Prognostic value of perfusion cardiovascular magnetic resonance with adenosine triphosphate stress in stable coronary artery disease

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Abstract

Background: Adenosine triphosphate (ATP) has been predominantly used in the Asia–Pacific region for stress perfusion cardiovascular magnetic resonance (CMR). We evaluated the prognosis of patients stressed using ATP, for which there are no current data.

Methods: We performed a retrospective longitudinal study from January 2016 to December 2020 and included 208 subjects with suspected obstructive coronary artery disease (CAD) who underwent ATP stress perfusion CMR. An inducible stress perfusion defect was defined as a subendocardial dark rim involving ≥ 1.5 segments that persisted for ≥ 6 beats during stress but not at rest. The primary outcome measure was a composite of major adverse cardiovascular events (MACE) including (1) cardiac death, (2) nonfatal myocardial infarction, (3) cardiac hospitalization, (4) late coronary revascularization. We compared outcomes in patients with and without perfusion defect using Kaplan–Meier and log rank tests. Significant predictors of MACE were identified using multivariable Cox regression analysis.

Results: Median follow-up was 3.3 years. Patients with no stress perfusion defect had a lower incidence of MACE (p < 0.001), including lower cardiac hospitalization (p = 0.004), late coronary revascularization (p = 0.001) and cardiac death (p = 0.003). Significant independent predictors for MACE were stress induced perfusion defect (p < 0.001, hazard ratio [HR] = 3.63), lower left ventricular ejection fractino (LVEF) (p < 0.001, HR = 0.96) and infarct detected by late gadolinium enhancement (LGE) (p = 0.001, HR = 2.92).

Conclusion: Perfusion defects on ATP stress are predictive of MACE which is driven primarily by cardiac hospitalization, late coronary revascularization and cardiac death. Significant independent predictors of MACE were stress induced perfusion defect, lower LVEF and infarct detected by LGE.

Keywords: Adenosine triphosphate, Stress, Cardiovascular magnetic resonance, Prognosis, Coronary artery disease

Introduction

Stress perfusion cardiac magnetic resonance (CMR) is a low-risk and non-invasive imaging modality for diagnosis of coronary artery disease (CAD) with high sensitivity, specificity and accuracy [1, 2]. Apart from its diagnostic accuracy, stress perfusion CMR is also recognized for its high prognostic value in risk stratification of patients...
of known or suspected CAD when using adenosine, dipyridamole and regadenoson as the vasodilator agent [3–10]. However, the prognostic value of adenosine triphosphate (ATP) as a vasodilator for stress CMR is not well-established. ATP has similar vasodilatory and hemodynamic changes to adenosine [11] and due to its lower cost and/ or licensing/ production issues of alternative pharmaceutical agents, it has been a commonly used alternative in the Asian Pacific region [11–14] and some European countries [15, 16]. Although ATP stress CMR might be assumed to have prognostic significance, this has never been demonstrated. Therefore, we performed this study to evaluate the prognostic significance of ATP stress CMR in order to confirm this hypothesis.

**Methods**

This study was approved by the Institutional Review Board of the Hong Kong West Cluster. Requirement for informed consent was waived. This study was a retrospective longitudinal study. Patients from the University of Hong Kong and Queen Mary Hospital’s database were identified from 1st January 2016 to 31st March 2019 and 1st January 2017 to 31st December 2017 respectively. Inclusion criteria were patients ≥ 18 years undergoing ATP stress CMR for suspected or known obstructive CAD. Exclusion criteria included coronary artery bypass grafts, known hypertrophic cardiomyopathy, myocarditis, implantation of cardiac pacemaker or implantable cardiac defibrillator, history of asthma or bronchospasm, incomplete notes to determine adequate stress and second or third-degree atrioventricular block. A total of 208 subjects were identified (see Fig. 1).

**CMR protocol**

A 3 T CMR scanner (Achieva, Philips Healthcare, Best, the Netherlands) with a 16-element phased array coil or a 1.5 T CMR scanner (Aera, Siemens Healthcare, Erlangen, Germany) with a 32-element phased array coil were used in all cases. Subjects were given ATP at an infusion rate of 0.14 mg/kg/min for at least 3 min, followed by an intravenous administration of gadoterate meglumine (injection rate: 3 to 4 mL/s, with a subsequent 30 mL saline flush at the same flow rate) to obtain the first-pass perfusion images using a T1 weighted fast gradient echo sequence for both scanners. [Philips Achieva: echo time (TE) 1.2 ms, repetition time (TR) 2.5 ms, flip angle 20°, field of view 320 mm x 320 mm, slice thickness 10 mm, Siemens Aera: TE 0.98 ms, TR 177 ms, flip angle 50°, voxel size 2.3 x 2.3 x 8 mm]. Three perfusion short-axis slice images (base, mid, apex) of the left ventricle were acquired. This was followed by acquisition of a short-axis cine stack using balanced steady-state free precession (bSSFP) (3 T Philips Achieva: TE/TR = 1.48/2.96 ms, flip angle 45°, slice thickness 8 mm, 25 cardiac phases; 1.5 T Siemens Aera TE/TR 1.28/40.17 ms, voxel size 1.2 x 1.2x6mm. flip angle 62°, slice thickness 8 mm, 25 phases) and analyzed with cmr42 software (Circle Cardiovascular Imaging, Inc., Calgary, Alberta, Canada) or

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**Fig. 1** Patient flow diagram

- HKU CMR Scans (n=666)
- QMH CMR Scans (n=651)
- Total CMR Scans (n=1317)
- Excluded cases:
  - 14 hypertrophic cardiomyopathy
  - 6 Inadequate stress response
  - 73 incomplete notes
  - 1 Coronary artery bypass graft
  - 2 permanent pacemakers in situ
  - 9 asthma
  - 1004 Non-stress CMR Scans
- Eligible Stress CMR Scans (n=208)
Syno Via (Siemens Healthineers). Long axis bSSFP cine images were acquired in the 2, 3 and 4-chamber orientations. Rest perfusion images were acquired in the same three short axis positions as the stress perfusion images at least 10 min after termination of ATP infusion. Inversion time scout images were acquired to determine the ideal inversion time for late gadolinium enhancement (LGE). LGE images were acquired 8–15 min after the second gadoterate meglumine injection for rest perfusion images. For the 3 T Philips Achieva, segmented phase sensitive inversion recovery (PSIR) LGE images were acquired (TE 3 ms, TR 6.1 ms, flip angle 25 degrees, slice thickness 8 mm). For the 1.5 T Siemens Aera, PSIR LGE images were acquired (TE 3–4 ms, TR 8–9 ms, flip angle 25 degrees, slice thickness 8 mm).

Adequate stress response
Adequate stress response to ATP was defined as two or more of the following criteria: (1) heart rate increase \( \geq 10 \) bpm, (2) systolic blood pressure decrease \( \geq 10 \) mmHg, (3) positive splenic switch-off sign, and (4) presence of stress symptoms (e.g. chest pain, shortness of breath, headache). Inadequate stress was defined as 0 or 1 of the above criteria. A subsequent 50% increased infusion rate would be given for an inadequate stress response [17]. If adequate stress response was still not achieved, no further infusion rate increase was delivered.

ATP perfusion and LGE assessment
Following previous publications on prognostic significance of regadenoson, adenosine and dipyridamole stress CMR [7, 8, 18], we identified significant inducible stress perfusion defects on the stress perfusion images (see Fig. 2) as previously described [19]. Briefly a stress-induced perfusion defect was defined as a subendocardial rim of reduced signal involving \( \geq 1.5 \) segments that persisted for \( \geq 6 \) beats during stress but not at rest without matching enhancement on LGE imaging [19, 20]. Rest perfusion defects and perfusion defects matching LGE were not regarded as stress induced perfusion defects. Reporting radiologists and cardiologists were blinded to the clinical outcome. Reporting was performed by either one or two radiologists/ cardiologists. At a minimum one of those reporting had level 3 accreditation. Myocardial LGE was quantified using the cmr42 software (Circle Cardiovascular Imaging, Inc.) [21]. LGE was identified as 5 standard deviations above the mean.

CMR ventricular function, volume analysis and image quality assessment
Left ventricular (LV) function and volumes were assessed using the bSSFP short axis cine images and analyzed with cmr42 software (Circle Cardiovascular Imaging, Inc.) to give the following CMR parameters: (1) LV end-diastolic volume, (2) LV end-systolic volume, (3) LV ejection fraction (LVEF), and (4) LV mass. Volumes and mass were corrected for body surface area using the Mosteller equation [22]. Image quality scoring of the perfusion and LGE images were performed using a Likert scale from 1 to 4. A score of 1 being excellent and 4 being non-diagnostic. Fifty cases were chosen at random. Mean and standard deviation for perfusion and LGE image quality scoring were 1.4 (SD 0.6) and 1.8 (SD 0.6).

Major adverse cardiovascular events
The subsequent hospital-related activities of the subjects were obtained through the territory-wide Electronic Patient Record system, including any clinical follow-ups, inpatient and outpatient care records, and examinations performed. The primary outcome measure of this study is a composite of major adverse cardiovascular events (MACE) consisting of (1) cardiac death, (2) non-fatal myocardial infarction (MI), (3) cardiac hospitalization, and (4) late coronary revascularization. Cardiac hospitalization included any in-patient hospital stay due to a cardiovascular events (i.e. heart failure or acute coronary syndrome), while late coronary revascularization includes percutaneous coronary intervention, and coronary artery bypass grafting more than 90 days post stress CMR. We recorded all cardiovascular events these subjects experienced, and their first events were used for analysis regarding composite MACE. For the annualized event rate, we used cardiac death and non-fatal
myocardial infarct events only in keeping with other publications and meta-analysis [8, 10].

**Statistical analysis**
Continuous variables are presented as mean ± standard deviations. Categorical variables are presented in
numbers with percentages in brackets. Student’s t-test was used to compare normally distributed variables. Mann–Whitney U test was used to compare non-normally distributed variables. Categorical variables were compared using Fisher’s exact test.

The outcomes of subjects with and without inducible perfusion defects on ATP stress CMR findings were compared using Kaplan Meier survival curve with log rank test. Sub-analysis of each type of MACE was also performed with Kaplan Meier survival curve and log rank test to determine the main drivers of the composite MACE outcome. A multivariable Cox regression model was created using the variables stress induced perfusion defect, LGE infarct and LVEF which all had a p-value < 0.05 on univariate Cox regression analysis. All statistical analyses were done using SPSS (version 26.0, Statistical Package for the Social Sciences, International Business Machines, Inc., Armonk, New York, USA).

Results
Subjects had a mean age of 61.2 ± 14.8 years and 123 were male (59.1%). Table 1 shows the characteristics of subjects with MACE compared to those without.

Adequate stress response to standard dose and a 50% higher infusion rate was achieved in 196 (94.2%) and 12 (5.8%) cases respectively.

ATP side-effects
One hundred patients (48.1%) experienced symptoms during ATP infusion. Side-effects included chest pain, shortness of breath, headache, palpitation and hot flushing. The symptoms were mild and resolved shortly after the ATP infusion was completed. No medical complications were encountered. See Table 2 for the frequency of different side-effects experienced by subjects during stress test.

Abnormal CMR findings
Out of 208 patients, 87 patients (male: female = 59:28) had abnormal CMR findings. Of these 87 patients, the patients had one or more of the following abnormalities: 35 (40.2%) had LVEF < 50%, 51 (58.6%) had MI detected by LGE, and 38 (43.7%) had stress induced perfusion defects. 6 patients (6.9%) had all three abnormalities, 25 (28.7%) had two of the three abnormalities, and 56 (64.4%) had only one of the three abnormalities.

Incidence of MACE composite endpoints
The median follow-up period was 3.3 years (interquartile range from 2.7 to 3.7 years).

Table 3 shows the incidence of MACE composites in patients with and without stress induced perfusion defects. Results of Kaplan Meier analysis showed that the primary endpoint of composite MACE was significantly different between patients with and without stress induced perfusion defects (p < 0.001) (Fig. 3). On sub-analysis of the individual endpoints, late coronary revascularization (p = 0.001), cardiac hospitalization (p = 0.004) and cardiac death (p = 0.003) were significantly different between the two groups (see Fig. 4a–d). There was no significant difference in non-fatal MI (p = 0.646) (see Fig. 4c).

The annualised event rate for patients with no stress induced perfusion defect was 0.4% vs 2.8% for patients with perfusion defects (Table 4).

Predictors for higher incidence rate of MACE
Subjects with MACE had significantly higher age, smoking rates, estimated glomerular filtration rate, prevalence of atrial fibrillation, LV end-diastolic volume index, LV end-systolic volume index, LV mass index, resting heart rate, LVEF < 50%/ lower LVEF, infarct detected by LGE, stress induced perfusion defect (see Table 1). Univariate Cox regression analysis of these factors is shown in Additional file 1: Table S2.

Using multivariable Cox regression analysis, stress induced perfusion defect (p < 0.001, hazard ratio [HR] = 3.63), lower LVEF (p < 0.001, HR = 0.96) and infarct detected by LGE (p = 0.001 h = 2.92) were identified as the predictors for higher incidence of MACE (Table 5).

Discussion
Our study showed that similar to other vasodilator stress agents, ATP stress CMR is also predictive of MACE. A stress induced perfusion defect on ATP stress CMR was associated with a higher risk of MACE (hazard ratio = 3.63) over a median follow-up of 3.3 years with an annualized event rate of 2.8%. The main drivers of this increased risk were the incidence of cardiac hospitalization, late coronary revascularization and cardiac death which were significantly higher in patients with stress induced perfusion defects on ATP stress CMR examinations. Alternatively, absence of a stress induced perfusion defect on ATP stress CMR had an annualized event rate of 0.4%. With multivariable cox regression analysis, stress induced perfusion defect, LVEF and MI detected by LGE were independent rick factors for MACE.

ATP has a short half-life of 20 s [23] and has vasodilatory effects like adenosine. Once ATP is infused intravenously, there is incremental cleavage of each phosphate compound. The resulting adenosine thus activates the $A_1$ and $A_2$ receptors producing the same vasodilatory effect as the more established intravenous adenosine infusion [24].
| General information                              | Subjects with MACE (n = 39) | Subjects without MACE (n = 169) | P value  |
|-------------------------------------------------|----------------------------|---------------------------------|---------|
| Age (yrs)                                        | 67.8 ± 12.8                | 59.8 ± 14.8                     | 0.001*  |
| Male                                            | 26 (66.7%)                 | 97 (57.4%)                      | 0.288   |
| Height (cm)                                     | 163.8 ± 10.4               | 163.5 ± 9.7                     | 0.847   |
| Weight (kg)                                     | 67.5 ± 13.3                | 67.3 ± 14.6                     | 0.932   |
| BMI (m²)                                        | 25.0 ± 3.8                 | 25.0 ± 4.2                      | 0.988   |
| Hypertension                                    | 26 (66.7%)                 | 90 (53.3%)                      | 0.128   |
| Diabetes                                        | 11 (28.2%)                 | 42 (24.9%)                      | 0.665   |
| Hyperlipidemia                                  | 14 (35.9%)                 | 64 (37.9%)                      | 0.819   |
| Smoking                                         | 9 (23.1%)                  | 11 (6.5%)                       | 0.002*  |
| Estimated glomerular filtration rate (mL/min/1.73m²) | 73.2 ± 23.8                | 80.5 ± 21.3                     | 0.025*  |
| Atrial fibrillation                             | 8 (20.5%)                  | 6 (3.6%)                        | <0.001* |
| Cardiac history                                 |                            |                                 |         |
| Heart failure                                   | 5 (12.8%)                  | 6 (3.6%)                        | 0.020*  |
| Myocardial infarction                           | 2 (5.1%)                   | 0 (0%)                          | 0.003*  |
| Coronary artery disease                         | 13 (33.3%)                 | 58 (34.3%)                      | 0.907   |
| Symptoms for CMR referral                       |                            |                                 |         |
| Chest pain                                      | 16 (41.0%)                 | 68 (40.2%)                      | 0.928   |
| Shortness of breath                              | 0                          | 8 (4.7%)                        | 0.166   |
| Palpitation                                     | 0                          | 6 (3.6%)                        | 0.232   |
| Dizziness                                       | 0                          | 2 (1.2%)                        | 0.495   |
| Loss of consciousness                           | 1 (2.6%)                   | 3 (1.8%)                        | 0.746   |
| CMR parameters                                   |                            |                                 |         |
| 1.5 T                                           | 16 (41.0%)                 | 71 (42.0%)                      | 0.910   |
| 3.0 T                                           | 23 (59.0%)                 | 98 (58.0%)                      | 0.910   |
| LV end-diastolic volume index (mL/m²)            | 101.1 ± 64.1               | 81.3 ± 23.1                     | 0.001*  |
| LV end-systolic volume index (mL/m²)             | 60.4 ± 65.4                | 33.8 ± 21.0                     | <0.001* |
| LV ejection fraction (%)                        | 50.2 ± 19.5                | 60.7 ± 12.6                     | <0.001* |
| LV mass index (g/m²)                            | 83.7 ± 39.7                | 60.9 ± 17.0                     | <0.001* |
| Heart rate at rest (bpm)                        | 76.4 ± 16.6                | 67.2 ± 12.3                     | <0.001* |
| Systolic blood pressure at rest (mmHg)           | 146.2 ± 22.7               | 139.9 ± 20.6                    | 0.103   |
| Diastolic blood pressure at rest (mmHg)          | 89.3 ± 12.1                | 85.1 ± 13.1                     | 0.241   |
| ATP infusion time (min)                         | 4.3 ± 0.7                  | 4.4 ± 0.8                       | 0.496   |
| Abnormal wall motion                            | 17 (43.6%)                 | 22 (13.0%)                      | <0.001* |
| Medications                                      |                            |                                 |         |
| Beta-blocker                                    | 20 (51.3%)                 | 68 (40.2%)                      | 0.208   |
| Calcium channel blocker                         | 9 (23.1%)                  | 52 (30.8%)                      | 0.342   |
| ACE inhibitor                                    | 15 (38.5%)                 | 37 (21.9%)                      | 0.031*  |
| Statin                                          | 27 (69.2%)                 | 96 (56.8%)                      | 0.155   |
| Aspirin                                         | 21 (53.9%)                 | 81 (47.9%)                      | 0.505   |
| Digoxin                                         | 0 (0%)                     | 1 (0.6%)                        | 0.630   |
| Side-effects                                     |                            |                                 |         |
| Chest pain                                      | 13 (33.3%)                 | 51 (30.2%)                      | 0.700   |
| Shortness of breath                              | 10 (25.6%)                 | 31 (18.3%)                      | 0.302   |
| Headache                                        | 3 (7.7%)                   | 14 (8.3%)                       | 0.903   |
| Palpitation                                     | 3 (7.7%)                   | 12 (7.1%)                       | 0.898   |
| Hot flushing                                    | 0 (0%)                     | 2 (1.2%)                        | 0.495   |
| Stress CMR findings                              |                            |                                 |         |
| LVEF < 50%                                       | 15 (38.5%)                 | 20 (11.8%)                      | <0.001* |
ATP is a readily accessible and less expensive in parts of the Asia Pacific region relative to other stress agents. The cost of ATP in our centre is approximately US$15 per patient whilst adenosine costs nearly US$70 per patient. An additional hurdle we have faced is the difficulty in obtaining adenosine and regadenoson in mainland China due to licensing and manufacturing issues. As such, centres in the Asia–Pacific frequently use ATP but the data supporting its use in CMR is not as extensive as other stress agents such as dobutamine, adenosine, dipyridamole and regadenoson [8, 18, 25]. Another issue with ATP is that centres in the Asia–Pacific region have sometimes mistaken adenosine and ATP as being the same agent. The current Society for Cardiovascular Magnetic Resonance guidelines has recently included ATP as a stress agent [26, 27] but the data supporting the imaging

### Table 1 (continued)

|                                      | Subjects with MACE (n = 39) | Subjects without MACE (n = 169) | P value |
|--------------------------------------|-----------------------------|---------------------------------|---------|
| Myocardial LGE                       | 21 (53.9%)                  | 30 (17.8%)                      | <0.001* |
| LGE (%)                              | 2.95 ± 7.13                 | 1.15 ± 4.63                     | 0.056   |
| Stress Induced Perfusion Defect      | 17 (43.6%)                  | 21 (12.4%)                      | <0.001* |

Data is presented as mean ± standard deviation or count with percentage in brackets

ATP adenosine triphosphate, ACE angiotensin converting enzyme, BMI body mass index, LV Left ventricle, LGE Late gadolinium enhancement; * = p < 0.05

### Table 2  
Frequency of ATP side-effects experienced by subjects during stress test

| Side-effect                  | Frequency |
|------------------------------|-----------|
| Chest pain                   | 64        |
| Shortness of breath          | 41        |
| Headache                     | 17        |
| Palpitation                  | 15        |
| Hot flushing                 | 2         |

### Table 3  
Incidence of composite endpoints in patients with and without stress inducible perfusion defects; MI, myocardial infarction

| Inducible Perfusion Defect | Late coronary revascularization | Cardiac hospitalization | Non-fatal MI | Cardiac death | Total |
|----------------------------|--------------------------------|-------------------------|--------------|---------------|-------|
| Present                    | 6                              | 10                      | 0            | 3             | 19    |
| Absent                     | 5                              | 17                      | 1            | 1             | 24    |
| Total number               | 11                             | 27                      | 1            | 4             | 43    |

ATP is a readily accessible and less expensive in parts of the Asia Pacific region relative to other stress agents. The cost of ATP in our centre is approximately US$15 per patient whilst adenosine costs nearly US$70 per patient. An additional hurdle we have faced is the difficulty in obtaining adenosine and regadenoson in mainland China due to licensing and manufacturing issues. As such, centres in the Asia–Pacific frequently use ATP but the data supporting its use in CMR is not as extensive as other stress agents such as dobutamine, adenosine, dipyridamole and regadenoson [8, 18, 25]. Another issue with ATP is that centres in the Asia–Pacific region have sometimes mistaken adenosine and ATP as being the same agent. The current Society for Cardiovascular Magnetic Resonance guidelines has recently included ATP as a stress agent [26, 27] but the data supporting the imaging

![Fig. 3](image-url)  

**Fig. 3** Incidence of composite major adverse cardiovascular events (MACE) between normal and abnormal stress test findings. Estimated cumulative incidence of composite MACE was significantly higher in subjects with abnormal stress findings (log rank p-value < 0.001)
protocol are very limited. Evidence and drug availability are crucial in the development of stress CMR services as some countries in this region have limited access to well

Fig. 4 Sub-analysis of the four parameters comprising the composite major adverse events end point (i.e. late coronary revascularization, cardiac hospitalization, non-fatal myocardial infarction and cardiac death) between patients with and without perfusion defects. Late coronary revascularization, cardiac hospitalization and cardiac death were significantly higher in subjects with stress induced perfusion defects (log rank p-value = 0.001, = 0.004 and = 0.003 respectively). There was no significant difference between the two groups in terms of non-fatal myocardial infarction.

Table 4 Annualized event rates for patients with and without stress inducible perfusion defects

| Inducible perfusion defect present (n = 38) | Inducible perfusion defect absent (n = 170) |
|-------------------------------------------|-------------------------------------------|
| Total number of non-fatal MI and cardiac death | 3 | 2 |
| Total patient years | 108.0 | 544.9 |
| Annualized event rate (per patient year) | 2.8% | 0.4% |

MI myocardial infarction

Table 5 Multivariable Cox regression model with stress induced perfusion defect, presence of LGE infarct and LVEF as variables. LVEF is a continuous variable

| Coefficient | p-value | Hazard ratio | 95% CI for Hazard ratio |
|-------------|---------|--------------|-------------------------|
| Stress induced perfusion defect | 1.289 | <0.001 | 3.630 | 1.879 | 7.012 |
| LVEF | -0.037 | <0.001 | 0.964 | 0.945 | 0.984 |
| LGE Infarct | 1.073 | 0.001 | 2.924 | 1.517 | 5.634 |

CI Confidence Interval, CMR Cardiovascular magnetic resonance, LGE Late gadolinium enhancement, LVEF left ventricular ejection fraction
established stress agents (i.e. adenosine, dipyridamole and regadenoson) due to licensing issues, cost and production. Thus, this study provides timely evidence for the utilization of ATP as a stress agent for stress CMR. So far, data supporting the use of ATP has been primarily in nuclear myocardial perfusion imaging studies and the protocols have been adapted for stress CMR [11, 14].

This study also demonstrates a safe and clinically feasible ATP protocol with a starting infusion rate of 0.14 mg/kg/min in which no patients experienced significant complications. The most common side effects of ATP infusion in our study were shortness of breath, chest pain and headache which largely agree with a previous report [13]. However, these side effects were mild and resolved within 5 min after ATP infusion was stopped. Indeed, we also demonstrated the feasibility of increasing the ATP infusion rate by 50% in patients not responding adequately. This 50% increase in infusion rate has been safely demonstrated in adenosine stress CMR previously [17] but not in ATP stress CMR. Some studies have suggested that ATP should be given at slightly higher infusion rates of 0.16 mg/kg/min initially [24]. However, our study shows that with an infusion rate of 0.14 mg/kg/min 94.2% of patients are adequately stressed.

Compared to other studies assessing the prognostic significance of stress CMR, our study showed similar findings of increased MACE in patients with stress induced perfusion defects on stress CMR [8, 18]. Furthermore, we showed that a normal ATP stress CMR indicates a lower likelihood of MACE and adds to the growing literature that stress CMR has significant prognostic value with different pharmacological stress agents [2, 10, 28]. Thus, the choice of pharmacological stress agent should be dependent on a center’s previous experience, the availability of the pharmacological agent and the cost implications for health care.

In our study, stress induced perfusion defect, lower LVEF and LGE detected infarcts were independent predictors of MACE. Our finding of LGE and stress induced perfusion defect as independent predictors of MACE is consistent with previous publications by Freed et al. and Pontone et al. which looked at regadenoson and dipyridamole respectively [8, 18].

Limitations

Our study has limitations. Firstly, this is a retrospective study in a Chinese population. Further research is needed to determine if this is generalizable to other populations worldwide. Secondly, our follow-up period is relatively short with relatively small number of patients with stress perfusion defects and a smaller number of patients with hard cardiovascular events. Thus, non-fatal MI although not significant in this study may actually be significant if the study length was increased and the number of subjects also increased. Nonetheless, our study still showed the prognostic value of ATP stress CMR for adverse cardiovascular events in Chinese population and data supporting the use of ATP stress CMR is required in this region to support the practice and development of stress CMR. Thirdly, we do not have other vasodilator agents like adenosine or dipyridamole for comparison to see if ATP is a comparable stress agent to more well-established stress agents for CMR. Lastly, not all patients underwent catheter/invasive coronary angiography to confirm the presence of obstructive CAD. Thus, a stress induced perfusion defect likely led to the patients undergoing catheter coronary angiography, however, the decision to revascularize was decided during the interventional procedure. In addition, our study follows previous studies in establishing the prognosis by not catheterizing all patients undergoing stress CMR [5, 8, 18].

Conclusion

ATP stress CMR has significant prognostic value. An abnormal ATP stress CMR with findings of stress induced perfusion defect is predictive of higher MACE events. Patients with suspected obstructive CAD without a stress induced perfusion defect on ATP stress CMR have an annualized event rate of 0.4% versus 2.8% if a stress induced perfusion defect is present.

Abbreviations

ATP: Adenosine triphosphate; bSSFP: Balanced steady-state free precession; CAD: Coronary artery disease; CMR: Cardiovascular magnetic resonance; HR: Hazard ratio; LAD: Left anterior descending coronary artery; LCX: Left circumflex coronary artery; LGE: Late gadolinium enhancement; LV: Left ventricle/ left ventricular; LVEF: Left ventricular ejection fraction; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; PSIR: Phase sensitive inversion recovery; RCA: Right coronary artery; TE: Echo time; TR: Repetition time.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12968-021-00770-z.

Additional file 1: Table S1. Patient characteristics of study population (without stress perfusion defect vs with stress perfusion defect). Table S2. Univariate Cox regression.

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Authors’ contributions

MYN, CYC contributed to study design. MYN, CYC, PMY were responsible for data acquisition and/or analysis. MYN, CYC, EYFW performed statistical
Globally, cardiovascular magnetic resonance (CMR) imaging has emerged as a valuable tool in the non-invasive assessment of cardiovascular disease (CVD) risk. This growing role is attributed to the multiparametric nature of CMR imaging, which can provide comprehensive information on cardiac structure and function, as well as non-invasive coronary artery disease (CAD) detection. This article introduces the advancements in CMR imaging and their implications for the management of CVD.

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