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Authors: Niya Mileva, Teodora Yaneva-Sirakova, Irina Hristova, Despina Georgieva, Greta Koleva, Dimitra Psalla, Ranko Georgiev, Dobrin Vassilev

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STUDY PROTOCOL

Rationale and design of the MICE study: exploration of the temporal relation between electrical and mechanical events during myocardial ischemia

Niya Mileva[1, 2* https://orcid.org/0000-0002-4666-0181], Teodora Yaneva-Sirakova[3*], Irina Hristova[4], Despina Georgieva[4 https://orcid.org/0000-0001-7622-3145], Greta Koleva[4 https://orcid.org/0000-0002-1270-5396], Dimitra Psalla[5], Ranko Georgiev[6], Dobrin Vassilev[1, 4]

[1]Medica Cor Hospital, Ruse, Bulgaria

[2]Medical Faculty, Medical University of Sofia, Sofia, Bulgaria

[3]Medical Institute of the Ministry of Interior, Cardiology Clinic, Sofia, Bulgaria

[4]Department of Health Care, University of Ruse "Angel Kanchev", Ruse, Bulgaria

[5]Laboratory of Pathology, School of Veterinary Medicine, Aristotle University of Thessaloniki, Greece

[6]Central Veterinary Clinic, Sofia, Bulgaria

Address for correspondence: Niya Mileva, MD, Medical University Sofia, ul. Georgi Sofiiski 1, 1431 Sofia, Bulgaria, tel: +35 9897983936, e-mail: nmileva91@gmail.com

*These authors contributed equally to this manuscript.

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Background

The contemporary treatment of coronary artery disease (CAD) is based on our understanding of the myocardial ischemic process and the hypothesis of "ischemic cascade" [1]. This concept was developed more than 30 years [1]. The term "cascade" indicates that the requirements from the previous step should be met for every consecutive stage to occur (Supplementary Figure 1). Thus, it postulates that at the time of acute ischemia, there is a reduction of blood flow (supply-demand mismatch), then left ventricular diastolic, followed by systolic dysfunction, electrocardiogram (ECG) abnormalities, and lastly-angina. A drop in oxygen supply reduces adenosine triphosphate production and results in lactic acidosis, which causes electrical dysfunction. This process is directly followed by cellular mechanical dysfunction [2]. It can be conferred that on a cellular level, biomechanical and electrical changes coincide. However, human circulation has collateral flow and other metabolic reserves on the tissue level [3, 4]. Thus, the exact metabolic consequences of oxygen supply-demand mismatch in the given heart remain unknown [3]. The speed of electrical and mechanical changes in the myocardium depends on many factors: the amount of affected myocardium, collateralization, myofilament isoforms, energy stores, etc. [4–9]. These factors were studied separately.

Based on current knowledge, there are a constellation of ischemia-induced processes at a cellular level and a cascade at the tissue level, which sounds highly improbable [10]. It is hypothesized herein, that ischemic changes (electrical and mechanical) in myocardial function are not uniform and depend on the extent of flow reduction and the location of the ischemic zone. For the reevaluation of the ischemic processes both on a cellular and tissue level, a simultaneous recording is needed of the mechanical and electrical activity at the same location in the heart.

According to available research, no experimental or clinical study has explored myocardial biochemical, mechanical, and electrical events simultaneously, at a single location, during ischemia until the present study. Preliminary observations during the percutaneous coronary intervention (PCI) in humans suggest that the movement of the PCI wire positioned in a coronary artery during ischemia should follow the general left ventricle (LV) wall mechanics at

that time [11]. In addition, animal-based experiments using a porcine model with simultaneous contrast-enhanced transesophageal (TOE) assessment of myocardial kinetics was performed. The results of these experiments showed excellent correlation between TOE and PCI wire assessment [12]. It has been demonstrated that the ECG signal acquired intracoronary should be at least as accurate as the conventional surface ECG, and it will provide precise simultaneous information from the same region of interest [11, 13]. The sequence of events is important, as the current understanding of diagnosis of myocardial ischemia is based on sequence of events during ischemic cascade. It is given a clear superiority in recommendations of imaging modalities over ECG stress testing [9]. The lower sensitivity and specificity of ECG stress test is explained based on ischemic cascade, while it is possible that the reason is the influence of different chest geometric factors [14]. This is mere speculation, but if the ischemic cascade existed, the prognostic implications of different ischemia provocative tests should be different, as mechanical contraction failure should signify a higher decrease in flow, i.e. higher grade stenoses, anatomic and/or functionally. According to available research, there is no publication supporting such a relationship.

Therefore, the objective of the current study is to explore the temporal relationship between electrical and mechanical events during early myocardial ischemia using a single PCI wire, which could be easily applied in clinical practice for patients undergoing invasive coronary angiography and PCI.

Methods

Study design

MICE is an investigator-initiated prospective, observational, single-center diagnostic performance study of 323 patients. Patients eligible for the study are those with chronic coronary syndrome that were referred for invasive coronary angiography and a significant stenosis. All patients will undergo conventional coronary angiography with a simultaneous recording of intracoronary ECG and left ventricular wall motion at rest, followed by exact measurements in a condition of induced acute ischemia. Detailed inclusion and exclusion criteria are described in Table 1.

The study protocol has been approved by the local Ethics Committee. All study subjects will be managed in accordance with the Declaration of Helsinki and provided with written informed consent prior to undergoing any study-specific procedures. This study is registered as www.clinicaltrials.gov number NCT04061525. The study leadership is composed of a principal investigator, a co-principal investigator and steering committee. Clinical events will be adjudicated by an independent clinical events committee.

Primary and secondary endpoints

Primary endpoint of the study is the feasibility of the method using a single PCI-wire for the evaluation of the sequence of occurrence of electrical and mechanical myocardial events during acute ischemia induction, assessed as percentage of successful simultaneous recordings of mechanical and electrical changes after ischemia induction by inflation of a coronary balloon into the target lesion.

The secondary endpoints include: 1) Proportion of patients in which mechanical events occurred as a first manifestation of ischemia; 2) Proportion of patients in which electrical events occurred as a first manifestation of ischemia; 3) Periprocedural myonecrosis evaluated by the extent of post-PCI troponin and Creatin phosphokinase MB fraction elevation 4) All-cause death at 12-month follow-up; 5) Cardiovascular death at 12-month follow-up; 6) Non-fatal myocardial infarction at 12-month follow-up; 7) New onset angina or heart failure symptoms at 12-month follow-up; 8) Target lesion revascularization at 12-month follow-up.

Patient selection

Patients eligible for the study will be those with chronic coronary syndrome that were referred for invasive coronary angiography and a significant, ≥ 50% diameter stenosis artery scheduled for intervention. Patients with acute coronary syndrome and hemodynamically unstable patients will be excluded from the protocol. Furthermore, patients with left bundle branch block, pacemaker stimulation, permanent atrial fibrillation, LV ejection fraction less than 40%, previous myocardial infarction in the area of interest, or Q-wave on surface ECG at the same zone. Also, patients with left main coronary artery stenosis, total coronary occlusion, previous coronary artery bypass grafting (CABG), primary cardiomyopathy, will be excluded.

Study procedures

Examination at rest

1. Invasive coronary angiography will be performed following standard protocol, after intracoronary nitroglycerin injection (100–200 μg). Then the projection providing the best visualization of the movements of the target coronary artery will be chosen.
2. After placement of a pressure measuring device (pressure wire or coronary pressure microcatheter) at least 10 mm below the distal edge of the coronary stenosis, nonhyperemic indexes will be recorded. A fractional flow reserve measurement will be performed using intracoronary papaverine injection (20 mg for left coronary artery and 15 mg for right coronary artery). After achievement of steady-state FFR is measured and then a pull-back for assessment of pressure step-ups will be performed.
3. A non-polymeric coronary guidewire 0.014” PCI wire is introduced in the target artery with a radiopaque part at least 10 mm distal from the coronary ostium and in a coronary artery segment with maximal movement amplitude of a coronary artery segment of interest. The radiopaque distal part of PCI wire should be located in mid to distal segment of the target artery with the highest amplitude of vessel contraction. The proximal outer end of the PCI wire is connected to a unipolar ECG electrode. Then the movement of the radiopaque part of the coronary wire and the icECG will be recorded for a baseline record of 5 cardiac cycles. Furthermore, the patient will be asked to report the severity of chest pain experiencing grading it from 1 being the lowest to 10 being the most severe pain during the remaining part of the procedure.

Ischemia induction

4. PCI balloon with a length of 6 to 10 mm and a diameter of 70–100% of the distal reference diameter of target vessel will be positioned on the PCI wire. The balloon will be inflated up to maximal configuration and will be kept dilated for a duration of 60 seconds. Every 10 seconds, a recording of the fluoroscopy (without contrast injection) for 3–5 consecutive cycles are performed. The icECG recording is obtained during the time of balloon inflation and the patient is asked to report the severity of chest pain if/when it appears. After 60 seconds the balloon will be deflated and removed from the artery. During the next 60 seconds the recording continues — wire movements on fluoroscopy are made after each 10 seconds interval. The whole procedure is digitally recorded by a

high-resolution camera capturing both icECG and the angiographic screen. The time of both monitors are synchronized for analysis of event timing.

Final evaluation

5. Final angiography and icECG will be recorded two minutes after the balloon dilatation. The patient is asked to report the severity of chest pain that is being experienced. Further treatment strategy (stent implantation, drug-eluting balloon inflation etc.) and medical therapy will be at the discretion of the treating physicians. Adherence to the ESC guideline recommendation is encouraged.

Intracoronary ECG analysis

Intracoronary ECG is acquired by attaching an alligator clip to 0.014-inch PCI wire (Runthrough, Terumo Japan; Sion Blue, Asahi, Japan, BMW Universal II, Abbott Vascular, USA) positioned in the distal third of a major coronary artery. The clamp is connected to a precordial ECG V1 — lead. In case of coronary stenosis at a bifurcation site, a second wire is allowed with recording function from the side branch with the same parameters as from the wire in the main vessel. A second wire is attached to the ECG V2 — lead.

The recorded intracoronary and surface ECG leads, with simultaneously recorded aortic blood pressure curves will be printed and analyzed consecutively. The speed of the ECG recording is 50 mm/s and ECG amplitude was calibrated as 10 mm/mV. Measurement of the ST-segment shift is based on the determination of the isoelectric line and the Junction-(J)-point. The isoelectric line represents the reference line for the measurement and is set at the TP-interval as recommended [13]. The J-point is defined as the transition of the QRS-complex to the ST-segment, 80 ms after the end of QRS — complex. Using these two markers the calculation of the ST-segment shift is performed as the difference in mV between the isoelectric line and the ST-amplitude at the J-point. The ST-segment elevation is equal to or more than 0.1 mV was accepted as a sign of ischemia.

Analysis of PCI-wire kinetics

Motion of the PCI wire will be recorded by fluoroscopy storing mode (at 7.5 frames per second) throughout the cardiac cycle, both at rest and during the ischemia induction. Various parameters described in detail in the supplementary material will be measured and compared

between the rest and acute ischemia phases (Supplementary Figures 1, 2). To ensure simultaneous recording of the events, the two monitors for angiography and hemodynamics were placed close to each other. A dedicated camera obtaining the full range of both monitors recorded the whole study. The recording was used for analysis and synchronization of the exact timing of each mechanical and electrical event. The timing of each mechanical event was matched with the records from the icECG. A detailed description is illustrated in (Supplementary Figure 2).

Statistical analysis

The MICE study is designed to assess: 1) the feasibility of the method for simultaneous evaluation of the consequence of electrical and mechanical myocardial changes during early myocardial ischemia using a single PCI wire. For the feasibility analysis, the rate of procedures with successful simultaneous recording of myocardial electrical and mechanical events during rest and ischemia induction will be calculated. The sample size was calculated based on previous data from COSIBRIA study [11], that 70% of patients have dynamic ST-segment elevation during coronary bifurcation PCI. If the same percentage is assumed in the current study, then 322.68 patients will be needed to detect differences in mechano-electrical coupling with 80% power and 95% level of confidence. Thus 323 patients will be needed. All analyses will be performed using Statistical Package for Social Sciences, version 25.0 (SPSS, PC version, Chicago, IL, USA) and R statistical software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient enrollment started in July 2022, and until July 2023, 69 patients and 82 vessels were included. Mean age was 67 ± 5, 74% were males, and 25% were diabetics. The target vessels assessed was LAD/diagonal in 56 of the cases (69%), LCX/OM in 20 cases (24%), and RCA in six cases (7%). Simultaneous recording of the mechanical and electrical changes after temporary ischemia induction was feasible and successful in 100% of the cases. In 55% (n = 45) of the vessels, the electrical changes with ST-elevation on intracoronary ECG were registered as the first manifestation of ischemia. In 36% (n = 30) the first ischemia manifestation was the reduction in the left ventricular contraction. In 9% (n = 7) of the cases electrical and mechanical changes were registered simultaneously and neither of the two events could be recorded as the

first to occur. The case example is illustrated in Figure 1. Completion of enrollment is expected in September 2024.

DISCUSSION

The diagnosis and treatment of myocardial ischemia caused by coronary artery disease still represent a significant problem. One of the reasons is that the current understanding of the ischemic process still relies on theconcept of “ischemic cascade”. This perception is implemented in clinical practice guidelines about patients with the CAD treatment strategy. According to the current recommendations, patients with ECG changes, especially those with accompanying chest pain, have the highest priority for invasive diagnostics and treatment [15–17]. However, previous data demonstrating the ischemic cascade theory reveals inconsistent results among investigators [18–20]. In some studies, a decreased flow was assumed to cause ischemia based on observations of relatively unchanged systolic blood pressure-heart rate product as a surrogate for oxygen consumption [6, 18]. Other studies accept flow disturbances as a surrogate of ischemia, which is questionable, considering a sizeable biological variation between people [7].

It is generally accepted that myocardial contraction ceases within seconds/minutes of interrupted or decreased coronary blood flow [1, 6, 21–23]. With the decrease in coronary blood flow, first, the function of the subendocardium is impaired, and with further reduction, the whole cardiac wall contraction stops. It should be noted that observations about the sequence of events are not concordant. Some studies report a simultaneous decrease in the extent of muscle contraction of the whole myocardial wall, probably because of the tethering effect between neighbor myofibrils. According to available research, there is no description of how the contraction and local pattern of left ventricular wall contraction interacts with the regional pattern of movement of coronary arteries. The research in that area was concentrated only on the assessment of global LV function and its relationship with atherosclerosis development [24–28].

The hypothesis herein, is that part of the inconsistency about the importance of ischemia as a clinical decision trigger is due to methods for its verification, which is a result of erroneous acceptance of the “ischemic cascade” dogma. For example, in the ISCHEMIA study, a couple of different tests were used to demonstrate ischemia — nuclear perfusion via SPECT or PET (showing metabolic changes during ischemia), echocardiography, cardiac magnetic resonance

(perfusion and mechanical consequences) and exercise ECG test [29]. The problem is that each of these tests demonstrates a different stage of the “ischemic cascade”, and as such, the result of each test is incomparable to each other.

According to available research, this is the first study to explore myocardial mechanical and electrical events simultaneously during ischemia in a man. The element of simultaneity in evaluating ischemic processes is critical to understanding which events have higher predictive value. Interventions demonstrating reduction of infarct size, based on epicardial ECG recording, later, failed to do so in clinical trials. Therefore, intracoronary ECG registration may provide much more accurate information in combination with a recording of mechanical events simultaneously. It is essential to examine which event occurs first and which factors are associated with discrepancies if/when they exist.

Intracoronary ECG was first developed to detect potential epicardial changes in an animal study [30]. It was demonstrated as a very sensitive tool for early ischemia detection [31–34]. It could also be used to assess the viability of myocardium during PCI and evaluate the adequacy of coronary collateral circulation [13, 35–37]. The present study demonstrated that icECG ST-segment elevation in side branches after coronary bifurcation stenting is equally sensitive and more specific for ongoing ischemia detection than FFR [38]. Furthermore, it was demonstrated that some changes in icECG after bifurcation stenting are associated with long-term mortality, and others have shown an increased rate of major adverse cardiovascular events [39–41]. Moreover, the experimental data has described a good sensitivity and specificity of epicardial electrodes for detecting ischemia, even in the subendocardial region [42].

All processes that develop during acute ischemia are deeply interconnected. Therefore, only the simultaneous registration of the mechanical and electrical changes could provide the exact diagnosis of acute ischemia. Thus, a method for concurrent registration of electrical and mechanical events using a single PCI wire was proposed. This method could be easily applied in everyday clinical practice allowing for a better understanding of the intricate process of myocardial ischemia. This, in its favor, may result in saving patients' lives and result in a reduction in medical costs. A further study is to prove the concept in a porcine model.

Limitations

The present study has several possible limitations. First, its observational nature. Second, the sample size is relatively small; nevertheless, the study is powered to assess the feasibility of the method using a single PCI wire for simultaneous evaluation of the events during early ischemia. It will provide a base for further studies, with bigger sample sizes to better understand the temporal relationship between ischemic mechanical and electrical changes in the myocardium. Furthermore, echocardiographic assessment during the protocol would provide additional information regarding left ventricular diastolic and systolic function.

CONCLUSIONS

This prospective, single-center study will determine the feasibility of a method for simultaneous registration for electrical and mechanical myocardial changes during acute ischemia using a single PCI wire in humans. This could allow for a better understanding of the ischemic process and benefit future diagnosis and therapy of patients with CAD.

Conflict of interest: The authors have nothing to disclose.

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References

1. Nesto R, Kowalchuk G. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol. 1987; 59(7): C23–C30, doi: 10.1016/0002-9149(87)90192-5, indexed in Pubmed: 2950748.
2. Kléber AG. Consequences of acute ischemia for the electrical and mechanical function of the ventricular myocardium. A brief review. Experientia. 1990; 46(11–12): 1162–1167, doi: 10.1007/BF01936928, indexed in Pubmed: 2253715.
3. Kalogeris T, Baines CP, Krenz M, et al. Cell biology of ischemia/reperfusion injury. Int Rev Cell Mol Biol. 2012; 298(1): 229–317, doi: 10.1016/B978-0-12-394309-5.00006-7, indexed in Pubmed: 22878108.

4. Amsterdam EA, Martschinske R, Laslett LJ, et al. Symptomatic and silent myocardial ischemia during exercise testing in coronary artery disease. Am J Cardiol. 1986; 58(4): 43B–46B, doi: 10.1016/0002-9149(86)90409-1, indexed in Pubmed: 3751902.

5. Reduto LA, Wickemeyer WJ, Young JB, et al. Left ventricular diastolic performance at rest and during exercise in patients with coronary artery disease. Assessment with first-pass radionuclide angiography. Circulation. 1981; 63(6): 1228–1237, doi: 10.1161/01.cir.63.6.1228, indexed in Pubmed: 7226471.

6. Berger HJ, Reduto LA, Johnstone DE, et al. Global and regional left ventricular response to bicycle exercise in coronary artery disease. Assessment by quantitative radionuclide angiocardiography. Am J Med. 1979; 66(1): 13–21, doi: 10.1016/0002-9343(79)90476-5, indexed in Pubmed: 420239.

7. Johnson NP, Gould KL. Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. JACC Cardiovasc Imaging. 2012; 5(4): 430–440, doi: 10.1016/j.jcmg.2011.12.014, indexed in Pubmed: 22498334.

8. Johnson NP, Gould KL. Physiological basis for angina and ST-segment change PET-verified thresholds of quantitative stress myocardial perfusion and coronary flow reserve. JACC Cardiovasc Imaging. 2011; 4(9): 990–998, doi: 10.1016/j.jcmg.2011.06.015, indexed in Pubmed: 21920337.

9. Weiss JN, Venkatesh N, Lamp ST. ATP-sensitive K+ channels and cellular K+ loss in hypoxic and ischaemic mammalian ventricle. J Physiol. 1992; 447(1): 649–673, doi: 10.1113/jphysiol.1992.sp019022, indexed in Pubmed: 1593462.

10. Maznyczka A, Sen S, Cook C, et al. The ischaemic constellation: an alternative to the ischaemic cascade — implications for the validation of new ischaemic tests. Open Heart. 2015; 2(1): e000178, doi: 10.1136/openhrt-2014-000178, indexed in Pubmed: 26196015.

11. Vassilev D, Dosev L, Rigatelli G, et al. Prediction of troponin elevation by means of intracoronary electrocardiogram during percutaneous coronary intervention of coronary bifurcation lesions (from COronary SIde Branch Residual IschemiA and COllateralization Assessment Study; COSIBRIA & Co Study. Kardiol Pol. 2016; 74(9): 943–953, doi: 10.5603/KP.a2016.0057, indexed in Pubmed: 27112944.

12. Yaneva-Sirakova T, Georgiev R, Mileva N, et al. Revisiting the “ischemic cascade” with contemporary methods. J Hypertens. 2023; 41(Suppl 3): e240, doi: 10.1097/01.hjh.0000941436.79075.c0.

13. Balian V, Galli M, Marcassa C, et al. Intracoronary ST-segment shift soon after elective percutaneous coronary intervention accurately predicts periprocedural myocardial injury. Circulation. 2006; 114(18): 1948–1954, doi: 10.1161/CIRCULATIONAHA.106.620476, indexed in Pubmed: 17060382.

14. Holland RP, Brooks H. The QRS complex during myocardial ischemia. An experimental analysis in the porcine heart. J Clin Invest. 1976; 57(3): 541–550, doi: 10.1172/JCI108309, indexed in Pubmed: 1249199.

15. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.

16. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.

17. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021; 42(14): 1379–1386, doi: 10.1093/eurheartj/ehaa575, indexed in Pubmed: 32860058.

18. Williams KA, Sherwood DF, Fisher KM. The frequency of asymptomatic and electrically silent exercise-induced regional myocardial ischemia during first-pass radionuclide angiography with upright bicycle ergometry. J Nucl Med. 1992; 33(3): 359–364, indexed in Pubmed: 1740703.

19. Nixdorff U, Erbel R, Wagner S, et al. Dynamic stress echocardiography for evaluating anti-ischemic drug profiles in post-MI patients. Int J Card Imaging. 1997; 13(6): 485–491, doi: 10.1023/a:1005882829544, indexed in Pubmed: 9415850.

20. Iskandrian AS, Bemis CE, Hakki A-H, et al. Ventricular systolic and diastolic impairment during pacing-induced myocardial ischemia in coronary artery disease: simultaneous hemodynamic, electrocardiographic, and radionuclide angiographic evaluation. Am Heart J. 1986; 112(2): 382–391, doi: 10.1016/0002-8703(86)90279-6, indexed in Pubmed: 3017084.

21. Morrow DA. Myocardial infarction: a companion to braunwald's heart disease. Elsevier Health Sciences 2016.

22. Forsythe L, George K, Oxborough D. Speckle tracking echocardiography for the assessment of the athlete's heart: is it ready for daily practice? Curr Treat Options Cardiovasc Med. 2018; 20(10): 83, doi: 10.1007/s11936-018-0677-0, indexed in Pubmed: 30146663.

23. Aroesty JM, McKay MG, Heller GV, et al. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. Circulation. 1985; 71(5): 889–900, doi: 10.1161/01.cir.71.5.889, indexed in Pubmed: 3986979.

24. Kähäri A, Emilsson K, Danielewicz M, et al. Circumflex artery motion; a new angiographic method for assessment of left ventricular function. Scand Cardiovasc J. 2003; 37(2): 80–86, doi: 10.1080/14017430310001195, indexed in Pubmed: 12775306.

25. Wandt B, Kähäri A, Zizala J, et al. Usefulness of coronary angiography for assessing left ventricular function. Am J Cardiol. 1998; 82(3): 384–386, doi: 10.1016/s0002-9149(98)00326-9, indexed in Pubmed: 9708672.

26. Konta T, Bett JHN. Patterns of coronary artery movement and the development of coronary atherosclerosis. Circ J. 2003; 67(10): 846–850, doi: 10.1253/circj.67.846, indexed in Pubmed: 14578617.

27. O'Loughlin A, Tang L, Moses D, et al. A novel quantitative index of coronary artery motion from multislice computed tomography and the location of coronary artery disease. Internat J Cardiov Cerebrov Dis. 2014; 2(1): 1–5, doi: 10.13189/ijccd.2014.020101.

28. Ghaffari S, Erfanparast S, Separham A, et al. The relationship between coronary artery movement type andStenosis severity with acute myocardial infarction. J Cardiovasc Thorac Res. 2013; 5(2): 41–44, doi: 10.5681/jcvtr.2013.009, indexed in Pubmed: 24251009.

29. Maron DJ, Hochman JS, O'Brien SM, et al. International study of comparative health effectiveness with medical and invasive approaches (ISCHEMIA) trial: rationale and design. Am Heart J. 2018; 201: 124–135, doi: 10.1016/j.ahj.2018.04.011, indexed in Pubmed: 29778671.

30. Hashimoto K, Corday E, Lang TW, et al. Significance of S-T segment elevations in acute myocardial ischemia. Evaluation with intracoronary electrode technique. Am J Cardiol. 1976; 37(4): 523–543, doi: 10.1016/0002-9149(76)90387-8, indexed in Pubmed: 1258786.

31. Meier B, Killisch J, Adatte J, et al. [Intracoronary electrocardiography during transluminal coronary angioplasty]. Schweiz Med Wochenschr. 1985; 115(45): 1590–1593, indexed in Pubmed: 2934812.

32. Friedman PL, Shook TL, Kirshenbaum JM, et al. Value of the intracoronary electrocardiogram to monitor myocardial ischemia during percutaneous transluminal coronary angioplasty. Circulation. 1986; 74(2): 330–339, doi: 10.1161/01.cir.74.2.330, indexed in Pubmed: 2942314.

33. Abboud S, Cohen RJ, Selwyn A, et al. Detection of transient myocardial ischemia by computer analysis of standard and signal-averaged high-frequency electrocardiograms in patients undergoing percutaneous transluminal coronary angioplasty. Circulation. 1987; 76(3): 585–596, doi: 10.1161/01.cir.76.3.585, indexed in Pubmed: 2957111.

34. Pande AK, Meier B, Urban P, et al. Intracoronary electrocardiogram during coronary angioplasty. Am Heart J. 1992; 124(2): 337–341, doi: 10.1016/0002-8703(92)90595-m, indexed in Pubmed: 1636577.

35. Wustmann K, Zbinden S, Windecker S, et al. Is there functional collateral flow during vascular occlusion in angiographically normal coronary arteries? Circulation. 2003; 107(17): 2213–2220, doi: 10.1161/01.CIR.0000066321.03474.DA, indexed in Pubmed: 12707241.

36. Tomai F, Crea F, Gaspardone A, et al. Mechanisms of cardiac pain during coronary angioplasty. J Am Coll Cardiol. 1993; 22(7): 1892–1896, doi: 10.1016/0735-1097(93)90775-v, indexed in Pubmed: 8245345.

37. Abaci A, Oguzhan A, Topsakal R, et al. Intracoronary electrocardiogram and angina pectoris during percutaneous coronary interventions as an assessment of myocardial viability: comparison with low-dose dobutamine echocardiography. Catheter Cardiovasc Interv. 2003; 60(4): 469–476, doi: 10.1002/ccd.10699, indexed in Pubmed: 14624423.

38. Vassilev D, Dosev L, Collet C, et al. Intracoronary electrocardiogram to guide percutaneous interventions in coronary bifurcations - a proof of concept: the FIESTA (Ffr vs. IcEcgSTA) study. EuroIntervention. 2018; 14(5): e530–e537, doi: 10.4244/EIJ-D-17-00189, indexed in Pubmed: 28829743.

39. Vassilev D, Mileva N, Nikolov P, et al. Predictors of long-term survival after provisional t-stenting strategy of coronary bifurcation lesion guided by intracoronary electrocardiography. Card Inn Appl. 2018; 138(Suppl_1): A15803-A.

40. Hishikari K, Kakuta T, Lee T, et al. ST-segment elevation on intracoronary electrocardiogram after percutaneous coronary intervention is associated with worse outcome in patients with non-ST-segment elevation myocardial infarction. Catheter Cardiovasc Interv. 2016; 87(4): E113–E121, doi: 10.1002/ccd.26072, indexed in Pubmed: 26152334.

41. Hishikari K, Yonetsu T, Lee T, et al. Intracoronary electrocardiogram ST-segment elevation in patients with non-ST-segment elevation myocardial infarction and its association with culprit lesion location and myocardial injury. EuroIntervention. 2014; 10(1): 105–112, doi: 10.4244/EIJV10I1A17, indexed in Pubmed: 24048173.

42. Aras K, Burton B, Swenson D, et al. Sensitivity of epicardial electrical markers to acute ischemia detection. J Electrocardiol. 2014; 47(6): 836–841, doi: 10.1016/j.jelectrocard.2014.08.014, indexed in Pubmed: 25242529.

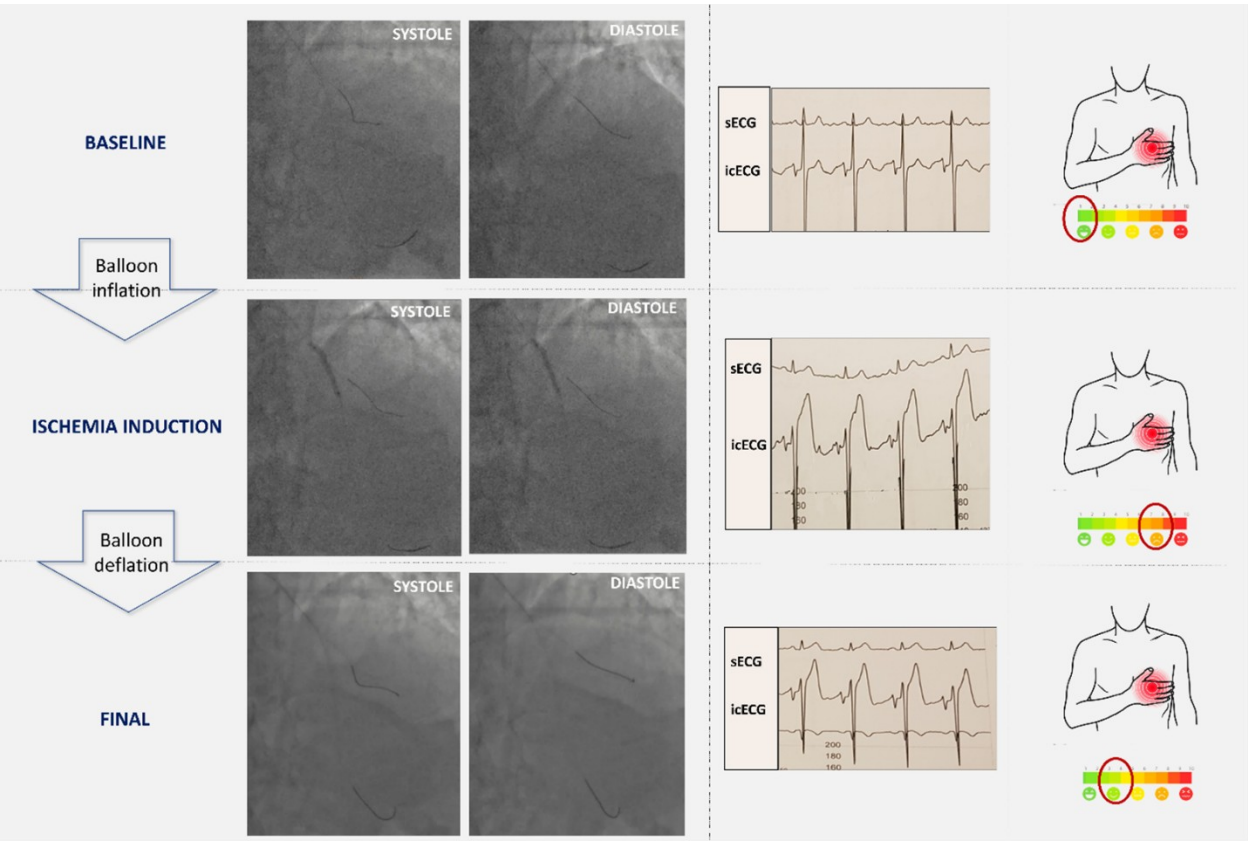

Figure 1. Case example; illustration of the mechanical and electrical events upon ischemia stimulation with balloon inflation; iECG — intracoronary electrocardiogram; sECG — surface electrocardiogram

Table 1 Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
1. Age ≥ 18 years 2. Willing and able to provide written informed consent 3. Patients with chronic coronary syndrome 4. Indication for invasive coronary angiography 5. Significant ≥ 50% diameter stenosis	1. Age < 18 or > 90-years old 2. Acute coronary syndromes 3. Hemodynamic instability 4. Left main coronary artery stenosis 5. Total coronary occlusion 6. Previous CABG 7. Left ventricular dysfunction EF < 40% 8. Previous myocardial infarction in the area of interest 9. Myocardial scar (Q-wave on superficial ECG) in the area of interest 10. Left or right bundle branch block 11. Atrial fibrillation/flutter 12. Pacemaker stimulation 13. Severe renal dysfunction, defined as an eGFR < 30 mL/min/1.73m^2 14. Cardiomyopathy (dilated, hypertrophic, amyloidosis, arrhythmogenic right ventricular dysplasia) 15. Left bundle branch block or baseline ST segment depression >1 mm 16. Unable to provide written IC

CABG — coronary artery bypass grafting; ECG — electrocardiogram; EF — ejection fraction; eGFR — estimated glomerular filtration rate; IC — informed consent