseteq, UK) was used. Subjects were placed in a prone position and moved so their heart was at magnet isocentre. Shimming was performed using a cardiac triggered, breath-held field map [6]. A slice-selective, cardiac gated 1-dimensional chemical shift imaging (1D-CSI) sequence was used with a 7cm slice selective pulse, with spatial pre-saturation of lateral skeletal muscle to avoid spectral contamination. 16 coronal phase-encoding steps were used, each 10mm thick (TR = heart rate, 96 averages, 20 mins). The first spectral line without skeletal muscle contamination was selected. Quantification of phosphocreatine (PCr), the γ resonance of adenosine triphosphate and 2,3-diphosphoglycerate (DPG) was performed using the AMARES time domain fit routine in the jMRUI processing software. After fitting the ATP peak area was corrected for blood contamination by 1/6 of the amplitude of the combined 2,3-DPG peak [7], and the PCr/ATP ratios were calculated and corrected for saturation, with T_1 values of cardiac phosphocreatine and ATP taken from the literature [8]. Flip angle correction was made using a gadolinium-doped 20mM phenyl phosphonic acid phantom at the centre of the coil [9,10].

Analysis of tagging data: The Cardiac Image Modelling package (University of Auckland) was used to analyse the tagging data by aligning a mesh on the tags between the endo- and epi-cardial contours. Circumferential strain and the rotation of the two planes were calculated throughout the cardiac cycle. Torsion between the two planes (taken as the circumferential-longitudinal shear angle) was calculated according to the method in [11] to account for the radius of the ventricle. Statistics (student t test and Pearson correlations) were performed with SPSS 17.0.

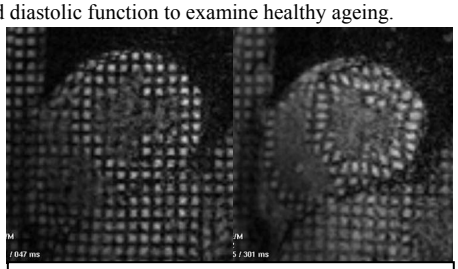

Fig 1 : Tagged images at *(left)* end diastole and *(right)* end systole

Table 1: Subject characteristics and key results

	18-40	*40-60*	*60+*
Ejection fraction (%)	58 ± 5	66 ± 5	60 ± 7
SBP/DBP (mmHg)	118/73	131/85	133/69
LV index (g/m^2)	52.8	52.2	54.1
Peak torsion (degrees)	6.6 ± 2	6.3 ± 2	7.6 ± 2

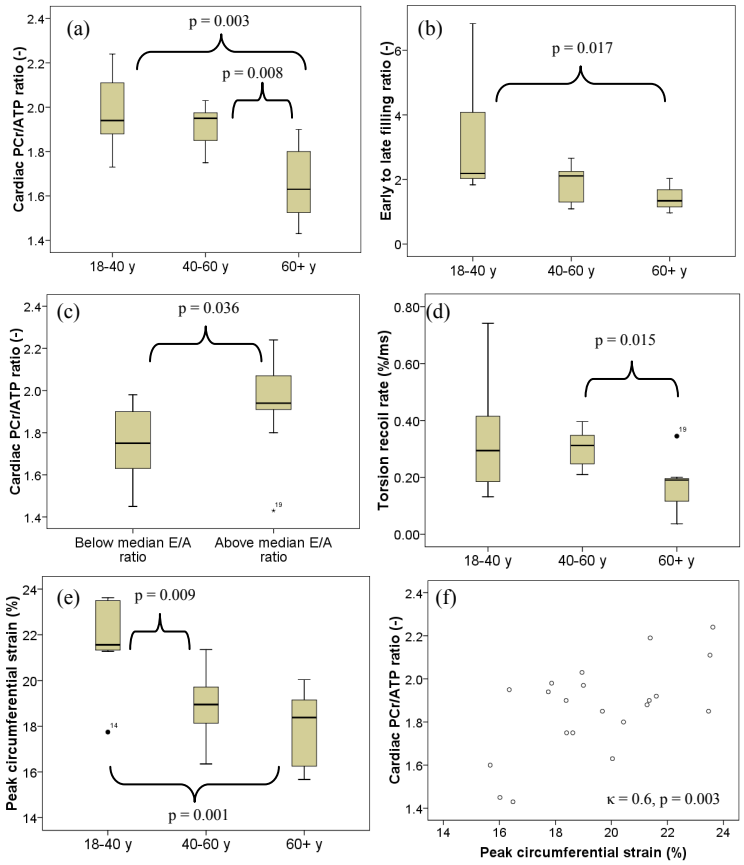

Fig 2: Group results and correlations

Results: Mean ages of the three groups were 31.2 ± 6.2y, 49.9 ± 8.7 y and 61.4 ± 1.6y respectively. LV index (LV mass divided by body surface area to standardise for body size), blood pressure or ejection fraction were similar between the three groups (table 1).

(i) Declining PCr/ATP ratio associated strongly with increasing age (κ = -0.60, p=0.002), which was most noticeable in the oldest group (fig 2a). (ii) The E/A ratio declines with age as expected (κ = -0.62, p = 0.002, fig 2b) consisting of separate significant reduction in early peak flow and a significant increase in late atrial flow: those subjects with below median E/A ratio have significantly lower PCr/ATP ratio (fig 2c) (iii) Importantly, in the context of diastolic filling, there is also a marked decrease in the recoil rate in the older age group, that is the maximum rate of torsion reduction after systole, expressed as % of maximum torsion lost per ms: a negative correlation is found with age (κ = -0.36, p = 0.05). The recoil rate also associates significantly with the E/A ratio (κ = 0.46, p = 0.04) and early filling rate (κ = 0.46, p = 0.04), suggesting a close relationship between the heart's capacity to rapidly dissipate torsion and good diastolic function. (iv) Peak circumferential strain declines with age (κ = 0.68, p <0.0005, fig 2e). Further, peak circumferential strain correlates strongly with cardiac PCr/ATP ratio (κ = 0.6, p = 0.003, fig 2f), associating impaired energetics with lower peak strain. There is a non-significant trend for peak torsion to increase in older age (table 1). These are similar findings to a previous study [4] though with reversed significance between torsion and peak circumferential strain.

Conclusion: This study has correlated phosphorus spectroscopy, cardiac tagging and diastolic function measurements in a female population of age varying from 18-65. The data clearly show that there is a direct relationship between both measurements of systolic and diastolic function and cardiac energetics, suggesting that this is an important mechanism in age-related decline in cardiac function. **Acknowledgements :** Lilian Fairbairn-Smith, Louise Morris, Carol Smith, Jessie Pairman, Katherine Wilton MRC grant G0500020, NIHR Biomedical Research Centre, Alistair Young, University of Auckland **References:** [1] Cacciaputi F *et al. J. Am. Geriatr. Soc.* 40:245 (1992), [2] Schocke MFH *et al. MRI* 2003;21:553, [3] Kostler *et al. MRM* 2006;56:907 [4] Oxenham H *et al. JCMR* 5:421 (2003), [5] Hollingsworth *et al. Proc. ISMRM* 2009;17:707, [6] Schar *et al. Proc. ISMRM* 2002;10:1735, [7] Conway MA *et al. Circulation* 1998;97:1716 [8] Tyler *et al. Proc. ISMRM* 2006;14:3099, [9] Buchli *et al. MRM* 1993;30:552, [10] Haase A *et al. JMR* 1984;56:401, [11] Buchalter *et al. Circulation* 1990;81:1236.