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Original Article

SAVEME (Myocardial Salvage After Rescue Angioplasty: Evaluation by Magnetic Resonance) Study: Rationale and Study Design

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ABSTRACT

Introduction: Atherosclerotic disease accounts for one-third of deaths annually, as it often leads to complications such as ST-elevation myocardial infarction (STEMI). Rescue percutaneous coronary intervention (PCI) is indicated in case of thrombolytic therapy failure administered in this scenario. However, the benefits regarding mortality rate reduction and the amount of myocardium that is actually salvaged are not well established. The development of new tools, including cardiac magnetic resonance imaging, to identify the myocardium at risk and the infarcted area has increased diagnostic accuracy. Differently from the context of primary PCI, little is known about the association between epicardial and microvascular coronary flow following rescue PCI and the salvaged myocardial area. The aim of this study is to evaluate whether there is an association between coronary flow and the salvaged myocardial area identified by magnetic resonance imaging.
Methods: This will be a prospective, open, single-center, intervention study. A total of 72 patients with STEMI who underwent rescue PCI after documented failure of the fibrinolytic therapy, and were transferred to our institution, will be selected, observing a pharmacoinvasive strategy.
Conclusions: At the end of this study, the authors expect to contribute to the knowledge about coronary flow and its association with the amount of salvaged cardiac muscle after rescue PCI. This type of information that can help to understand which cases can benefit the most from rescue PCI.

Estudo SAVEME (Salvamento Miocárdico Após Angioplastia de Resgate: Avaliação por Ressonância Magnética). Racional e desenho do estudo

Palavras-chave:
Infarto do miocárdio
Terapia fibrinolítica
Imagem por ressonância magnética

RESUMO

Introdução: A doença aterosclerótica é responsável por um terço dos óbitos ocorridos anualmente, pois frequentemente leva a complicações como infarto do miocárdio com supradesnivelamento do segmento ST (IMCST). A intervenção coronária percutânea (ICP) de resgate é indicada caso ocorra falha da terapia trombolítica administrada neste cenário. No entanto, os benefícios, em termos de redução da taxa de mortalidade e da quantidade de miocárdio efetivamente salvo, não são bem estabelecidos. O desenvolvimento de novas ferramentas, entre elas a ressonância magnética cardíaca, para identificar a área miocárdica em risco e infartada, elevou a acurácia diagnóstica. Diferentemente do contexto da ICP primária, pouco se sabe sobre a relação entre o fluxo coronário epicárdico e microvascular após a ICP de resgate e a área de miocárdio salva. O objetivo deste estudo é avaliar se existe relação entre tais fluxos e a área de miocárdio salva identificada pela ressonância magnética.

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Métodos: Estudo prospectivo, aberto, unicêntrico, de intervenção. Serão selecionados 72 pacientes com IMCST que tiverem realizado ICP de resgate após falha documentada da terapia fibrinolítica transferidos para este serviço, obedecendo uma estratégia fármaco-invasiva.
Conclusões: Ao término desta pesquisa, esperamos contribuir para o conhecimento sobre o fluxo coronariano e sua relação com a quantidade de músculo cardíaco salvo após a ICP de resgate. Esta é uma informação que pode ajudar a entender quais casos mais se beneficiam da ICP de resgate.

Introduction

Although primary percutaneous coronary intervention (PCI) was shown to be superior to fibrinolysis, the latter is still the most commonly used therapeutic strategy, mainly due to logistic difficulties in transferring patients to carry out primary PCI in a timely fashion.[1-3] In 30 to 50% of cases, thrombolysis cannot restore adequate flow to the culprit artery (Thrombolysis in Myocardial Infarction – TIMI < 3).[4] These patients have higher early and late mortality when compared with those who achieve TIMI flow 3.[5] Additionally, a change in myocardial perfusion assessed by TIMI Myocardial Perfusion Grade (TMPG) may persist, despite normal epicardial flow. This change is associated with greater thrombotic load, larger infarct size, and worse and slower resolution of ST-elevation, as well as worse survival in the short and long terms.[6-13]

Rescue PCI is indicated in cases of fibrinolytic failure; it also aims to treat the culprit lesion, reestablishing normal epicardial flow and myocardial perfusion. However, the level of recommendation class IIa for this procedure in the guidelines reflects the fact that the benefits are not well established in terms of mortality rate reduction and the amount of myocardium that is actually salvaged.[14-19] Thus, a number of studies have tried to evaluate this treatment, assessing predictors of mortality, vascular complication rates, and differences in mortality reduction between developed and emerging countries.[20-22]

Cardiac magnetic resonance (CMR) is an imaging modality that may provide additional insight into the underlying pathophysiology of myocardial perfusion failure observed by TMPG. It allows assessing not only myocardial function, but also the extent of the myocardial infarction, estimating the size of the possible area at risk, myocardial viability, and the degree of persistent microvascular obstruction after reperfusion therapy.[23-27]

Appelbaum et al. evaluated the association between TMPG and the persistent microvascular obstruction measure assessed by CMR performed at 1 week and after 3 months in 21 patients with ST-elevation myocardial infarction (STEMI) treated with primary PCI. After the procedure, TIMI 3 flow was observed in 90% of patients, altered TMPG (0/1 or 2) in 48%, and evidence of persistent microvascular obstruction at the CMR in 52%. An association was observed between altered TMPG and persistent microvascular obstruction at the CMR (90% persistent microvascular obstruction in patients with TMPG 0/1 or 2 vs. 18% persistent microvascular obstruction in those with TMPG 3; $p < 0.01$) and with a larger infarct size (17.3 vs. 5.2%; $p < 0.01$, respectively).[28]

Another study, which assessed 50 patients with failed thrombolytic therapy who underwent rescue PCI and follow-up with CMR (performed within 6 days), showed a small amount of salvaged myocardium (3 ± 4%) and no difference between patients with TIMI flow ≤ 2 or 3 (3.3 ± 3.6% in those with TIMI 0-2 vs. 3.0 ± 3.7% in those with TIMI 3; $p = 0.80$) or among those who underwent early vs. late rescue PCI. Also, no associations were observed between ST resolution or presence of TIMI 3 flow after the rescue PCI and the amount of salvaged myocardium. These associations were not listed as pre-specified outcomes for analysis and cannot be considered conclusive.[29]

Bodí et al.[30] compared the outcomes related to left ventricular alterations in the pharmacoinvasive strategy (151 patients) and primary PCI (93 patients). The CMR performed after 1 week showed a similar extent of the area at risk in both groups (29 ± 15% vs. 29 ± 17%; $p = 0.9$). Non-significant differences in infarct size, salvaged myocardial area, persistent microvascular obstruction, ejection fraction, and end-diastolic and end-systolic volumes were detected at the CMR performed at 1 week and after 6 months ($p > 0.2$ in all cases). Patients treated with rescue PCI (n = 35) were evaluated separately and compared with patients in the successful thrombolysis and primary PCI groups. The rescue PCI group had worse ejection fraction, left ventricular mass, myocardial area at risk, and infarct size ($p \leq 0.05$ in all cases), as well as a trend towards greater microvascular obstruction ($p = 0.06$) in the initial CMR than the other groups. At the CMR performed after 6 months, no significant differences were observed in the parameters evaluated between the three groups.[30]

The few studies in the literature shown here used diverse analysis criteria post-acute myocardial infarction, and it is not clear which is the best period for CMR outcomes to be analyzed.

Our hypothesis is that there is an association between the alteration in TMPG and in the TIMI flow at the end of rescue PCI and the size of myocardial infarction and microvascular obstruction observed at the post-PCI CMR.

The main objective of this study is to evaluate TMPG and TIMI flow after rescue PCI and to establish an association with the CMR findings related to infarct size and post-PCI microvascular obstruction.

Methods

Study design and patient selection

This will be a prospective, open, interventional, single-center study carried out at *Hospital São Paulo* of *Escola Paulista de Medicina*, *Universidade Federal de São Paulo*, in São Paulo (SP). Seventy-two patients with STEMI submitted to rescue PCI after documented fibrinolytic therapy failure, transferred to this service, will be selected.

Patients older than 18 years, with STEMI, who underwent thrombolysis within 12 hours of symptom onset will be included.

Thrombolytic therapy failure will be defined by an electrocardiogram performed 60 minutes after the thrombolytic agent administration, showing a resolution of the ST-segment < 50% when compared to the initial electrocardiogram, associated or not with persistent chest pain or hemodynamic instability. Once the thrombolytic treatment failure is identified, the Interventional Cardiology team must be urgently called in to perform the rescue PCI.

Patients with a new or presumed new left bundle branch block will be excluded from the study. Other exclusion criteria reflect the known contraindications to CMR or the use of adjuvant medications to percutaneous treatment; impossibility to perform pre-procedure CMR (*e.g.*, pre-existing pacemaker and hemodynamic instability among others) or impossibility to perform post-procedure CMR (severe heart failure, low output, and need for pacemaker due to high-

grade atrioventricular block, among others); history of intolerance, allergic reaction, or contraindication to any of the study medications, including the paramagnetic contrast agent (gadolinium), dual antiplatelet therapy or heparin; stroke in the last 3 months; peptic ulcer in the last 6 months; hemorrhagic diathesis or coagulopathy; or refusal to receive blood transfusion.

The study is registered with in clinicaltrials.gov (protocol NCT02517255). The schedule indicates that patients will be included by the second semester of 2016.

Overall objective

The main study objective is to assess TMPG and TIMI flow after rescue PCI and to establish an association with the CMR findings related to infarct size and the microvascular obstruction carried out after the PCI.

Specific objectives

The following are the primary objectives:

- To evaluate the association between the increase in TMPG after successful rescue PCI (defined as the presence of residual lesion < 30% and TIMI flow 3) and the indices of acute myocardial infarction size and persistent microvascular obstruction measured by CMR during hospitalization within 7 days and 3 and 6 months after acute myocardial infarction.
- To evaluate the association between the change in epicardial TIMI flow after successful rescue PCI and indices of acute myocardial infarction size and persistent microvascular obstruction, measured by CMR performed during hospitalization within 7 days and 3 and 6 months after the acute myocardial infarction.
- To establish whether there is a significant difference between the CMR evaluation in the acute myocardial infarction extension and persistent microvascular obstruction at 3 and 6 months after acute myocardial infarction.

The following are the secondary objectives:

- To identify the clinical and angiographic characteristics associated with the occurrence of microvascular obstruction in patients with TMPG 3.
- To evaluate the association between alterations in the 12-lead electrocardiogram (resolution of ST-elevation and the sum of the ST-segment and Q-wave elevation voltage) before and after PCI with indices of acute myocardial infarction size and persistent microvascular obstruction measured by CMR.
- To compare TMPG and indices of acute myocardial infarction size and persistent microvascular obstruction after successful rescue PCI among the following indications of rescue PCI: (a) persistent precordial pain, refractory to clinical treatment; (b) ST-segment resolution < 50% in the worst lead at the electrocardiogram performed at least 60 minutes after thrombolytic therapy administration; and (c) association of items (a) and (b).
- To evaluate the association between time of chest pain onset to rescue PCI and TMPG and the indices of acute myocardial infarction size and persistent microvascular obstruction.
- To evaluate the association between time to fibrinolysis and time to rescue PCI with the amount of salvaged myocardium.

Rescue percutaneous coronary intervention description

Patients will be treated according to the standard STEMI protocol. Catheterizations will be conducted through the femoral approach and following the pharmacoinvasive strategy.[31] The use of glycoprotein IIb/IIIa inhibitor, the choice of access (radial or femoral) and catheter diameter, as well as the use of thromboaspiration will be at the interventionist's discretion.

The angiographic projections used will be those that allow optimal evaluation of the TIMI flow and TMPG in the infarct-related artery, as well as adequate quantitative coronary angiography analysis.

Intracoronary adenosine should be performed after the rescue PCI prior to final imaging assessment, in order to provide maximal epicardial and microvascular coronary vasodilation. The administered dose will be that recommended by Grygier et al.,[32] namely: 2 mg of adenosine diluted in 10 mL of 0.9% saline solution for the left coronary artery and 1 mg of adenosine diluted in 10 mL of 0.9% saline solution for the right coronary artery.[32]

Protocol for obtaining coronary angiography images

After the PCI, four imaging assessments will be performed for analysis, divided into two sequences. In the first sequence, intracoronary nitroglycerin will be administered at a dose of 100 to 300 mcg, and two angiograms (30 frames/second) will be performed in at least two projections, being at least one in the cranial-left anterior oblique view (right coronary artery), caudal-right anterior oblique view (left circumflex artery), and cranial-right anterior oblique view (left anterior descending artery). In the second sequence, intracoronary adenosine will be administered at a dose of 600 mcg, and two angiograms will be performed (30 frames/second) in at least two projections, being at least one in the cranial-left anterior oblique view (right coronary artery), caudal-right anterior oblique view (left circumflex artery), and cranial-right anterior oblique view (left anterior descending artery).

Cardiac magnetic resonance technique and analysis

CMR will be performed during hospitalization within 7 days (baseline) and at 3 and 6 months after the acute myocardial infarction. Late CMRs should evaluate the evolution of infarct area and cardiac function compared with baseline CMR.

In the initial study, steady-state free precession (SSFP) sequences will be used, in the long and short axes of the heart, for function assessment; T1-weighted sequences for resting perfusion; T2-weighted sequences for edema evaluation; and the inversion-recovery technique will be used to assess the area of necrosis/fibrosis (late enhancement). In the exams performed at 3 and 6 months, pharmacologic stress perfusion (dipyridamole) will be added to the protocol. Images will be evaluated by two physicians who have at least 3 years of experience with the method, and divergences will be resolved by a third-party examiner who has over 10 years of experience. These physicians will have no access to clinical information or laboratory test results prior to image assessment.

TMPG analysis

Myocardial blush will be evaluated distally to the culprit lesion by a single examiner who has over 10 years of experience in coronary angiography. Projections will be chosen to minimize overlapping of non-infarcted territories over those of the culprit artery. The duration of filming must exceed three cardiac cycles in the myocardial blush washout phase. Care will be taken not to confuse venous system filling with blush. The blush will be evaluated at the same stage of the cardiac cycle, as it may be less intense during diastole. TMPG grades are defined as:[9]

- Grade 0: contrast fails to enter the microvasculature. There is absence of or minimal ground-glass appearance (blush) or opacification of the myocardium in the region perfused by the culprit artery, indicating lack of tissue perfusion.
- Grade 1: the contrast enters slowly, but fails to exit the microvasculature. There is a ground glass appearance (blush) or myocardial opacification in the region perfused by the culprit artery, which does not disappear from the microvasculature;

the contrast remains until the next injection (approximately 30 seconds between injections).

- Grade 2: Contrast entry and exit from the microvasculature is delayed. There is ground glass appearance (blush) or myocardial opacification in the region perfused by the culprit artery, which persists strongly at the end of the washout phase (i.e., the contrast persists strongly after three cardiac cycles and does not decrease, or only minimally decreases in intensity, during the washout phase).
- Grade 3: Adequate contrast entry and exit from the microvasculature. There is ground glass appearance (blush) or myocardial opacification in the region perfused by the culprit artery, which usually disappears or discretely persists at the end of the washout phase (i.e., the contrast disappears or discreetly persists after three cardiac cycles, and noticeably decreases in intensity during the washout phase, similar to a non-culprit artery).

TIMI flow analysis

TIMI flow will be evaluated by a single examiner as follows: Grade 0, if there is absence of anterograde flow beyond the point of occlusion; Grade 1, if the contrast goes beyond the obstruction area but fails to completely opacify the distal coronary bed; Grade 2, if the contrast goes beyond the obstruction and opacifies the distal coronary bed, but more slowly than normal; and Grade 3, if the flow is normal.[4,33]

The TMPG, TIMI flow, and quantitative coronary angiography analyses will be performed independently of the study investigators.

Data analysis

Qualitative data will be analyzed as absolute frequencies and percentages, and quantitative data will be described as mean and standard deviation, or as median and interquartile range, according to each variable distribution.

Initially, patients will be divided into subgroups according to the TPMG and TIMI grade, which will be compared in relation to clinical and angiographic characteristics. Pearson's chi-squared test or Fisher's exact test will be used for the qualitative variables, as necessary. For comparisons of the quantitative variables, analysis of variance (ANOVA) models will be used for data with normal distribution; non-parametric methods will be used for models with other distributions.

To evaluate the association between flow (TPMG and TIMI) and infarct size observed at 7 days, 3 and 6 months, ANOVA models with repeated measurements will be adjusted considering two factors: flow (Grades 0, 1, 2, and 3) and time of evaluation (7 days, 3 and 6 months). In these models, comparisons will be made between groups (flow 0 vs. 1, 2 and 3), as well as intragroup (comparisons between 7 days, 3 and 6 months). In the obstruction analysis, models of generalized estimating equations (GEE) with binomial distribution will be applied. Results will be expressed as odds ratios and 95% confidence intervals. In both analyses (infarct size and obstruction), in addition to the flow, clinical and angiographic characteristics (univariate and multivariate analysis) will be investigated.

The software Statistical Package for Social Science (SPSS), version 19.0, will be used for the statistical calculations.

Conclusions

At the end of this study, the authors expect to contribute to the knowledge about coronary flow and its association with the amount of salvaged myocardium after rescue percutaneous coronary intervention. This information can help to understand which cases can benefit the most from rescue percutaneous coronary intervention.

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Conflicts of interest

The authors declare no conflicts of interest.

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