Contrast enhanced-cardiovascular magnetic resonance imaging in patients with pulmonary hypertension

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Received 14 January 2005; revised 15 April 2005; accepted 22 April 2005; online publish-ahead-of-print 17 May 2005

Aims To determine the presence and extent of delayed contrast enhancement (DCE) in patients with pulmonary hypertension (PHT) using contrast enhanced-cardiovascular magnetic resonance imaging (ce-CMR).

Methods and results Twenty-five patients with PHT underwent ce-CMR and right heart catheterization. Right ventricular (RV) and left ventricular (LV) volumes, ejection fraction, mass, and DCE mass were determined with ce-CMR. Mean pulmonary artery pressure (mean PAP) averaged 43 (12) mmHg and cardiac output 4.3 (1.2) L/min. DCE was demonstrated in 23 out of 25 patients. DCE was confined to the RV insertion points (RVIPs) in seven patients and extended into the interventricular septum (IVS) in the remaining 16 patients. In these 16 patients, septal contrast enhancement was associated with IVS bowing. The extent of contrast enhancement correlated positively with RV end-diastolic volume/body surface area, RV mass, mean PAP, and pulmonary vascular resistance and correlated inversely with RV ejection fraction.

Conclusion DCE was present within the RVIPs and IVS of most patients with PHT studied. Extent of DCE correlated with RV function and pulmonary haemodynamics. DCE was associated with IVS bowing and may provide a novel marker for occult septal abnormalities directly relating to the haemodynamic stress experienced by these patients.

KEYWORDS
Pulmonary hypertension; Cardiovascular magnetic resonance imaging; Right ventricle; Gadolinium

Introduction
Pulmonary hypertension (PHT) results from a variety of conditions which affect the pulmonary circulation. Causes of PHT occurring on the arterial side of the pulmonary circulation include pulmonary arterial hypertension (PAH) and chronic thrombo-embolic PHT (CTEPH). These conditions, which account for the majority of patients referred to tertiary PHT centres, are characterized by elevated pulmonary vascular resistance (PVR), rising pulmonary arterial pressure (PAP), and, ultimately, right ventricular (RV) failure. Although recent therapeutic advance has improved the short-to-medium term outlook for such patients, early death due to progressive RV failure remains inevitable in many.¹,²

Greater understanding of the pathophysiological processes involved in the evolution of RV failure in PHT may facilitate better targeting of the treatments currently available and allow physicians monitoring patients with PHT to anticipate an individual's decline and the need for therapeutic intervention or referral for transplant.

Cardiovascular magnetic resonance (CMR) imaging is widely recognized as an accurate and reproducible means of measuring RV volume,³ RV mass,⁴ and pulmonary arterial flow⁵,⁶ in patients with PHT. Contrast enhanced-CMR (ce-CMR) imaging has the potential to provide additional information regarding the mechanisms of RV failure in this condition. Delayed contrast enhancement (DCE) is well established as a marker of myocardial abnormalities in a variety of illnesses. Myocardial infarction, fibrosis, and inflammation have all been shown to result in DCE using gadolinium as an intravenous (iv) CMR contrast agent.⁷–⁹ This technique has yet to be utilized to interrogate the RV myocardium in PHT.

We hypothesized that
(i) myocardial abnormalities might exist in patients with PAH and CTEPH;
(ii) ce-CMR could identify these abnormalities;
(iii) the extent of any contrast enhancement seen would relate to the severity of haemodynamic disturbance;
(iv) the pattern of DCE would provide some insight into the pathophysiological processes underlying RV failure in this context.

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Methods

Patients

We performed a cross-sectional study of 25 consecutive patients attending for diagnostic assessment at the Scottish Pulmonary Vascular Unit in Glasgow, UK. No selection criteria were applied to the study population other than an underlying diagnosis of either PAH or CTEPH, reached by conventional diagnostic methods. All 25 patients underwent diagnostic right heart catheterization and ce-CMR; the final diagnoses reached in these patients are summarized in Table 1.

Twelve control subjects, with no history of any cardiorespiratory disease, underwent CMR imaging, without contrast enhancement, to provide local control values for ventricular dimensions and function. The control subjects were staff of the Western Infirmary, Glasgow, UK. Controls were approached individually and were well matched for age, sex, and systemic blood pressure to the PHT cohort. All subjects gave informed written consent to a study protocol that had been approved by the institutional review committee. Demographic data for the study population are summarized in Table 2.

At the time of the study, no patient had received any specific treatment (other than anticoagulation with warfarin) for PHT. None of the patients had a previous diagnosis of ischaemic heart disease (IHD) or a history of previous myocardial infarction.

Twenty-three out of 25 patients underwent ce-CMR within 24 h of right heart catheterization. The other two patients underwent ce-CMR within 4 days of invasive assessment.

CMR image acquisition

ce-CMR imaging was performed on a 1.5 T MRI scanner (Sonata Magnetom, Siemens, Germany) using a protocol that has been described in detail elsewhere. An identical CMR protocol was employed in the assessment of control subjects with the omission of contrast enhanced imaging. Fast imaging at steady state precession (SSFP) cines (TrueFISP by Siemens) were utilized throughout for the acquisition of contrast enhanced imaging. Fast imaging at steady state precession is particularly prone to artefacts caused by cardiac or chest wall movement. Only areas of contrast enhancement that persisted on these 'swapped phase' images were included in subsequent quantification of areas of contrast enhancement. Any areas of contrast enhancement were also compared directly with the pre-contrast cine image corresponding with the contrast enhanced image in terms of both slice position and time frame to further exclude artefact, especially that caused by partial volume effect and blood pool residing behind trabeculated myocardium.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Final diagnoses reached in 25 patients with PHT</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>Number of patients</td>
</tr>
<tr>
<td>PAH</td>
<td>19</td>
</tr>
<tr>
<td>Idiopathic PAH</td>
<td>12</td>
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<tr>
<td>Associated PAH</td>
<td>7</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>5</td>
</tr>
<tr>
<td>Repaired congenital left-to-right shunt</td>
<td>2</td>
</tr>
<tr>
<td>CTEPH</td>
<td>6</td>
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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Group demographics for 25 patients with PHT and 12 control subjects</th>
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<tbody>
<tr>
<td>PHT ( (n = 25) )</td>
<td>Controls ( (n = 12) )</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 (+ 14)</td>
</tr>
<tr>
<td>Sex ( (%: %) )</td>
<td>17:8</td>
</tr>
<tr>
<td>Systemic BP (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>125 (+ 17)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>78 (+ 9)</td>
</tr>
<tr>
<td>Mean BP</td>
<td>96 (+ 12)</td>
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</table>

Values are mean (+ SD) unless stated.

All MR images were analysed by a single operator (K.G.B.) using the Argus analysis software (Siemens, Erlangen, Germany). Individual scans were coded by number and analysed in batches by K.G.B. who was blinded to the identity and haemodynamic results of any given subject at the time of analysis. RV and LV volumes [RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV)] were determined by manual planimetry of selected SA images, as described previously. Particular methodological points of note included the deliberate inclusion of trabeculations and papillary muscles in all analyses, as discussed by previous authors. Definition of the most basal ventricular slice to be included in the right and to a lesser extent in the LV analysis has proved difficult in the past. In an attempt to overcome this problem, the most basal ventricular image (RV or LV), once identified visually, was cross-referenced with the horizontal long axis view before its inclusion in the final analysis to ensure this slice was indeed ventricular and not atrial. Right and left ventricular stroke volume (RVSV and LVSV), ejection fraction (RVEF and LVEF), and mass (RW and LW) were determined as previously described. RV mass was determined as RV free wall mass, the interventricular septum (IVS) was considered part of the LV. RW index (RMI) was determined as RMI/LVM. For correlation analyses, RV volumes were corrected for body surface area (BSA).

Contrast enhanced-CMR image analysis

Areas of contrast enhancement were first identified visually. Mean signal intensities (+ SD) for areas of contrast enhancement and for an adjacent reference area of non-enhancing myocardium were our own study, or are of particular importance, include the use of a traditional left ventricle (LV) short axis (SA) cine stack for the acquisition of both RV and LV images. Pre-contrast imaging parameters, which were standardized for all subjects, included: TR/TE/flip angle/voxel size/FoV = 3.14 ms/1.6 ms/60/2.2 x 1.3 x 8.0 mm/340 mm. Eight millimetre imaging slices were used with a 2 mm interslice gap. Gadolinium-diethylene triaminopentaacetic acid (Gd-DTPA) was employed as an iv contrast agent and was administered at a dose of 0.2 mmol/kg. After a 10 min interval, a second stack of SA images, using copied slice positions, was acquired using a contrast sensitive segmented inversion recovery technique. [Implemented by Siemens as an inversion recovery Turbo FLASH (fast low angle shot)]. Again standardized scan settings were used for the contrast enhanced imaging in all subjects and specific parameters included TR/TE/flip angle/voxel size/FoV number of segments = 11.6 ms/4.3 ms/20/2.2 x 1.3 x 8.0 mm/23. The inversion time for the TurboFLASH sequence was optimized on an individual patient basis. Successful nulling of normal myocardium was deemed to have been achieved once the LV myocardium appeared black and homogenous. Generally speaking, an inversion time between 240 and 280 ms was required to achieve this. Artefact on the contrast enhanced images was excluded by the acquisition of 'swapped phase' images through slice planes which appeared to demonstrate intramyocardial contrast enhancement. This technique involves the 'swapping' of the phase-encoding and frequency-encoding directions, as the phase-encoding direction is particularly prone to artefacts caused by cardiac or chest wall movement. Only areas of contrast enhancement that persisted on these 'swapped phase' images were included in subsequent quantification of areas of contrast enhancement. Any areas of contrast enhancement were also compared directly with the pre-contrast cine image corresponding with the contrast enhanced image in terms of both slice position and time frame to further exclude artefact, especially that caused by partial volume effect and blood pool residing behind trabeculated myocardium.
then determined using the Siemens Mean Curve software (Siemens, Erlangen, Germany). DCE was defined as an area of visually identified contrast enhancement with a mean signal intensity (SI) that was more than two standard deviations higher than the mean SI of an adjacent area of reference myocardium, which although nulled had a mean SI significantly above zero. DCE volume was determined by planimetry of any areas of contrast enhancement meeting these criteria. DCE mass was calculated by multiplying DCE volume by myocardial density (1.05 g/cm³) and is used in the subsequent correlations and discussion as the absolute measured value of contrast enhancing tissue seen.

Although DCE has previously been described within the RV insertion points (RVIPs) in conditions such as hypertrophic cardiomyopathy (HCM), no universally accepted definition of their extent has been agreed for the purposes of CMR imaging. We have therefore defined the boundaries of the RVIPs arbitrarily employing a method described in detail and illustrated in Figure 1.

**Cardiac catheterization**

Right heart catheterization was performed using techniques described elsewhere. Cardiac output (CO) was determined by thermodilution, allowing the determination of PVR by mean PAP—pulmonary artery occlusion pressure (PAOP)/CO. We were unable to calculate PVR in one patient due to a technically unsatisfactory PAOP measurement.

Chronic pulmonary thrombo-embolism was considered as a cause of PHT in all subjects studied. Isotope perfusion lung scanning and CT pulmonary angiography were performed in all and if any suspicion remained regarding the presence of significant thromboembolic disease, selective pulmonary angiography was performed in the catheterization laboratory.

**Statistical analysis**

A power calculation, aiming for a power of 90% and assuming a Type I error of 0.05, suggested that only four patients with PHT and four controls were needed to demonstrate significant differences in contrast enhancement if present. This calculation employed mean values and standard deviations from a previous study of contrast enhanced-CMR in patients with myocardial infarction [in which mean (SD) SI of contrast enhanced regions was 330% (±195%) of that of reference areas].

For all variables, a normal distribution was verified using histograms and Kolmogorov–Smirnov tests. For demographic, haemodynamic, and ce-CMR variables, mean values ± one standard deviation (±SD) were calculated. Correlations between normally distributed CMR and haemodynamic variables were tested by Pearson’s method and correlation involving non-normally distributed variables was assessed using Spearman’s rho test; all tests were two-tailed. Mean SI values for areas of DCE vs. reference areas were compared by a paired t-test. An independent sample (unpaired) t-test (equal variances not assumed) was used to compare RV and LV measurements acquired in the 25 PHT patients studied with (i) the 12 control subjects assessed in our own laboratory and (ii) previously published normal mean values. This method was also used to compare differences in mean DCE mass between subgroups of patients with different aetiologies of PHT and gender and to compare systemic blood pressure measurements in PHT patients with controls. A significance level of 5% was used in all tests. No adjustment was made to P-values to account for multiple testing. All statistical analyses were performed using SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA). All values in the subsequent results and discussion sections are presented as mean (±1SD) unless otherwise stated.

**Results**

**Right heart catheterization**

Invasive measurements acquired in the PHT patients are summarized in Table 3.

**Pre-contrast CMR imaging**

Ventricular dimensions and systolic function of PHT patients and control subjects are presented in Table 4.

In summary, LV measurements within PHT patients were within previously published normal limits; however, LVEDV and LVSV were significantly lower in the PHT cohort when compared with local controls. Within the control population, both LV and RV measurements were within previously published normal limits.

In PHT patients, RV volumes and RV mass were significantly increased, and RVEF significantly depressed in

<table>
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<tr>
<th>Table 3</th>
<th>Results of right heart catheterization in 25 patients with PHT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (±SD)</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>72 (±20)</td>
</tr>
<tr>
<td>Systolic PAP</td>
<td>23 (±9)</td>
</tr>
<tr>
<td>Diastolic PAP</td>
<td>43 (±12)</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>4.3 (±1.2)</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>9 (±5)</td>
</tr>
<tr>
<td>PVR (mmHg/L/min)</td>
<td>7 (±5)</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>66 (±8)</td>
</tr>
</tbody>
</table>

PA Oxygen saturation (%)
Table 4 Ventricular dimensions and function by cardiac magnetic resonance imaging in patients with PHT and control subjects

<table>
<thead>
<tr>
<th></th>
<th>PHT (n = 25)</th>
<th>Controls (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVa (mL)</td>
<td>179 (± 60)</td>
<td>128 (± 46)</td>
<td>0.009</td>
</tr>
<tr>
<td>ESVa (mL)</td>
<td>104 (± 58)</td>
<td>45 (± 22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>75 (± 27)</td>
<td>83 (± 29)</td>
<td>0.38</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>45 (± 17)</td>
<td>65 (± 7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mass (g)</td>
<td>86 (± 34)</td>
<td>48 (± 18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV mass index</td>
<td>0.88 (± 0.25)</td>
<td>0.41 (± 0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVb (mL)</td>
<td>90 (± 25)</td>
<td>116 (± 36)</td>
<td>0.01</td>
</tr>
<tr>
<td>ESVb (mL)</td>
<td>29 (± 17)</td>
<td>31 (± 14)</td>
<td>0.6</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>63 (± 17)</td>
<td>85 (± 24)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>70 (± 11)</td>
<td>74 (± 7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Mass (g)</td>
<td>97 (± 27)</td>
<td>120 (± 51)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Values are mean (±SD) unless stated.
*EDV, end-diastolic volume.
*ESV, End-systolic volume.

Discussion

The aim of the current study was to determine whether we could detect myocardial abnormalities in patients with PHT using ce-CMR imaging. In addition, we sought to identify any relationship that might exist between the extent of contrast enhancement and pulmonary haemodynamics and to explore potential mechanisms of DCE in these patients.

DCE was demonstrated in the vast majority of patients in our study (23 out of 25 subjects). The two subjects in whom DCE was not demonstrated both had low pulmonary artery pressures (PAPs) at invasive assessment (mean PAP 30 and 34 mmHg, respectively) and normal RV anatomy and function at CMR (RV ejection fractions 68% and 71%, respectively). All areas of DCE observed in our study were located within the mid-wall of the ventricular myocardium at either the RVIPs in isolation, in seven patients, or within both the RVIPs and the IVS in the remaining 16 patients.

In our study, DCE mass correlated with various haemodynamic variables. Septal contrast enhancement was particularly associated with the presence of IVS bowing;\textsuperscript{16} in all 16 patients in whom septal contrast enhancement was demonstrated, bowing of the IVS was also seen. Only one patient demonstrated IVS bowing without significant septal contrast enhancement (in this subject, contrast enhancement was present but was confined to the RVIPs).

There were no significant differences in DCE mass in patients of different genders or different aetiologies. However, the numbers of patients in these subgroups were small making it difficult to draw significant conclusions from these results.

Potential mechanisms of contrast enhancement

The physiological mechanism(s) responsible for the contrast enhancement seen in our study are unknown. In general, DCE is thought to result from delayed clearance of gadolinium from a relatively expanded extracellular volume within fibrotic or necrotic myocardial compartments.\textsuperscript{19,20}

Potential biological mechanisms for the contrast enhancement seen in our study are explored below.

Myocardial ischaemia

The exclusive and consistent mid-wall contrast enhancement pattern demonstrated in our study is not typical of ischaemic injury. DCE in acute and chronic myocardial infarction characteristically involves the sub-endocardium and extends tranmurally depending on the size of the infarct.\textsuperscript{7,21} In addition, previous authors have found no evidence of reversible myocardial ischaemia within either the RVIPs or the IVS using stress myocardial scintigraphy in patients with PHT.\textsuperscript{22}
Myocardial fibrosis

The mid-wall contrast enhancement pattern we report appears most similar to that recently described in several studies of patients with HCM using ce-CMR. These studies have demonstrated similar contrast enhancement to that seen in our own study within both the RVIPs and the other focal areas throughout the heart, including the IVS. Contrast enhancing foci in HCM have recently been shown to correlate histologically with areas of increased myocardial collagen. Although autopsy studies of the hearts of patients with HCM had, in the past, demonstrated gross muscle fibre disarray and destruction of the circumferential, mid-wall component of the ventricular myocardium within the RVIPs, it is only since the publication of the more recent CMR studies referenced earlier that this distribution of fibrosis has become recognized as the pattern typical of HCM.

Despite an extensive review of the literature we have been unable to find any similar autopsy studies which describe the histopathological appearances seen within the RVIPs and IVS of human subjects with PHT. This makes any speculation that similar mechanisms of DCE might exist in patients with PHT uncertain.

Elevated RV afterload

One possible precipitant for myocardial abnormalities in the setting of PHT is elevated RV afterload. DCE mass in our study correlated positively with RV mass and RVMI; both variables which have been associated with the degree of RV hypertrophy present in patients with PHT. However, pure afterload-induced myocardial hypertrophy seems an unlikely cause of the fibrosis suggested by the contrast enhancement seen in our study. Such a global insult to the RV myocardium cannot, in our opinion, explain the consistent, exclusive deposition of contrast enhancement within the RVIPs and the IVS.

The localized nature of the contrast enhancement pattern demonstrated in our study therefore suggests that there is an additional factor precipitating what appears most likely to be fibrotic change within the areas described.

Mechanical wall stress

The RVIPs are regions of a particular mechanical stress, even under normal physiological conditions. In severe PHT, these mechanical stresses are amplified as elevation of RV chamber pressures results in the generation of a physiologically abnormal leftward trans-septal pressure gradient. This gradient is manifested physiologically as the paradoxical, leftward displacement of the IVS seen during early LV diastole (i.e. late RV systole) in a proportion of patients with PHT (Figure 4). It is of note that in our study, all 16 patients in whom there was evidence of septal contrast enhancement also showed clear evidence of IVS bowing.

Animal studies have, in addition, shown that the middle, circumferential layer of the LV myocardium, which by conventional CMR terminology includes the areas identified within the RVIPs and IVS in our own study, is subject to maximal hoop stress (defined as force generated per unit...
area of myocardium) during the course of normal ventricular contraction.27

In a rodent model of hypobaric–hypoxic PHT, the RVIPs (within 3 days of hypoxia) and later the IVS were also identified by McKenzie et al.28 as the earliest sites of immuno-reactive-atrial natriuretic peptide expression and so proposed as the areas of ventricular myocardium subject to the earliest and most intense increases in mechanical wall stress as a result of developing PHT and rising RV chamber pressures.28

Summary of potential mechanisms of DCE

It is clear from the aforementioned discussion that, at present, we can only speculate upon the nature of the physiological processes responsible for the contrast enhancement pattern demonstrated in our study. However, it appears most likely from the available data that these areas represent myocardial fibrosis within the mid-wall, circumferential muscle compartment of the RVIPs and IVS which result in DCE via abnormalities of contrast kinetics analogous to those recently described in HCM.24 Elevated mechanical wall stress within these areas appears a likely precipitant of these focal myocardial abnormalities.

However, definitive proof of the cellular processes underlying contrast enhancement in PHT will require correlation between areas of DCE at CMR and autopsy specimens from patients with this condition.

Additional findings

In keeping with previous CMR studies of patients with PHT, we found evidence of RV dilatation, RV hypertrophy, and RV systolic dysfunction.3,4,18 LVEDV and LVSV were diminished in our study in PHT patients in comparison with the controls, but were still within previously published normal ranges. Similar relative abnormalities within the LV have been reported in previous CMR studies of patients with PHT,18 although an explanation for these left-sided structural changes remains elusive.
Study limitations

The work we have reported here involves relatively small numbers of patients, this in part reflects the relatively low prevalence of PHT in the general population. The hypothesis we have proposed to explain the DCE observed in our study remains a speculation pending further investigation. None of the patients in our study had undergone coronary angiography to formally exclude IHD which is an important cause of DCE. However, the contrast enhancement pattern seen in our study was not suggestive of ischaemic myocyte injury and a diagnosis of IHD was not considered likely in any patient studied based on the presenting clinical picture.

Clinical implications

Contrast enhanced-CMR imaging provides a novel method of identifying and quantifying myocardial abnormalities in patients with PHT, abnormalities which have thus far gone undetected. Our study, in combination with the work of others,18,26,29 emphasizes the importance of IVS dysfunction in the evolution of RV failure in PHT.

Given the correlations of DCE mass with existing markers of disease severity in PHT, this measure may prove useful in the prognostic classification of patients presenting with PAH or CTEPH.

Acknowledgements

Chest, Heart & Stroke Scotland, Edinburgh, UK and the British Heart Foundation, London, UK are acknowledged for their support.

References