Effect of Myocardial Viability Assessed by Cardiac Magnetic Resonance on Survival in Patients With Severe Left Ventricular Dysfunction

Jonathan Yap; Fang Yi Lim; Fei Gao, PhD; Sinead Z. Wang; Shoen C.S. Low; Thu Thao Le, PhD; Ru-San Tan

Background: Myocardial viability assessment in revascularization of ischemic heart failure remains controversial. This study evaluated the prognostic utility of cardiac magnetic resonance (CMR) late gadolinium enhancement (LGE) in ischemic heart failure.

Methods and Results: This study retrospectively analyzed subjects with ischemic heart failure and left ventricular ejection fraction (LVEF) ≤35%, who underwent CMR at a single center in 2004–2014 before undergoing coronary artery bypass grafting (CABG) or optimal medical therapy (OMT). Analyses were stratified by treatment. Myocardial segments were deemed non-viable if LGE exceeded 50% wall thickness. Overall and anterior viability were assessed. Outcomes were all-cause mortality, cardiovascular (CV) mortality and major adverse CV events. Among 165 subjects (mean (±SD) age 57.5±8.5 years, 152 males), 79 underwent CABG and 86 received OMT. A greater number of non-viable segments was significantly associated with higher all-cause and CV mortality in the CABG group (adjusted hazard ratios 1.17 [95% confidence interval (CI) 1.01–1.37; P=0.04] and 1.25 [95% CI 1.01–1.56; P=0.045], respectively), but not in the OMT (P>0.05) group. Anterior wall viability did not affect outcomes.

Conclusions: The extent of myocardial viability assessed by LGE appeared to identify patients with a differential survival benefit from CABG in this retrospective, small cohort study. These findings raise interesting hypotheses that need to be validated in larger prospective studies.

Key Words: Cardiac magnetic resonance late gadolinium enhancement; Myocardial viability; Revascularization; Severe ischemic left ventricular dysfunction; Survival
with contemporary OMT, unlike with DSE and SPECT. The aim of this study was to investigate the association between myocardial viability assessed by LGE and clinical outcomes after either CABG or OMT in patients with ischemic HF.

**Methods**

**Study Population**
This was a single-center retrospective analysis of clinical outcomes in consecutive ischemic HF patients who had undergone myocardial viability assessment using CMR as part of workup for consideration of surgical revascularization. The recruitment period was from 1 September 2004 to 28 February 2014. All subjects had severely impaired LVEF (≤35%) on CMR. In each patient, the decision for subsequent CABG or OMT was reached based on clinical team review of clinical status, multimodality imaging results (including LGE), and the patient’s wishes. This study has been registered with the Research Registry (www.researchregistry.com, UIN: 4711) and was approved by the SingHealth Centralised Institutional Review Board (2014/604/C). The study was conducted in accordance with the Declaration of Helsinki. Clinical data, baseline demographics, CV risk factors, significant comorbidities, cardiac catheterization reports, CMR findings, and procedural details of CABG were garnered from a review of patients’ medical charts.

**CMR Imaging**
All patients underwent CMR on a 1.5-T CMR scanner (Avanto; Siemens). Cine CMR and, after gadolinium contrast administration, LGE sequences were performed at standard long-axis 2-, 3-, and 4-chamber and a parallel stack of contiguous short-axis slices. LVEF and left ventricular volumes were calculated using standard methods. The CMR wall motion score index was calculated from the 17-segment model, with each segment assigned a score based on systolic motion, as follows: 1: normal; 2, hypokinesia; 3, akinesia; 4, dyskinesia; 5, aneurysmal/scar. A CMR LGE score index was calculated from the 17-segment model, with each segment assigned a score based on the extent of hyperenhancement as follows: 0, 0% hyperenhancement; 1, contemporary OMT, unlike with DSE and SPECT. The aim of this study was to investigate the association between myocardial viability assessed by LGE and clinical outcomes after either CABG or OMT in patients with ischemic HF.

**Table 1. Baseline Characteristics of the Entire Study Population and in CABG or OMT Groups Separately**

| Characteristic                        | Whole cohort (n=165) | CABG (n=79) | OMT (n=86) |
|--------------------------------------|---------------------|-------------|------------|
|                                      | Viable (n=64)       | Non-viable (n=15) | P-value | Viable (n=49) | Non-viable (n=37) | P-value |
| Age (years)                          | 58±8.8              | 54±9.9      | 0.13      | 60±10.0       | 56±9.0           | 0.065   |
| Male sex                             | 152 (92)            | 14 (93)     | 1.00      | 44 (90)       | 35 (95)          | 0.69    |
| Ethnicity                            | Chinese 106 (64)    | 5 (33)      | <0.01     | 31 (63)       | 21 (57)          |         |
|                                      | Malay 34 (21)       | 7 (42)      |           | 16 (33)       | 7 (19)           |         |
|                                      | Indian 21 (13)      | 6 (40)      |           | 1 (2)         | 7 (19)           |         |
|                                      | Other 4 (2)         | 0 (0)       |           | 1 (2)         | 2 (5)            |         |
| BMI (kg/m²)                          | 24.8±4.2            | 24.6±4.2    | 0.72      | 24.9±4.1      | 25.0±4.3         | 0.98    |
| Comorbidities                        |                     |             |           |               |                  |         |
| Hypertension                         | 87 (53)             | 8 (53)      | 1.00      | 24 (49)       | 19 (51)          | 1.00    |
| Hyperlipidemia                       | 102 (62)            | 10 (67)     | 0.75      | 25 (51)       | 20 (54)          | 0.83    |
| Diabetes                             | 83 (50)             | 10 (67)     | 0.26      | 25 (51)       | 17 (46)          | 0.67    |
| COPD                                 | 5 (3)               | 1 (7)       | 0.47      | 1 (2)         | 1 (3)            | 1.00    |
| Smoker                               | 86 (52)             | 13 (87)     | 0.04      | 19 (39)       | 18 (49)          | 0.39    |
| Prior MI                             | 95 (58)             | 12 (80)     | 0.08      | 25 (51)       | 24 (65)          | 0.27    |
| Prior PCI                            | 135 (82)            | 14 (93)     | 1.00      | 26 (73)       | 29 (79)          | 0.62    |
| Prior CABG                           | 0 (0)               | 0 (0)       | –         | 0 (0)         | 0 (0)            | –       |
| Prior symptomatic HF                 | 71 (43)             | 6 (40)      | 1.00      | 20 (41)       | 17 (46)          | 0.67    |
| Prior valvular heart disease*        |                     |             |           |               |                  |         |
| Mitral regurgitation                 | 84 (51)             | 7 (47)      | 0.18      | 25 (51)       | 16 (43)          | 0.92    |
| Mitral stenosis                      | 0 (0)               | 0 (0)       | –         | 0 (0)         | 0 (0)            | –       |
| Aortic regurgitation                 | 11 (7)              | 1 (7)       | 1.00      | 4 (8)         | 1 (3)            | 0.78    |
| Aortic stenosis                      | 1 (1)               | 0 (0)       | 1.00      | 0 (0)         | 0 (0)            | –       |
| Tricuspid regurgitation              | 49 (0)              | 5 (33)      | 0.21      | 18 (37)       | 8 (22)           | 0.10    |
| Atrial fibrillation                  | 13 (8)              | 1 (7)       | 1.00      | 4 (8)         | 3 (8)            | 1.00    |
| Prior stroke                         | 26 (16)             | 1 (7)       | 0.68      | 12 (24)       | 4 (11)           | 0.16    |
| Renal impairment                     | 15 (9)              | 0 (0)       | 0.58      | 6 (12)        | 4 (11)           | 1.00    |
| Creatinine (μmol/L)                  | 106±51              | 99±27       | 0.72      | 108±50        | 104±32           | 0.62    |
| Peripheral vascular disease          | 4 (2)               | 1 (7)       | 0.19      | 2 (4)         | 1 (3)            | 1.00    |
| Presentation                         |                     |             |           |               |                  |         |
| STEMI                                | 24 (15)             | 3 (20)      |           | 4 (8)         | 12 (32)          |         |
| NSTEMI                               | 57 (35)             | 1 (7)       |           | 21 (43)       | 2 (5)            |         |

(Table 1 continued the next page.)
1–25% hyperenhancement; 2, 26–50% hyperenhancement; 3, 51–75% hyperenhancement; 4, 76–100% hyperenhancement. Anterior segments were defined as basal anteroseptal, basal anterior, mid-anteroseptal, mid-inferoseptal, mid-anterior, apical septal, apical anterior, apical lateral, apical inferior, and apex. Non-viable segments were defined as segments having >50% hyperenhancement. Primary analysis was performed with viability as a continuous variable. Secondary analysis was performed using viability as a dichotomous variable with a cut-off of ≥4 non-viable segments defined as non-viable. Sensitivity analyses were also performed at a range of other cut-off values (5, 6, and 7 non-viable segments).

Outcomes
Subjects were followed up until a common end-of-study date, namely 1 January 2015. The primary outcome measure was all-cause mortality. Secondary outcome measures were CV mortality and major adverse CV events (MACE) comprising CV death, non-fatal myocardial infarct, non-fatal stroke, and coronary revascularization with either CABG or percutaneous coronary intervention (PCI). Outcomes were obtained from national registries and a review of patients’ health records.

Statistical Analysis
Subjects were stratified into CABG and OMT groups for analysis. As these groups were non-randomized with inherent biases related to the complex clinical decision-making process, all analyses were performed separately in each group. Baseline demographics and risk factors were reported and compared between subjects with dichotomous left ventricular overall viable vs. non-viable status using descriptive statistics, Fisher’s exact test or a t-test as appropriate. Survival time was measured from recruitment to the date of outcomes or date of censor (1 January 2015). Hazard ratios (HRs) for outcomes and their corresponding 95% confidence intervals (CIs) for overall and anterior territory viability status were derived using a Cox proportional hazards model. We tested the constant proportional hazards on the basis of Schoenfeld residuals and no violation to the proportional hazards assumption was observed. Two-tailed P<0.05 was considered statistically significant. Stata version 13 (StataCorp, College Station, TX, USA) was used for all analyses.

Results
Study Population
Of a total of 165 enrolled subjects (mean ±SD age 57.5±8.5 years, 152 males), 79 underwent CABG and 86 received...
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Table 2. Outcomes for the Study Population

| CABG         | Overall viable (n=64) | Overall non-viable (n=15) | Anterior viable (n=68) | Anterior non-viable (n=11) | OMT          | Overall viable (n=49) | Overall non-viable (n=37) | Anterior viable (n=56) | Anterior non-viable (n=30) |
|--------------|----------------------|---------------------------|------------------------|---------------------------|--------------|-----------------------|--------------------------|------------------------|--------------------------|
| All-cause mortality | 11 (17)               | 7 (47)                    | 14 (21)                | 4 (36)                    | 21 (43)      | 13 (35)               | 22 (39)                  | 12 (40)                |                          |
| CV mortality  | 6 (9)                 | 5 (33)                    | 8 (12)                 | 3 (27)                    | 19 (39)      | 10 (27)               | 19 (34)                  | 10 (33)                |                          |
| MACE         | 19 (30)               | 9 (60)                    | 23 (34)                | 5 (45)                    | 25 (51)      | 17 (46)               | 27 (48)                  | 15 (50)                |                          |

Data are given as n (%). "Non-viable" was defined as ≥4 non-viable segments. CV, cardiovascular; MACE, major adverse cardiac events. Other abbreviations as in Table 1.

Table 3. Effect of Viability Assessment by CMR on Outcomes in the CABG and OMT Groups

| Overall viability | All-cause mortality | MACE | CV mortality | All-cause mortality | MACE | CV mortality |
|-------------------|---------------------|------|--------------|---------------------|------|--------------|
| CABG              | HR (95% CI)         | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Continuous*       | 1.19 (1.01–1.41)    | 0.04  | 1.13 (0.90–1.30) | 0.07  | 1.29 (1.03–1.60) | 0.03  |
| Dichotomous       | 2.34 (0.90–6.13)    | 0.08  | 2.02 (0.91–4.49) | 0.09  | 3.58 (1.08–11.9) | 0.04  |

| CABG              | HR (95% CI)         | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
|-------------------|---------------------|------|--------------|-------------------|------|--------------|
| Anterior viability| Continuous*         | 1.13 (0.93–1.38) | 0.21 | 1.09 (0.93–1.28) | 0.28 | 1.19 (0.93–1.52) | 0.18 |
| Dichotomous       | 1.53 (0.50–4.71)    | 0.46  | 1.22 (0.46–3.24) | 0.69 | 2.17 (0.57–8.34) | 0.26  |

Primary analysis was performed with viability as a continuous variable. Secondary analysis was performed using viability as a dichotomous variable with a cut-off of ≥4 non-viable segments defined as non-viable. *Per unit increase in the number of non-viable segments. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,2.

OMT. The mean (±SD) duration of follow-up was 3.9±2.7 years. Table 1 summarizes the baseline demographics and clinical characteristics of the study population.

Effect of Overall Myocardial Viability on Outcomes

The number of outcome events per group is given in Table 2. On univariate analysis, a unit increase in the number of non-viable left ventricular wall segments was significantly associated with higher incident all-cause mortality (HR 1.19; 95% CI 1.01–1.41; P=0.04) and CV mortality (HR 1.29; 95% CI 1.03–1.60; P=0.03) in the CABG group, but not in the OMT group. This remained significant after adjustment for confounders of age, body mass index, atrial fibrillation, and diabetes for overall mortality (adjusted [aHR] 1.17; 95% CI 1.01–1.37; P=0.04) and after adjustment for confounders of age, body mass index, and diabetes for CV mortality (aHR 1.25; 95% CI 1.01–1.56; P=0.045). A unit increase in left ventricular non-viable wall segments was associated with a non-significant trend for increased MACE events in the CABG group (HR 1.13; 95% CI 0.99–1.30; P=0.07), but not in the OMT group (HR 1.01; 95% CI 0.92–1.10; P=0.85). Analyses using dichotomous left ventricular overall viability status at a threshold of 4 non-viable segments demonstrated a significant effect on CV mortality in the CABG group (HR 3.58; 95% CI 1.08–11.9; P=0.04); this remained significant after adjustment for the above confounders (aHR 3.86; 95% CI 1.11–13.4; P=0.03). However, this dichotomous cut-off did not demonstrate a significant effect on all-cause mortality in either the CABG (HR 2.34; 95% CI 0.90–6.13; P=0.30) or OMT (HR 0.74; 95% CI 0.37–1.48; P=0.40) group. There was also no significant effect on MACE using this dichotomous cut-off in either group. Additional sensitivity analyses performed at other cut-off values (5, 6, and 7 non-viable segments) also did not yield any significant findings (Table 3; Figures 1-2).

Effect of Anterior Viability on Outcomes

The presence of anterior territory viability, either continuous or dichotomous, did not significantly affect all-cause mortality and MACE outcomes in either the CABG or OMT group (Table 3). Additional sensitivity analyses performed at other cut-off values did not yield any significant findings.

Comparison of CMR and SPECT

In all, 63 patients underwent both CMR and SPECT. Of the 19 patients with at least moderate ischemia on SPECT, CMR showed viability in 18. Of the 44 patients with nor or mild ischemia on SPECT, CMR showed viability in at
High perioperative mortality. STICH, the only contemporary randomized controlled trial of CABG plus OMT vs. OMT alone in severe ischemic cardiomyopathy (Hypothesis 1), showed neutral primary mortality outcomes on an intention-to-treat analysis, a result that had to be interpreted in light of the high degree of treatment cross-overs. Per-protocol analysis demonstrated mortality benefits in subjects who actually underwent CABG compared with OMT alone. This benefit favoring CABG persisted when mortality rates between the original randomization treatment arms were compared, after excluding survivors who withdrew, in the STICH Extension Study (STICHES) that followed subjects up to 10 years.

In severe left ventricular dysfunction, selecting patients with sufficient viable myocardium that may recover contractile function after revascularization is a reasonable and appealing management approach. Various investigators reported that revascularization of viable myocardium significantly improved both global and segmental func-

Discussion

Few studies have investigated the association between myocardial viability assessment by LGE and clinical outcomes in patients with ischemic HF treated with either CABG or OMT. In the present study, an increasing number of non-viable wall segments on LGE was significantly associated with both all-cause and CV mortality in surgically revascularized patients, with a non-significant trend towards more MACE events. Anterior territory LGE extent did not have a significant effect on outcomes in either group.

In patients with severe ischemic left ventricular dysfunction (LVEF ≤35%), the post-CABG improvement in symptoms and survival is counterbalanced by recognized high perioperative mortality. STICH, the only contemporary randomized controlled trial of CABG plus OMT vs. OMT alone in severe ischemic cardiomyopathy (Hypothesis 1), showed neutral primary mortality outcomes on an intention-to-treat analysis, a result that had to be interpreted in light of the high degree of treatment cross-overs. Per-protocol analysis demonstrated mortality benefits in subjects who actually underwent CABG compared with OMT alone. This benefit favoring CABG persisted when mortality rates between the original randomization treatment arms were compared, after excluding survivors who withdrew, in the STICH Extension Study (STICHES) that followed subjects up to 10 years.

In severe left ventricular dysfunction, selecting patients with sufficient viable myocardium that may recover contractile function after revascularization is a reasonable and appealing management approach. Various investigators reported that revascularization of viable myocardium significantly improved both global and segmental func-

Figure 1. Kaplan-Meier curves for all-cause mortality in patients with viable vs. non-viable myocardium who underwent (A) coronary artery bypass grafting or (B) optimal medical therapy.

Figure 2. Kaplan-Meier curves for major adverse cardiac events (MACE)-free survival in patients with viable vs. non-viable myocardium who underwent (A) coronary artery bypass grafting or (B) optimal medical therapy.
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Table 4. Comparison of CMR and SPECT

| CABG (n=34) | OMT (n=29) |
|-------------|------------|
| **No or mild ischemia on SPECT (n=20)** | **Moderate-severe ischemia on SPECT (n=14)** | **No or mild ischemia on SPECT (n=24)** | **Moderate-severe ischemia on SPECT (n=5)** |
| <4 Non-viable segments on CMR (n=14) | ≥4 Non-viable segments on CMR (n=6) | <4 Non-viable segments on CMR (n=13) | ≥4 Non-viable segments on CMR (n=1) |
| 2 deaths | 2 deaths | 3 deaths | 0 death |
| (1 CV death) | (1 CV death) | (3 CV deaths) | (0 CV death) |
| ≥4 Non-viable segments on CMR (n=10) | <4 Non-viable segments on CMR (n=5) | ≥4 Non-viable segments on CMR (n=5) | ≥4 Non-viable segments on CMR (n=0) |
| 7 deaths | 3 deaths | 3 deaths | 0 death |
| (6 CV deaths) | (3 CV deaths) | (3 CV deaths) | (0 CV deaths) |

SPECT, single photon emission computed tomography. Other abbreviations as in Tables 1,2.

The findings of the present study may potentially have some effect on patient selection for surgical revascularization among patients with ischemic HF, but this will have to be validated further. Although we did not find a specific dichotomous cut-off value for viability that affected all-cause mortality, a cut-off of 4 non-viable segments seemed to identify a group with less CV mortality with CABG. The use of viability as a continuous variable was also significant for both overall and CV mortality. Thus, CMR viability assessment may be used by the clinician in the overall patient assessment as an additional tool to aid in the complex decision-making process for revascularization in this fragile group. The decision for revascularization in this group of patients is always difficult and multifactorial. In cases where the decision may be less than straightforward, the presence of viability may provide the heart team with some evidence to lean towards revascularization. This has to be taken into account on a case-by-case basis, looking at the patient as a whole.

We also analyzed anterior territory viability because prior studies have shown that the prognostic benefit in revascularization arises primarily from revascularization of the left main or left anterior descending artery. In this study, anterior viability did not affect outcomes in either group, but the small number of patients may mean that the study is not powered to show any potential differences, and this needs to be validated in further studies. However, in the present study, overall viability appears to be a stronger predictor of outcomes than anterior viability in those predicting functional recovery than a combination of PET and SPECT (97% vs. 87%), and has a higher negative predictive value than the combination of PET and SPECT (93% vs. 77%), suggesting a possible advantage in identifying viability. In the present study we found that an increase in the number of non-viable segments on LGE was significantly associated with higher all-cause and CV mortality in patients who underwent CABG. The differences between the results of the present study and those of the STICH and PARR-2 trials may be accounted for, at least in part, by differences in the imaging modality of viability assessment, with LGE being more accurate. In the present study, of the 44 patients with no or mild ischemia on SPECT, 28 had viability demonstrated on CMR. Of these 28 patients, 14 underwent CABG, with only 1 CV mortality in this group. This explanation is strengthened by corroborative evidence. In a cohort of 144 patients with ischemic cardiomyopathy, Gerber et al found that, in the presence of dysfunctional viable myocardium as determined by LGE, revascularization had a significantly higher effect on survival than medical treatment (HR 4.56; 95% CI 1.93–10.90).

In all the studies described above, LGE had not been used for the assessment of myocardial viability. LGE is an accurate tool for determining myocardial viability, whereby gadolinium-based contrast causes hyperenhancement of scarred infarcted tissue due to increased extracellular volume. Fibrosis <50% of wall thickness is deemed viable. Thus, viable and infarcted myocardium may be identified independent of wall motion and infarct age, and with close correlation to histologic findings. LGE has been well validated in both preclinical and clinical studies in animals and humans, and has been shown to be a strong prognostic factor for all-cause mortality and MACE. Several studies have suggested that CMR provides a better assessment of viability than SPECT and PET. SPECT overestimates scar tissue, causing significant variation from LGE in terms of the mean number of segments classified as scar. Conversely, PET underestimates scar tissue relative to CMR due to lower spatial resolution than CMR, with Klein et al reporting that 11% of segments defined as viable on PET having some degree of LGE on CMR, suggesting non-viability. In another study, Kuhl et al showed that LGE is more sensitive in

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who are revascularized by CABG. This may indicate the importance of the whole left ventricle rather than a particular distribution, especially in this group of patients with severe globally impaired left ventricular function.

**Study Limitations**

There are several limitations that require consideration. First, this study is a retrospective review and has its inherent biases. CABG and OMT were non-randomized. Patient decision may have influenced treatment choice, and data on patients who were recommended to have CABG but decided on OMT were not available. Hence, we stratified the analysis of the cohort based on treatment received to study the effect of viability in each stratum. Second, this study was performed on a small cohort of patients, and the findings need to be confirmed in a randomized controlled trial with sufficient patient numbers and well-defined criteria for treatment assignment. Third, the use of CMR LGE in patients with advanced chronic kidney disease is limited in view of the potential of nephrogenic systemic fibrosis. Finally, data were not available for comparisons of patients who underwent both DSE and CMR; we did, however, perform a subset analysis on those who had concomitant SPECT and CMR.

**Conclusions**

In the present retrospective small cohort study, the extent of myocardial viability assessed by LGE appeared to identify patients with a differential survival benefit among those undergoing CABG, but not in medically treated patients. These findings raise interesting hypotheses that will need to be validated in larger prospective randomized controlled trials.

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**Disclosures**

None.

**IRB Information**

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