Heart Institute of the Clinical Hospital of the University of São Paulo Medical School (InCor-HCFMUSP)

Department of Hemodynamics and Interventional Cardiology

Research Protocol

Title:

Effects of Papaverine on Microvascular Resistance in Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention (PAP-MICRO TRIAL)

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- **Abstract:**

Background:	Microvascular disease is one of the main components of coronary artery disease, especially in acute myocardial infarction (AMI). Despite this, it has not yet been possible to establish effective therapies for reversing microvascular dysfunction. The present study seeks to evaluate the effect of intracoronary papaverine on microvascular resistance after angioplasty in patients with AMI.
Objectives:	**Primary:** To evaluate improvement in QFR-IMR after the use of intracoronary papaverine vs. placebo. **Secondary:** Assessment of infarct size; area of microvascular compromise on magnetic resonance imaging; troponin curve and BNP levels before and after PCI and after papaverine infusion.
Population:	Patients aged >18 years with a diagnosis of AMI (with or without ST-segment elevation), Killip class I or II, who have undergone successful PCI of the culprit lesion.
Materials and Methods:	Randomized, prospective, multicenter, placebo-controlled, double-blind clinical trial. An infusion of papaverine or saline will be administered at the end of PCI of the culprit artery, with subsequent analysis of the acquired images to calculate microvascular resistance by means of QFR-IMR. For the analysis, an alpha of 5%, power of 95%, and a sample size of 100 patients were established.
Analysis of Results:	Description in percentages, means, and medians, with univariate and multivariate assessment based on tests appropriate to the distribution of the data.

- **Principal Investigator:** Dr. Carlos Augusto Homem de Magalhães Campos
- **Associate Investigator:** Pedro Guimarães Silva
- **Host Institution:** Heart Institute – HCFMUSP

1. Introduction and Rationale

Microvascular disease in the context of cardiomyopathies

The establishment of myocardial ischemia involves a series of causal and associated elements which, when combined, contribute to oxygen deprivation of the cardiomyocytes.(1,2) The classically described model of myocardial ischemia, in which the formation of atherosclerotic plaque in the epicardial vessels culminates in limitation of blood flow to viable myocardium, proves insufficient to explain several clinical scenarios, especially INOCA (ischemia with non-obstructed coronary arteries), ANOCA (angina with non-obstructed coronary arteries), and MINOCA (myocardial infarction with non-obstructed coronary arteries). A new view of the pathophysiology of coronary artery disease (CAD) highlights the leading role of coronary microvascular disease (CMD) in the context of angina/ischemia, understanding it not only as a determining element for the development of the functional and anatomical alterations found in ischemic myocardium, but also as a prognostic factor for outcomes such as death, acute myocardial infarction, and the development of heart failure and hospitalization.(3)

CMD refers to a set of alterations at the level of the microcirculation which result in impairment of coronary blood flow and, consequently, myocardial ischemia. Periarteriolar fibrosis, medial-intimal hypertrophy, microembolism, and sympathetic hypertonia are among the known mechanisms that precipitate the increase in microvascular resistance and make up CMD.(1–4) The mechanism by which these alterations in the functionality of the microcirculation occur is still not well established. Oxidative stress mediated by the production of reactive

oxygen species (ROS) causes inflammation and a consequent imbalance in cytokine production, with excessive synthesis of vasoconstrictor substances, such as endothelin-1, associated with a reduction in the production of vasodilator agents such as nitric oxide (NO).(5,6) In addition, in situations of pronounced myocardial hypertrophy, such as hypertrophic cardiomyopathy, aortic stenosis, and poorly controlled arterial hypertension, the disproportion between the large muscle mass and the insufficient microvascular network causes ischemia and replacement of viable myocardium by fibrotic tissue, which contributes to even greater rarefaction of the capillary network and ischemia.(4) In conditions such as Takotsubo syndrome and Prinzmetal's angina, vasospasm at the arteriolar level corresponds to the microvascular component responsible for the alterations and symptoms described in these presentations.(3)

In acute coronary syndromes (ACS), the causal elements additionally include the impact of in-situ thrombosis of atherosclerotic plaques and microembolization with concomitant occlusion of the capillary networks, giving rise to the slow-flow/no-reflow phenomena (whether spontaneously or resulting from mobilization of the thrombotic burden during the attempt at recanalization by percutaneous intervention). To this are added the vasospastic reflex and the inflammation arising from myocardial ischemia/necrosis of greater proportions than in stable arterial disease, with concomitant endothelial dysfunction and vasotonic imbalance polarized toward vasoconstriction.(7,8)

The clinical and prognostic relevance of microvascular disease is already established in several scenarios, especially in patients with coronary artery disease. The detection of elevated indices of microvascular resistance, whether by invasive or non-invasive methods, is associated with a greater occurrence of

adverse outcomes, ranging from a higher incidence of angina to a greater occurrence of non-fatal AMI, hospitalization, and cardiovascular death.(4,5,8–10) This association can be found even in patients without obstructive lesions on coronary angiography. Reports indicate that approximately 40% of patients with angina in the absence of obstructive lesions have primary microvascular angina (pMVA) as the underlying cause.(2,11)

To date, few advances have been made in the therapeutic field aimed at treatment directed at CMD.(4) The contemporary approach focuses especially on the control of risk factors, with no validated alternatives that demonstrate the capacity to reverse the anatomical and functional alterations of the compromised microvasculature. The present work proposes to investigate the effects of papaverine as a therapy for the treatment of CMD in cases of AMI in the acute phase undergoing percutaneous revascularization.

Methods for assessing microvascular physiology: microvascular resistance and its clinical impacts

The nature of CMD makes it necessary to employ different techniques that enable parameters of microvascular physiology to be obtained. The methods available today can be classified as invasive and non-invasive.(4)

Advances in artificial intelligence and in the ability to analyze contrast flow in the coronary bed have allowed the development of software of significant accuracy for determining the severity of coronary stenoses, and can even estimate fractional flow reserve (FFR) values non-invasively and with good correlation with data obtained by means of intravascular catheters.(12,13)

Papaverine: molecular characteristics, pharmacokinetics, pharmacodynamics, and clinical use

Papaverine is a true alkaloid, a natural derivative of opium, obtained from the poppy (*Papaver somniferum*). It is well established as one of the main drugs with vasodilator action, being used for the management of erectile dysfunction, intestinal/gastric spasms, bronchospasm, and especially peripheral and coronary arterial vasodilation.(14–19) Its use in the context of interventional cardiology is already established in the management of coronary slow-flow/no-reflow during percutaneous coronary intervention (PCI) and in the performance of invasive studies that require the induction of pharmacological hyperemia (FFR).(16,17,19,20)

It is a highly bioavailable molecule (80%), with a high rate of protein binding (~90%) and a half-life of 90–120 min. It undergoes hepatic metabolism, with subsequent renal excretion. Its pharmacodynamics consists of the inhibition of cAMP and cGMP phosphodiesterases, with elevation of serum levels of cAMP and cGMP and reduction of the influx of calcium ions (Ca^{2+}) into the intracellular environment.(14,15)

The elevation of cGMP causes an increase in the activity of protein kinase G (PKG), whose action is to reduce the influx of Ca^{2+} (an essential element for muscle contraction) and to increase the efflux of potassium (K^{+}), culminating in hyperpolarization of the action potential. The elevation of cAMP and cGMP, as well as the fall in Ca^{2+} levels, cause a reduction in the activity of myosin light-chain kinase (MLCK), which is responsible for the activation of myosin. In parallel, they are responsible for the increased action of myosin light-chain

phosphatase (MLCP), which acts by dephosphorylating the myosin molecule and favoring muscle relaxation and vasodilation.(15)

Papaverine is one of the methods employed to promote the optimal hyperemic stimulus for performing FFR. Its action after intracoronary injection lasts around 30–60 s, being more effective than adenosine or adenosine triphosphate in ensuring maximal vasodilation.(19) Its use is already provided for and substantiated in the package insert, with approval by ANVISA and support for use by the intra-arterial route (Ministry of Health Registration: MS 1.0387.0032. Date of last package insert revision: 02/04/2021).

The use of intracoronary papaverine after PCI can be justified by pathophysiological mechanisms distinct from those that justify its use in inducing maximal hyperemia for FFR assessment. During FFR, papaverine is administered with the diagnostic objective of transiently reducing coronary vascular resistance to the lowest possible level, producing maximal hyperemia and allowing assessment of the functional relevance of a stenosis. Papaverine induces intense and predictable coronary vasodilation, reaching levels of hyperemia comparable to those obtained with adenosine and ATP, which is why it has been widely used in coronary physiology studies.

On the other hand, at the end of PCI, especially in complex or calcified lesions or those associated with a high atherothrombotic burden, the main limitation of myocardial flow frequently no longer lies in the epicardial circulation, but in the microcirculation. Phenomena such as distal embolization, endothelial edema, reflex arteriolar vasoconstriction, and microvascular obstruction may result in persistent tissue hypoperfusion, even in the presence of apparently satisfactory

angiographic flow. In this situation, the intracoronary administration of papaverine assumes a therapeutic role, promoting intense arteriolar vasodilation, reduction of microvascular resistance, and improvement of effective myocardial perfusion.

The most direct clinical evidence for this concept was provided by Ishihara et al., who demonstrated significant improvement of the no-reflow phenomenon after primary PCI in patients with acute myocardial infarction. The intracoronary administration of papaverine increased angiographic coronary flow and significantly reduced the number of frames required for the progression of contrast, suggesting restoration of microvascular perfusion. These findings reinforce the notion that the drug acts not only as a hyperemic agent for physiological assessment, but also as a modulator of microcirculatory function in situations of compromised reperfusion.

From a physiological perspective, the rationale for its use after PCI is based on the recovery of the microcirculation, which is recognized as an independent prognostic determinant after coronary procedures. The persistence of microvascular dysfunction is associated with a greater extent of myocardial necrosis, worse contractile recovery, and a higher incidence of cardiovascular events.

Thus, whereas in FFR papaverine is employed to artificially create a condition of maximal hyperemia intended for diagnostic measurement, its administration at the end of PCI seeks to restore tissue perfusion in a territory potentially affected by procedural microvascular injury, constituting a physiologically distinct and potentially beneficial use.

The use of intra-arterial doses of 10 to 40 mg is provided for in the package insert for papaverine and ratified by ANVISA, with the most recent opinion issued in 2021. Although the study by Ishihara et al. employed a smaller amount (10 mg) for the assessment of no-reflow, the 20 mg intracoronary dose is well documented in the physiology literature for the induction of maximal hyperemia during coronary functional assessment (FFR), having been used by De Bruyne et al. in comparative studies with adenosine and ATP. In those studies, 20 mg produced profound and consistent hyperemia, serving as a reference for maximal reduction of microvascular resistance. Since the use of 20 mg doses did not result in higher rates of arrhythmias or adverse events and was associated with optimal vasodilation of the microcirculation, this dose was chosen for use in the study given the large thrombotic burden and microcirculatory dysfunction anticipated in the study's target population.

The work in question centers on the hypothesis that the hyperemic optimization effect promoted by papaverine, with concomitant immediate reduction of microvascular resistance in a scenario of significant microcirculatory impairment, may result in a reduction of infarct size and less ischemia in the setting of acute coronary artery disease. These analyses will be carried out by means of the study of the microcirculation after papaverine infusion in patients with ACS undergoing percutaneous coronary intervention.

Objectives

Primary

To evaluate improvement in Quantitative Flow Ratio - Index of Microcirculatory Resistance (QFR-IMR®) after the use of intracoronary papaverine vs. placebo.

Secondary

Assessment of infarct size by means of cardiac magnetic resonance imaging, as well as scar area, area of microvascular occlusion/ischemia, presence of segmental dysfunction and ejection fraction, and TIMI classification for the assessment of coronary flow on angiography.

Assessment of the troponin curve and BNP levels before and after PCI and after papaverine infusion.

Safety outcomes: occurrence of hypotension and/or cardiogenic shock, anaphylaxis, need for the use of vasopressor drugs or hemodynamic support; progression to unstable bradyarrhythmia and/or need for temporary pacemaker implantation; development of non-sustained, unstable, or pulseless ventricular tachycardia, ventricular fibrillation, need for CPR and/or defibrillation/cardioversion, transient ischemic attack or stroke, and death related to the intervention.

2. Methodology

Study design

The present study is proposed as a randomized, double-blind, multicenter, placebo-controlled clinical trial.

Setting

The study will be conducted on the premises of the Heart Institute of the Hospital das Clínicas, University of São Paulo Medical School, a tertiary and quaternary level public cardiology hospital; at Hospital Agamenon Magalhães, a public hospital belonging to the Health Department of the Government of Pernambuco; at the Hospital de Clínicas of the Federal University of Paraná (CHC-UFPR); and at the Institute of Cardiology of Rio Grande do Sul (IC/FUC). The patients studied will be those whose care/treatment is provided at the Hemodynamics and Interventional Cardiology Service, with those responsible for data collection and analysis being affiliated with this department.

The parties responsible for conducting the study are the following:

- **Study Sponsor:** Heart Institute of the Hospital das Clínicas, University of São Paulo Medical School (InCor-HCFMUSP).
- **Financial Sponsor:** São Paulo Research Foundation (FAPESP).
- **Host Institution:** Heart Institute of the Hospital das Clínicas, University of São Paulo Medical School (InCor-HCFMUSP).
- **Co-Participating Institutions:** Hospital Agamenon Magalhães; Hospital de Clínicas of the Federal University of Paraná (CHC-UFPR); and Institute of Cardiology of Rio Grande do Sul (IC/FUC).
- **Principal Investigator:** Prof. Dr. Carlos Augusto Homem de Magalhães Campos.

The parties involved in the study will have the following responsibilities:

- **Principal Investigator/Supervisor:** Responsible for the overall coordination of the project, review of the progress and accuracy of data

collection, and adherence to the established research protocol. Will provide technical and theoretical guidance to all research participants, having the final word regarding the progress of the project and the inclusion or exclusion of selected patients.

- **Executing Investigator/Supervisee:** Responsible for the execution of the project, development of data collection tools, selection of patients, and collection of information, whether directly from the included patients or through review of medical records.
- **Host Institution:** The study will be based at the Heart Institute (InCor-HCFMUSP), with the other participating centers (Hospital Agamenon Magalhães, CHC-UFPR and IC/FUC) serving the purpose of recruiting and enrolling patients in accordance with the determinations of the present project.
- **FAPESP:** Responsible for the funding and financial support for the acquisition of supplies and materials, whether of permanent use or not, necessary for carrying out the research.
- **Pharmacy:** Responsible for storing and dispensing the previously acquired pharmacological supplies, in accordance with the guidance provided in the package insert.
- **Clinical Care Team:** Will consist of the group of physicians authorized by the Research Team to participate in the present project. It will be composed of: 1 – physicians with specialization in Interventional Cardiology and specific training for image acquisition during coronary angiography in accordance with the protocol established for angiographic analysis by the QFR-IMR software; 2 – cardiologists responsible for the

clinical management of patients in the in-hospital setting. The interventional cardiologists will perform the diagnostic (coronary angiography) and therapeutic (PCI) procedures for the patients and will be responsible for administering the medications according to randomization, as well as for acting accordingly in the event of adverse events arising or not from the administration of the infusion of the therapy under study. The clinical cardiologists will be responsible for the management, prescription, follow-up, and evaluation of the treated patients, with documentation of relevant clinical data in the medical record.

- **Research Team:** Will be composed of the Principal Investigator, the Executing Investigator, the Clinical Care Team, and other co-supervisors of the said research project. It will be responsible for evaluating and communicating the progress of the project for the information of the Principal Investigator and for adjusting requirements as necessary.
- **Person Responsible for Randomization:** The randomization of selected patients will be carried out by the Executing Investigator with the aid of the REDCap digital tool for randomization and data masking.
- **Person Responsible for Safety:** The Executing Investigator will be responsible for the safety assessment of the interventions performed by the Clinical Care Team under the guidance of the Principal Investigator.
- **Person Responsible for Adverse Event Reporting:** The Executing Investigator will be responsible for recording and reporting any and all adverse events related to the research observed by him or by members

of the clinical care team, regardless of severity, under the coordination and guidance of the Principal Investigator.

Population

Inclusion Criteria

- Age ≥ 18 years.
- Diagnosis of acute myocardial infarction with or without ST-segment elevation (STEMI or NSTEMI), confirmed by current clinical, electrocardiographic, and laboratory criteria.
- Patients undergoing PCI of the culprit lesion with angiographic success, regardless of the initial thrombotic burden.
- Killip class I or II at the time of enrollment.
- Capacity to understand the objectives, risks, and benefits of the study and to provide Informed Consent, or consent by a legal representative when permitted by applicable legislation and regulations.
- Agreement to participate in the study and to comply with the procedures set out in the protocol.

Exclusion Criteria

- Absence of indication or clinical benefit for percutaneous reperfusion.
- Diagnosis of unstable angina without elevation of biomarkers consistent with acute myocardial infarction.
- Prior history of acute myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention.
- Concurrent participation in another interventional clinical study.

- Inability to comply with the procedures set out in the protocol.
- Refusal to sign the Informed Consent Form.
- Known or suspected non-ischemic cardiomyopathy under investigation.
- Pregnancy, defined by patient report, positive laboratory test, or clinical suspicion at the time of enrollment. Women of childbearing potential without confirmation of pregnancy status may undergo investigation in accordance with institutional routine.
- Known hypersensitivity to papaverine, opiate derivatives, iodinated contrast, or gadolinium, considered clinically relevant and documented in the medical record or in a reliable medical history.
- Second-degree Mobitz II atrioventricular block, 2:1 atrioventricular block, or complete atrioventricular block documented on the admission ECG or during the current clinical presentation. Patients with permanent pacemakers may be included.
- Prolonged corrected QT interval (QTc) on admission, defined as QTc > 500 ms, preferably calculated using Bazett's formula.
- Current use of medications known to be associated with significant QT prolongation and increased risk of torsades de pointes, when their discontinuation is not clinically feasible before the intervention.
- Killip class III or IV on admission.
- Need for vasoactive support (norepinephrine, epinephrine, vasopressin, or equivalent), inotropic support (dobutamine, milrinone, or equivalent), or mechanical circulatory assistance before the completion of PCI.
- Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² or need for dialysis therapy.

- Contraindication to cardiac magnetic resonance imaging, including incompatible devices, severe uncontrolled claustrophobia, or known hypersensitivity to gadolinium.

Women of childbearing potential without confirmation of pregnancy status may undergo investigation in accordance with institutional routine, taking into account primarily a report of current or possible pregnancy. Pregnancy testing will not be performed routinely.

The patients included in the present work will all be admitted to InCor within the scope of the Brazilian Unified Health System (SUS). All research-related interventions will be carried out in the context of the patient's hospitalization for an urgent/emergency procedure due to ACS, with the use of papaverine in these contexts being something already provided for in the routine clinical practice of Interventional Cardiology. Therefore, the patient selected for the research in question will not be placed at additional elective risk that would justify the need for insurance or the right to indemnification. Comprehensive and free care will be provided, as for any patient treated for AMI, by InCor-HCFMUSP and its clinical staff. The participant may contact the Research Team at any time during hospitalization to communicate any questions.

Cardiac magnetic resonance imaging with gadolinium will be performed only in participants without contraindications to the examination, following assessment of renal function. Participants with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², on dialysis, with known hypersensitivity to gadolinium, with devices incompatible with magnetic resonance imaging, with non-compatible metallic bodies, or with severe uncontrolled claustrophobia will not undergo the

examination. All participants will undergo standardized safety screening prior to CMR.

The main risks include discomfort related to the enclosed environment of the equipment, anxiety, claustrophobia, and allergic reactions to the contrast agent, which are generally rare. The examination will be performed under the supervision of a trained team and in an environment with support for the management of complications. Any clinically relevant incidental findings will be communicated to the participant and to the attending physician for assessment and follow-up in accordance with institutional routine.

Intervention

The intervention will consist of the intracoronary injection of a fixed dose (2 mL, totaling 20 mg) of papaverine solution (dilution of 10 mg/mL in distilled water) to be administered at the end of PCI of the culprit lesion identified at the time of catheterization. Randomization to the use of papaverine or saline will be determined by the REDCap software and only after all standard treatment for the clinical presentation of AMI has been completed by the Clinical Care Team in accordance with the institution's standard procedure, with no measure or resource being withheld. Clinical care will prevail over the research protocol, permitting the use of clinically indicated therapies even if this entails protocol deviation, rescue therapy, or unblinding.

Opaque syringes containing the papaverine solution or placebo (0.9% saline solution) will be used, coded for the purposes of subsequent analysis. The opaque syringes will be prepared and stored by a designated member of the Research Team in fixed quantities throughout the project, taking into account the

viability of the solution after preparation, and using sterile technique. Each syringe will be represented by a 7-digit alphanumeric code, generated by computer by another investigator who will be responsible for masking. Each syringe will then be designated to draw from the ampoule previously de-identified by the Research Team corresponding to one of two groups coded by color (e.g., blue or green), which will arbitrarily correspond to placebo or papaverine, known exclusively to the investigator responsible for masking, who will participate neither in the administration of the intervention nor in the analysis of the data. The designation as placebo or intervention will be known only to the investigator responsible for masking and will not be revealed until the end of the study. After preparation, the investigator responsible for drawing up the syringe must not provide the member of the clinical care team with any information about the syringe preparation process.

The administration of the intervention (placebo or papaverine) will be carried out immediately after the end of PCI, and after randomization of the patient previously selected and in agreement to participate in the study in question. The papaverine or placebo will be administered immediately after dilution, in the Catheterization Laboratory, aiming for maximum viability and lowest risk of contamination, with immediate infusion after preparation. The use of papaverine is therapeutic in nature for the management of the microvascular component of AMI, even in the absence of no-reflow/slow flow visible on angiography.

The papaverine to be used will be acquired specifically for the present study, being provided for in the budget already established and requested for purchase from the InCor Pharmacy. The Pharmacy, as well as the supply and materials department of the InCor Hemodynamics and Interventional Cardiology Unit, will

be responsible for storage and temperature control in accordance with the package insert until dispensing for the examinations related to the project, as well as for disposal in the event of expiry or unsuitability. Expiry date and batch number will be information provided at the time of purchase.

After PCI, blood samples will be collected from the hospitalized patient for assessment of laboratory parameters (complete blood count, troponin, BNP, creatinine). Prior to discharge, the patient will undergo cardiac magnetic resonance imaging (CMR) to determine segmental dysfunction and ejection fraction and to assess infarct size and the presence of signs of microvascular occlusion. For better elucidation of microvasculature dysfunction, studies will be performed to determine T1, T2, and T2* maps (weighting for the study of hematoma) and aspects of epicardial and microvasculature flow. The post processing analysis of the CMR images will be performed with the aid of the Medis Suite MR®, a specialized software that will be provided by Medis Medical Imaging® as a sponsor of our study.

The analysis of microvascular parameters by means of the QFR-IMR calculation software will also be blinded, such that an independent examiner unaware of the group to which the patient of the images under analysis was allocated will provide the values relating to microvascular resistance.

After participation in the study, all patients will continue to receive follow-up and clinical treatment in accordance with the care guidelines in force for acute myocardial infarction and according to the judgment of the attending physician, regardless of allocation group. Accordingly, there is no need to make the investigational intervention available after the end of participation.

Standard-of-care procedures and research-specific procedures

Standard-of-care procedures correspond to those indicated regardless of participation in the study, including clinical assessment, routine laboratory tests, electrocardiogram, coronary angiography, PCI of the culprit lesion, administration of medications recommended by current guidelines, and the usual in-hospital follow-up of acute myocardial infarction.

Research-specific procedures include randomization to intracoronary administration of papaverine or placebo at the end of PCI, coronary physiological analysis using QFR-IMR parameters, and the performance of cardiac magnetic resonance imaging for the assessment of infarct size and microvascular obstruction. Non-participation in the study will not entail any detriment to the standard clinical care offered to the patient.

Criteria for rescue therapy and management of complications

1. Slow-flow/No-reflow

Defined as a reduction in epicardial coronary flow (TIMI < 3) or acute deterioration of angiographic flow after percutaneous coronary intervention, in the absence of significant residual mechanical obstruction. Initially, mechanical causes must be ruled out, including coronary dissection, acute stent thrombosis, stent underexpansion, malapposition, or critical residual lesion. Once the absence of these conditions is confirmed, intracoronary papaverine will be administered as a bolus into the target vessel. After administration, a new angiographic assessment will be performed to verify the recovery of coronary flow and myocardial perfusion. If the condition persists, additional intracoronary

vasodilators and other supportive measures may be used at the operator's discretion.

2. Coronary vasospasm

Characterized by the presence of transient coronary narrowing associated or not with chest pain, ischemic electrocardiographic changes, or impairment of distal flow. Initial treatment will consist of the administration of intracoronary nitrate. If reduced flow persists or an associated microvascular component is suspected, intracoronary administration of papaverine may be considered after mechanical complications have been ruled out.

3. Persistent chest pain

In the presence of persistent chest pain after the intervention, immediate clinical, electrocardiographic, and angiographic assessment must be performed to rule out acute thrombosis, coronary dissection, side-branch occlusion, or other mechanical complications. In the absence of structural changes and in the face of suspected microvascular dysfunction or impaired distal perfusion, intracoronary papaverine may be used as an adjuvant therapeutic measure.

4. Hemodynamic instability

Considered in the presence of clinical signs of hypoperfusion, progressive hemodynamic deterioration, need for vasoactive support, or development of cardiogenic shock. In such cases, investigation must be immediately initiated to identify the underlying cause, including mechanical complications, persistent ischemia, arrhythmias, or acute ventricular impairment. Advanced supportive measures, including volume expansion, vasoactive agents, mechanical

circulatory assist devices, and ventilatory support, may be employed according to clinical need.

5. Arterial hypotension

Defined as systolic blood pressure below 90 mmHg or mean arterial pressure < 65 mmHg, accompanied or not by symptoms. In the event of hypotension, possible causes related to the procedure, to the use of vasodilators, or to the patient's clinical course must be assessed. Management will include volume replacement, adjustment of medications, appropriate positioning of the patient, and use of vasopressors when clinically indicated.

6. Bradyarrhythmias

Defined as a heart rate below 50 bpm associated with symptoms, hemodynamic instability, or significant conduction disturbances. Treatment will follow current recommendations for advanced cardiovascular support, including intravenous administration of atropine, use of chronotropic agents, and implantation of a temporary pacemaker when necessary. The administration of papaverine must be discontinued if a temporal association with the event is suspected.

7. Supraventricular tachyarrhythmias

These include atrial fibrillation, atrial flutter, or other supraventricular tachycardias with clinical repercussions. Management will be carried out in accordance with institutional protocols, including ventricular rate control, pharmacological or electrical cardioversion, and hemodynamic stabilization, as clinically indicated.

8. Ventricular tachyarrhythmias

These include sustained ventricular tachycardia, polymorphic ventricular tachycardia, torsades de pointes, and ventricular fibrillation. Considering the potential for QT interval prolongation associated with papaverine, all patients will remain under continuous electrocardiographic monitoring during and after its administration. In the event of ventricular arrhythmias, the infusion or administration of the drug will be immediately discontinued and advanced life support measures will be adopted, including correction of electrolyte disturbances, administration of magnesium sulfate when indicated, synchronized electrical cardioversion, or defibrillation, according to the type of arrhythmia and the clinical condition of the patient.

9. Safety monitoring

All patients undergoing intracoronary administration of papaverine will remain under continuous monitoring of electrocardiogram, heart rate, blood pressure, and peripheral oxygen saturation during the procedure and in the immediate subsequent period. Adverse events, cardiovascular complications, and rescue interventions will be systematically recorded for analysis of the safety and efficacy of the protocol.

Variables

Information will be obtained by means of patient interviews, medical record entries, and during the percutaneous coronary intervention:

Demographic data and anthropometry: sex; age, weight, height.

Past medical history: allergies; presence of systemic arterial hypertension; diagnosis of chronic kidney disease (GFR < 60 mL/min/1.73 m²); report of

diabetes mellitus; need for insulin therapy; presence of obesity (BMI ≥ 30 kg/m²); prior diagnosis of CAD, history of acute myocardial infarction or prior percutaneous coronary intervention with or without stent implantation; prior diagnosis of heart failure; ejection fraction on the most recent echocardiogram; history of hemorrhagic or ischemic stroke; history of coronary artery bypass graft surgery; current or past smoking; smoking burden; current or past alcohol use; use of anticoagulants, beta-blockers, oral vasodilators (ACE inhibitors, calcium channel blockers, oral nitrates); continuous use of ASA and/or other antiplatelet agents and whether they were prescribed in the acute setting; use of illicit substances (cocaine, cannabis, or others).

Data relating to the intervention: time between the onset of symptoms consistent with the diagnosis of ACS and the performance of the percutaneous intervention; form of presentation of the ACS (unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction); Killip classification on arrival at the service (whether I or II); presence of angina and its intensity (scale of 0 to 10); need for a coronary vasodilator for the control of chest pain; TIMI classification at baseline, after PCI, and after infusion; presence of significant thrombosis on angiography; evidence of slow-flow/no-reflow; use of intracoronary aspiration therapy and/or glycoprotein IIb-IIIa inhibitor; presence of left main coronary artery lesion; angiographic pattern of the lesions (single-, two-, or three-vessel disease) and the value obtained by calculation of the SYNTAX score; total PCI time; success/failure of the intervention; number of stents implanted; occurrence of complications (dissection/occlusion/perforation); occurrence of ventricular fibrillation/unstable or pulseless ventricular tachycardia/cardiorespiratory arrest with need for defibrillation (before or after

infusion); intraprocedural death; occurrence of a neurological event (TIA or stroke) after the procedure.

Laboratory and functional assessment: complete blood count, glycated hemoglobin, creatinine, troponin before the intervention and every 6 hours after reperfusion for a minimum period of 24 hours after PCI; BNP before and after the intervention; infarct size, percentage of fibrosis of the ventricular mass, size of the area of ischemia/microvascular occlusion, ejection fraction, segmental dysfunction, presence of intracavitary thrombus or other structural complications.

Blood sample collection

The blood samples provided for in the study will be collected, whenever possible, concurrently with routine standard-of-care laboratory tests, with the aim of minimizing additional venipunctures. Serial measurements of troponin, BNP, complete blood count, creatinine, and other tests provided for in the protocol will be performed.

The estimated volume of blood collected exclusively for research purposes will be approximately 10 to 20 mL per assessment during hospitalization, totaling up to 60 mL per participant throughout the study. Whenever available and compatible with the established collection windows, results obtained in routine clinical care may be used for research purposes, reducing the need for additional collections.

Sample size calculation

The primary endpoint will be the QFR-IMR of the culprit vessel, compared between the intracoronary papaverine and saline arms by analysis of covariance

(ANCOVA), with adjustment for baseline QFR-IMR measured after primary percutaneous coronary intervention. We adopted a population standard deviation of 5.0 mmHg·s/dm, derived from the distribution of QFR-IMR in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary PCI, in which the median was 26.4 mmHg·s/dm (interquartile range 22.9 to 29.7) in a cohort of 475 patients.(21)

We defined the minimum clinically relevant difference as 3.0 mmHg·s/dm. This value corresponds to approximately 60% of the QFR-IMR gradient observed between patients with and without microvascular obstruction on cardiac magnetic resonance imaging (28.7 versus 23.6 mmHg·s/dm) and represents a conservative fraction of the 5.0 mmHg·s/dm increment associated with a 29% increase in the risk of heart failure (hazard ratio 1.29, 95% confidence interval 1.10 to 1.52).(21) An QFR-IMR threshold of 25 to 27 mmHg·s/dm consistently discriminates high-risk patients after STEMI in independent cohorts,(21–23) which reinforces the prognostic relevance of a reduction of this magnitude. We assumed a within-subject correlation of 0.7 between the baseline and final QFR-IMR measurements, consistent with the reproducibility described for modeled angiographic indices, which reduces the residual variance by a factor of $(1 - \rho^2)$ in the ANCOVA framework.

With 90% power, a two-tailed significance level of 0.05, and 1:1 allocation, the study requires 30 participants per arm. Adding an estimated loss of 15%, the final sample size will be 35 participants per arm, totaling 70 participants. To better establish safety and efficacy in acute coronary syndrome, we determined a sample size for conducting the study of 100 patients in total, with 1:1 allocation between the placebo and intervention groups.

Sample losses and missing data

For the sample size calculation, an overall loss rate of approximately 15% was considered, encompassing withdrawals, losses to follow-up, and limitations in obtaining the examinations set out in the protocol. This estimate includes the inability to perform cardiac magnetic resonance imaging (CMR) due to contraindication, clinical instability, or refusal by the participant, as well as the occurrence of angiographic images inadequate for analysis of QFR-IMR parameters as a result of insufficient quality, vessel overlap, or technical limitations of acquisition.

Every effort will be made to minimize losses to follow-up and missing data by means of prospective monitoring, structured scheduling of assessments, and systematic review of image quality. Participants who discontinue the study after randomization will have the data already collected included in the analyses, whenever permitted by the consent and by applicable ethical standards. The frequency and reasons for losses will be recorded and reported in the final analysis of the study.

Randomization method

Randomization will be carried out by means of the REDCap® (Research Electronic Data Capture) platform, using a specific module for random allocation of participants. The randomization sequence will be generated electronically before the start of recruitment, in a 1:1 ratio between the study groups, by an investigator not involved in the enrollment of participants or in the assessment of outcomes.

The randomization list will be incorporated into the REDCap® system with access restricted to authorized users, ensuring allocation concealment until the completion of eligibility assessment and enrollment of the participant. The system will automatically release the group assignment only after definitive registration of the participant, preventing prior access to the randomization sequence by the investigators responsible for recruitment.

If randomization blocks are used to ensure balance between the groups throughout the study, the block size will remain confidential and restricted to those responsible for generating the sequence. Stratification will not be performed, unless specifically provided for in a subsequent version of the protocol.

All randomization records, including date, time, responsible user, and allocated group, will remain stored electronically in REDCap®, allowing full traceability of the process. Any deviations from the randomization procedure, allocation errors, or breaches of concealment will be documented, justified, and reported in the study records, and will be taken into account in the final analyses in accordance with the previously defined statistical plan.

Stratification will not be performed in the randomization process by type of acute myocardial infarction (AMI) or reperfusion strategy. However, considering the inclusion of patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), as well as patients who did or did not undergo prior thrombolysis, pre-specified subgroup analyses will be performed to assess the consistency of results across these populations.

The analyses will include, at a minimum, comparison of efficacy and safety outcomes according to: (i) type of AMI (STEMI versus NSTEMI) and (ii) prior thrombolysis (yes versus no). Such analyses will be exploratory in nature and will be interpreted with caution, as the study is not specifically powered to detect differences between subgroups.

Method for assessing the microcirculation: QFR-IMR

Microvascular resistance will be assessed through the use of the QFR software (Medis Medical Imaging ©, Version 3.1) and specifically by means of QFR-IMR: a dedicated tool that provides an angiography-derived assessment of Index of Microcirculatory Resistance (IMR). This method uses three-dimensional reconstruction of the coronary artery and computational analysis of contrast flow to estimate the resistance of the microcirculation without the need for guidewires with pressure or thermodilution sensors. In this way, it permits physiological assessment of the microcirculation in a less invasive manner that is more readily applicable in the context of acute myocardial infarction (AMI).(13) For providing the QFR-IMR software for the carrying out of this study, Medis Medical Imaging acts as a sponsor for thar part of the trial.

On this basis, the measurement of microvascular dysfunction will be carried out by means of blind analysis of the images obtained through coronary angiography, employing the QFR-IMR method as the instrument. These IMR measurements will be calculated and confirmed by physicians with training in interventional cardiology who are certified to interpret this method by the developing company. All assessors will be blinded as to which group the patient under analysis was allocated to (saline or papaverine).

The reference values adopted will be those validated in the literature for angiography-derived indices of microvascular resistance. Values < 25 U will be considered consistent with preserved microvascular function, values between 25 and 40 U will indicate intermediate impairment, and values > 40 U will be considered consistent with significant microvascular dysfunction. The analysis of IMR will be carried out treating it as a spectrum (continuous variable), being categorized only for the purposes of secondary assessment. Studies conducted in patients with AMI have demonstrated an association between elevated angiography-derived microvascular resistance values and a greater occurrence of microvascular obstruction, a greater extent of myocardial necrosis, worse ventricular recovery, and an increased risk of adverse cardiovascular events after percutaneous coronary intervention.(13)

The analyses will be performed by assessors trained and certified in the use of the QFR-IMR platform, following a standardized protocol for angiographic acquisition and image processing, and remaining blinded to treatment allocation. The use of QFR-IMR parameters in the context of AMI is supported by studies that have demonstrated good correlation with the invasive index of microcirculatory resistance (IMR), in addition to adequate reproducibility and prognostic value for identifying residual microvascular dysfunction after primary PCI.

The measurements will use the images obtained during coronary angiography and PCI of the index procedure. The assessment will subdivide the images into 3 groupings: those obtained at the beginning of the procedure (termed pre-infusion), at the end of PCI (post-infusion), and after the infusion of the syringe containing saline or papaverine (post-medication). Subsequently, the absolute

values of microvascular resistance will be calculated for each of the groupings and the values obtained will be compared in order to assess the impact of the intervention on the microcirculation. IMR values > 25 will be classified as elevated and consistent with the presence of significant microvascular disease.

The primary endpoint of the study consists of the assessment of microvascular resistance by QFR-IMR, used as markers of the integrity of the coronary microcirculation after PCI. The rationale for its use is based on evidence that microvascular dysfunction constitutes an important prognostic determinant after acute myocardial infarction, being associated with microvascular obstruction, the no-reflow phenomenon, and inadequate myocardial reperfusion.

Elevated microvascular resistance values correlate with larger infarct size, less recovery of left ventricular function, a higher incidence of heart failure, readmissions for cardiovascular causes, and an increased occurrence of major adverse cardiovascular events. Thus, although the primary endpoint is physiological, it represents a biologically plausible and clinically relevant surrogate endpoint for cardiovascular outcomes of greater impact.

The clinical outcomes of the study, including ventricular function, symptoms, heart failure, readmissions, cardiovascular events, and mortality, will be analyzed as secondary and exploratory outcomes, allowing assessment of whether any benefits observed in the microcirculation translate into measurable clinical repercussions. However, the study was not powered to demonstrate statistically significant differences in these clinical outcomes.

Quality control of angiographic images

Angiographic acquisitions intended for physiological analysis will be performed according to a standardized protocol, using projections with adequate separation of the coronary segments, minimization of vessel overlap, absence of significant foreshortening of the vessel, and complete filling of the coronary bed with contrast. Whenever possible, at least two angiographic projections with a minimum angular difference of 25° will be obtained to permit adequate three-dimensional reconstruction and analysis of QFR-IMR parameters.

The images will be acquired after the completion of PCI and stabilization of the final angiographic result, using digital acquisition at 30 frames per second for optimal image resolution and accurate IMR outputs. All examinations will be stored in DICOM format on a secure institutional server, with coded identification of the participants and access restricted to authorized investigators.

Examinations with insufficient quality, significant vessel overlap, inadequate contrast filling, excessive motion, or inability to perform three-dimensional reconstruction will be classified as non-analyzable. When technically feasible and without additional risk to the participant, new acquisitions may be performed during the procedure itself. For quality control, a sample of the analyses may be submitted to independent assessment by a second observer, with measurements repeated in cases of relevant discrepancy or technical doubt.

The assessment of the images will be carried out by an investigator blinded to the allocation or randomization of the patients, independently of the clinical care team, with analysis by at least 2 assessors for verification and reduction of bias. The images will be stored in an independent archive, as well as in the digital

system and in the patient's medical record, as determined by regulatory standards.

Reimbursement of expenses

Participants and, where applicable, their companions will be entitled to reimbursement of expenses directly related to participation in the study, including costs of transportation, meals, and parking necessary for attending visits and procedures performed exclusively for research purposes.

Reimbursement will be provided upon presentation of receipts for the expenses or a simplified declaration, in accordance with the institutional standards in force. Payment will be made by the research center within 30 days of the request and verification of the corresponding documentation. The amount reimbursed will be limited to expenses actually incurred and compatible with the procedures set out in the protocol, and does not constitute remuneration or financial incentive for participation. The principal investigator and the administrative team of the study will be responsible for the review, recording, and operationalization of the reimbursement process.

Cardiac risks associated with intracoronary administration of papaverine

Intracoronary papaverine has a widely known safety profile in interventional cardiology; however, its administration may be associated with potentially serious cardiovascular events, especially in patients with prior electrical instability, electrolyte disturbances, or complex coronary artery disease.

- **Arterial hypotension:** resulting from the systemic vasodilator effect, generally transient, possibly requiring volume expansion and, in selected cases, vasopressor support.
- **Sinus bradycardia:** may occur during or after intracoronary administration, usually in a transient manner, but potentially associated with hemodynamic repercussions.
- **Cardiac conduction disturbances:** these include atrioventricular block of varying degrees and transient intraventricular blocks, particularly in procedures involving the right coronary artery or in patients with prior conduction system abnormalities.
- **QT/QTc interval prolongation:** a known pharmacological effect of papaverine, related to increased susceptibility to malignant ventricular arrhythmias.
- **Torsades de pointes:** polymorphic ventricular tachycardia associated with QT prolongation, potentially self-limited or progressing to hemodynamic instability and ventricular fibrillation.
- **Ventricular tachycardia:** may occur in sustained or non-sustained form, requiring continuous monitoring and treatment in accordance with advanced life support protocols.
- **Ventricular fibrillation:** a rare event, but described in the literature, particularly after high intracoronary doses or in predisposed patients, potentially requiring immediate electrical defibrillation.
- **Need for electrical defibrillation:** may be necessary in cases of ventricular fibrillation or pulseless ventricular tachycardia.

- **Need for a temporary pacemaker:** may occur in situations of severe bradycardia, advanced atrioventricular block, or electrical instability with hemodynamic repercussions.

All participants will undergo continuous electrocardiographic and hemodynamic monitoring during and after the administration of papaverine, allowing early identification and immediate treatment of any arrhythmic or hemodynamic complications. Resuscitation, cardioversion/defibrillation, and temporary cardiac pacing equipment will be readily available throughout the procedure.

Emergency infrastructure for administration of the intervention

The administration of intracoronary papaverine will be performed exclusively in a catheterization laboratory with advanced support for cardiovascular emergencies. All participants will remain under continuous electrocardiographic monitoring, pulse oximetry, and invasive or non-invasive hemodynamic monitoring, in accordance with institutional routine.

The procedure room will be equipped with a defibrillator capable of synchronized cardioversion and defibrillation, complete material for cardiopulmonary resuscitation (CPR), an oxygen therapy system, equipment for advanced airway management, and a temporary pacemaker, available for immediate implantation when clinically indicated.

Emergency medications will be readily available, including vasopressors, inotropes, atropine, antiarrhythmics, sedatives, and other drugs used in advanced cardiovascular life support protocols. The intervention will be conducted by qualified interventional cardiologists, with the support of a

multiprofessional team trained in the management of cardiovascular emergencies and cardiopulmonary resuscitation.

In the event of an adverse event or complication related to the procedure, the institutional emergency protocol will be immediately activated, with identification of the event, adoption of appropriate therapeutic measures, clinical stabilization of the participant and, when necessary, transfer to an intensive care unit or continuation of support in a specialized hospital environment. All events will be recorded and followed up in accordance with the study's safety monitoring plan.

Safety Monitoring Plan

1. Objective

The purpose of this plan is to ensure the early identification, appropriate management, systematic recording, causality assessment, and timely reporting of adverse events (AEs) and serious adverse events (SAEs) occurring during individuals' participation in the study, ensuring the protection of participants and compliance with Good Clinical Practice (ICH-GCP), CNS Resolution No. 466/2012, and other applicable regulations.

2. Definitions

Adverse Event (AE)

Any unfavorable medical occurrence observed in a participant included in the study, regardless of the existence of a causal relationship with the procedure or investigational product.

Serious Adverse Event (SAE)

Any event that results in at least one of the following conditions will be considered serious:

- Death;
- Imminent risk of death;
- Unplanned hospitalization or prolongation of existing hospitalization;
- Persistent or significant incapacity or disability;
- Congenital anomaly or birth defect;
- Clinically significant event that, in the investigator's judgment, may place the participant at risk or require intervention to prevent any of the above conditions.

3. Clinical monitoring and surveillance period

All participants will be monitored continuously from the signing of the Informed Consent Form until the end of the follow-up period defined in the protocol.

Monitoring will include:

- Serial clinical assessment during hospitalization;
- Continuous electrocardiographic monitoring during the procedure;
- Continuous hemodynamic monitoring during and immediately after the intervention;
- Laboratory assessment in accordance with institutional routine and as established by the protocol;
- Systematic recording of symptoms, clinical signs, and intercurrent events;
- Review of medical records, ancillary tests, and hospitalization reports.

4. Identification and recording of adverse events

All adverse events observed by the investigator or spontaneously reported by the participant will be recorded on a specific safety form and in the study database.

For each event, the following must be documented:

- Clinical description of the event;
- Date and time of onset;
- Date and time of resolution;
- Intensity;
- Seriousness;
- Action taken;
- Clinical course;
- Final outcome;
- Causality assessment.

5. Classification of intensity

Events will be classified as to intensity as:

Mild

Transient event, well tolerated, without significant interference in usual activities and without the need for specific intervention.

Moderate

Event that produces relevant discomfort and may require clinical or therapeutic intervention.

Severe (intensity)

Disabling or clinically important event that substantially interferes with the participant's clinical condition.

The classification of intensity is independent of the regulatory definition of a Serious Adverse Event (SAE).

6. Causality assessment

The relationship between the event and the procedure or investigational product will be assessed by the principal investigator according to the following criteria:

- Definitely related;
- Probably related;
- Possibly related;
- Unlikely to be related;
- Not related.

The assessment will consider:

- Temporal relationship;
- Biological plausibility;
- Presence of alternative factors;
- Response to discontinuation of the intervention;
- Previously available scientific evidence.

7. Events of special interest

Considering the pharmacological profile of intracoronary papaverine, the following will be considered events of special interest:

Cardiovascular

- Persistent no-reflow;

- Slow-flow;
- Coronary vasospasm;
- Recurrent chest pain;
- Reinfarction;
- Stent thrombosis;
- Cardiogenic shock;
- Significant hypotension.

Arrhythmic

- Symptomatic bradycardia;
- Advanced atrioventricular block;
- Ventricular tachycardia;
- Polymorphic ventricular tachycardia;
- Torsades de pointes;
- Ventricular fibrillation;
- New-onset atrial fibrillation.

Electrocardiographic

- Significant prolongation of the QT or QTc interval.

8. Follow-up of events

All adverse events will be followed until:

- Complete resolution;
- Clinical stabilization;
- Return to baseline condition;
- Determination of permanent sequelae;

- Death.

Follow-up may include additional clinical assessments, laboratory tests, imaging examinations, and specialist consultations according to clinical need.

9. Reporting of serious adverse events

Immediate notification

Every SAE must be reported to the principal investigator immediately upon becoming known.

Reporting deadline

SAEs must be reported to the sponsor and to the Research Ethics Committee within 24 hours of their initial identification.

Follow-up reports must be submitted as new information becomes available.

10. Safety monitoring and review committee

The principal investigator and the executing investigator will conduct periodic review of the accumulated safety data, including:

- Frequency of adverse events;
- Frequency of serious adverse events;
- Unexpected events;
- Events potentially related to papaverine;
- Need for protocol modifications.

If a significant risk to participants is identified, the following may be recommended:

- Temporary suspension of recruitment;

- Protocol revision;
- Discontinuation of the intervention;
- Early termination of the study.

11. Criteria for discontinuation of the intervention

Administration of the intervention must be immediately discontinued in the following situations:

- Sustained ventricular tachycardia;
- Torsades de pointes;
- Ventricular fibrillation;
- Severe QTc prolongation associated with clinical instability;
- Refractory hypotension;
- Unexpected serious adverse reaction attributed to the intervention;
- Any condition that represents an unacceptable risk to the participant in the investigator's judgment.

12. Periodic safety reports

Consolidated safety reports will be prepared periodically during the conduct of the study and at its conclusion, containing:

- Total number of AEs and SAEs;
- Distribution by seriousness and causality;
- Events of special interest;
- Corrective measures implemented;
- Overall assessment of the safety profile of the intervention.

These reports will be made available to the Research Ethics Committee and to the competent regulatory authorities, as applicable.

Definitions and Safety Reporting Flow

Adverse Event

Reporting: record on the data collection form and follow until resolution, stabilization, or the end of follow-up.

Serious Adverse Event

Any event that results in at least one of the following conditions:

- Death;
- Imminent risk of death;
- Unplanned hospitalization or prolongation of hospitalization;
- Persistent or significant incapacity or disability;
- Congenital anomaly or birth defect;
- Clinically relevant event requiring intervention to prevent any of the above conditions.

Reporting: notify the Principal Investigator immediately upon identification and the sponsor and REC within 24 hours. Supplementary information must be forwarded as it becomes available.

Unexpected Adverse Event

An event whose nature, severity, frequency, or clinical course is not consistent with the previously known information about the investigational product, the scientific literature, or the study protocol.

Reporting: follow the SAE flow when serious; when not serious, record and report in the periodic safety reports.

Adverse Reaction Related to the Investigational Product (ADR)

An adverse event for which there is a reasonable possibility of a causal relationship with the investigational product, classified as definite, probable, or possible by the investigator.

Reporting: record, assess causality, and follow until resolution. When serious or unexpected, report as an SAE within 24 hours.

Causality Assessment

The causal relationship will be classified by the investigator as:

- Definite;
- Probable;
- Possible;
- Unlikely;
- Not related.

The assessment will consider temporality, biological plausibility, alternative factors, and clinical course.

Type of occurrence	**Recording**	**Notification to the Principal Investigator**	**Notification to the REC/Sponsor**
Non-serious AE	Immediate	As per study routine	Periodic reports
Non-serious ADR	Immediate	As per study routine	Periodic reports
SAE	Immediate	Within 24 hours	Within 24 hours
Related unexpected SAE	Immediate	Within 24 hours	Within 24 hours, with supplementary updates when applicable

Unblinding in emergency situations

Unblinding will be permitted exclusively in exceptional situations in which knowledge of the intervention received by the participant is considered indispensable for immediate clinical decision-making and may directly impact their safety or therapeutic management. Unblinding must not be carried out for operational convenience, scientific interest, or routine assessment of study outcomes.

Unblinding may be carried out in the following situations:

- Occurrence of a serious adverse event (SAE) in which knowledge of the treatment administered is essential for defining medical management;
- Unexpected serious adverse reactions with potential risk to life;
- Severe or refractory hemodynamic instability without a clearly identified cause;
- Malignant ventricular arrhythmias potentially related to the investigational product;
- Need for emergency medical intervention in which information about the participant's allocation could substantially modify the treatment;
- Express determination by the attending medical team when lack of knowledge of the intervention represents an additional risk to the participant.

Persons responsible for unblinding

The request for unblinding must be made by the principal investigator or, in their unavailability, by a formally designated sub-investigator trained for this function. In immediate clinical emergencies, the attending physician responsible for care

may request unblinding directly, provided that the justification is duly documented.

Access to allocation information

The information regarding the participant's allocation will remain stored in a secure randomization system under the responsibility of the study coordination. Access will occur exclusively by the authorized investigator or by the professional formally designated for this purpose. The opening of the code must be limited to the participant involved in the emergency, preserving the blinding of the other participants and of the research team whenever possible.

Recording of unblinding

Every unblinding must be recorded on a specific form containing, at a minimum:

- Identification of the participant;
- Date and time of the request;
- Name and role of the professional who authorized and carried out the unblinding;
- Detailed clinical justification;
- Circumstances that motivated the decision;
- Information disclosed;
- Actions taken after learning of the allocation;
- Clinical outcome of the event.

The record will be incorporated into the medical chart, the study database, and the essential documents of the research.

Communication to the competent bodies

Every unblinding must be communicated to the Research Ethics Committee (REC) in accordance with the study's standard operating procedures. In cases classified as serious adverse events, notification will follow the pharmacovigilance and safety flows, including communication to the competent regulatory authorities when required.

Preservation of the integrity of the study

Whenever possible, unblinding must occur only for the professionals directly involved in the participant's care, with outcome assessors, statisticians, and other members of the research team remaining blinded. All occurrences will be periodically assessed by the principal investigator and by those responsible for study monitoring in order to verify the potential impact on methodological integrity and the validity of the results.

Final report

The total number of unblindings, their justifications, and respective outcomes will be described in the final study report and taken into account in the safety analyses and interpretation of the results. This procedure aims to ensure the protection of participants without unnecessarily compromising the scientific validity of the research.

The establishment of an independent Data and Safety Monitoring Board (DSMB) is not warranted for the present study owing to its single-center nature, limited sample size, and use of intracoronary papaverine, a drug with well-established use and a widely known safety profile in interventional cardiology practice. The intervention will be performed exclusively in the catheterization laboratory setting, under continuous clinical, electrocardiographic, and hemodynamic

monitoring, with previously defined criteria for the management of adverse events and discontinuation of the intervention. Safety monitoring will be conducted by the Principal Investigator, with systematic review of adverse events and communication to the Research Ethics Committee in accordance with the regulatory requirements in force, which is considered sufficient to ensure the safety of participants and the integrity of the study.

Method of analysis of results

Primary hypothesis

The primary hypothesis of the study is that intracoronary administration of papaverine at the end of PCI reduces microvascular resistance, assessed by QFR-IMR, in comparison with standard treatment without papaverine.

Analysis population

The primary analysis will be carried out according to the intention-to-treat (ITT) principle, including all randomized participants according to the group to which they were originally allocated. In addition, a per-protocol analysis will be carried out as a sensitivity analysis, including only participants who complete the protocol without major deviations.

Analysis of the primary endpoint

The primary endpoint, expressed as a continuous variable, will initially be assessed for distribution by means of the Shapiro-Wilk test. Variables with a normal distribution will be presented as mean ± standard deviation and compared between groups by means of Student's t-test for independent

samples. Variables with a non-normal distribution will be described as median and interquartile range and compared by the Mann-Whitney test.

Analysis of secondary endpoints

Secondary continuous variables will be analyzed using the same criteria applied to the primary endpoint. Categorical variables will be presented as absolute frequencies and percentages, and compared by the chi-square test or Fisher's exact test, as appropriate. Effect measures will be presented as mean difference, relative risk (RR), or odds ratio (OR), accompanied by 95% confidence intervals.

Binary clinical outcomes, including the occurrence of heart failure, readmission, major cardiovascular events, and mortality, will be analyzed by logistic regression when applicable. Should time-dependent outcomes be assessed, Kaplan-Meier curves and the log-rank test may be used.

Handling of missing data

Missing data will initially be described in terms of frequency and pattern of occurrence. For the primary endpoint, when appropriate, multiple imputation may be employed if the proportion of missing data exceeds 5%. Sensitivity analyses will be performed to assess the impact of missing data on the main results.

Safety analysis

The safety population will include all participants who receive the intervention provided for in the protocol. Adverse events and serious adverse events will be presented by treatment group as absolute frequencies and percentages.

Comparisons between groups will be carried out by the chi-square test or Fisher's exact test. Cardiovascular events of interest will be specifically described, including hypotension, bradyarrhythmias, atrioventricular blocks, QT interval prolongation, torsades de pointes, ventricular tachycardia, ventricular fibrillation, and the need for defibrillation or a temporary pacemaker.

Control of multiplicity

As this is a study with a single primary endpoint, the significance level will be set at $\alpha = 0.05$ (two-tailed) for the main analysis. The analyses of secondary endpoints will be considered exploratory and interpreted in a hierarchical and contextualized manner, with no formal adjustment for multiplicity being planned. The respective p-values and 95% confidence intervals will be presented to allow adequate interpretation of the results.

Statistical software

Statistical analyses will be performed using validated statistical software, such as R (R Foundation for Statistical Computing) or SPSS (IBM Corp.), with a significance level of 5% being adopted for all inferential tests.

Analysis populations

- **Intention-to-treat (ITT):** will include all randomized participants, analyzed according to the group to which they were originally allocated, regardless of the intervention received, rescue therapy, protocol deviations, or unblinding. This will be the primary efficacy population.

- **Per-protocol (PP):** will include participants who complete the study without major protocol deviations and with data available for assessment of the primary endpoint.
- **Safety:** will include all participants who receive the study intervention, analyzed according to the treatment actually received.
- **Rescue therapy, deviations, and unblinding:** Participants who undergo rescue therapy, or who have protocol deviations or unblinding, will remain included in the ITT analysis. Major deviations may determine exclusion from the PP analysis. All such occurrences will be recorded, described, and taken into account in sensitivity analyses, when applicable.

Secondary endpoints

1. Assessment by cardiac magnetic resonance imaging (CMR)

Time of measurement: Up to 30 days after the procedure, depending on institutional availability.

Variables assessed: infarct size (% of left ventricular mass), scar area (% of left ventricular mass), presence and extent of microvascular obstruction (MVO), presence of segmental dysfunction, and left ventricular ejection fraction (%).

Method of analysis: comparison between groups by Student's t-test or Mann-Whitney test, according to the distribution of the data.

Clinical interpretation: smaller infarct size, lesser extent of MVO, and higher ejection fraction will be interpreted as markers of better myocardial reperfusion and preservation of ventricular function.

2. Angiographic coronary flow (TIMI)

Time of measurement: immediately after PCI and after the study intervention.

Unit of measurement: TIMI classification (0 to 3).

Method of analysis: comparison between groups by the chi-square test, Fisher's exact test, or models for ordinal variables, when applicable.

Clinical interpretation: higher proportions of TIMI 3 flow will be considered indicative of better coronary reperfusion.

3. Cardiac biomarkers

Variables assessed: troponin and BNP.

Time of measurement: pre-procedure, post-PCI, and after administration of the intervention, in accordance with the study schedule.

Unit of measurement: absolute values according to the institutional laboratory method.

Method of analysis: comparison of absolute and relative changes between groups by parametric or non-parametric tests for continuous measures.

Clinical interpretation: lower levels of troponin and BNP may suggest a lesser extent of myocardial injury and less hemodynamic compromise.

4. Safety outcomes

Time window: from the procedure until hospital discharge.

Events assessed:

- Arterial hypotension;
- Cardiogenic shock;

- Anaphylaxis;
- Need for vasopressor drugs;
- Need for mechanical circulatory support;
- Unstable bradyarrhythmia;
- Need for a temporary pacemaker;
- Non-sustained ventricular tachycardia;
- Sustained/unstable ventricular tachycardia;
- Pulseless ventricular tachycardia;
- Ventricular fibrillation;
- Need for cardiopulmonary resuscitation;
- Need for cardioversion/defibrillation;
- Transient ischemic attack (TIA);
- Stroke;
- Death related to the intervention.

Method of analysis: absolute frequency and percentage, with comparison between groups by the chi-square test or Fisher's exact test.

Clinical interpretation: a lower incidence of adverse events and serious adverse events will be interpreted as a better safety profile of the intervention.

Priority of secondary endpoints: the CMR parameters will constitute the secondary efficacy endpoints of greatest clinical relevance, followed by the cardiac biomarkers and angiographic parameters. Safety outcomes will be analyzed independently and reported for all participants exposed to the intervention.

Data Governance and Personal Data Protection

The processing of data will be carried out in compliance with the Brazilian General Data Protection Law (LGPD – Law No. 13,709/2018). The institution will act as Data Controller, being responsible for decisions relating to the processing of the information, while the investigators and platforms used for storage and management will act as Processors. Participants may exercise their rights through the institutional channels made available by the institution and stated in the Informed Consent Form.

Demographic, clinical, laboratory, angiographic, electrocardiographic, and imaging data necessary for the execution of the research will be collected, including sensitive personal data relating to health. The information will be coded by a unique identifier, with directly identifiable data kept separately and with restricted access. Storage will be carried out in a secure electronic environment (REDCap® and protected institutional servers), with access control limited to authorized professionals.

The processing of data will have as its legal basis the participant's consent, the conduct of health research, and compliance with applicable regulatory obligations. The data may be shared exclusively for the purposes of monitoring, auditing, statistical analysis, and scientific publication, always confidentially and observing the principles of necessity and minimization. Records will be retained for the period required by the ethical and regulatory standards in force, and will subsequently be coded or deleted when applicable.

The REDCap® platform

The REDCap® platform is hosted on a secure institutional server and protected by individual authentication mechanisms, per-user access control, and encryption. Access will be restricted to authorized members of the research team, by means of personal credentials and permission profiles defined according to their roles in the study.

The platform maintains a complete audit trail, recording the entry, modification, viewing, and export of data, with identification of the user and the date and time of each operation. Periodic backups will be performed in accordance with institutional information security policies, ensuring the recovery of data in the event of system failure or unavailability.

Randomization will be implemented by a specific REDCap® module, with restricted access and concealment of the allocation sequence until definitive enrollment of the participant. Participants' identifiable data will be stored separately from the study's analytical database, using a unique identification code, so as to ensure confidentiality, traceability, and protection of participants' identity during all stages of the study.

Work plan and Timeline

- Recruitment: 6 months
- Analysis of results: 6 months
- Preparation and writing of the final work: 3 months

Total: 15 months

MONTHS	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
RECRUIT	X	X	X	X	X	X									

MENT															
ANALYSIS OF RESULTS							X	X	X	X	X	X			
Preparation and writing of the final work													X	X	X

Study stopping rules

The study may be temporarily suspended or permanently terminated by the Principal Investigator if an unacceptable risk to participants is identified. The criteria for discontinuation include:

1. Occurrence of an unexpected serious adverse event related to the intervention with potential risk to life or death;
2. Frequency of serious adverse events related to the procedure or to the investigational product higher than expected based on the literature and on the previously known risk profile;
3. Identification of an unfavorable safety pattern suggesting a causal relationship with the intervention;
4. Determination by the Research Ethics Committee, competent regulatory authority, or sponsor;
5. Evidence that continuation of the study compromises the safety of participants or the scientific integrity of the research. Following suspension, a detailed analysis of the events that occurred will be carried out in order to decide on resumption, modification of the protocol, or permanent termination of the study.

An individual's participation will be discontinued in the following situations:

- **Withdrawal of consent:** request by the participant or their legal representative for discontinuation of participation in the study, without the need for justification.
- **Serious adverse event:** occurrence of a serious adverse event that, in the investigator's judgment, renders continued participation inappropriate or unsafe.
- **Clinical or hemodynamic instability:** development of a clinical condition that represents an additional risk to the participant or interferes with the safe conduct of the study.
- **Pregnancy:** confirmation of pregnancy during the period of participation, when applicable.
- **Inability to follow up:** loss to follow-up, inability to attend the scheduled assessments, or any condition that makes adequate collection of study data unfeasible.
- **Reasoned medical decision:** determination by the investigator, based on clinical or safety criteria, that remaining in the study is not in the participant's best interest.
- **Critical protocol deviation:** occurrence of a relevant violation of the prescribed procedures that compromises the safety of the participant or the scientific validity of the data.

In all cases, the reason for discontinuation will be documented in the study records and, whenever applicable, the participant will be followed until the resolution or stabilization of ongoing safety events.

Withdrawal of consent and use of previously collected data

The participant may withdraw their consent to participate in the study at any time, without prejudice to their medical care. In such a situation, no new information will be collected after the withdrawal is formalized.

The data obtained up to the date of withdrawal may be retained and used for the purposes of scientific analysis, safety, methodological integrity of the study, and compliance with ethical and regulatory requirements, provided that they have been previously anonymized or coded and in compliance with the LGPD and with the Informed Consent Form. Should the participant expressly request the deletion of their data, the request will be reviewed taking into account the legal, regulatory, and scientific limitations applicable to clinical research.

The participant's decision, as well as the extent of the use of data already collected, will be duly recorded in the study documentation, with confidentiality and protection of personal information being ensured.

Communication of clinically relevant findings

All clinically relevant findings identified during the performance of the study's examinations and procedures, including changes on electrocardiogram, echocardiogram, cardiac magnetic resonance imaging, laboratory tests, or events detected during follow-up, will be promptly assessed by the research team.

When the findings present potential diagnostic, prognostic, or therapeutic impact, the participant will be informed in a timely manner so that the clinical

measures deemed appropriate may be adopted. The results will be recorded in the medical chart and in the study documentation, as applicable.

Communication will follow institutional clinical care pathways, preserving the confidentiality of the data and prioritizing the safety of the participant, especially in cases of findings that require further investigation or immediate clinical intervention.

Protocol deviations

Protocol deviations will be classified according to their potential impact on participant safety, data integrity, and the scientific validity of the study.

- **Minor deviation:** an occurrence without relevant impact on participant safety or on the assessment of outcomes, such as delays within the permitted visit windows or minor documentary inconsistencies.
- **Major deviation:** an occurrence with potential impact on the conduct of the study or on data quality, including failures in procedures prescribed by the protocol, assessments not performed, or incorrect administration of research procedures.
- **Critical protocol violation:** an occurrence that significantly compromises participant safety, the ethical aspects of the research, or the validity of the results, including enrollment of an ineligible participant, failure in the consent process, or improper breaking of the randomization.

All deviations will be recorded on a specific form, assessed by the Principal Investigator, and classified as to severity and impact. When applicable, they will be reported to the Research Ethics Committee in accordance with the institutional standards in force. Participants with major deviations or critical

violations will remain included in the intention-to-treat (ITT) analysis, and may be excluded from the per-protocol (PP) analysis, as defined in the statistical plan.

Monitoring and auditing plan

The study will be subject to periodic monitoring conducted by the principal investigator, with a frequency proportional to the rate of participant enrollment and the operational complexity of the protocol. Monitoring activities may take place on site or remotely.

The scope of monitoring will include verification of participant eligibility, obtaining and filing of the Informed Consent Form, checking of the data recorded in the electronic database against the corresponding source documents, oversight of randomization, control of the investigational product, review of adverse events and serious adverse events, assessment of protocol deviations, and verification of compliance with the protocol, Good Clinical Practice (ICH-GCP), and applicable regulatory requirements.

Audits may be carried out by the institution, the sponsor, the Research Ethics Committee, or the competent regulatory authorities. All essential study records will remain available for inspection, ensuring traceability, data integrity, protection of participants, and regulatory compliance throughout the conduct of the research.

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Materials and Resources

The resources required to conduct the present study are itemized by unit value:

Item	No.	Unit value	Total value
Cardiac magnetic resonance imaging study with contrast (gadolinium)	100	R$ 1,900.00	R$ 190,000.00
Ampoule of papaverine 50 mg/mL, 2 mL (unit)	100	R$ 15.70	R$ 1,570.00
Ampoule of distilled water (10 mL)	200	R$ 0.82	R$ 164.00
Opaque plastic injection syringe with screw thread (20 mL)	200	R$ 6.30	R$ 1,260.00
Ampoule of 0.9% saline solution (10 mL)	200	R$ 0.11	R$ 22.00
A4 printing paper (pack of 100 sheets)	10	R$ 15.00	R$ 150.00
Permanent-use material: laptop for data analysis	1	R$ 20,000.00	R$ 20,000.00
SPSS SOFTWARE LICENSE	1	R$ 6,648.37	R$ 6,648.37
Transportation/meal and accommodation expenses for those involved in the study	100	R$ 2,000	R$ 200,000.00
TOTAL			**R$ 419,814.37**

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Publication and dissemination plan

The results of the study will be analyzed and disseminated in scientific journals, at conferences, and through other appropriate academic channels, regardless of whether or not they confirm the hypothesis initially proposed. Positive, negative,

or inconclusive results will be reported transparently, in accordance with the principles of scientific integrity and good practice in clinical research.

Publications and presentations will use exclusively aggregated and anonymized data, with no possibility of individual identification of participants. After completion of the study, participants may request access to a summary of the overall results of the research in accessible language, subject to regulatory limitations and the schedule for analysis and publication of the data.

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Addendum I. Angiographic Acquisition Protocol for QFR-IMR Analysis

A1. Purpose and scope

This addendum specifies the angiographic acquisition standards required for the derivation of the angiography-based Index of Microcirculatory Resistance (QFR-IMR, Medis Medical Imaging ©, QFR version 3.1) in the PAP-MICRO trial. It supplements the sections “Method for assessing the microcirculation: QFR-IMR” and “Quality control of angiographic images” of the main protocol. Because QFR-IMR requires quantification of contrast flow velocity in addition to three-dimensional vessel reconstruction, its acquisition requirements are more restrictive than those of a standard QFR analysis; wherever a discrepancy exists, the specifications of this addendum prevail for all acquisitions intended for QFR-IMR analysis.

A1.1. Target vessels

QFR-IMR analyses will be performed in the culprit vessel treated during the index percutaneous coronary intervention (PCI). The inclusion criteria of the main protocol do not restrict eligibility to any particular coronary artery, and therefore any of the three major epicardial vessels may be the target of the analysis; only one target vessel will be analysed per participant. The left anterior descending artery (LAD) and the right coronary artery (RCA) are expected to account for most of the analyses and are the vessels for which the acquisition standards of this addendum were primarily developed, since they allow reproducible angulation pairs with minimal overlap and foreshortening and consistent identification of a distal anatomical landmark for frame counting across serial acquisitions. When the culprit vessel is the left circumflex artery (LCx) or one of its marginal branches, the angulation pair specified for that

vessel in Table A1 will be used and all remaining requirements of this addendum apply unchanged. Because overlap and foreshortening are typically greater in the LCx territory, particular attention must be paid to the visibility of the distal landmark used for frame counting; acquisitions in which this landmark cannot be identified will be classified as non-analyzable in accordance with section A9.

A2. Acquisition time points and number of acquisitions

Angiographic images for QFR-IMR will be acquired at three time points of the index procedure, corresponding to the three analysis groupings defined in the main protocol: (i) pre-infusion, at the beginning of the procedure; (ii) post-infusion, after completion of PCI and stabilization of the final angiographic result; and (iii) post-medication, after the intracoronary infusion of the syringe containing saline or papaverine. Each time point requires two acquisitions of the target vessel from two different angulations, resulting in three paired acquisitions (six angiographic runs) per participant.

The pair of angulations is selected for each participant at the pre-infusion time point and must be reproduced identically at the post-infusion and post-medication time points. Field of view, magnification, table position, source-to-image distance and frame rate must also be kept constant across the three time points, so that contrast flow velocity and QFR-IMR values remain directly comparable within the same participant. The angulation pair actually used, together with the acquisition parameters, will be recorded in the electronic case report form (REDCap®) for every participant.

A3. Recommended angiographic projections

The angulation pairs recommended for this study are presented in Table A1. They follow the angulation recommendations of the QFR 3.1 user manual, adapted to the vessels that may be treated in this trial. For the RCA, the pair including the posterolateral and posterior descending branches will be used when those branches are to be contained in the analysis, ensuring that the entire RCA is included in the acquisition.

Table A1. Recommended angiographic projections for QFR-IMR acquisitions.

Target vessel	First projection	Second projection
LAD	RAO 35° + CRANIAL 25°	AP 0° + CRANIAL 45°
LAD – alternative, when AP 0° + CRANIAL 45° is not feasible	RAO 35° + CRANIAL 25°	LAO 30° + CRANIAL 20°
LCx and its marginal branches	LAO 10° + CAUDAL 25°	RAO 25° + CAUDAL 25°
RCA	LAO 50° + CAUDAL 0°	LAO 30° + CRANIAL 30°
RCA including the posterolateral and posterior descending branches	LAO 30° + CRANIAL 30°	AP 0° + CRANIAL 25°

Irrespective of the pair selected, the two projections must differ by at least 25° (optimally between 35° and 50°) and should be as perpendicular as possible to the target vessel. Minor patient-specific adjustments of these angulations are permitted at the pre-infusion acquisition in order to obtain an optimal view of the vessel without foreshortening or overlap, particularly at the level of the culprit lesion. Once the pair has been defined and judged adequate at the pre-infusion time point, it becomes fixed for that participant: the same angulations must be used for the post-infusion and post-medication acquisitions. For example, if RAO 35° + CRANIAL 25° and AP 0° + CRANIAL 45° provide adequate visualisation of

the LAD without foreshortening or overlap at the pre-infusion time point, these same two projections will be repeated at post-infusion and post-medication, yielding three paired acquisitions (six angiographic runs) for that participant. Any change of angulation between time points precludes the within-patient comparison and will be recorded as a protocol deviation.

Before each acquisition, a short test injection of contrast is advisable to detect severe overlap or foreshortening; if present, the C-arm should be rotated or angulated approximately 5° further, and the corrected angulation must then be maintained for all subsequent time points of that participant.

A4. Acquisition frame rate

Because QFR-IMR derives contrast flow velocity from the number of frames elapsed between two anatomical events, the acquisition frame rate directly determines the temporal resolution of the measurement. For this study, acquisitions must be performed at 25 to 30 frames per second. Where the installed equipment or radiation-dose considerations do not allow this range, a minimum of 15 frames per second is acceptable, and the frame rate actually used must be documented. The frame rate must be identical at the three time points of the same participant. This requirement is more restrictive than the general minimum of 12.5 frames per second stated in the QFR 3.1 user manual for standard QFR analysis.

A5. Contrast injection

Contrast injection for QFR-IMR acquisitions should preferably be performed with an automated power injector, using a fixed flow rate and volume that are kept constant across the three time points of the same participant, in order to

minimise operator-dependent variability in contrast flow velocity. Where an automated injector is not available, injection must be performed manually in a brisk and uniform manner, sustained throughout the acquisition, so that the progression of the contrast column can be tracked reliably during quantification of coronary flow velocity. The following technical conditions apply to all acquisitions:

A guiding or diagnostic catheter of 5F or larger is recommended (4F is the minimum acceptable size) in order to support a brisk contrast injection.

The catheter must be completely filled with contrast before the injection, avoiding premature contrast leakage.

The injection should aim for complete opacification of the target vessel over approximately three full cardiac cycles.

Intracoronary nitroglycerin should be administered before the first acquisition of each time point, unless contraindicated by the haemodynamic status of the participant.

The table must not be moved, nor the field of view or magnification changed, during or immediately after the injection.

The participant should be asked to hold their breath during the acquisition whenever clinically feasible.

The entire target vessel, including the distal landmark used for frame counting, must be visible in both projections.

Acquisitions must comply with the input requirements of the QFR software: grayscale DICOM XA images, square pixels (aspect ratio 1:1),

isocenter calibration data present, fixed angulation (rotational angiography is not supported), and a minimum of five image frames.

A6. Haemodynamic data to be recorded at each acquisition

Because QFR-IMR is computed from the product of a pressure term and a flow velocity term, mean aortic pressure must be recorded at each of the three acquisition time points, simultaneously with the corresponding angiographic runs. Mean aortic pressure will be obtained from the guiding catheter with the transducer at the mid-axillary level, after adequate zeroing and flushing of the system, and with a stable pressure waveform free of damping or ventricularisation. Heart rate at the moment of each acquisition will also be recorded, as will the systolic and diastolic aortic pressures. All values will be entered in the electronic case report form together with the acquisition time, so that each QFR-IMR measurement can be paired with the haemodynamic conditions under which it was obtained.

A7. Selection of the distal analysis point

The placement of the distal point differs from that used in a standard QFR analysis. For QFR-IMR, the distal point must not be advanced into the most distal portion of the vessel: it will be positioned at approximately two-thirds of the vessel length measured from the ostium, that is, at the transition between the middle and distal thirds of the vessel, and never within the terminal third. This convention reproduces the position at which the sensor of a pressure-temperature guidewire is conventionally placed for invasive IMR measurement by thermodilution, and therefore preserves comparability between angiography-derived and invasive microcirculatory resistance values. Proximal and distal

points must be placed on the same anatomical landmark in both projections; where the software indicates a possible mismatch between views, the points will be repositioned before any correction of the pathline or of the lumen contours. The same landmarks will be used for the pre-infusion, post-infusion and post-medication analyses of a given participant.

A8. Manual frame counting for the estimation of contrast flow velocity

When manual frame counting is required for the estimation of contrast flow velocity, the start and end frames will be defined according to the following rules:

Start frame (A): column of contrast extending across 70% of the arterial lumen, with antegrade motion.

End frame (B): contrast enters (but does not necessarily fill) a distal landmark.

When necessary, the start and end point markers will be adjusted within the application (C).

The distal landmark used to define the end frame must be an unambiguous anatomical structure, such as a side branch or a bifurcation, located within the analysed segment; the same landmark must be used for the three time points of a given participant and by both independent analysts. As a rule, frame counting will be performed preferentially on the projection in which the motion of the contrast column is visibly faster and best visualised, that is, the projection offering the clearest depiction of the advancing contrast front and of the distal landmark, with the least overlap and foreshortening of the analysed segment. When both projections are equivalent in this respect, the projection with the

higher-quality opacification will be chosen. The projection selected for counting will be kept constant across the three time points of the same participant and will be recorded in the electronic case report form.

A9. Quality control, non-analyzable acquisitions and deviations

Acquisitions with insufficient opacification, severe overlap of the analysed segment, significant foreshortening, excessive table or respiratory motion, a frame rate below 15 frames per second, absence of isocenter calibration data, or in which the distal landmark is not visible will be classified as non-analyzable. Whenever technically feasible and without additional risk to the participant, the acquisition will be repeated during the same procedure using the angulation pair already assigned to that participant. Any change in angulation, frame rate, injection method, field of view or landmark between the three time points, as well as the absence of a mean aortic pressure recording at any time point, will be documented as a protocol deviation in accordance with the section “Protocol deviations” of the main protocol. All acquisitions will be stored in DICOM format on the secure institutional server with coded participant identification, and will be analysed by two assessors certified in QFR-IMR and blinded to treatment allocation, as described in the main protocol.