The Role of Cardiovascular Magnetic Resonance as a Gatekeeper to Invasive Coronary Angiography in Patients Presenting with Heart Failure of Unknown Etiology

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Abstract

Background: In patients presenting with new onset heart failure (HF) of unclear etiology the role of coronary angiography (CA) is unclear. CA has conventionally been performed to differentiate underlying coronary artery disease from dilated cardiomyopathy, but it is associated with a risk of complications and may not detect an ischemic etiology due to arterial recanalization or an embolic episode. In this study, we assessed the diagnostic accuracy of a cardiovascular magnetic resonance (CMR) protocol incorporating late gadolinium and magnetic resonance coronary angiography as a non-invasive gatekeeper to CA in determining the etiology of HF in this subset of patients.

Methods and Results: 120 consecutive patients underwent CMR and CA. The etiology was ascribed by a consensus panel who utilized the results of the CMR scans. Similarly, a separate consensus group ascribed an underlying etiology by using the results of CA. The diagnostic accuracy of both these strategies was compared against a "gold-standard" panel who made a definitive judgment by reviewing all clinical data. The study was powered to show non-inferiority between the two techniques. LGE-CMR had a sensitivity of 100%, a specificity of 96% and a diagnostic accuracy of 97% which was equivalent to CA (sensitivity of 93%, specificity of 96% and a diagnostic accuracy of 95%). Using LGE-CMR as a gatekeeper to CA was also found to be a cheaper diagnostic strategy in a decision tree model (£974 vs £1321, p=0.001).

Conclusions: LGE-CMR is a safe, clinically effective and economical gatekeeper to CA in patients presenting with HF of uncertain etiology.

Key Words: gadolinium, magnetic resonance imaging, heart diseases, cardiomyopathy

Introduction

Heart failure (HF) is a common disorder associated with a significant morbidity, mortality and financial burden to healthcare services. The most common underlying cause is coronary artery disease (CAD), accounting for over half of all cases, followed by non-ischemic dilated cardiomyopathy (DCM).[1] Identification of the etiology is important as management of the underlying condition differs; treatment of CAD may require revascularisation and secondary prevention measures such as aspirin and statins, whereas pharmacotherapy remains the mainstay of treatment in DCM. In addition, an etiology of CAD portends a worse prognosis.[2] Accordingly, current guidelines recommend a thorough clinical assessment utilising a careful history, physical examination coupled with laboratory investigations, electrocardiography and echocardiography to try and ascertain the underlying cause and severity of HF.[3] The same guidelines recommend invasive x-ray coronary angiography (CA) in any patients presenting with chest pain or significant ischemia unless the patient is not eligible for revascularization of any kind.

The situation is less clear in those patients who do not present with chest pain and in whom coronary artery disease has not been excluded by means of CA. In patients with diabetes mellitus where ischemia may be silent or in young patients who may have coronary anomalies, CA may be justifiable. However, in older patients with HF but no angina there is no data to suggest that revascularization would improve clinical outcome.[4] Any revascularization performed would be in the hope of improved symptoms as a result of augmented ventricular function. Whilst generally safe and providing hemodynamic data in addition to coronary imaging, the invasive nature of CA carries an inherent morbidity and

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mortality risk.[5] There are also issues of radiation burden, patient discomfort and significant cost. Whilst angiography is often regarded as the gold-standard, what is also now clear is that this investigation alone may not be sufficient to make the correct diagnosis as several transplant and post-mortem studies have shown that CA can misdiagnose the etiology of HF.[6, 7]

We have previously demonstrated that late gadolinium enhanced cardiovascular magnetic resonance (LGE-CMR) may have a role in excluding coronary artery disease as the underlying cause of HF. The pattern of late enhancement seen on LGE-CMR differs in patients with HF due to DCM and CAD. A subendocardial pattern of late enhancement is seen in patients with CAD whereas the majority of patients with DCM have either no late enhancement or a patchy midwall pattern that is not related to the territory of a coronary artery.[8] In addition, other groups have provided data to suggest that magnetic resonance coronary angiography (MRCA) can robustly exclude disease of either the left main coronary artery or proximal three-vessel disease with 100% sensitivity and 100% negative predictive value.[9] We therefore hypothesized that in patients presenting with recent onset HF of uncertain etiology with no obvious ischemic basis, LGE-CMR was a non-invasive, safe and cost-effective alternative to CA and could therefore act as a gatekeeper.

Methods

Patient Population

Patients with recently-diagnosed HF (symptom onset < 6 months prior to enrollment, n=124) were prospectively recruited between July 2004 and August 2006 from consecutive referrals seen at 6 HF clinics in south-east England. All patients had a diagnosis of HF with reduced LVEF based on standard criteria [3, 10] All patients were clinically stable in NYHA I-III HF and were aged 35 or older and were scheduled to undergo CA as part of their clinical work-up for HF. Exclusion criteria for the study included any prior history, ECG or biochemical evidence of CAD. Patients with chest pain or significant valvular disease were also not enrolled. In addition, as the scanning protocol involved MRCA, patients with atrial fibrillation were also excluded as the MRCA sequences utilized perform poorly in the context of a highly variable R-R interval. Finally, all patients with standard contraindications to CMR were also excluded. The recruited patients therefore had HF of uncertain etiology with no clinical evidence of CAD and were in sinus rhythm.

On recruitment, patients underwent CMR with both myocardial LGE and MRCA. Patients also underwent CA as part of their standard clinical investigation. All patients were recruited prior to undergoing CA and none were denied a CMR scan as a consequence of the CA findings in cases where CA was performed prior to LGE-CMR. The project was approved by the local institutional Ethics committee. All participants gave written informed consent.

Cardiovascular Magnetic Resonance

Cine CMR (Siemens Sonata 1.5T [n=42] and Siemens Avanto [n=78]) was performed using steady-state, free precession breath-hold cines (TE [Echo time]/TR [Repetition time]

1.6/3.2ms, flip angle 60°) in long-axis planes and sequential contiguous 7mm short-axis slices (3mm gap) from the atrioventricular ring to the apex. LGE images were acquired 10 minutes after intravenous gadolinium-DTPA (Schering; 0.1 mmol/kg) in identical short-axis (SA) planes using an inversion-recovery gradient echo sequence. Inversion times were adjusted to null normal myocardium (typically 320 to 440 ms; pixel size 1.7 x 1.4mm). In all patients, imaging was repeated for each SA image in 2 separate phase encoding directions to exclude artifact. LGE was only deemed to be present, when the area of signal enhancement could be seen in both phase-swapped images and in a cross-cut long axis image.

MRCA was performed in all patients. We used using a free-breathing navigator based fat-suppressed balanced steady state free precession sequence (SSFP) (TE = 1.47ms, TR = 3.5ms). Phase ordering with automatic window selection (PAWS)[11] was implemented to maximize the respiratory efficiency. For the left main (LMS), left anterior descending (LAD), and left circumflex coronary arteries (LCx), a 3-dimensional volume was imaged using a three-point planscan tool with the centre of the volume focussed on the left main coronary artery. Changes in the antero-posterior and left-right angulation by 5 degrees were made to ensure maximal coverage of the proximal LAD and LCx. The right coronary artery (RCA) was similarly imaged with the aid of the three-point planscan tool. Each volume consisted of 8 x 3mm slices, reconstructed to 16 x 1.5mm slices. A field of view of 300mm x 300mm with a 320 x 320 matrix yielded an in-plane pixel size of 0.9mm x 0.9mm. A partial Fourier factor of 6/8 was implemented in the in-plane phase encoding direction and 25% over-sampling was performed in the through-plane phase encoding direction. Imaging was performed during the mid-diastolic rest period, the duration and onset of which were determined from

viewing a four-chamber cine acquisition.[12] The number of phase encode steps acquired per cardiac cycle was dependent on the duration of this rest period and varied from 20 – 40, resulting in an acquisition window of 70 – 140ms and an acquisition duration ranging from 60 – 120 cardiac cycles (assuming 100% respiratory efficiency).

CMR image analysis

Ventricular volumes and function were measured for the left ventricle using standard techniques,[13] and analyzed using semi-automated software (CMRtools, Cardiovascular Imaging Solutions, London, UK). The presence of late enhancement was predefined as regions with an increase in signal intensity of greater than 2SD of remote normal myocardium. Coronary stenosis on MR angiography was predefined as >50% in any of the major epicardial vessels.

Assessment of Etiology

This was assessed by three independent consensus groups: 1) A CMR arm; 2) A conventional X-ray angiogram arm; and 3) A 'gold-standard' group had access to and reviewed all clinical and imaging data.

CMR Arm: For analysis of the CMR scans for etiology of HF, a consensus group of 3 expert cardiologists reviewed the CMR scans using a pre-defined algorithm (figure 1). The CMR consensus group was presented with the patient's clinical history including risk factors for coronary artery disease. They were blinded to the X-Ray angiography data. All data were anonymized. The cine and LGE sequences were presented. Cine imaging was carefully

analyzed for regional and global hypokinesia and correlated with late gadolinium images. If subendocardial LGE was present, the cardiologists were directed to recommend proceeding to CA with the view that there was evidence of underlying CAD due to evidence for prior myocardial infarction. In the absence of subendocardial LGE (ie either no LGE, or presence of midwall LGE), the MRCA images were reviewed. If the MRCA images revealed LMS or severe proximal 3 vessel disease, the Cardiologists were also directed to recommend proceeding to CA to definitively exclude CAD as the underlying etiology. In the absence of both subendocardial LGE and LMS/proximal 3 vessel disease on MRCA, a diagnosis of DCM was ascribed by the consensus panel with the implication that CA was not required for further evaluation of the underlying etiology.

Conventional X-Ray Angiography Arm: A separate consensus group of 3 experienced cardiologists with expertise in coronary intervention was presented with the clinical history and the CA images (including left ventriculograms) in an anonymized format. These physicians were blinded to the CMR data, and all data were anonymized. The cardiologists were asked to independently ascribe an underlying etiology for the HF using a structure based on a standardized definition of ischemic cardiomyopathy as proposed by Felker et al.[14] To summarize, patients were ascribed an underlying etiology of CAD if there was obstructive coronary artery disease of >50% in the left-main vessel, or of >75% stenosis in i) either the proximal LAD or ii) $\geq$ 2 epicardial coronary arteries. Single vessel disease not involving the proximal LAD was treated as non-ischemic as the extent of LV dysfunction would be considered to be out of proportion to the extent of CAD.

Standardized coronary anatomy was used to delineate the distribution of coronary artery disease.[15] The 3rd consensus group member's view was only required in cases where there was disagreement between the 2 primary group members.

Gold-standard Arm: A final independent and separate consensus group of 3 Cardiologists reviewed all the anonymized data and ascribed a "gold-standard" etiology based on review of all the clinical data including tissue characterization information from LGE-CMR as well as luminographic data from CA. Based on the permutations of CAD and LGE pattern seen, the gold-standard group categorized etiologies into 1 of 6 groups as follows: (see figure 2)

1. Non-ischemic DCM: Either no LGE or midwall LGE on CMR and unobstructed coronary arteries on CA. (True DCM)

2. Heart failure secondary to CAD: Ischemic pattern of LGE that involves the subendocardium in 3 or more segments with at least one stenosis of >75% seen in coronary artery(ies)[16] subtending the affected area of infarction evident on CA. (True CAD).

3. Non-ischemic DCM with bystander infarct: Small area of subendocardial LGE affecting <2 of 17 segments in a globally hypokinetic LV with unobstructed coronary arteries on CA. (DCM with bystander infarct).

4. Non-ischemic DCM with bystander CAD: Either no LGE, or midwall LGE with coronary stenosis(es) considered insufficient to explain the extent of LV dysfunction. (DCM with bystander CAD ie disease not affecting the left main stem/proximal LAD or significant ≥ 2 vessel disease).

5. Heart failure due to ischemic heart disease with unobstructed coronary arteries: 3 or more segments of subendocardial/transmural LGE in a perfusion territory typical of a coronary artery with associated regional hypokinesia and unobstructed coronary arteries on CA ie probable recannalization, spasm or embolic episode. (Myocardial infarction with unobstructed coronary arteries).

6. Heart failure due to CAD with no subendocardial LGE but severe proximal 3 vessel disease/LMS disease on CA. (Severe proximal CAD on CA without infarction)

Follow-Up of Patients

As an additional check, to corroborate the findings of the gold-standard consensus group, follow up data were collected prospectively in all recruited patients. Patient events were recorded by communication with patients, their cardiologists and general practitioners. Medical records were reviewed following attendance at outpatient clinics or hospitalization.

All patients were directly contacted at enrolment and at 6 monthly intervals during follow up. No patient was lost to follow up. The data was reviewed to determine if there was any change in subsequent clinical diagnosis when compared to the initial diagnosis ascribed by the gold-standard consensus group.

Diagnostic Cost Comparison

A decision tree model was constructed with LGE-CMR positioned as a gatekeeper to CA (see figure 3). Using the latest cost data from the 2008-2009 United Kingdom National Health Service tariffs, the cost of a coronary angiogram without complications is set at £1,255.[17] As no national NHS tariff for CMR had yet been set at the time of this study, the cost of a CMR

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scan was set at £600 in line with current charges in UK NHS centres. The cost of using LGE-CMR as a gatekeeper to coronary angiography was compared to using traditional method of utilizing only coronary angiography by implementing the above costs. The accuracy of each test was factored into the cost comparison by indexing the total cost of each strategy over the number of correct diagnoses.

Statistical Analysis

Prior to enrolment, a sample size calculation was performed in order to power the study to demonstrate equivalence between LGE-CMR and CA in diagnosing the underlying etiology of HF.[18] The sample size for this study was calculated assuming that x-ray coronary angiography correctly classifies the etiology on 90% of occasions and this value is the same for LGE-CMR. The study was powered at 80% with an alpha error of 0.05 to classify equivalence as a difference of less than 10% between the two diagnostic strategies. With these assumptions, 111 patients in each group were required and the protocol aimed for recruitment of 122 patients assuming a 10% drop out rate. All patients were recruited to both LGE-CMR and CA groups. Each consensus group was blinded to either LGE-CMR or CA data as appropriate thereby validating the inclusion of the same patients in both groups.

All continuous variables are expressed as mean +/- SD, and the distribution of categorical variables is expressed as frequencies. To evaluate the relative accuracy of LGE-CMR and CA in diagnosing the underlying etiology of HF, calculations of sensitivity, specificity, positive predictive and negative predictive values (PPV and NPV) were performed with the gold standard consensus group diagnosis being the comparator. Comparison of the costs for the 2 diagnostic strategies was compared using the Mann-Whitney U statistic which was

corrected for ties. For all statistical tests used, a p value of <0.05 was deemed to be statistically significant. Stata v10 was used for all statistical analyses.

Results

Baseline Characteristics

The baseline characteristics of the patients are summarized in table 1. Of the 124 patients recruited, 4 patients did not complete the study: 2 patients were unable to tolerate LGE-CMR scanning due to claustrophobia; 1 patient was found to have moderate to severe aortic regurgitation by CMR, which had not been identified by echocardiography, and subsequently had aortic valve surgery; 1 patient declined CA after undergoing a LGE-CMR and was therefore excluded. The final cohort therefore comprised of 120 patients in whom full LGE-CMR with MRCA was carried out without complications. The same patients also underwent CA, with 2 patients suffering complications requiring hospitalization (1 femoral artery hematoma ; 1 small occipital infarct periprocedurally). LGE-CMR was performed prior to CA in 81 out of 120 (68%) cases. Overall, 13 (11%) patients were admitted with acutely decompensated heart-failure as their index presentation. These patients were treated with routine anti-failure therapy and recruited to the study after stabilization and with a median interval of 43 days (range 4-115 days) between presentation and their CMR scan. The NYHA status in table 1 reflects the functional class at the time of the scan rather than the time of index clinical presentation. Patients had been started on conventional anti-failure therapy prior to undergoing their scan. In keeping with guidelines, a large proportion of patients were on treatment with angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta blockers.[19]

Interobserver Agreement in Consensus Groups

In the CMR consensus group, the diagnosis was unanimous in a large majority of cases, and a majority decision was only required in 6 (5%) cases. In the CA consensus group, the

diagnosis was unanimous in a large majority of cases, and a majority decision was only needed in 3 (2.5%) cases. Finally, in the "gold-standard" consensus group, a majority decision was needed in only 1 case.

Diagnostic Accuracy

After review of all clinical, LGE-CMR and CA data, the gold-standard consensus group deemed that 91 of the 120 cases had an underlying non-ischemic etiology and were therefore classified as DCM. The remaining 29 cases were deemed to represent HF secondary to CAD. Table 2 summarizes the breakdown of cases into subgroups as outlined in the methods section.

The decision tree (figure 3) presents the diagnostic findings of LGE-CMR and CA respectively as well as the number of correct and incorrect diagnoses. In summary, 87 of 91 (96%) cases of DCM were correctly diagnosed by LGE-CMR. In the decision tree model, these 87 patients would theoretically be able to avoid undergoing CA thereby avoiding its associated risks as well as providing a significant cost saving in the diagnostic cascade. Four patients with an eventual diagnosis of DCM were put forward for CA in view of a limited area of bystander infarct. In 4 cases, LGE-CMR showed no evidence of prior infarction and hence CA was not indicated. However, in 2 of these cases CA documented obstructive disease in the mid LAD and in 2 other cases, mid vessel obstructive lesions were seen in the Cx and RCA respectively. All cases had severe global hypokinesia and severe LV dysfunction with no evidence of prior infarction on CMR and for this reason the gold standard group ascribed a diagnosis of DCM with "bystander" CAD.

LGE-CMR correctly identified all 29 patients who were ascribed CAD as the underlying etiology. In 2 of these cases, an etiology of CAD was ascribed despite unobstructed coronary arteries. This view was reached by virtue of the observation that there was a large territory of subendocardial/transmural LGE consistent with the supply of at least 1 major epicardial artery with relatively well preserved wall thickening in other unaffected areas. There were no cases where LGE-CMR suggested a diagnosis of DCM and corresponding CA documented significant LMS, proximal LAD or 3 vessel disease. Of patients with a diagnosis of DCM, 25 had a midwall pattern of fibrosis.

CA also correctly identified 87 of 91 cases (96%) of DCM. As stated above, four patients were incorrectly ascribed as having CAD when the gold standard diagnosis was DCM. CA identified all but 2 cases of HF due to CAD.

The sensitivity, specificities, positive/negative predictive values and overall diagnostic accuracy for both LGE-CMR and CA are presented in table 3.

Cost Savings of Using LGE-CMR as a Gatekeeper

Assuming the costs for each investigation as stated in the methods section, applying the results from this study, the cost of using the conventional approach of CA to evaluate underlying etiology would be £1255 per patient. As CA has a diagnostic accuracy of 95%, the cost per correct diagnosis would be approximately £1321.

If LGE-CMR was used as a gatekeeper, all 120 patients would undergo LGE-CMR at a cost of £600 per scan. However, 87 patients would subsequently be spared CA representing a net

saving of approximately £655 per patient. Conversely, 33 patients would undergo both LGE-CMR and CA thereby costing £1855 per patient. Using these figures, the net cost per patient using LGE-CMR as a gatekeeper to CA would be significantly cheaper at £945 per patient (p=0.001). As LGE-CMR has a diagnostic accuracy of 97%, the cost per correct diagnosis would be approximately £974, which represents a 26% cost saving on using coronary angiography alone.

Clinical follow up of recruited patients

Follow up data were obtained for all 120 recruited patients with a mean follow up duration of 44.3 +/- 11.5 months. In the 87 patients in whom DCM was diagnosed on the basis of unobstructed coronary arteries and no subendocardial late enhancement on CMR (true DCM), the diagnosis did not change during the follow up period. In addition, the diagnosis in the 27 patients with LV dysfunction secondary to CAD as identified by both subendocardial scarring on CMR and significant coronary stenoses on CA (true CAD) did not change during follow up.

In 10 cases, the findings of LGE-CMR and CA were at odds and the eventual "correct" diagnosis was formed by the gold-standard consensus group who reviewed all the clinical data. In the 4 cases of DCM with bystander CAD, only 1 patient underwent urgent revascularization 2 years after enrollment following an admission with NSTEMI. This patient was not revascularized following initial angiography as the clinician had felt the diagnosis to be DCM. In the other 3 cases, the patients had not presented subsequently with typical ischemic symptoms and their respective clinicians had treated the patients as DCM with pharmacotherapy and device therapy as appropriate.

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In the 4 cases with DCM and bystander infarction, the clinicians continued treatment with a working diagnosis of DCM. Two of these patients also received a statin. Finally, in 2 cases where the diagnosis was one of prior myocardial infarction with unobstructed coronary arteries, both patients were treated with antifailure therapy as well as aspirin and a statin. One of these patients received an ICD as he had subsequently presented with sustained ventricular tachycardia.

Discussion

The main finding of this study is that LGE-CMR appears to be highly effective in detecting the basis of cardiac dysfunction in patients with newly-diagnosed HF in whom the etiology is unclear. It is clinically effective and economically viable as a gatekeeper to CA.

Specifically, these patients have neither prior history of ischemic heart disease nor any chest pain that may represent underlying CAD. Current guidelines for the management of HF state that there is little evidence for benefit from revascularization in these groups but offers no firm guidance on a non-invasive alternative. This is also particularly important as nearly half of patients with HF and low EF have normal or near normal coronary arteries on angiography with an underlying myocardial disorder responsible for the clinical presentation. At present this is not fully characterized unless an endomyocardial biopsy is performed.

Identification of the condition responsible for the cardiac structural and/or functional abnormalities may be important, as some conditions that lead to LV dysfunction are potentially treatable and/or reversible.[3] Conventional imaging often has a low yield in

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detecting the underlying cause and as a consequence present guidelines do not advocate routine angiography. This is however at odds with the practice of many healthcare providers and autopsy data on the underlying etiology. A major strength of CMR is its ability to provide tissue characterization in-vivo yielding information on the underlying etiology and risk stratification plus guiding device implantation.[19-21] Importantly, this information is incremental to coronary anatomy findings alone. There is therefore an opportunity to reappraise the role of non-invasive imaging in identifying the underlying cause and management plan in this cohort of patients.

Clinical Implications

The cohort studied was representative of those normally encountered in a heart failure service. Most were in at least NYHA III at the time of their original index presentation. They had been stabilized on antifailure therapy reflected by an improvement in functional status by the time of recruitment; the clinical challenge was to elucidate the underlying etiology.

Our data demonstrates that LGE-CMR shows diagnostic equivalence to CA in revealing the underlying etiology of this poorly studied cohort. In addition, the positioning of LGE-CMR as a gatekeeper to CA allows for the safe avoidance of CA in approximately 75% of this cohort who had DCM. This represents an opportunity to allow a significant cost saving in the management of these patients in a non-invasive manner with no ionizing radiation exposure or need for in-patient stay. Other advantages are that within a single test, data is provided on biventricular function, tissue characterization, viability as well as risk stratification.[19]

Two prior studies have quoted modest success in comparing LGE-CMR to CA in this type of cohort, but without additional MRCA to exclude severe proximal disease.[16, 22] Both these studies suggest an overall sensitivity of 81-86% with a specificity of 91-93% in determining the presence of obstructive CAD. However, the authors acknowledged that the presence of obstructive CAD did not in itself represent an underlying etiology of ischemia-driven heart failure because of coincidental and non-contributory CAD. Indeed, in our study defining the gold standard for diagnosis of CAD as the contributory etiology of HF as a 70% lesion in at least 1 vessel would produce similar sensitivity/specificity figures to those obtained by Soriano et al.[16] A further study[23] addresses this flaw to a certain extent by using a validated definition for "ischemic cardiomyopathy" which allows for the presence of single vessel disease without a history of prior myocardial infarction to represent non-ischemic heart failure.[14] Both studies also did not have any mechanism in their CMR protocol to detect the uncommon but important group of patients in whom CAD may contribute to HF by virtue of severe proximal 3 vessel disease without prior infarction. The use of MRCA in our study design addresses this potential pitfall. Our study utilized the refined, validated and more realistic definition for "ischemic cardiomyopathy" which precludes the scenario of a single lesion in either the circumflex or right coronary artery being deemed sufficient to cause global hypokinesia with resultant severe LV dysfunction. The present study is unique in being the first that is adequately powered to assess the diagnostic accuracy of LGE-CMR at baseline as a gatekeeper to CA when compared against a robust gold-standard. Most importantly, its findings are also validated against prospective clinical follow-up.

The use of a "gold standard" consensus group with access to a full dataset of CMR based tissue characterization and coronary disease burden from CA was best equipped to provide

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the most accurate etiology. This is because they were afforded the opportunity to integrate the severity of coronary disease with the extent of prior infarction and to consider whether the location and severity of any documented CAD would be adequate to cause ischemic myocardial hibernation. This study also advocates a more rigorous classification of the underlying etiology in patients with HF based on a combination of luminal angiography and myocardial tissue characterization. These have been broadly classified into 6 subsets from the findings of the gold-standard group and also challenges the traditional dichotomy of ischemic versus non-ischemic cardiomyopathy.

Other smaller studies have been performed assessing LGE-CMR in a similar role with respect to the management of heart failure.[24, 25] However, these studies included patients with chest pain or clinical features of CAD and therefore a comparison with our study is not strictly valid. Pilz et al have also used a "gatekeeper" model to argue for a role for adenosine stress CMR in a different cohort of patients with a class II indication for CA. Their data shows that the rates of CA in this cohort who have an intermediate probability of CAD could be reduced by over 80%.[26] In our protocol, the use of first pass perfusion was considered but was decided against as it has been demonstrated from nuclear studies that perfusion defects may be present in non-ischemic cardiomyopathies.[27, 28] The use of first pass perfusion would therefore not necessarily help in discriminating an underlying ischemic from non-ischemic etiology.

CT coronary angiography represents a real non-invasive alternative to conventional CA.[29] However, it has a significant radiation burden and is not at present used to provide tissue characterization data at acceptable levels of radiation exposure. It is therefore subject to

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the same diagnostic pitfalls as conventional CA.[30, 31] There has also been interest in the role of stress and contrast echocardiography in a similar cohort.[32] This has the advantage of portability and whilst it provides important information on function and ischaemia, it lacks detailed tissue characterization and hence cannot delineate different patterns of fibrosis. Interpretation is also more operator dependent. Nuclear techniques have the advantage of long term outcome data but also do not reliably distinguish patterns of fibrosis characteristic to the underlying etiology and carry a significant radiation burden. Increasingly, the presence of fibrosis *per se* has been shown to be of important prognostic significance and this information is not obtained by these alternative techniques.

Limitations

LGE-CMR was carried out within 37 +/-29 days of CA. Although short, this period represents a potential opportunity for a clinical event between the 2 procedures being performed. However, none of the patients had evidence of new cardiac events, required hospitalization or had any form of therapy changed between their respective LGE-CMR and CA. The gold-standard diagnosis was provided by highly experienced cardiologists who were familiar with the performance and interpretation of CA and LGE-CMR. However, the consensus view they provided was effectively an opinion. This is potentially contentious in the group of patients who represent a "grey area" where LGE-CMR and CA provided potentially contradictory conclusions. However, validation of their opinion in all these "grey cases" was provided by 3.5 year follow up data which showed that all the ascribed diagnosis by the consensus group was mirrored by the patients' own physicians and clinical outcomes. In addition, the diagnosis only changed in 1 patient with features of DCM on LGE-CMR and single vessel CAD where 2 years after enrollment he re-presented with an acute coronary syndrome which

represented a new and unrelated event. Repeat CA in this patient demonstrated a clear progression of CAD which warranted revascularization with PCI. None of the patients with bystander CAD required or underwent revascularization with a view to evaluating any subsequent improvement in LV function. In addition, due to improving clinical status, none of the patients required or underwent myocardial biopsy. In patients, with a predominant DCM phenotype but with concurrent CAD, potentially, angiography provides useful information that could be missed by CMR alone. However, recent trials indicate that this is unlikely to affect outcomes in this cohort. Most notably in the CORONA trial[33], statins had no significant benefit in patients with heart-failure, regardless of etiology. Reflecting this, there was no adverse outcome overall, based on their management plan.

At times, the findings in this subgroup of "grey cases" may be difficult to synthesize. They present a diagnostic and management dilemma for clinicians and further work is therefore needed in uncovering the prognosis in this group compared to patients with "true DCM" (no CAD on CA and no subendocardial LGE on CMR). LGE-CMR does however appear to provide some assistance in reaching the right clinical decision in this under-recognized group.

The MRCA sequence required a regular ECG to obtain images of adequate spatial resolution. For this reason, patients with atrial fibrillation were excluded. We also excluded all patients with chest pain even though this symptom may be present in heart failure of either etiology. It was felt that any patients with symptoms suggesting possible angina ought to have coronary angiography to ensure they were not denied the chance of revascularization as a therapeutic option.

CT coronary angiography may have provided higher sensitivities and specificities in the exclusion of coronary artery disease but with an increased radiation burden along with the risks associated with iodine-based contrast agents. Detailed tissue characterisation is also not currently possible with CT. MRCA was included in our protocol to ensure that we did not miss patients with severe proximal coronary disease but no infarction. However, no such patients were encountered suggesting that this is an important but uncommon presentation.[24]

It should also be noted that the cohort we studied consisted predominantly of patients with mild to moderate heart failure in sinus rhythm and no symptoms consistent with myocardial ischemia, and may not apply to patients with more severe or advanced heart failure. This is also relevant to MRCA which may have a different and potentially lower negative predictive value in a broader cohort of heart-failure Patients where there is a higher burden of CAD. Finally, the potential cost-savings of this procedure will depend upon local/national relative reimbursement rates for both CMR and CA, and hence this data is most applicable to healthcare services such as the UK where CMR is less expensive than CA.

Conclusions

CMR is a safe, clinically effective and fiscally prudent gatekeeper to CA in patients presenting with new onset HF with no features of chest pain or prior myocardial infarction. It is of particular value in clarifying the underlying pathophysiology in patients who are likely to have dual pathology by establishing the dominant etiology. Additional information is provided on biventricular assessment, tissue characterization, risk stratification and likelihood to benefit from device therapy. Unique aspects of our study compared to previous work are comparison of findings with a gold-standard panel including CMR and

angiography rather than CA alone, and in addition, corroboration of these findings through subsequent clinical follow-up. Our study also suggests the need for a paradigm shift from a simple classification of ischemic vs non-ischemic etiologies in this cohort, based on luminography, to one that refines the Felker criteria incorporating myocardial tissue characterization. Further studies are required to identify the prognosis in this cohort with particular focus on the subgroup of grey cases in whom there appears to be concurrent CAD with non-ischemic DCM.

Acknowledgements

Conflicts of Interest/Disclosures

Professor Dudley Pennell is a Consultant to Siemens and a Director of Cardiovascular Imaging Solutions Ltd. Professor Martin Cowie has Consultancy agreements with Pfizer, Takeda and Servier.

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<u>Figure legends</u>

Figure 1: Pre-defined decision algorithm for CMR consensus panel to decide whether to proceed to invasive x-ray coronary angiography (CA). The algorithm states that the presence of subendocardial late gadolinium enhancement (LGE) should trigger the decision to proceed to CA. In cases where, subendocardial LGE is not present, magnetic resonance coronary angiography (MRCA) images should be reviewed before deciding whether CA is required. The review of MRCA should exclude proximal severe 3 vessel disease or left main stem (LMS) disease before a scan be labelled as dilated cardiomyopathy (DCM).

Figure 2: Late gadolinium enhanced cardiovascular magnetic resonance (LGE-CMR) and associated coronary angiogram (CA) images of diagnosis subtypes. Six different diagnoses are graphically represented with LGE-CMR images followed by CA images of the left coronary artery (LCA) and right coronary artery (RCA). True dilated cardiomyopathy (DCM) as depicted in row a) shows an LGE-CMR image with no subendocardial LGE and unobstructed coronary arteries on CA. In row b), true coronary artery disease (CAD) is depicted with a circumflex territory infarct on CMR (arrows) as well as a severe proximal circumflex artery stenosis (arrows). In row c) a small area of subendocardial LGE(arrows) is seen in a severely dilated LV with severe global systolic impairment and unobstructed coronary arteries representing DCM with bystander infarct. In row d) distal disease of the left anterior descending artery is seen (arrows) with no evidence of subendocardial LGE (DCM with bystander CAD). In row e) a large apical infarct is seen on LGE-CMR in the context of unobstructed coronary arteries suggesting ischemic heart failure (HF) with unobstructed coronary arteries. Finally, the images in row f) show a possible scenario of ischemic heart failure without infarction. There is no LGE on CMR but severe proximal 3 vessel disease

including left main stem disease on CA (arrows). No patient in our study had this scenario and therefore the images are for illustration only.

Figure 3: A decision tree model summarizing the results of the decisions made by the late gadolinium enhanced cardiovascular magnetic resonance (LGE-CMR), coronary angiography (CA) and gold standard consensus panel groups. The model delineates the role of LGE-CMR with incorporated magnetic resonance coronary angiography (MRCA) as a gatekeeper to CA. In this model, 87 (73%) of the recruited cohort safely avoided CA and were correctly ascribed a diagnosis of DCM by LGE-CMR. The relative diagnostic performance of using LGE-CMR against CA is represented by the true and false positive (TP/FP) as well as true and false negative (TN/FN) numbers presented at the end of the decision tree.

Table legends

Table 1: Baseline characteristics of the study group. DCM- dilated cardiomyopathy ; CAD- coronary artery disease; CMR- cardiovascular magnetic resonance; NYHA – New York Heart Association heart failure class; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin 2 receptor blocker; LV - left ventricle; EDVI – end-diastolic volume index; ESV- end-systolic volume index; EF- ejection fraction.

Table 2: Final categorization of etiology as ascribed by Gold Standard Consensus Panel. DCM – dilated cardiomyopathy; CAD- coronary artery disease; CA: invasive x-ray coronary angiography.

Table: 3: Table showing sensitivity, specificities, positive predictive values (PPV), negative predictive values (NPV) and diagnostic accuracy of late gadolinium-enhanced (LGE-CMR) and invasive x-ray coronary angiography (CA) vs the gold standard consensus group diagnosis (columns 2 and 3).

Table 1: Baseline Characteristics at time of CMR Scan

Characteristic	n=120
Age (years) (SD)	57 (11)
Male sex (%)	96 (80)
Family history of DCM (%)	7 (6)
Family history of CAD (%)	20 (17)
History of diabetes (%)	20 (17)
History of hypertension (%)	56 (47)
History of smoking (%)	29 (24)
History of alcohol excess (%)	7 (6)
Preceding flu like illness (%)	11 (9)
Heart Failure duration prior to enrollment in days (SD)	63 (39)
Interval between CMR and Coronary Angiogram (days) (SD)	37 (29)
NYHA Class at time of enrollment (%)	
I	29 (24)
II	75 (63)
III	16 (13)
Medication (%)	
Aspirin	56 (47)
ACEI/ARB	110 (92)
Beta Blocker	84 (70)
Spironolactone	24 (20)
Digoxin	2 (2)
Diuretics	73 (61)
Anticoagulation	11 (9)
Amiodarone	4 (3)
Statins	56 (47)
CMR Dimensions and Function (SD)	
LVEDVI (mL/m^2)	130 (48)
LVESVI (mL/m^2)	84 (48)
LVEF (%)	39 (13)
LV MassI (g/m^2)	113 (37)

Table 2: Gold-standard Consensus Panel Categorization list

Diagnosis	N (%)
<u>DCM</u>: True DCM	83 (69)
<u>CAD:</u> True CAD	27 (23)
<u>DCM:</u> Bystander infarct	4 (3)
<u>DCM:</u> Bystander CAD	4 (3)
<u>CAD:</u> MI with unobstructed coronary arteries on CA	2 (2)
<u>CAD:</u> Severe proximal CAD on CA with no infarction	0 (0)

Table 3: Diagnostic accuracy of LGE-CMR and CA

	LGE-CMR (95% CI)	CA (95% CI)
Sensitivity %	100 (88-100)	93 (77-99)
Specificity %	96 (89-99)	96 (89-99)
PPV %	88 (72-97)	87 (70-96)
NPV %	100 (96-100)	98 (92-100)
Diagnostic accuracy %	97	95