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The impact of dark-blood versus conventional bright-blood late gadolinium enhancement on the myocardial ischemic burden

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ABSTRACT

Purpose: In perfusion cardiovascular magnetic resonance (CMR), ischemic burden predicts adverse prognosis and is often used to guide revascularization. Ischemic scar tissue can cause stress perfusion defects that do not represent myocardial ischemia. Dark-blood late gadolinium enhancement (LGE) methods detect more scar than conventional bright-blood LGE, however, the impact on the myocardial ischemic burden estimation is unknown and evaluated in this study.

Methods: Forty patients with CMR stress perfusion defects and ischemic scar on both dark-blood and bright-blood LGE were included. For dark-blood LGE, phase sensitive inversion recovery imaging with left ventricular blood pool nulling was used. Ischemic scar burden was quantified for both methods using >5 standard deviations above remote myocardium. Perfusion defects were manually contoured, and the myocardial ischemic burden was calculated by subtracting the ischemic scar burden from the perfusion defect burden.

Results: Ischemic scar burden by dark-blood LGE was higher than bright-blood LGE (13.3 ± 7.4% vs. 10.3 ± 7.1%, $p < 0.001$). Dark-blood LGE derived myocardial ischemic burden was lower compared with bright-blood LGE (15.6% (IQR: 10.3 to 22.0) vs. 19.3 (10.9 to 25.5), median difference −2.0%, $p < 0.001$) with a mean bias of −2.8% (95% confidence intervals: −4.0 to −1.6%) and a large effect size ($r = 0.62$).

Conclusion: Stress perfusion defects are associated with higher ischemic scar burden using dark-blood LGE compared with bright-blood LGE, which leads to a lower estimation of the myocardial ischemic burden. The prognostic value of using a dark-blood LGE derived ischemic burden to guide revascularization is unknown and warrants further investigation.

1. Introduction

In patients with known or suspected coronary artery disease (CAD), the myocardial ischemic burden (MIB) is the strongest predictor of major adverse cardiac events, superior to left ventricular (LV) function and scar burden [1]. Consequently, the functional assessment of myocardial ischemia and the corresponding MIB is recommended to guide revascularization [2]. Stress perfusion cardiovascular magnetic resonance (CMR) has high concordance with invasive fractional flow reserve and is a method of choice for the non-invasive detection and quantification of myocardial ischemia [2–4]. When assessed by stress perfusion CMR, a MIB threshold of ≥12.5% (2/16 myocardial segments)

Abbreviations: CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; CI, confidence interval; ICC, intraclass correlation coefficient; ISB, ischemic scar burden; LGE, late gadolinium enhancement; LOA, limits of agreement; LV, left ventricular; LVEF, left ventricular ejection fraction; MIB, myocardial ischemic burden; PDB, perfusion defect burden; PSIR, phase-sensitive inversion-recovery; ROI, region of interest; SD, standard deviations.

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is associated with worse prognosis and is often used to guide revascularization decision making [1,5,6].

The presence of inducible ischemia is inferred from subendocardial perfusion defects on visual assessment of stress perfusion CMR [7]. Following myocardial infarction, over time the necrotic cardiomyocytes are replaced by fibrotic tissue, which can be identified using late gadolinium enhancement (LGE) imaging [8]. As these myocardial scar patterns can cause perfusion defects on stress perfusion imaging, the current Society of Cardiovascular Magnetic Resonance position statement recommends perfusion images to be read in conjunction with LGE images [7]. Matched perfusion / LGE defects are not considered a sign of myocardial ischemia, rather a consequence of reduced capillary density and therefore do not contribute to the MIB [7].

Conventional bright-blood LGE imaging is the reference standard for the non-invasive assessment of myocardial scar by CMR [9]. This method aims to null the signal of normal myocardium while the blood pool and scar tissue appear hyperenhanced. A consequence of this approach, however, is relatively low contrast experienced between the blood pool and areas of subendocardial scarring. This often makes the scar-blood border difficult to delineate and hinders the identification of scar as well as the assessment of the apparent scar volume [10,11]. Numerous dark-blood LGE methods with additional magnetization preparation have been proposed to increase scar-to-blood contrast for improved visualization of ischemic scar [12]. Recently, a dark-blood LGE method not requiring additional magnetization preparation was proposed [13]. By using a shorter inversion time to null the LV blood pool instead of normal myocardium, the blood pool appears a darker grey on a standard phase-sensitive inversion-recovery (PSIR) image with improved scar-blood contrast [13]. When compared with conventional bright-blood PSIR LGE, greater detection of myocardial infarction was achieved with superior image quality and increased observer confidence [11]. This increased sensitivity for ischemic scar detection by dark-blood LGE may impact the MIB estimation when read in conjunction with stress perfusion imaging.

The aim of this study was to quantify the impact of utilising dark-blood LGE versus conventional bright-blood LGE on the MIB estimation.

2. Materials and methods

2.1. Population

Retrospective inclusion of patients who underwent adenosine stress perfusion CMR with both dark-blood and bright-blood LGE imaging with the following criteria 1) Evidence of an ischemic pattern LGE on visual assessment of both dark-blood and bright-blood LGE; 2) Perfusion defects on visual assessment of stress perfusion imaging. All patients were instructed to refrain from caffeine for 24 h prior to the CMR examination. All patients gave written informed consent (regional ethics committees: 15/NS/0030 & 18/ES/0115) and the study was conducted according to the Declaration of Helsinki.

2.2. CMR protocol

All CMR examinations were performed using a clinical 3 Tesla system (Achieva TX, Philips Healthcare, Best, the Netherlands) equipped with a 32-channel cardiac phased-array coil. A routine CMR protocol was used to obtain short-axis cine images for assessment of ventricular function. First-pass stress perfusion imaging was performed using an ECG-triggered saturation-recovery spoiled gradient-echo sequence. Three short-axis LV slices were acquired during adenosine-induced hyperemia (140–210 μg/kg/min) to cover the basal, mid and apical ventricular levels [14]. Typical sequence parameters were: TR 2.2 ms, TE 1.0 ms, flip angle 15°, acquired resolution 2.6 × 2.6 mm^2, reconstructed resolution 1.3 x 1.3 mm^2, slice thickness 10 mm, SENSE acceleration factor 1.8. During hyperaemia, an intravenous bolus of 0.075 mmol/kg of gadobutrol (Gadovist, Bayer Pharmaceuticals, Berlin, Germany) was administered at 4.0 ml/s followed by a 25 ml saline flush. Patients were asked to perform a breath-hold during the first pass of contrast. A second bolus of 0.075 mmol/kg of gadobutrol was administered for rest perfusion imaging (not analysed in this study). Patient total contrast dose was 0.15 – 0.165 mmol/kg of gadobutrol (27 patients also received a pre-bolus of 0.0075 mmol/kg of gadobutrol with each contrast injection – not utilised in this study).

2.3. LGE imaging

LGE imaging was performed at least thirteen minutes after first contrast injection. First, dark-blood LGE was acquired in the three standard LV long-axis and a stack of short-axis views using an ECG-triggered segmented spoiled gradient-echo PSIR sequence acquired during a breath-hold. Typical sequence parameters were: TR 3.5 ms, TE 2.0 ms, flip angle 25°, TFE factor 25, PSIR reference readout flip angle 5°, acquired resolution 1.61 × 1.61 mm^2, reconstructed resolution 0.65 × 0.65 mm^2, slice thickness 8 mm. Immediately after, long and short-axis bright-blood LGE images were acquired using the same sequence. For both methods, a Look-Locker sequence was performed to determine the correct inversion time (LV blood nulling for dark-blood LGE, normal myocardium nulling for conventional bright-blood LGE). All images were acquired in the mid-diastolic resting period. The mechanism for the blood-nulled PSIR LGE method has previously been described in detail [13].

2.4. Image analysis

Images were anonymized and presented in random order. All analyses were performed using the dedicated certified software package cvi42 (v5.12.2, Circle Cardiovascular Imaging Inc., Calgary, AB, Canada). The LV short-axis cine stack was analysed for determining LV volumes, mass, and ejection fraction (LVEF). Dark-blood and bright-blood LGE and perfusion images were analysed in different sittings by consensus of two experienced observers. LGE analysis did not consider long-axis LGE images.

2.5. LGE scar quantification

Three of the short-axis LGE PSIR slices were selected to best match the slice locations of the three short-axis perfusion slices. On these slices the total LGE volume was quantified using the semi-automated 'signal threshold versus reference mean' method with the threshold set at > 5 standard deviations (SD) above the mean signal intensity of reference myocardium [15]. Epicardial and endocardial boundaries were manually contoured. Reference myocardium was defined by a manually drawn region of interest (ROI) in an area of remote myocardium without visually apparent LGE or image artefacts, with the enhancement overlay turned off. For consistency, ROIs were preferentially placed in the anteroseptal segment if free of enhancement / artefact. Once satisfied with myocardial contours and ROI placement, the enhancement overlay was turned on to enable manual exclusion of non-ischemic enhancement / artefact from the scar quantification. Observers were blinded to enhancement values / results during the LGE analysis. One patient had evidence of microvascular obstruction on the basal LV slice of both LGE methods. As the focus of this work was to evaluate the impact of the LGE methods on the MIB estimate, the area of no-reflow was manually contoured and added to the hyperenhanced area.

To evaluate the intraobserver reproducibility of the semi-automated quantification of dark-blood LGE, LGE quantification analysis was repeated by the same observers in consensus in 10 randomly selected cases following a 2-week interval.

2.6. Myocardial ischemic burden quantification

Stress perfusion image window width and level were adjusted for

optimal contrast within the LV myocardium [7]. Endocardial and epicardial contours were manually drawn on the dynamic with maximal observed myocardial contrast following peak LV signal intensity. Perfusion defects were manually contoured [16]. Contiguous defects were contoured as a whole, while non-contiguous defects were contoured separately. The perfusion defect burden (PDB) was calculated by dividing the sum perfusion defect area by the sum myocardial area as contoured on the three perfusion slices and expressed as a percentage. LGE and perfusion contours were then visually inspected side by side. Enhanced ischemic scar not associated with a visual perfusion defect within the same myocardial segment was manually excluded from the scar quantification [17]. The remaining ischemic scar burden (ISB) for each LGE method was then calculated by dividing the sum hyperenhanced area by the sum myocardial area of the three LGE slices and expressed as a percentage. The MIB was calculated by subtracting the ISB from the PDB. Any negative values were set to zero to represent no ischemia.

2.7. Statistical analysis

Normality of data was tested using the Shapiro-Wilk test. Group means / medians were compared using a paired samples *t*-test or Wilcoxon signed-rank test as appropriate. McNemar's test was used to evaluate paired dichotomous data. Linear correlations were assessed using Pearson's or Spearman's correlation coefficient as appropriate. Agreement between dark-blood and bright-blood LGE ISB and MIB estimates was examined using Bland-Altman analysis and linear regression. Agreement between dark-blood and bright-blood LGE methods to classify MIB $\geq$ 12.5% or $<$ 12.5% was measured using Cohen's kappa statistic (κ) and reported with 95% confidence intervals. Intraobserver reproducibility of semi-automated LGE quantification was assessed using an average measures two-way mixed model intraclass correlation coefficient (ICC). The statistical significance of differences in reproducibility was assessed by a Wilcoxon rank comparison of the squared differences [15]. All statistical tests were two-tailed and significance was set at $p < 0.05$. Data are presented as mean $\pm$ standard deviation unless otherwise stated. Statistical analysis was performed using SPSS Statistics (version 26, International Business Machines, Armonk, NY, USA).

3. Results

3.1. Study population

Fifty patients were identified of which nine patients were excluded due to inadequate image quality (3 perfusion imaging; 2 dark-blood LGE; 1 bright-blood LGE; 3 dark and bright-blood LGE). One patient was excluded due to significant ventricular thinning on perfusion imaging, deemed unsuitable for reliable contouring. Consequently, CMR data from 40 patients (33 male, mean age 65 years) were included in the analysis. Clinical characteristics are described in Table 1.

3.2. Ischemic scar burden

As per the study design, all patients had ischemic pattern hyperenhancement. 31 of 40 (78%) patients had a higher ISB with dark-blood LGE compared with bright-blood LGE. Mean ISB by dark-blood LGE was higher than bright-blood LGE (13.3 $\pm$ 7.4% vs. 10.3 $\pm$ 7.1%, $p < 0.001$). A strong positive linear relationship was found for ISB between the two LGE methods ($r = 0.857$, $p < 0.001$, Fig. 1A) with a mean bias of 3.0% (bias 95% confidence intervals (CI): 1.7 to 4.2, 95% limits of agreement (LOA): −4.6 to 10.6%, Fig. 1B).

3.3. Intraobserver reproducibility of semi-automated LGE quantification

Intraobserver ICC for quantified LGE from dark-blood and bright-blood methods were 0.96 and 0.85, respectively, with no significant difference between intraobserver reproducibility ($p = 0.386$).

Table 1
Population characteristics.

Parameter	n = 40
Age, years (range)	65 (35–80)
Male gender, n (%)	33 (83)
Clinical history, n (%)	
Dyslipidaemia	36 (90)
Hypertension	29 (73)
Diabetes	18 (45)
Smoking	34 (85)
Previous revascularization	23 (58)
CMR data	
LV EDVi (ml/m^2)	95 (IQR: 83 to 112)
LV ESVi (ml/m^2)	51 (IQR: 41 to 67)
LV EF (%)	46 $\pm$ 10
Indexed LV mass (g/m^2)	54 $\pm$ 11

Results are expressed as mean $\pm$ standard deviation / median (interquartile range). CMR: cardiovascular magnetic resonance; LV: left ventricular; EDVi: indexed end-diastolic volume; ESVi: indexed end-systolic volume; EF: ejection fraction; IQR: interquartile range.

3.4. Myocardial ischemic burden

The PDB was 30.0 $\pm$ 13.3%. Dark-blood LGE indicated a lower MIB than bright-blood LGE in 30 of the 40 patients (75%). Group MIB had non-normal distribution although MIB group differences were normally distributed. Median MIB calculated using dark-blood LGE was lower compared with bright-blood LGE (15.6% (IQR: 10.3 to 22.0) vs. 19.3 (10.9 to 25.5), median difference −2.0%, $p < 0.001$). A strong positive linear relationship was found for MIB calculated using the two LGE methods ($r_s = 0.921$, $p < 0.001$, Fig. 2A) with a mean bias of −2.8% (bias 95% CI: −4.0 to −1.6%, 95% LOA: −10.2 to 4.7%) Fig. 2B). The effect size of using dark-blood LGE on the MIB estimation was large compared to using bright-blood LGE ($r = 0.62$). Four patients had zero MIB with dark-blood LGE vs. one patient with bright-blood LGE ($p = 0.250$).

MIB was calculated as $\geq$ 12.5% by both LGE methods in 26 out of 40 patients (65%) and as $<$ 12.5% by both methods in 11 patients (27.5%, including one patient with an MIB of zero by both methods). In two patients (5%), the calculated MIB was $\geq$ 12.5% using bright-blood LGE while $<$ 12.5% when using dark-blood LGE. In one patient (2.5%), the MIB was $\geq$ 12.5% using dark-blood LGE while $<$ 12.5% when using bright-blood LGE (Fig. 2A). There was strong agreement between the two LGE methods around the MIB threshold of 12.5%. ($\kappa = 0.83$, 95% CI: 0.64 to 1.00). Fig. 3 presents 2 case examples demonstrating the impact of dark-blood LGE on the MIB compared with conventional bright-blood LGE.

4. Discussion

This is the first study to directly evaluate the impact of a dark-blood LGE method on the estimation of the MIB compared with conventional bright-blood LGE. The main finding of this study is; within segments containing stress perfusion defects, dark-blood LGE identifies more ischemic scar than conventional LGE, which reduces the estimated MIB when read in conjunction with stress perfusion imaging.

4.1. Ischemic scar burden

We observed that the ISB was higher using dark-blood LGE compared with conventional bright-blood LGE. Whilst our calculated ISB was derived only from segments containing stress perfusion defects, this finding is consistent with several recent studies that compared dark-blood LGE methods with conventional bright-blood LGE for the detection of ischemic scar. Using visual assessments of scar burden, studies by

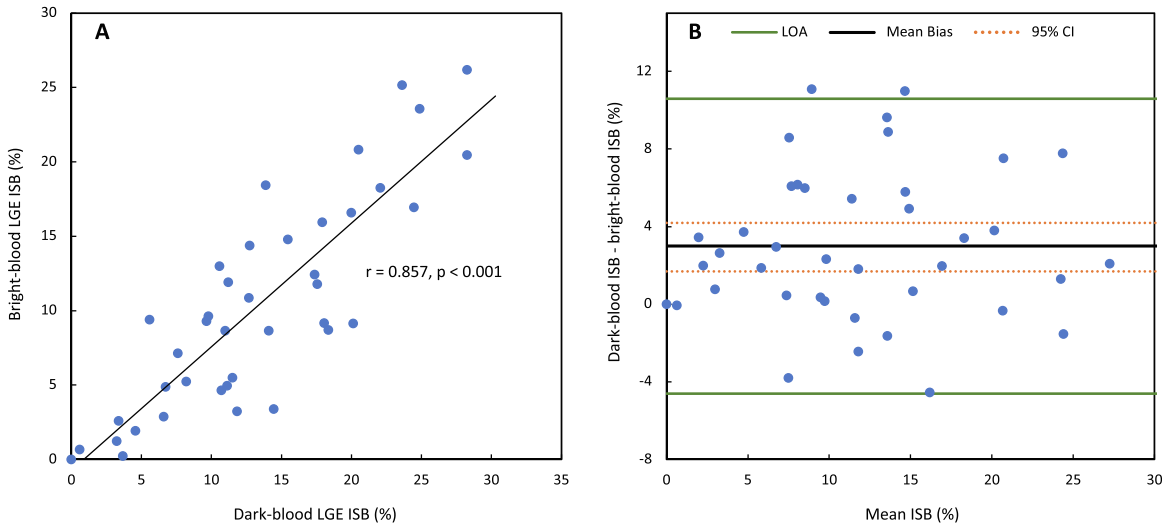

Fig. 1. Correlation and agreement of the dark-blood and bright-blood late gadolinium enhancement (LGE) ischemic scar burden (ISB). **(A)** Linear regression for ISB using dark-blood and bright-blood LGE. **(B)** Corresponding Bland-Altman plot. CI: confidence intervals.

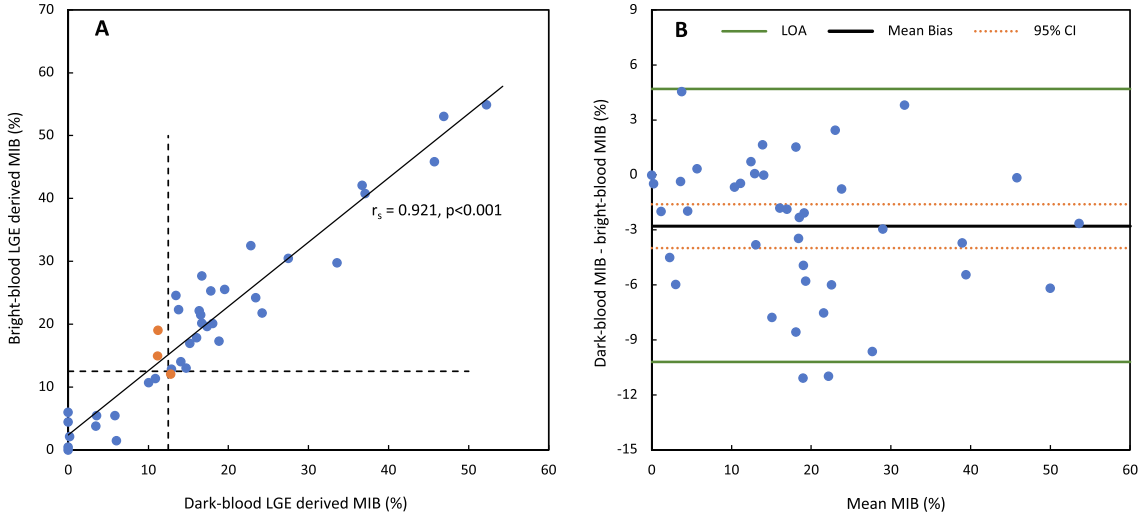

Fig. 2. Correlation and agreement of the dark-blood and bright-blood late gadolinium enhancement (LGE) derived myocardial ischemic burden (MIB). **(A)** Regression analysis for the MIB using dark-blood and bright-blood LGE in conjunction with stress perfusion images. Dashed gray lines indicate the 12.5% MIB threshold. Orange data points represent patients with disagreement around the 12.5% MIB threshold between the two LGE methods. **(B)** Corresponding Bland-Altman plot. CI: confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Francis et al., Holtackers et al. and Foley et al., all found higher scar burdens with dark-blood LGE compared with bright-blood LGE, due to a combination of increased scar transmurality, increased identification of segments with subendocardial scar, or both [10,11,18].

Using a semi-automated quantification of scar burden, Foley et al. did not report a significant difference between a dark-blood and bright-blood LGE method. However, a study by Song et al. did demonstrate a significant mean increased scar burden of between 1.3% and 1.6% with a dark-blood LGE method over conventional bright-blood LGE [19]. We observed a larger difference in ISB in our study, however, this may be explained by use of the full-width half-maximum LGE quantification method in the Foley and Song studies, which may underestimate scar volume with dark-blood LGE [20]. To the best of our knowledge, no semi-automated LGE quantification methods have been validated against histology for use with dark-blood LGE, however, using a 5-SD threshold we found dark-blood LGE had excellent intraobserver reproducibility. A semi-automated threshold approach was utilised in favour of manual contour delineation of scar as the latter is susceptible to changes in window width and level settings, as well as high inter-observer variability [15].

4.2. *Myocardial ischemic burden*

Accurate assessment of the MIB by CMR is important as it carries prognostic value that can be used to guide revascularization [1,4]. Evidence of any ischemic burden on perfusion CMR is associated with adverse prognosis [21], which progressively worsens when the burden of ischemia increases [1,5,6]. The recently reported International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial found that a significant *peri*-procedural event rate offset any longer-term prognostic benefit offered by revascularization of ischemic territories [22]. These findings underline the need for the careful selection of patients being referred for coronary revascularization. An accurate estimate of the ischemic burden is an important measure to understand patient risk. When combined with perfusion imaging, in 75% of cases we observed a lower burden of myocardial

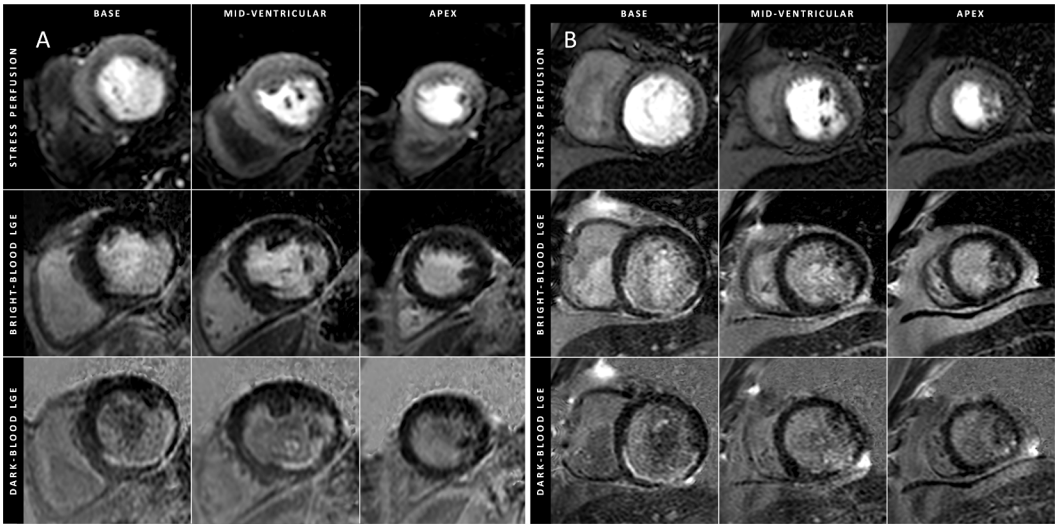

Fig. 3. Case examples: Stress perfusion (top), bright-blood late gadolinium enhancement (LGE) (middle), and dark-blood LGE images (bottom) for two patients. **(A)** Widespread perfusion defects can be observed at the basal and mid ventricular levels and in the inferior apical segment. Reduced contrast at the blood-scar boundary with bright-blood LGE imaging led to underestimation of ischemic scar volume when compared to dark-blood LGE, which reduced the calculated myocardial ischemic burden (MIB) (dark-blood ischemic scar burden (ISB) 17.6% vs. bright-blood ISB 11.8%, MIB 16.4% vs. 22.2%, respectively). **(B)** Extensive stress perfusion defects can be seen at all ventricular levels with associated ischemic scar throughout the basal inferioseptum, inferior, inferolateral and mid to apical inferior segments on both LGE images. Greater scar conspicuity with dark-blood LGE led to a higher quantified scar volume, particularly withinin the mid inferior perfusion defect, and a reduced estimation of the MIB (dark-blood ISB 17.4% vs. bright-blood ISB 12.4%, MIB 16.6 % vs. 21.5%, respectively).

ischemia with dark-blood LGE compared with bright-blood LGE. Whilst we observed strong agreement around the 12.5% MIB threshold, this is likely due to inclusion of patients with ischemic heart failure (mean LVEF 46%) and their associated high ischemic burdens, substantially higher than the clinical 12.5% threshold (median dark-blood MIB 15.6%, bright-blood 19.3%). We found a significant MIB mean bias of −2.8% with dark-blood LGE, which corresponded to a large effect size suggesting there is potential to reclassify patients with burdens of ischemia close to the 12.5% threshold. It is noteworthy that the 12.5% MIB threshold utilised in this study is validated and derived from segmental analyses of ischemia [6]. We report ischemic burdens derived in a pixelwise-like fashion. The prognostic impact of this approach was beyond the scope of this study, however, these findings warrant further investigation as they could have potential clinical impact relating to revascularization decision making and patient management.

5. Limitations

1) No histological reference standard was available in this study and therefore this work is unable to comment on which LGE method provides the most accurate measure of scar. However, the dark-blood LGE method used in this study was recently validated against histology in a porcine animal model. Dark-blood LGE demonstrated superior visualization and quantification of scar size compared with conventional bright-blood LGE, with histopathology as reference standard [23]. 2) As per the local scanning protocol at our centre, dark-blood LGE images were acquired before conventional bright-blood LGE. Although a randomized order would have been a preferable study design, this limitation in fact gives conventional bright-blood LGE an advantage in terms of improved scar-to-blood contrast due to the increased contrast washout from the blood pool [24]. 3) Manual exclusion of potential LGE extending beyond a perfusion defect within a myocardial segment was not performed as, without the ability to overlay the perfusion and LGE images, this could have introduced a potential observer bias. 4) In areas where the extent of ischemic scar reaches 100% transmurality, differences in ISB between LGE methods would not impact the MIB. No adjustment was made for this in the analysis as to do so is difficult given the often fluctuating nature of scar transmurality even within myocardial segments.

6. Conclusions

In patients with coronary artery disease, stress perfusion defects are associated with a higher ISB when measured with dark-blood LGE compared with conventional bright-blood LGE, which reduces the estimated MIB. The prognostic value of using a dark-blood LGE derived MIB to guide revascularization is unknown and warrants further investigation.

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CRediT authorship contribution statement

Russell Franks: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Robert J. Holtackers:** Software, Writing – review & editing, Visualization. **Ebraham Alskaf:** Methodology, Formal analysis, Investigation, Writing – review & editing. **Muhummad Sohaib Nazir:** Conceptualization, Methodology, Validation, Writing – review & editing. **Brian Clapp:** Writing – review & editing, Supervision. **Joachim E. Wildberger:** Writing – review &

editing, Supervision. **Divaka Perera:** Writing – review & editing, Supervision. **Sven Plein:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Amedeo Chiribiri:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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