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Normal age-related changes in left ventricular function: Role of afterload and subendocardial dysfunction

Jehill D. Parikh [a,b,1], Kieren G. Hollingsworth [a,b,1], Dorothy Wallace [a,b,1], Andrew M. Blamire [a,b,1], Guy A. MacGowan [c,d,e,*,1]

[a] Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom
[b] Newcastle Magnetic Resonance Centre, Newcastle University, Newcastle upon Tyne, United Kingdom
[c] Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom
[d] Centre for In Vivo Imaging, Newcastle University, Newcastle upon Tyne, United Kingdom
[e] Dept. of Cardiology, Freeman Hospital, Newcastle upon Tyne, United Kingdom

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ABSTRACT

Background: In normal ageing, both vascular and ventricular properties change, and how these affect left ventricular function is not clear.
Methods: 96 subjects (ages 20–79) without cardiovascular disease underwent cardiac magnetic resonance (MR) imaging for measurement of global function, diastolic function (E/A ratio), MR tagging for measurement of torsion to shortening ratio (TSR, ratio of epicardial torsion to endocardial circumferential shortening, with increase in TSR suggesting subendocardial dysfunction relative to the subepicardium), and phase contrast MR imaging measurement of central aortic pulse wave velocity (PWV). The Vicorder device was used to measure carotid to femoral PWV.
Results: Univariate correlations established that the 4 principal age-related changes in the left ventricular function were: 1) diastolic function: E/A ratio ($r: -0.61$, $p < 0.00001$); 2) global systolic function: cardiac output ($r: -0.49$, $p < 0.00001$), 3) structure: end-diastolic volume index ($r: -0.39$, $p < 0.0001$), and 4) systolic strains: TSR ($r: 0.49$, $p < 0.0001$). Multiple linear regression analysis showed that age was the dominant factor in predicting changes in cardiac output and E/A ratio (both $p < 0.01$). Increased TSR was significantly related to reduced cardiac output and end-diastolic volume index ($p < 0.05$ and $p < 0.01$ respectively). Measures of vascular stiffness were not significantly related to any of these variables, but increased effective arterial elastance (afterload) was significantly related to reduced E/A ratio ($p < 0.05$).
Conclusions: In this group of normal ageing subjects, afterload but not vascular stiffness is significantly related to diastolic dysfunction. Increased TSR, suggesting relative subendocardial dysfunction, has a significant role in reductions of cardiac output and end-diastolic volume index.

1. Introduction

To understand how ageing with cardiovascular risk factors can lead to heart failure in the elderly, it is firstly important to understand how normal ageing affects left ventricular function. Vascular stiffening increases from the 3rd decade or earlier in normal subjects [1]. This is thought to affect the heart by enhanced arterial wave reflections creating a greater afterload on the heart [2]. To date, studies showing relationships of vascular ageing to changes in left ventricular systolic and diastolic function have concentrated on community-based subjects, in whom there are significant proportions of conditions such as hypertension and diabetes mellitus that will increase vascular stiffness [3–5]. In normal ageing without cardiovascular disease, the relationships between vascular stiffness may not be as pronounced. A major purpose of this study was therefore to comprehensively study the relationship of normal age-related changes in vascular stiffness and afterload with changes in left ventricular function.

Magnetic resonance imaging can accurately assess changes in left ventricular blood pool volumes with age [6]. Vascular function was assessed by several parameters, each of which has distinguishing features. Pulse wave velocity (PWV) was assessed with the Vicorder device which measures pulse wave velocity from carotid to femoral arteries [7–9]. PWV was also measured with phase contrast MRI (PC MRI), which measures velocity in the descending thoracic aorta (Central MR PWV). Velocities will be lower in the central vessels, so these measures

* Corresponding author at: Dept of Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN, United Kingdom.
E-mail address: guy.macgowan@nuth.nhs.uk (G.A. MacGowan).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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are not identical [10,11]. The augmentation index (AI) measures the late systolic wave reflection that poses an afterload on the left ventricle. Arterial elastance is a measure of afterload that is based on the pressure-volume framework and represents the ratio of end-systolic pressure to stroke volume [12]. Potentially the measures of vascular stiffness and afterload differ in that afterload represents the whole of the ejection time whereas vascular stiffness represents a distinct time in late systole when wave reflections might affect left ventricular function [13].

Torsion, and the ratio of torsion to endocardial circumferential shortening (TSR) are also known to increase with normal ageing [14]. TSR is a measure of the subepicardial influence over the subendocardium, with relative dysfunction in the subendocardium increasing TSR (Fig. 1), though its relevance to changes in left ventricular function are not clear. We determined the relationship of measures of vascular stiffness, afterload and torsion to age-related changes in global systolic and diastolic function.

2. Methods

2.1. Subjects

Ninety-six subjects (41 males, 55 females) aged between 20 and 79 years were recruited into six discrete age bands, with 16 subjects in each decade 20–29, 30–39, 40–49, 50–59, 60–69 and 70–79 years. The subjects were screened with a 12-lead electrocardiogram, fasting lipid profile, and blood pressure measurements. Subjects with hypertension (systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 90 mm Hg), were excluded from the study, as well as any other cardiovascular diagnosis, diabetes mellitus or dialysis-dependent renal failure, or any treatment with antihypertensive therapy. There were 9 patients that were deemed not suitable for the study after attending for a screening visit. These were 2 patients aged 40–49, 1 50–59, 4 60–69 and 2 70–79. The reasons for failing the screening visit: were 7 had BP > 150 systolic or 90 diastolic, 1 patient was on a thiazide diuretic, and 1 patient had musculoskeletal problems making MR imaging problematic. Informed written consent was obtained for all patients, and this study was approved by a UK National Health Service Research Ethics Committee (NRES Committee North East — Newcastle & North Tyneside 1, reference number 12/NE/0057, and ClinicalTrials.Gov identifier NCT01504828). All subjects had measurements of pulse wave velocity by the Vicorder device and the MRI on the same day within 2 h.

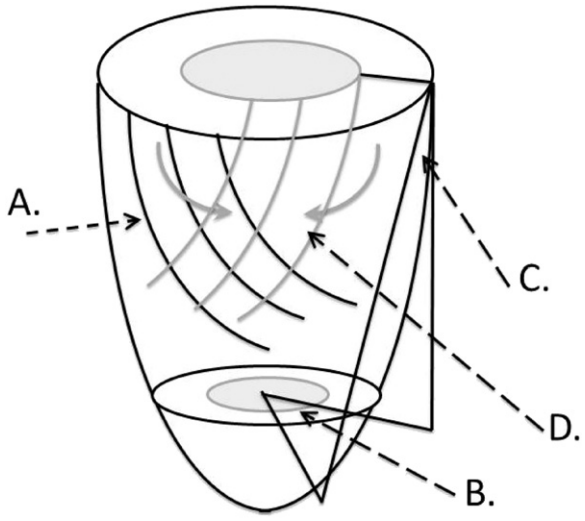

Fig. 1. Illustration of epicardial torsion and endocardial circumferential shortening used in the calculation of the torsion to shortening ratio (TSR) and the relationship to subepicardial and subendocardial fibre orientations. Epicardium is black and endocardium grey. A. Obliquely oriented subepicardial fibres produce rotation of the apex with respect to the base (B.) in a counterclockwise direction when looking from the apex to base, which is quantified in terms of the circumferential-longitudinal shear angle (C.). Epicardial torsion acts on the subendocardium with its greater mechanical advantage due to its larger radius, forcing subendocardial fibre bundles to shorten in a direction at almost 90° away from the subendocardial fibre direction (D.). This subepicardial to subendocardial interaction is quantified as the torsion to shortening ratio (TSR), and an increase in the TSR suggests subendocardial dysfunction relative to the subepicardium.

2.2. Vicorder based measurements of vascular stiffness

The Vicorder device (Skidmore Medical, UK) is an inflatable cuff-based device that simultaneously measures the upstroke of carotid and femoral pulsations to calculate pulse wave velocity, and has been evaluated extensively by comparing with invasive measurements and other tonometric devices [7–9]. The Vicorder measurements were performed by trained research nurses. Patients laid on an examination couch, with the head raised to approximately 30°, so that the skin and muscles over the carotid were relaxed. PWV was measured by a cuff placed over the right carotid and the right thigh. The length between the carotid and femoral arteries was done by measuring the length between the suprasternal notch and the mid-point of the thigh cuff. Other measurements with the Vicorder device were done with a cuff placed on the right upper arm. These included oscillatory blood pressure measurement and using a global transfer function central aortic pressures and AI [15].

2.3. Central MR PWV

A Philips Achieva 3T scanner and a 6 channel receiver array coil were employed to acquire cardiac MRI data as previously described, and validated against the Vicorder measures of PWV [16]. Briefly, phase contrast (PC) MRI flow data were acquired at two slice locations in descending aorta approximately 10 cm apart, using high temporal resolution sequence (repetition time (TR) = 5 ms; echo time (TE) = 2.9 ms; flip angle (FA) = 10°; number of excitations (NEX) = 1; slice thickness = 8 mm, parallel imaging sensitivity encoding (SENSE) factor 2, field of view (FOV) = 300 mm × 225 mm, reconstructed voxel size = 1.17mm^2, velocity encoding (V_{enc}) = 150 cm/s, 44 phases, breath hold duration ~19 s) [17]. The Q-flow analysis package (Philips, ViewForum version 3) was employed for region of interest analysis, to extract time-velocity curves from the PC MRI acquisitions and to estimate precise distance (ΔX) between the two slice locations. The time-velocity curves were then employed to compute transit time (ΔT) using an in-house Matlab based program and determine pulse wave velocity PWV = ΔX/ΔT [17]. Additional scout images were acquired to facilitate positioning of the PC MR acquisitions and to ensure that the slices were positioned perpendicular to aorta at both locations.

2.4. Cardiac cine imaging

Details of cardiac cine imaging have been previously reported in detail [18]. Briefly, these include short-axis balanced steady-state free precession images which were acquired covering the left ventricle (FOV = 350 mm, TR/TE = 3.7/1.9 ms, acceleration factor 17, FA 40°, slice thickness 8 mm, 0 mm gap, 14 slices, 25 phases, resolution 1.37 mm). Image analysis was performed using the cardiac analysis package of the ViewForum workstation (Philips) to obtain measures of systolic and diastolic function as previously detailed. The following hemodynamic parameters were derived: effective arterial elastance (Ea = end-systolic pressure (systolic blood pressure × 0.9) / stroke volume normalised to body surface area), end-systolic elastance (Ees = end-systolic pressure / end-systolic volume normalised to body surface area), and ventricular-arterial coupling by the ratio of Ees/Ea. Assessment of diastolic function from cine images was performed by calculating the ratio of peak early and late left ventricular filling rates (E/A ratio), and the early filling percentage was calculated as the volume increase from end-systole to the midpoint divided by the stroke volume and multiplied by 100. The eccentricity ratio (left ventricular mass in g over the end-diastolic volume in ml) was calculated as a measure of concentric remodelling. Longitudinal shortening was determined in the four-chamber view by determining the perpendicular distance from the plane of the mitral valve to the apex in systole and diastole. The myocardial wall thickness at systole and diastole was determined at the same level as the cardiac tagging, and radial thickening was calculated.

2.5. Cardiac tagging and regional strains

Tagged short axis images were obtained at the same session. A turbo-field echo sequence with acceleration factor 9 was employed (TR/TE/FA/NEX = 4.9/3.1/10/1, parallel imaging SENSE factor 2, FOV 350 × 350 mm, voxel size 1.37 × 1.37 mm, tag spacing of 7 mm) [18]. 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 epicardial contours, and is described in detail elsewhere [14,18]. The epicardial torsion between the two planes (taken as the circumferential-longitudinal shear angle defined on the epicardial surface) was calculated [19]. Circumferential strain was measured for both the whole myocardial wall and the endocardial third of the wall thickness. The ratio of the peak torsion (in radians) [20], and the peak circumferential strain in the endocardial third of the myocardium (subendocardium, %) was derived and is referred to as the torsion to shortening ratio, TSR (Fig. 1) [18,20,21]. The recoil of torsion in early diastole is a measure of active relaxation [22] was expressed as the torsion recoil rate (which is normalised for peak torsion, %/ms).

2.6. Data and statistical analysis

The strategy was to determine how measures of vascular function and afterload (MR and Vicorder PWV, AI, and effective arterial elastance) changed with age, and identify which parameters of systolic, diastolic function and strains were most strongly related to age by the Pearson correlation method. We then used the Bonferroni correction procedure for multiple comparisons when comparing measures of vascular stiffness with left ventricular function. Those variables that were significantly related with this univariate