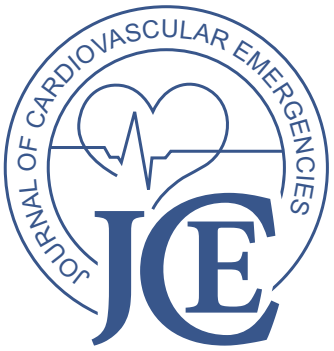

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Stem Cells in Ischemic Cardiac Injury

Vulnerable Plaque

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Aims and scope

The Journal of Cardiovascular Emergencies is the official journal of the Transylvanian Association of Transvascular Therapy and Transplantation Kardiomed, Tîrgu Mureș, Romania, and is published quarterly.

The Journal of Cardiovascular Emergencies aims to publish top quality papers related to acute conditions in any cardiovascular pathology.

The journal will mainly focus on recent advances in the field of diagnosis and treatment of the most common causes of cardiovascular emergencies, including acute coronary syndromes, acute heart failure, acute aortic diseases, pulmonary embolism, peripheral arterial diseases or cardiac arrhythmia. Interdisciplinary approaches will be extremely welcomed, presenting new advances in the approach of different other pathologies (i.e. stroke) from the cardiovascular perspective.

The Journal of Cardiovascular Emergencies will publish high-quality basic and clinical research related to these topics, in a common approach that will integrate the clinical studies with the pre-clinical work dedicated to discovery of new mechanisms involved in the development and progression of acute cardiovascular conditions.

Especially in the case of acute coronary syndromes, the journal will try to provide the entire cardiology community with the perspective of the regional cardiology networks in Central and Eastern European countries, reflecting the regional model of care in cardiovascular acute conditions.

The journal will primarily focus on publishing original research papers, but also other types of materials (such as review articles, case reports, state-of-the-art papers, comments to editor, etc) will be extremely welcomed.

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EDITORIAL

The Hemodynamic Impact of Unstable Coronary Plaques — Do We Have the Evidence?

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In the last years, estimation of the functional relevance of a coronary artery stenosis has raised an increased interest, and new imaging-derived parameters have been proposed as promising tools for this application. Invasive FFR represents nowadays the gold standard for the estimation of lesion significance, while noninvasive CT-FFR has been proposed as an alternative technique with good sensitivity and positive predictive value for predicting an FFR <0.8, which is the reference value for classifying a lesion as significant.

Transluminal attenuation gradient (TAG) by computed tomography angiography (CTA) has been suggested to represent a faster alternative to invasive FFR or to noninvasive FFR-CT for assessing lesion-specific ischemia. In a recent meta-analysis, corrected coronary opacification decrease was an independent predictor of major adverse cardiac events (MACE) in patients with coronary artery stenosis, adding long term prognostic value over clinical predictors or classical biomarkers.[1] The usefulness of TAG in plaque characterization is especially obvious in highly calcified lesions, in which the presence of calcium precludes good quality imaging of the coronary plaques.[2] In these cases, TAG can significantly contribute to the reclassification of stenosis degree and to choosing the most appropriate therapeutic strategy.

It has been proposed that noninvasive CTA-based lesion-specific ischemia will represent the gatekeeper to the cardiac catheterization laboratory in a close future, as soon as the technique and its application will be validated by large trials.[3] TAG, myocardial perfusion, and CT and CT-FFR are the most common studied imaging tools for the assessment of lesion-specific ischemia, because ischemia-guided revascularization can significantly improve patient outcomes.[4] CT-FFR proved superior to TAG, CTA-evaluated stenosis degree or the combination of the two in terms of diagnostic accuracy in the DISCOVER-FLOW and DeFACTO studies.[5]

However, little is known in present about the role of plaque vulnerability degree in increasing the functional significance of a stenosis. Morphological and functional quantitative plaque assessment using CTA can provide us relevant information on the presence of vulnerability markers inside an atheromatous plaque, with the concomitant calculation of parameters reflecting functional significance such as TAG, myocardial perfusion, or CT-FFR.[6] A study on a limited number of patients, published in this number of JCE by Orzan et al. shows a good correlation between noninvasive TAG and invasive FFR ($r = 0.7$, $p = 0.01$) in the culprit lesions of patients with acute coronary syndromes, at the same time proving that the presence of vulnerability markers inside a plaque (an increased amount of necrotic core or a higher plaque burden) are associated with higher TAG values.[7] These findings suggest that the presence of vulnerability features inside a coronary plaque could increase the functional significance of a coronary lesion, and that vulnerable plaques could have a stronger impact on the myocardial ischemia than non-vulnerable ones with the same morphological severity.

However, the value of this interesting study is significantly altered by the low number of cases enrolled, being actually a pilot study. This could also represent an explanation for the lack of statistical significance in many of

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the associations studied, as the number of cases was not sufficient to generate statistical power. A future extension of the study should provide not only a higher number of patients for data validation, but also more applications of CTA such as myocardial perfusion imaging or shear stress assessment at the site of vulnerable lesions, in order to explore all the potential inter-relations between vulnerable plaques and associated ischemia. This could be particularly important as there are no large studies published so far to elucidate the hypothesis that vulnerable plaques can have an increased impact on the distal blood flow, causing more severe ischemia as compared with stable plaques.

The role of inflammation in the complex process of atheromatous plaque formation is also not negligible, and the authors mention the potential role of inflammation and local shear stress in plaque progression. Taking into consideration that an augmented inflammation can lead to plaque vulnerabilization, at the same time altering the local coronary blood flow and shear stress distal to the plaque, an extension of this study could also address the relation between the elevation of inflammatory biomarkers, the alteration of coronary flow, and the resulting myocardial ischemia. In this way, the study could provide the necessary evidence to demonstrate that plaque vulnerabilization can lead to an increased functional significance of the lesion, reflected in a lower coronary perfusion distal to the lesion and a more severe lesion-specific ischemia.

CONFLICT OF INTEREST

Nothing to disclose.

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REVIEW

Monitoring Acute Myocardial Infarction Complicated with Cardiogenic Shock — from the Emergency Room to Coronary Care Units

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ABSTRACT

Cardiogenic shock remains the leading cause of death in patients hospitalized for acute myocardial infarction, despite many advances encountered in the last years in reperfusion, mechanical, and pharmacological therapies addressed to stabilization of the hemodynamic condition of these critical patients. Such patients require immediate initiation of the most effective therapy, as well as a continuous monitoring in the Coronary Care Unit. Novel biomarkers have been shown to improve diagnosis and risk stratification in patients with cardiogenic shock, and their proper use may be especially important for the identification of the critical condition, leading to prompt therapeutic interventions. The aim of this review was to evaluate the current literature data on complex biomarker assessment and monitoring of patients with acute myocardial infarction complicated with cardiogenic shock in the Coronary Care Unit.

Keywords: acute myocardial infarction, cardiogenic shock, biomarkers, coronary care unit monitoring

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Cardiogenic shock (CS) remains the leading cause of death in patients hospitalized for acute myocardial infarction (AMI), occurring in 7% to 10% of AMI patients.[1–4] In-hospital mortality rates for CS complicating AMI are reaching 50%, and short-term prognosis is linked to the severity of hemodynamic disturbances.[5] Several studies have suggested that short-term mortality in CS ranges between 42% and 48%, and that most patients will succumb due to multiple organ failure as a consequence of organ hypoperfusion.[6–8]

CS implies a systolic blood pressure lower than 90 mmHg for more than 30 minutes, caused by a severe myocardial dysfunction, leading to systemic hypoperfusion. The clinical signs of CS can vary from decreased diuresis and indicators of peripheral vasoconstriction to altered mental status.[9]

Hemodynamic changes in CS trigger various biochemical pathways due to tissue ischemia, elevated systemic inflammation, cellular apoptosis, neurohormonal activation, and extracellular matrix degradation.[10–13] CS patients undergo rapid changes in their clinical, biochemical, and hemodynamic status, either due to the disease itself, or secondary to the multitude of therapeutic interventions. The proper determination and use of complex biomarkers

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that illustrate such changes may be highly important for identifying the critical condition, leading to prompt therapeutic interventions, as well as for risk stratification.[14] Novel biomarkers have been under intensive research in the last years in an attempt to identify predictors for the evolution of this critical disease.

Nevertheless, AMI patients complicated with CS require immediate diagnosis and management that should include a continuous monitoring in the Coronary Care Unit (CCU) besides invasive or noninvasive therapies. A careful monitoring could be helpful for the immediate detection of changes in the clinical, hemodynamic, and biochemical status, resulting in the timely initiation of the appropriate intervention and thus reducing mortality.

The aim of this article was to review the current literature data on complex biomarker assessment and monitoring of patients with AMI complicated with CS in the CCU.

SERUM BIOMARKERS IN AMI COMPLICATED WITH CARDIOGENIC SHOCK

The most used biomarkers in acute cardiovascular settings include myocardial injury enzymes, parameters that express hemodynamic stress, systemic inflammation markers, as well as other emerging biomarkers such as extracellular matrix degradation indicators or micro-RNAs. These biomarkers can be extremely important in monitoring response to treatment and for risk stratification in critical care conditions, helping to better guide the therapy of acute heart failure patients and leading to improvement in clinical management and outcomes.[15,16]

MARKERS FOR MYOCARDIAL INJURY IN THE EMERGENCY ROOM

Creatine kinase (CK) is an enzyme that was described in 1965 as a biomarker for myocardial injury, having a sensitivity of 90%, but a low specificity for the detection of myocardial infarction.[17] CK is detected in the serum at 12 hours from the onset of myocardial damage, peaks in 24 to 35 hours and normalizes in 48 to 72 hours, this dynamic making it inappropriate for early diagnosis of AMI. Despite its low specificity (increasing as well in other conditions such as hemolysis, muscle damage, rhabdomyolysis, burns, trauma, sepsis, or pregnancy), the creatine kinase assay is still used for the diagnosis of AMI due to its relatively low costs and wide availability.[18,19]

CK-MB (creatine kinase - myocardium brain) is one of the three major isoenzymes of CK, found in high concentrations in the cardiac muscle, as well as in lower levels in the brain and skeletal muscles.[20] CK-MB presents similar releasing patterns to that of CK, and shows high specificity and sensitivity in detecting AMI, being more reliable in the 12–24-hour time window from the onset of AMI. Nevertheless, CK-MB has been shown effective in identifying AMI patients presenting in the emergency department with acute chest pain with a nonspecific ECG, thus allowing timely reperfusion therapies.[21,22]

The current gold standard biomarker for myocardial infarction is considered to be cardiac troponin, which is highly specific for the cardiac muscle.[23] Troponin assays have become widely available and are used in cardiovascular emergency settings, as they allow the identification of acute myocardial infarction at 6 hours from the onset of symptoms, having a sensitivity of 80.75% and a specificity of 63.8%.[24,25] The newer high-sensitivity assays can detect lower levels of troponin (3 pg/mL) within a shorter time from MI onset (3 to 4 hours from the onset of symptoms).[24] Despite its high diagnostic accuracy, false positive results may be encountered, caused by troponin elevation in conditions with increased oxygen demand, reduced cardiac output, or ventricular strain, such as heart failure, pulmonary embolism, or septic shock.[26] Other non-cardiac causes for elevated troponin levels are anemia, renal failure, pulmonary disorders, ischemic and hemorrhagic cerebrovascular events, or intense exercise.[27,28] Also, an increased level of troponin in heart failure patients has been linked to poorer outcomes, regardless of the presence of AMI, and elevated high-sensitive troponin expresses a considerably higher amount of myocardial injury in patients with heart failure, thus being a useful risk stratification biomarker.[29–31] Moreover, a sub-study of the Global Registry of Acute Coronary Events (GRACE) on 16,318 non-ST elevation myocardial infarction patients revealed that increased levels of troponin were associated with higher rates of cardiac arrest, new heart failure, cardiogenic shock, and death.[32]

Myoglobin is a myocardial necrosis marker that can be detected in the blood stream within the first 3 hours from the onset of MI symptoms, but it lacks myocardial specificity, as it is raised in skeletal muscle damage, trauma, electrical cardioversion, renal disease, and patients with genetic muscular disorders.[19] The kinetics of plasmatic myoglobin levels have been shown to be a reliable way for assessing the coronary artery patency following thrombolytic therapy in MI patients; increased baseline levels of this enzyme were observed in patients who did not respond to streptokinase, while there was a significantly higher myoglobin release among responders to thrombolysis as compared to non-responders.[33]

The Heart-Type Fatty Acid Binding Protein (H-FABP) is one of the most abundant proteins in the cardiac muscle, absent from the plasma or interstitial fluid, that is released during an episode of myocardial necrosis.[34] H-FABP is released into the blood stream within 2 hours from symptom onset, with a peak at 4 to 6 hours, having an over 80% sensitivity in diagnosing AMI. Serial determinations of H-FABP are useful for the diagnosis of AMI, for identifying patients in need of reperfusion therapies, for detecting re-infarctions, as well as for estimating the infarct size.[35] As in case of myoglobin, the levels of H-FABP can be elevated in other non-cardiac conditions such as renal failure, muscular trauma, traumatic cardiopulmonary resuscitation, or intramuscular injections, causing interference with the results of the assays. Some studies have questioned the role of myoglobin and H-FABP in the early detection of AMI, stating that cardiac troponins are more specific and possess higher diagnostic accuracy.[36,37]

BIOMARKERS FOR RISK ASSESSMENT IN THE CORONARY CARE UNIT

No reliable indicators have been established for the early risk assessment of developing heart failure or CS in AMI patients; however, various biomarkers that reflect the evolution towards ventricular dysfunction have been shown to associate with poorer outcomes after an acute coronary event.

Soluble ST 2 (sST2) is a novel marker expressing inflammation and interstitial fibrosis associated with heart failure that is up-regulated during myocardial strain as well as post-AMI. Soluble ST 2 has been shown to illustrate progressive decongestion in acute heart failure, and it has been demonstrated that circulating levels of sST2 decreased after 1 month in cases where mechanical circulatory assisting devices were used.[38–40]

Natriuretic peptides (NP) with the 3 isoenzymes: atrial NP, brain NP (BNP), and NT-proBNP, act as protective hormones that counteract the physiologic abnormalities of myocardial dysfunction and injury.[41] BNP has also diagnostic and prognostic value in myocardial infarction, as a serum level higher than 30 pmol/L was shown to be highly sensitive for diagnosing AMI, with a negative predictive value of 96%.[42] Furthermore, BNP is an efficient risk stratification tool for short- and long-term major adverse cardiac events following an AMI. In combination with echocardiographic assessment of left ventricular ejection fraction, BNP leads to an increased predictive capacity for death, heart failure, and repeated ischemic episodes.[42,43]

Co-peptin is a plasmatic peptide that increases in critical conditions such as shock, sepsis, stroke, or cardiovascular diseases, carrying diagnostic and prognostic value for myocardial injury. Persistently elevated levels of co-peptin after 3 to 5 days post-AMI are associated with higher rates of mortality and re-admissions for heart failure, and if associated with NT-proBNP assessment, it provides a more accurate risk prediction tool in AMI patients.[44,45]

INFLAMMATORY BIOMARKERS IN ACUTE CORONARY SYNDROMES AND CRITICAL CONDITIONS

The systemic inflammatory response occurring in cardiogenic shock due to AMI is caused by myocardial necrosis, generalized tissue hypoperfusion, and hypoxia.[46] Several inflammatory cytokines, including interleukins (IL-6, IL8), tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), and soluble adhesion molecules, show increased levels in AMI complicated with CS.[47–49] The elevated baseline levels of inflammatory biomarkers have high predictive power for the development of CS and mortality in this patient population. A sub-study of the COMMA trial showed that increased values in the serum levels of IL-6, TNF-α, and CRP predicted the combined mortality and CS in AMI patients.[50]

C-reactive protein is an acute inflammatory response protein that can be elevated in subjects with atherosclerosis. This biomarker expresses an enhanced inflammation, and is especially increased in acute coronary syndromes. Furthermore, an increased level of CRP has been linked to worse outcomes following an acute coronary event.[51–56] Elevated plasmatic CRP concentrations are associated with the worsening of the hemodynamic and neurohormonal state of heart failure patients, being a valuable predictor for ischemic and non-ischemic complications.[57] Also, elevated levels of high-sensitive CRP (hs-CRP) have been associated with increased short-term death rates in AMI patients who underwent primary coronary angioplasty.[58–60]

Interleukin-6 is the main promoter of CRP production at the level of the liver, being involved in acute inflammation, macrophage activity, hemato- and thrombopoiesis, and stem cell function. Also, the plasma concentration of IL-6 was shown to independently predict 30-day mortality in AMI patients with CS.[49] A study on 75 AMI patients who underwent primary angioplasty found significant correlations between increased levels of IL-6 and CRP and impairment of left ventricular systolic and diastolic function, as well as a good predictive power of these biomarkers for the development of systolic and diastolic dysfunction at 6 months.[61]

Pentatraxin-3 (PTX-3) is a novel biomarker linked with the inflammatory response in heart failure patients, being shown to correlate with poor evolution of heart failure and with major adverse cardiac events in patients with known diastolic heart failure.[62,63] Also, PTX-3 levels have been proposed as prognostic markers for adverse events in patients with unstable angina and myocardial infarction.[64]

Procalcitonin is an inflammatory response biomarker produced by the parathyroid gland, which has been correlated with the severity of organ injury in AMI and CS, being used as a guiding tool for treatment and risk stratification in severe heart failure patients.[65–68]

EMERGING BIOMARKERS IN MYOCARDIAL INFARCTION – EXTRACELLULAR MATRIX REMODELING AND MIRNAS

The extracellular matrix (ECM) is the complex network within the intercellular space that has critical signaling functions. ECM provides the mechanical support for the myocardial fibers to perform their mechanical and biochemical function, and regulates cell proliferation, adhesion, and migration.[69] Following myocardial infarction, cardiac cells undergo necrosis and are replaced by a scar that is mainly composed by ECM components. Several components of the ECM have been linked to cardiac fibrosis and remodeling after an acute cardiac event. Galectin-3 is a complex biomarker that is elevated in patients with important ventricular remodeling following AMI complicated with acute heart failure. The PRIDE trial demonstrated that elevated levels of Galectin-3 are highly predictive for 60-day mortality rates and re-admissions in the hospital for acute heart failure.[70–74]

Matrix metalloproteinases (MMPs), with their various isoenzymes, are biomarkers involved in the degradation of ECM components, together with serine proteases.[75] MMP-2 is activated during cardiac injury due to increased oxidative stress, resulting in the cleavage of intracellular contractility substrates in the cardiac myocytes such as troponin I and myosin light chain.[76] Concentrations of MMP-1 were shown to be significantly higher in patients with reduced systolic function. At the same time, MMP-2, MMP-9, and MMP-7, which express an enhanced collagen turnover, were more increased in subjects with diastolic dysfunction.[77] According to the I-PRESERVE trial results, elevated levels of MMPs were associated with a higher incidence of the composite end-point of death due to heart failure, repeated hospitalizations, and all-cause mortality in patients with diastolic heart failure.[78]

Non-coding micro-ribonucleic acids (miRNAs) have recently emerged as useful risk stratification tools for the development of heart failure following an AMI. The identification of this new class of biomarkers could contribute to triggering prompt therapeutic intervention for preventing this potentially fatal complication.[79] Many gene alterations have been examined for myocardial infarction response and the integration of mRNA and messenger RNAs in a genetic profile, which could help in elucidating the mechanisms of MI development, providing novel biomarkers for risk stratification following an acute coronary event.[80–82] However, these promising tools are yet to be applied in clinical practice and require further research.

HEMODYNAMIC MONITORING IN THE CORONARY CARE UNIT

Various devices can be used in the CCUs, in order to provide essential information regarding the clinical and hemodynamic status of complicated AMI cases.

NONINVASIVE MONITORING IN THE CCU

One the most useful devices in the CCUs are represented by continuous surface electrocardiogram (ECG) monitoring systems, which offer continuous monitoring for 2–3 days following an AMI, or throughout the entire period of hemodynamic instability. These systems allow the early identification of arrhythmias and conduction disturbances as well as ST-segment and T-wave changes.[83] ST-segment and T-wave changes can reveal repeated episodes of ischemia in the early post-AMI period, or can indicate an inefficient reperfusion therapy, which can serve as predictors for negative outcomes.[84–88] Furthermore, it has been demonstrated that more than three ischemic events, or more than one hour repeated ischemic event on the continuous ECG tracing records indicate a three-vessel coronary artery disease or severe coronary atherosclerosis.[84,87,88]

The evaluation of arterial oxygen saturation with the use of pulse oximetry is used for noninvasively detecting the ventilatory status of the patients in the CCU. The technique is based on the photometric analysis of the pulse wave in the fingernail, requiring a systolic blood pressure of more than 85 mmHg. Therefore, clinical situations in which the patients present hypovolemia, low blood pressure, CS, or other types of shock associated with decreased tissular perfusion, can impair the evaluation of ventilatory status using this method.[89] Tissular hypoperfusion is the most common event that proceeds multiple organ dysfunction during shock.[90] Another method for the noninvasive assessment of tissue oxygenation includes near-

infrared spectroscopy (NIRS), a technique that monitors muscular tissue oxygenation (StO_2) using infrared light absorption, through placement of a noninvasive sensor at the level of the thenar eminence. It has been shown that the normalization of StO_2 levels is associated with improved outcomes in patients with hemorrhagic shock, and that low levels of the same parameter were correlated with the development of multiple organ dysfunction of trauma patients.[90–93]

The evaluation of body temperature can offer important information on the overall status of the critically ill patient, as fever is a negative prognostic factor that can indicate elevated systemic inflammation or infection, while a decreased peripheral temperature is a sign of decreased tissue perfusion.[94–98] Body temperature is assessed through peripheral (tympanic membrane, temporal artery, axillary, or oral), or central (pulmonary artery catheter, urinary bladder, esophageal, or rectal) methods. However, a meta-analysis on 75 studies that assessed the accuracy of peripheral thermometry for the estimation of core body temperature stated that peripheral thermometers should not be used if the body temperature will influence the therapeutic management, as they do not present an acceptable clinical accuracy.[99,100] Fever can be an appropriate response to infection, and one study showed a lower in-hospital mortality rate in patients with peak temperatures of 39–39.4 ºC compared to peak temperatures of 36.5–36.9 ºC (OR, 0.56; 95% CI 0.48-0.66).[101]

Diuresis monitoring (urine output on a given time frame) is of essence in the CCU, as it can provide relevant information on the renal function and hydration status of the patient, helping to guide fluid and diuretic therapy.[94] A normal urine output ranges between 0.5–1 mL/kg/h, while the presence of oliguria, a diuresis of less than 500 mL over a 24-hour period, might indicate a decreased renal perfusion that could be related to the onset of acute heart failure.[102,103] The presence of oliguria in critically ill subjects with AMI is a sensitive marker of acute kidney injury, and it has been shown to be linked to higher mortality rates in these patients.[104,105] Patients with CS secondary to AMI present decreased arterial pressure and an overall organ hypoperfusion, which leads to hypotension-induced renal injury. The main cause of acute kidney insufficiency in critically ill AMI patients is acute circulatory failure, through a pre-renal mechanism.[106] A mean arterial pressure (MAP) of over 65 mmHg is required to avoid organ failures, including renal dysfunction.[107] An additional cause of renal dysfunction in patients with AMI is contrast-induced nephropathy, a complication of contrast media administration during coronary angiography and the third most common cause of hospital-acquired acute renal injury.[108]

MONITORING HEMODYNAMIC STATUS IN THE CCU

Usually, continuous recording of blood pressure and cardiac output (CO) is essential for the optimization of diuretic, inotropic, and vasodilator therapies in critical patients admitted in the CCU.[109] The finger-cuff technology can provide continuous noninvasive monitoring of BP and cardiac output, using a cuff placed around the finger for continuous BP measurement and beat-to-beat cardiac output calculation through pulse contouring.[110] Several studies have shown that this method is comparable to invasive monitoring systems.[111,112]

The noninvasive evaluation of stroke volume and cardiac output can be achieved using thoracic electrical impedance, ultrasound, and pulse contour analysis.[113,114] The parameters assessed with cardio-impedance methods are the fluid content of the thoracic cavity, which has a negative correlation with thoracic impedance, ventricular preload, and left ventricular contractility, thus allowing the estimation of cardiac output, systemic vascular resistance, and the overall mechanical function of the left ventricle. However, systems that use electrical impedance to estimate CO cannot be used in certain situations that include septic shock, aortic valve replacement, uncontrolled hypertension, arrhythmias, the presence of an intra-aortic balloon pump, body weight of more than 155 kg or less than 30 kg, as well as a heart rate above 200 beats per minute.[115–117] Pulse contour analysis systems are based on the fact that the area under the systolic segment of the arterial pulse wave is correlated with the stroke volume.[118] The first and most used device that uses pulse wave contour and thermo-dilution for CO evaluation is the minimally invasive PiCCO system (PULSION medical system, Munich, Germany), which requires a central venous line for cold saline injection and an arterial cannulation for placement of the temperature sensor that records the thermodilution curve.[119] In addition, the PiCCO system can assess intrathoracic blood volume, global end-diastolic volume, and extravascular lung water, allowing the measurement of cardiac preload and pulmonary edema quantification.[120] The Non-Invasive Cardiac Output (NICO) monitoring device is based on partial re-inhalation of CO_2, using Fick's equation applied to carbon dioxide, and its accuracy is comparable to that of the gold standard thermodilution technique.[121]

Although transthoracic echocardiography cannot provide continuous hemodynamic measurements, it is the

best bedside method to repeatedly evaluate the cardiac function, regional wall motion abnormalities, left ventricular ejection fraction, pulmonary artery pressure, aortic flows, and stroke volume, as well as acute complications occurring during the acute ischemic events, such as valve regurgitation, cardiac tamponade, left ventricular wall or papillary muscle rupture.[122–124] Transesophageal echocardiography is a useful tool in hemodynamically unstable patients under mechanical ventilation; despite of the associated inter and intraprocedural variability, the method has been validated in agreement to the thermodilution method in measuring the cardiac output.[125,126] Moreover, the esophageal Doppler flexible probe can measure the aortic flow by multiplying the cross-sectional area with the velocity, which will allow the estimation of the left ventricular stroke volume. The major limitation of this method is that it provides measurements from the descending aorta (only 70% of the total flow), and that discrepancies appear in case of aortic coarctation, aneurysms, or in the presence of an intra-aortic balloon pump.[127] Nevertheless, the evaluation of stroke volume with esophageal Doppler has been shown to be in concordance with well-established invasive methods.[128,129]

INVASIVE MONITORING OF HEMODYNAMIC PARAMETERS IN THE CORONARY CARE UNIT

Invasive monitoring in the CCU is performed when the hemodynamic status of the patients is not stabilized and requires additional invasive measures.[130]

The invasive evaluation of blood pressure is achieved by placing a catheter in a superficial artery (radial, femoral, or pedis artery), which is connected to a transducer that transforms the mechanical pulse wave into a pressure curve. Analysis of the invasive arterial pressure waveform allows the estimation of CO and ventricular ejection fraction, and the invasive measurements are performed simultaneously with the noninvasive evaluation of blood pressure.[131,132]

Central venous pressure (CVP) is a marker that illustrates intravascular volume and right ventricular function, being measured by inserting a catheter in the superior caval system (subclavian or internal jugular vein), with continuous ECG recording, under local anesthesia. An increased CVP is suggestive of decreased ventricular function, increased venous return, increased systemic vascular resistance or elevated intrathoracic pressures. The assessment of CVP is of utmost importance in hemodynamically unstable AMI patients, as it guides fluid administration in this critical condition.[133]

The invasive assessment of CO and stroke volume is performed by Swan Ganz catheterization using the thermodilution method, which also allows the evaluation of right cardiac pressures and the pulmonary capillary wedge pressure, being largely used in CCUs for invasive hemodynamic monitoring.[134–137] Other invasively assessed parameters used in the CCU for critical AMI patients are those reflecting ventricular contractility such as the left ventricular stroke volume and the mechanical work, which can indicate whether inotropes or vasodilator therapies are required.[138,139]

The pressures in the right ventricular and pulmonary artery illustrate the pulmonary circulation, while the capillary wedge pressure reflects the end-diastolic pressure in the left ventricle, indicating the preload alteration and estimating the systolic and diastolic function of the left heart chambers.[140,141] Furthermore, the pulmonary capillary wedge pressure evaluation provides information on the hemodynamic impact of various acute complication of MI such as ischemic mitral regurgitation, interventricular septum defect, or newly developed intracardiac shunts of papillary muscle rupture with acute mitral regurgitation.[142]

CONCLUSION

CS is a life-threatening complication of AMI that requires intensive monitoring of the hemodynamic, biochemical, and inflammatory status, being essential in providing a proper and complex diagnostic and therapeutic management, as well as for accurate risk stratification. Complex serum biomarker panels able to identify early changes in the clinical status, to detect high risk patients, and to evaluate response to treatment should be introduced in current clinical practice for a proper and prompt therapeutic intervention. Also, various invasive and noninvasive monitoring techniques should be used as complementary tools for guiding diagnosis and treatment in acute coronary care units.

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH

A Comparative Preliminary Study on CT Contrast Attenuation Gradient Versus Invasive FFR in Patients with Unstable Angina

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ABSTRACT

The **aim** of this preliminary study was to assess the effectiveness of transluminal contrast attenuation gradient (TAG) determined by computed tomographic angiography (CTA), for the evaluation of the functional significance of coronary artery stenoses in patients with acute coronary syndromes produced by vulnerable coronary plaques, and to demonstrate the correlation between this new parameter and the vulnerability markers of the culprit lesions. **Material and methods:** This is a preliminary pilot study on 10 patients with acute coronary syndromes – unstable angina type, who underwent CTA for the assessment of coronary lesions, followed by invasive angiography and the determination of fractional flow reserve (FFR) prior to a revascularization procedure. Patients were divided into 2 groups, according to their FFR values: Group 1 consisted of 6 patients with an FFR value <0.8 (functionally significant lesion), and Group 2 consisted of 4 patients who presented an FFR value >0.8 (functionally non-significant lesion). **Results:** FFR values were 0.64 ± 0.07, 95% CI: 0.5–0.7 in Group 1, and 0.86 ± 0.05, 95% CI: 0.7–0.9 in Group 2. Plaques associated with an FFR<0.8 presented a higher amount of plaque volume (192.7 ± 199.7 mm3 vs. 42.1 ± 27.3 mm3, p = 0.1), necrotic core (66.7 ± 72.9 mm3 vs. 10.0 ± 9.3 mm3, p = 0.1), and fibro-fatty tissue (29.7 ± 37.4 mm3 vs. 6.2 ± 3.8 mm3, p = 0.2). At the same time, TAG significantly correlated with the presence of a functionally significant lesion. Coronary lesions associated with low FFR presented significantly higher values of TAG along the plaque as compared with lesions with FFR values >0.8 (TAG values 22.1 ± 5.8 HU vs. 11.7 ± 2.5 HU, p = 0.01). Linear regression identified a significant correlation between TAG and FFR values as a measure of functional significance of the lesion (r = 0.7, p = 0.01). **Conclusions:** Contrast attenuation gradient along the culprit lesion, determined by CTA, correlates with the FFR values and with CT markers of plaque vulnerability, indicating that the presence of vulnerability features inside a coronary plaque could increase the functional significance of a coronary lesion.

Keywords: contrast atenuation, vulnerable coronary plaque, computed tomographic angiography, fractional flow reserve

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INTRODUCTION

Coronary atherosclerosis represents one of the most devastating diseases worldwide, and acute coronary syndromes (ACS) are the most severe form of this condition. The costs related to the complex investigations of ACS and the associated treatment are constantly increasing; however, the mortality of patients with acute myocardial infarction remains very high, reaching 20% in the absence of timely initiation of reperfusion treatment.[1,2]

New cardiac imaging technologies have been developed in recent years in an attempt to identify imaging markers associated with an increased vulnerability of the coronary plaques, hoping that prompt treatment of these lesions could prevent the progression of the disease towards the development of an acute coronary event. Such a technique is represented by computed tomography angiography (CTA), which is able not only to identify the presence of vulnerability markers inside the plaque, but also to quantify the amount of its components on the basis of CT density. However, the decision to stent or not a vulnerable plaque that is not hemodynamically significant remains challenging for the interventionist.[3–5]

Usually, the severity of a coronary artery stenosis is estimated on the basis of coronary angiography, by calculating the narrowing degree of the coronary lumen. However, intravascular ultrasound (IVUS) studies demonstrated that not all culprit lesions that have triggered an acute coronary syndrome produce a significant narrowing of the coronary lumen.[6,7] At the same time, the PROSPECT trial demonstrated that the amount of plaque burden evaluated by IVUS was the strongest predictor of mortality in patients with vulnerable plaques.[8] Also, the COURAGE trial demonstrated the non-superiority of visual cineangiography-guided revascularizations compared to the correct medication in regards to mortality, myocardial infarction, and other cardiovascular complications.[9,10]

At the same time, a new technology represented by the estimation of fractional flow reserve (FFR) has been suggested and implemented in cath labs in recent years, in order to provide a robust tool for the assessment of the functional significance of a coronary stenosis. FFR, an invasive technique that measures the intraluminal pressure after stenosis compared to the pressure proximal to stenosis with the aid of a special transducer similar to a coronary guide, rapidly became a gold standard for assessing the functional significance of a coronary artery stenosis. FFR is defined as the ratio between the mean distal and proximal pressure to stenosis, and a rate of less than 0.8 is considered a strong indicator of a significant stenosis.[11,12] The FAME and FAME II trials demonstrated that a percutaneous coronary intervention (PCI) strategy based on the functional signification of the coronary stenosis is preferable to the classical strategy based on angiographic aspect.[11,13] However, the exact relation between the functional significance of a coronary lesion and the vulnerability degree of this plaque is still under investigation.

Multiple CTA-derived markers have been proposed for plaque characterization, in stable or unstable plaques.[14,15] The plaque burden, the amount of low-density plaque, or the remodeling index are vulnerability markers easily calculated on CTA images using modern post-processing software. At the same time, it has been proposed that the degree of attenuation of contrast material along the stenosis, determined by CTA, could serve as a functional parameter expressing the hemodynamic significance of a coronary artery stenosis.[12,16,17]

The aim of this preliminary study was to assess the effectiveness of transluminal contrast attenuation gradient (TAG) determined by CTA, for the evaluation of the functional significance of coronary artery stenoses in patients with acute coronary syndromes produced by vulnerable coronary plaques, and to demonstrate the correlation between this new parameter and the vulnerability markers of the culprit lesions.

MATERIAL AND METHODS

This is a preliminary pilot study on 10 patients with ACS – unstable angina type, who underwent CTA for the assessment of coronary lesions, followed by invasive angiography and determination of FFR prior to a PCI procedure.

Patients with other forms of ACS (acute myocardial infarction, with or without ST-segment elevation), hemodynamically unstable patients, or patients with significant kidney dysfunction were excluded from the study.

The study protocol was approved by the ethics committee of the institution where the procedures were performed, and written informed consent was obtained from each participant included in the study. All study procedures have been carried out according to the principles stipulated in the Declaration of Helsinki.

Prior to the CTA examination, all patients received beta-blockers, in order to obtain a heart rate below 60/min, and 1 mL/kg of ionic contrast media was administrated through an intravenous 18-gauge line at a flow rate of 6.1 mL/s, followed by a 150 mL saline chaser at the same flow rate.

Image acquisition was performed with a Siemens Somatom 128-slice CT equipment (Siemens, Erlangen, Germany), followed by automated and manual reconstruction

and evaluation of the coronary artery. Post-processing and image analysis for the quantification of coronary plaque components have been carried out using the QANgioCT RE software (Medis, Leiden, The Netherlands), which allowed atherosclerotic plaque characterization and quantification of plaque components such as: plaque volume, lesion length, mean and maximum plaque burden, fibrous fatty volume, necrotic core volume, % stenosis, and TAG expressed in mean HU/mm.

TAG was calculated as the difference in the contrast density along the coronary stenosis, between the segment located 1 mm proximal to the stenosis and the segment located 1 mm distal to the lesion (Figure 1).

Following CTA examination, all patients underwent invasive angiography and FFR calculation using the Optis Integrated System (St Jude Medical, St Paul, Minnesota, USA), and Aeris Agile Tip pressure wire catheters (St Jude Medical, St Paul, Minnesota, USA) for invasive FFR determination.

Patients were divided into 2 groups, according to their FFR values: Group 1 consisted of 6 patients with an FFR value <0.8 (functionally significant lesion) and Group 2 consisted of 4 patients who presented an FFR value >0.8 (functionally non-significant lesion).

Statistical analysis was performed using the GraphPad InStat 3.0 software (GraphPad Software, San Diego, USA). For comparing the characteristics of all patients between Group 1 and Group 2, Fisher's exact test (or Student's t-test for age) was used. Continuous values were expressed as mean ± standard deviation, and statistical significance was determined using the Mann-Whitney test. Linear regression was used for assessing the correlation between FFR values and TAG. Statistical significance was considered for p values <0.05 and all p values were two-sided.

RESULTS

Baseline characteristics of the study population are presented in Table 1. There were no statistically significant differences between the study groups in relation to age, gender, and cardiovascular risk factors (smoking status, hypertension, obesity, dyslipidemia) (Table 1).

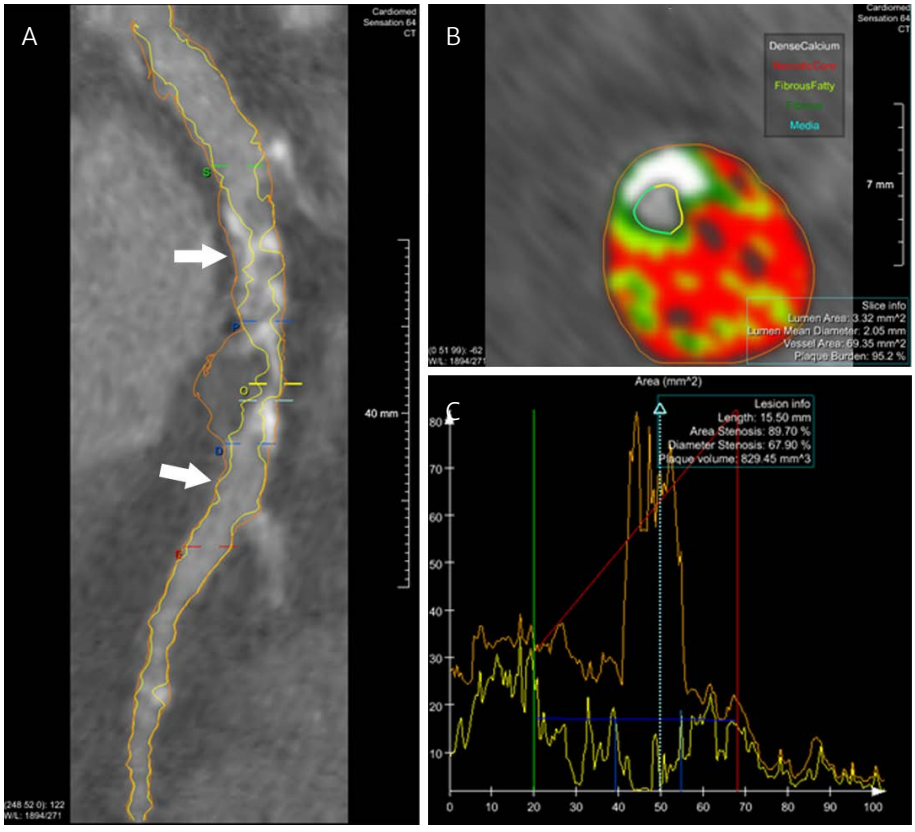

FIGURE 1. Automated post-processing of a coronary vulnerable plaque. **A** – reference points for calculation of the attenuation gradient between the segment located proximal and distal to the plaque (arrows); **B** – color coded representation of plaque components based on contrast density and quantification of plaque burden, fibrofatty tissue and necrotic core; **C** – graphical representation of quantification of plaque components based on contrast density

TABLE 1. Patient characteristics in the study groups

	Group 1 FFR <0.8 n = 6	Group 2 FFR >0.8 n = 4	p value
Age, years	68.5 ± 7.2	69.2 ± 9.5	0.7
Gender, male	3 (50.0%)	3 (75.0%)	0.5
Hypertension	3 (50.0%)	2 (50.0%)	1
Hyperlipidemia	3 (50.0%)	2 (50.0%)	1
Obesity (BMI >25 km/m^2)	2 (33.3%)	2 (50.0%)	1
Smoker*	3 (50.0%)	1 (25.0%)	0.5
Diabetes	1 (16.5%)	1 (25.0%)	1

*past or present

FFR values were 0.64 ± 0.07, 95% CI: 0.5–0.7 in Group 1, and 0.86 ± 0.05, 95% CI: 0.7–0.9 in Group 2.

The CT analysis of plaque characteristics revealed that lesion length and stenosis severity were statistically significantly higher in Group 1 as compared with Group 2 (p <0.0001). At the same time, functionally significant plaques presented an elevated expression of vulnerability markers inside the plaques as compared to functionally non-significant plaques (Figure 2). Plaques associated with an FFR<0.8 presented a larger plaque volume (192.7 ± 199.7 mm^3 vs. 42.1 ± 27.3 mm^3, p = 0.1), necrotic core (66.7 ± 72.9 mm^3 vs. 10.0 ± 9.3 mm^3, p = 0.1) and fibro-fatty tissue (29.7 ± 37.4 mm^3 vs. 6.2 ± 3.8 mm^3, p = 0.2) (Table 2). However, the differences were not sta-

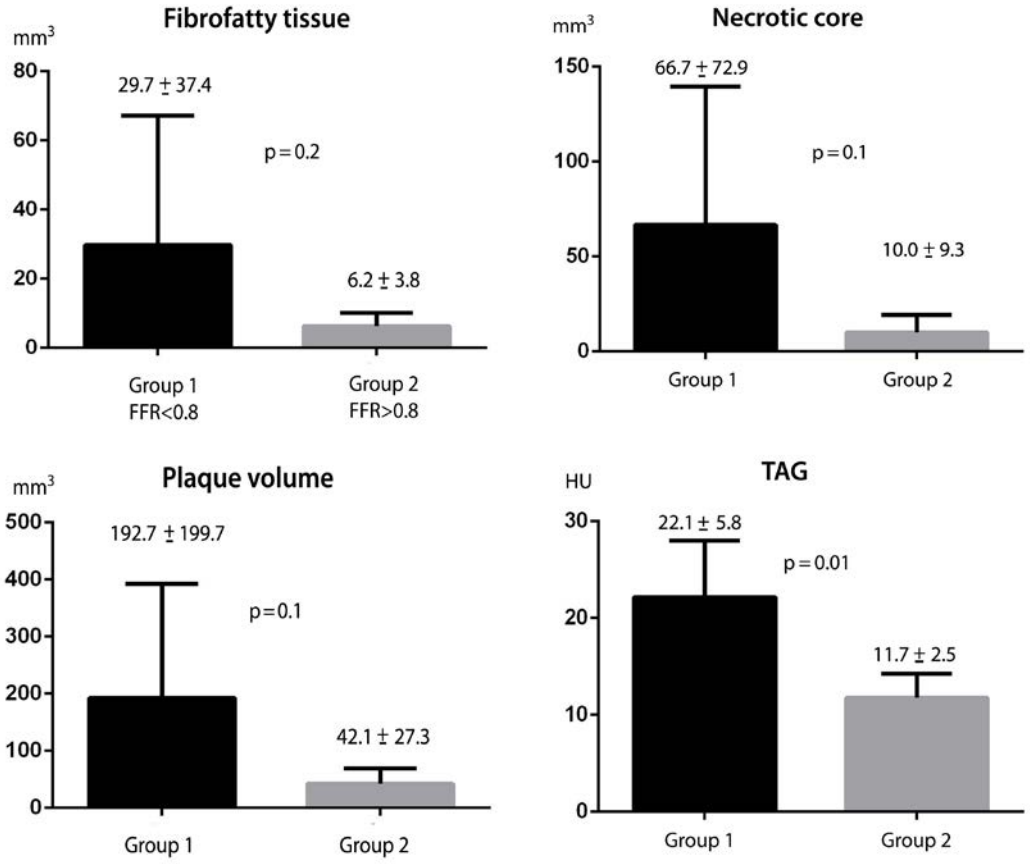

FIGURE 2. Plaque characteristics and TAG values in the culprit lesions of the group with FFR <0.8 vs. the group with FFR >0.8

TABLE 2. Plaque characteristics in the study groups

	Group 1 FFR <0.8 n = 6	Group 2 FFR >0.8 n = 4	p value
Lesion length (mm)			<0.0001
Mean ± SD	9.9 ± 3.6	3.2 ± 1.7	
95% confidence interval	6.1–13.7	0.4–6.0	
% stenosis (%)			<0.0001
Mean ± SD	82.7 ± 8.3	40.1 ± 5.1	
95% confidence interval	74.0–91.5	32.0–48.3	
Plaque burden (%)			0.4
Mean ± SD	76.7 ± 8.2	72.3 ± 6.6	
95% confidence interval	68.1–85.3	61.7–82.9	
Plaque volume (mm^3)			0.1
Mean ± SD	192.7 ± 199.7	42.1 ± 27.3	
95% confidence interval	-16.8–402.3	-1.3–85.5	
Plaque thickness (μm)			0.6
Mean ± SD	3.3 ± 1.6	2.9 ± 1.1	
95% confidence interval	1.5–5.1	1.2–4.7	
TAG (HU)			0.01
Mean ± SD	22.1 ± 5.8	11.7 ± 2.5	
95% confidence interval	16.0–28.2	7.7–15.7	
Fibro-fatty tissue (mm^3)			0.2
Mean ± SD	29.7 ± 37.4	6.2 ± 3.8	
95% confidence interval	-9.5–69.0	0.1–12.4	
Necrotic core tissue (mm^3)			0.1
Mean ± SD	66.7 ± 72.9	10.0 ± 9.3	
95% confidence interval	-9.8– 143.2	-4.7–24.8	

TAG – trans-stenotic attenuation gradient

tistically significant, probably due to the limited number of cases.

At the same time, TAG significantly correlated with the presence of a functionally significant lesion. Coronary lesions associated with low FFR presented significantly higher values of TAG along the plaque as compared with lesions with FFR values >0.8 (TAG values 22.1 ± 5.8 HU vs. 11.7 ± 2.5 HU, p = 0.01) (Figure 3).

Linear regression identified a significant correlation between TAG and FFR values as a measure of functional significance of the lesion (r = 0.7, p = 0.01), indicating that the decrease in FFR in functionally significant plaques is directly correlated with the decrease in contrast density along the plaque, as expressed by an increased contrast gradient along the lesion.

DISCUSSION

CTA has become one of the most extensively used and useful imaging techniques in cardiology, and its relevance in patients with vulnerable coronary plaques is nowadays widely accepted.[18]

Despite of a multitude of studies that assessed the role of CTA in evaluating plaque vulnerability, according to our knowledge there are no published data so far regarding the role of CTA in assessing vulnerability markers in relation to the functional significance of a coronary lesion.[19–23]

FFR remains the gold standard for assessing the hemodynamic significance of a coronary artery stenosis; however, this remains an invasive technique that could prove to be unnecessary in cases with no significant lesions. Therefore the validation of new imaging-derived markers able to assess the functional significance of a coronary lesion using a noninvasive route could play a significant role in the reduction of unnecessary invasive coronary interventions.

The CT-based calculation of FFR (CT-FFR) has been also introduced in recent years as a new parameter for the estimation of lesion severity on a noninvasive route, using computational fluid dynamics and the simulation of

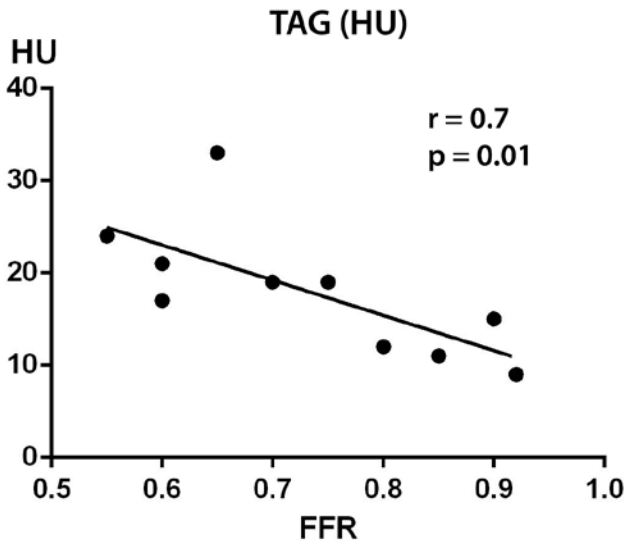

FIGURE 3. Correlation between TAG and FFR in culprit lesions of patients with unstable angina

coronary flow.[24] Also, coronary shear stress, calculated using computational fluid dynamics, has been proposed to be associated with plaque vulnerability in unstable coronary lesions. Several recent studies proved that unstable plaques exhibit reduced shear stress in the region located immediately distal to the vulnerable coronary plaque.[25] However, all these techniques based on coronary flow simulation and computational post-processing are time-consuming and require significant skills and experienced operators, being difficult to be performed in a timely fashion, as requested in many cardiovascular emergencies.

In recent studies, TAG and CT-FFR have shown their superiority as compared with invasive FFR in intermediate lesions with a stenosis degree between 30% and 70%, showing good sensitivity and specificity for discriminating between significant and non-significant lesions.[12]

As compared with the gold standard (FFR), TAG presents the advantage that it does not require the administration of vasodilators drugs, while FFR requires adenosine administration. It is also important to mention that the presence of coronary calcification could impact the quality of TAG measurement, an impediment that is not encountered when using the invasive FFR approach. Corrective applications of CT post-processing techniques have been proposed to overcome this disadvantage, such as TAG with corrected contrast opacification (TAG-CCO) and TAG with the exclusion of calcified coronary segments (TAG-ExC). Some studies have shown that in comparison to classical coronary angiography, TAG-ExC can improve the coronary CT angiography specificity, while TAG-CCO has a limited contribution in addition of the information of CTA alone.[23,26]

In this pilot study, we demonstrated that TAG could be considered a new imaging-derived parameter able to estimate the functional significance of coronary lesions, being significantly increased in coronary lesions classified as significant based on FFR assessment, the currently validated gold standard. At the same time, TAG was associated with CT markers of plaque vulnerability, such as necrotic core or plaque volume, indicating that TAG can be considered a marker indirectly associated with plaque vulnerability. This could also open the hypothesis that vulnerable coronary plaques have a higher impact on the functional significance of a coronary lesion, probably via complex mechanisms related to the alteration of the local dynamic forces in the coronary flow, a process in which local inflammation could play a certain role.

LIMITATION OF THE STUDY

One major limitation of this study is that the TAG and FFR evaluations were made in different moments; therefore, the information provided by the two imaging tools could not be entirely superposable.

On the other hand, the small number of patients included in this pilot study makes it hard to generalize the conclusions. However, this study opens new perspectives for challenging a hypothesis that could be further explored in larger scale studies.

CONCLUSION

In patients with unstable angina, contrast attenuation gradient along the culprit lesion, determined by CTA, could serve as a promising tool for the estimation of the functional significance of the lesion, being highly correlated with FFR values. At the same time, TAG correlates with CT markers of plaque vulnerability, indicating that the presence of vulnerability features inside a coronary plaque could increase the functional significance of a coronary lesion.

CONFLICT OF INTEREST

Nothing to declare.

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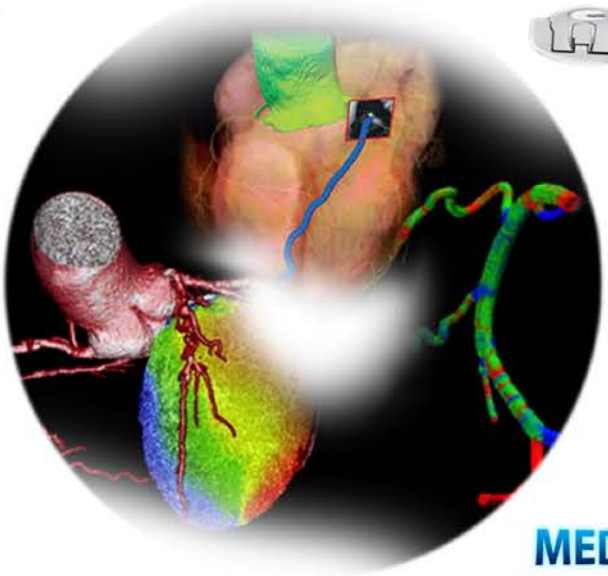

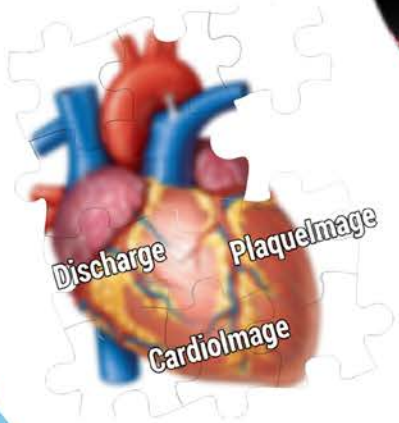

1. DISCHARGE

DIAGNOSTIC IMAGING STRATEGIES FOR PATIENTS WITH STABLE CHEST PAIN AND INTERMEDIATE RISK OF CORONARY ARTERY DISEASE: COMPARATIVE EFFECTIVENESS RESEARCH OF EXISTING TECHNOLOGIES - *FINANȚAT DE COMISIA EUROPEANĂ, PROGRAMUL CADRU FP7, 2014*

2. CARDIOIMAGE

PLATFORMĂ IMAGISTICĂ MULTIMODALĂ RMN/CT DE ÎNALTĂ PERFORMANȚĂ, DESTINATĂ APLICĂRII MEDICINII COMPUTAȚIONALE, NANOPARTICULELOR ȘI IMAGISTICII HIBRIDE ÎN CERCETAREA BOLILOR ATEROTROMBOTICE *FINANȚAT DE AUTORITATEA NAȚIONALĂ PENTRU CERCETARE ȘTIINȚIFICĂ, PROGRAMUL OPERAȚIONAL*

3. PLAQUEIMAGE

CREȘTEREA CAPACITĂȚII DE CERCETARE ÎN DOMENIUL IMAGISTICII PLĂCII CORONARIENE VULNERABILE, BAZATĂ PE TEHNOLOGII AVANSATE DE NANOPARTICULE, IMAGISTICĂ DE FUZIUNE ȘI SIMULĂRI COMPUTAȚIONALE - *FINANȚAT DE AUTORITATEA NAȚIONALĂ PENTRU CERCETARE ȘTIINȚIFICĂ, PROGRAMUL OPERAȚIONAL COMPETITIVITATE, 2016*

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CLINICAL UPDATE

Cardiac Stem Cell-based Regenerative Therapy for the Ischemic Injured Heart — a Short Update 2017

Mariann Gyöngyösi, Dominika Lukovic, Katrin Zlabinger, Ljubica Mandic, Johannes Winkler, Alfred Gugerell

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ABSTRACT

Cell therapy for the ischemic injured heart has been largely investigated in the last two decades, and most of the small cohort and randomized clinical studies, as well as meta-analyses led to the conclusion that cell-based human regenerative therapy is safe and effective in term of reducing adverse clinical outcomes and increasing left ventricular performance. Both the in vitro and in vivo rodent animal models of ischemic heart failure using bone marrow-derived mononuclear cells promised marvelous success in regeneration of the heart suffering from ischemic burden. However, in certain patient groups, stem cell studies failed to reach the primary endpoint, showing no effect of this regenerative therapy. This brief overview addresses the contradictory results between human cardiac regenerative studies and the very positive rodent experiments.

Keywords: stem cells, ischemic heart diseases, cardiac regeneration

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Cell therapy for the ischemic injured heart has been investigated in the last two decades. Both the in vitro and in vivo rodent animal models of ischemic heart failure using bone marrow-derived mononuclear cells promised marvelous success in regeneration of the heart suffering from ischemic burden. Numerous positive findings of these experiments led to sustained enthusiasm for the clinical translation of cardiac regeneration. The triggers for cardiac cell-based therapies from the late 1990s included the differentiation of bone marrow mesenchymal stem cells into cardiomyocyte-like cells; enhanced angiogenesis when bone marrow-derived stem cells were injected into the infarcted left ventricular wall. World-wide well-known researchers reported that a certain fraction of bone marrow cells expressing c-kit marker, and also hematopoietic cells with CD34+ markers could give rise to new vessels and cardiomyocytes; the mobilization of bone marrow cells either spontaneously or using specific factors in the post-infarction period leads to the homing of these c-kit and CD34+ bone marrow cells in the myocardial infarction region, and these cells reduce infarct size and improve survival in animal models. Accordingly, over a decade, hundreds of clinical reports have emerged about the use of cell-based cardiovascular regenerative therapy for patients with ischemic heart disease with the hope of clinically relevant regeneration of the human ischemic injured myocardium by using bone marrow cells, but also peripheral progenitors, cardiospheres, or mesenchymal

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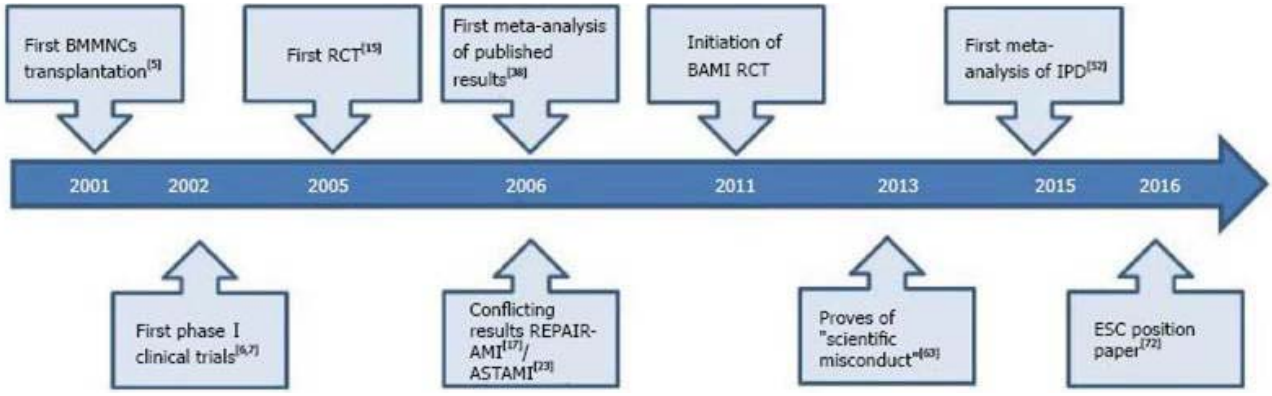

FIGURE 1. Fifteen years of bone marrow mononuclear cell therapy in acute myocardial infarction — time line chart.

From Micheu MM, Dorobantu M. Fifteen years of bone marrow mononuclear cell therapy in acute myocardial infarction. World J Stem Cells 2017; 9(4): 68-76. (reprinted with permission)

stem cells from diverse origins. Most of the small cohort and randomized clinical studies, as well as meta-analyses led to the conclusion that the cell-based human regenerative therapy is safe and effective in term of reducing adverse clinical outcomes and increasing left ventricular performance. However, after the first clinical study with no evidence of the beneficial effect of bone marrow-origin cell therapy in acute myocardial infarction, published in 2006, the number of trials and meta-analyses with neutral outcomes is increasing.[1–6] In 2014, the DAMASCENE group has revealed several discrepancies in published clinical trials with regenerative medicine.[7] In 2017, it is likely that

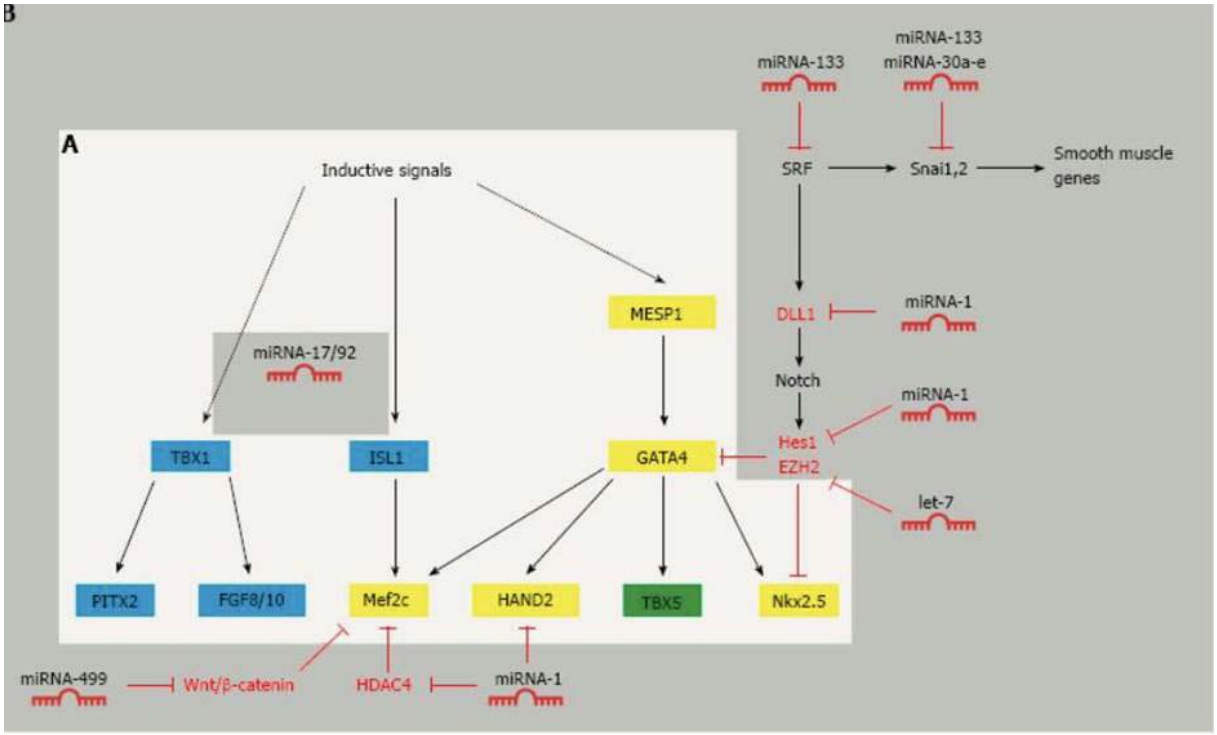

FIGURE 2. The complex web of transcription factors in cardiac specification and their regulation by microRNAs. A: Crosstalk between transcription factors involved in the formation of the first and second heart field (light grey box). MESP1, GATA4, Mef2c, HAND2 and Nkx2.5 are central transcription factors in the first and second heart field (yellow). TBX5 is only expressed in the first heart field (green). ISL1 and TBX1 are expressed in the second heart field (blue); B: MicroRNA-mediated regulation of cardiac transcription factors during cardiomyocyte differentiation (dark grey box).

From Kamps JA, Krenning G. Micromanaging cardiac regeneration: Targeted delivery of microRNAs for cardiac repair and regeneration. World J Cardiol. 2016 Feb 26;8(2):163-79. (reprinted with permission).

one type of cell-based regenerative therapy, namely the intracoronary bone marrow-origin cell therapy is safe, but it offers no functional or clinical benefit (Figure 1).

There are other groups of patients who have chronic ischemic heart failure or refractory angina pectoris and are symptomatic in spite of maximal medical treatment and need cardiac regenerative therapy with anti-ischemic and anti-remodeling effect. The majority of these patients received cell or gene therapy, or manipulated autologous or allogeneic cells intramyocardially, percutaneously. Although the last updated Cochrane meta-analysis summarizing several small randomized study results reported a benefit of cell therapy in this patient population, the most recent randomized multicenter CHART-1 trial (intramyocardial injection of cardiopoietic cells for heart failure) failed to reach the primary endpoint, showing no effect of this regenerative therapy in this patient population.[8]

Why are the human cardiac regenerative studies contradictory to the very positive rodent experiments? There are endless explanations, such as comorbidities of the patients, "sick cell in sick patients" if autologous cells are used, or inappropriate cell dose and type, or the recipient milieu (e.g., inflammatory status or lack of cell homing signals).

According to the rising skepticism in the cardiac regeneration field, the question arises, whether cardiac cell-based therapy for heart disease should be continued in humans? Recognizing the scant evidence of efficacy of the first approaches of cardiac regeneration therapies, the second and third generations of cells and cell therapies are currently under way also in the clinic. Furthermore, refinement of the concepts of cell reprogramming continues, novel gene therapies or tissue engineering, or the local stimulation of endogenous remnant cardiac stem cells with secretomes, exosomes, or other cardiopoietic or immune-modulatory approaches are under testing. Additionally, the role of cell-realted, exosome-bound, cell-free circulating, or locally released oligonucleotids (e.g., non-coding RNAs) is under investigation in the cardiac regeneration processes (Figure 2).

Summarizing the experiences of the past, a position paper has recently been published with facts and clear guidelines for cardiac cell-based therapies.[9] According to the continuous effort to improve clinical regenerative therapies, large clinical multicenter randomized studies are under way with novel concepts regarding the mechanism of action, such as the European Commission-supported SCIENCE (percutaneous intramyocardial delivery of allogeneous stem cell for treatment of heart failure) or the ReGenHeart (percutaneous intramyocardial gene therapy for refractory angina pectoris). We, in the Department of Cardiology, Medical University of Vienna are participants in both of these trials, with the aim to achieve better quality of life of patients through treatment of therapy-resistant heart failure and angina pectoris, and to provide novel information regarding the biological mechanism of action.

CONFLICT OF INTEREST

None declared.

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CASE SERIES

Coronary Artery Malformations Presenting as Acute Coronary Syndromes: A Case Series

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ABSTRACT

Coronary artery malformations are rare congenital abnormalities, which present non-specific symptoms such as atypical chest pain, malignant arrhythmia, or sudden cardiac death. The proper diagnosis of these abnormalities in emergency conditions can be very difficult, and noninvasive imaging techniques, such as computed tomography or magnetic resonance imaging, along with the gold standard represented by invasive coronary angiography, remain the most frequently used modalities for diagnosing these rare cases. We present four cases of coronary anomalies represented by an abnormal origin of the coronary arteries from the coronary ostium, presenting in emergency conditions with symptoms of acute myocardial infarction, which were diagnosed by urgent angiography.

Keywords: coronary artery malformation, coronary ostium, congenital heart diseases

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INTRODUCTION

Coronary artery malformations are rare congenital abnormalities, most of them consisting in an abnormal origin of a coronary artery, with or without clinical impact.[1] Due to their non-specific symptoms, such as atypical chest pain, malignant arrhythmia, or sudden cardiac death, caused by the reduction of blood flow in the coronary artery having an abnormal origin, the proper diagnosis of these abnormalities in emergency conditions can be very difficult.[2,3] Non-invasive imaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), along with the gold standard represented by invasive coronary angiography, remain the most frequently used modalities for diagnosing these rare cases.[4] The therapeutic algorithm is represented by conservative treatment (avoidance of heavy physical burden, use of beta-blockers), coronary angioplasty, or surgical intervention in the most severe cases.[5]

In this paper we present four cases of coronary anomalies represented by an abnormal origin of the coronary arteries from the coronary ostium, presenting in emergency conditions with symptoms of acute myocardial infarction, which were diagnosed by urgent angiography.

The patients agreed to the publication of their data and the institution where the patients had been admitted approved the publication of the cases.

CASE 1

A 66-year-old female patient with a history of hypertension and diabetes, with recurrent episodes of chest pain, dyspnea, and fatigue in the past, was admitted to

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our department accusing intense angina and diaphoresis. Physical examination was normal, and electrocardiography showed sinus rhythm with negative T waves in the inferior leads DII, DIII, aVF. The laboratory tests revealed a minimal elevation of creatine phosphokinase (CK 359 U/L). Echocardiography parameters were in normal ranges. However, the left ventricle was hypertrophic, with a left ventricular ejection fraction of 53%. Due to the presence of recurrent angina symptoms, an invasive angiography was performed in order to assess possible coronary lesions and revealed the separate origin of the left descendent artery (LAD) and left circumflex artery (LCX) from two different coronary ostia located in the left side of the Valsalva sinus (Figure 1A). The LCX presented an ostial lesion and the LAD multiple, non-significant lesions, while the right coronary artery (RCA) was hypoplastic (Figure 1B). The patient received antiplatelets, statins, and diuretics, and was recommended to avoid intensive physical exertion. At the 6-month follow-up, the evolution of the patient was favorable, with significant regression of the symptoms.

CASE 2

A 63-year-old female patient, without any cardiovascular history, presented to our emergency room with intensive chest pain started 10 hours prior to presentation, associated with dyspnea and nausea. Electrocardiography revealed sinus rhythm and elevation of the ST segment with 2 mm in the right chest leads (V7, V8, V9). Coronary angiography performed in emergency revealed the common origin of the RCA and LCX from the right Valsalva sinus, with an acute thrombotic occlusion of the LCX (Figure 2A) and a severe lesion on the distal segment of the LAD. Two drug-eluting stents were implanted in the LCX and in the distal part of the LAD, with optimal TIMI III flow (Figure 2B). During the procedure the patient received 100 IU/kg/min heparin and the loading dose of eptifibatide, followed by continuous administration on the station. The next day after the intervention, she presented altered neurological status and obnubilation associated with diaphoresis. The emergency CT revealed a hemorrhagic stroke, therefore anticoagulation therapy was interrupted. During hospitalization, the cardiologic status remained stable. The patient was discharged with recommendations and a therapeutic plan (antiplatelet, statin, beta-blocker), and the neurological status of the patient presented a slow, but favorable evolution.

CASE 3

A 60-year-old male, smoker, with a history of diabetes and dyslipidemia, presented with unstable angina that was relieved by administration of nitroglycerin, associ-

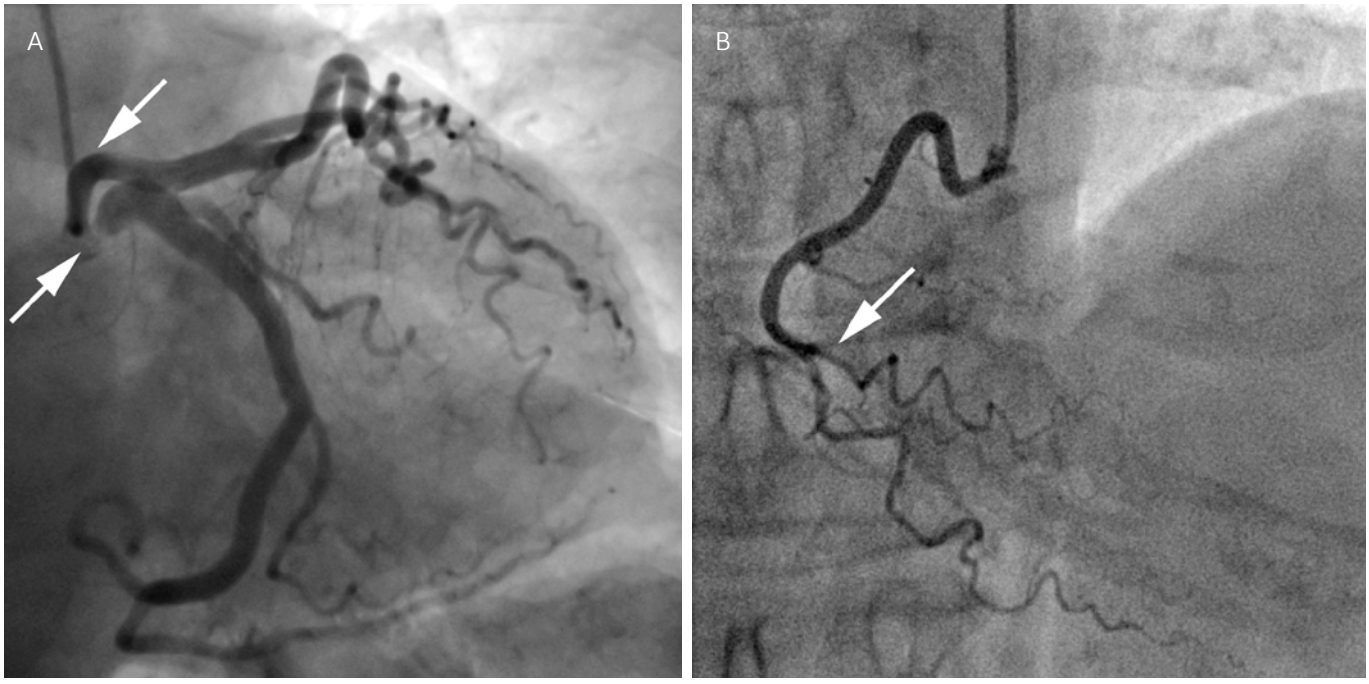

FIGURE 1. Case 1. **A** – Separate origin of the LAD and LCX from two different coronary ostia located in the left side of the Valsalva sinus (arrow); **B** – Hypoplastic RCA

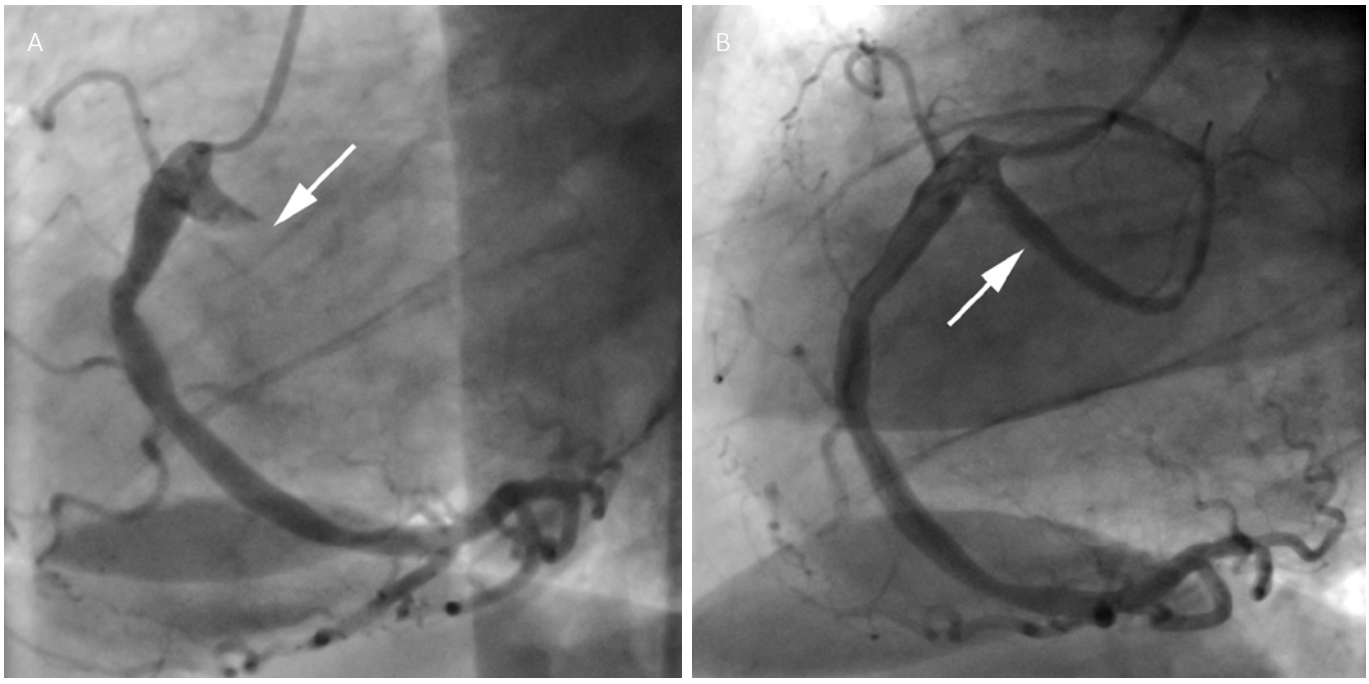

FIGURE 2. Case 2. **A** – Common origin of the RCA and LCX from the right Valsalva sinus with an acute thrombotic occlusion of the LCX (arrow); **B** – LCX recanalization after PCI and implantation of a drug eluting stent (arrow)

ated with vegetative symptoms. The patient reported that the chest pain started a week ago, during medium physical effort. The electrocardiogram showed negative T waves in the inferior leads, and echocardiography parameters were within normal ranges, with a good left ventricular ejection fraction. Coronary angiography showed the separate origin of the LAD and LCX, with lesions about 30–40% on the coronary arteries, without any hemodynamic significance

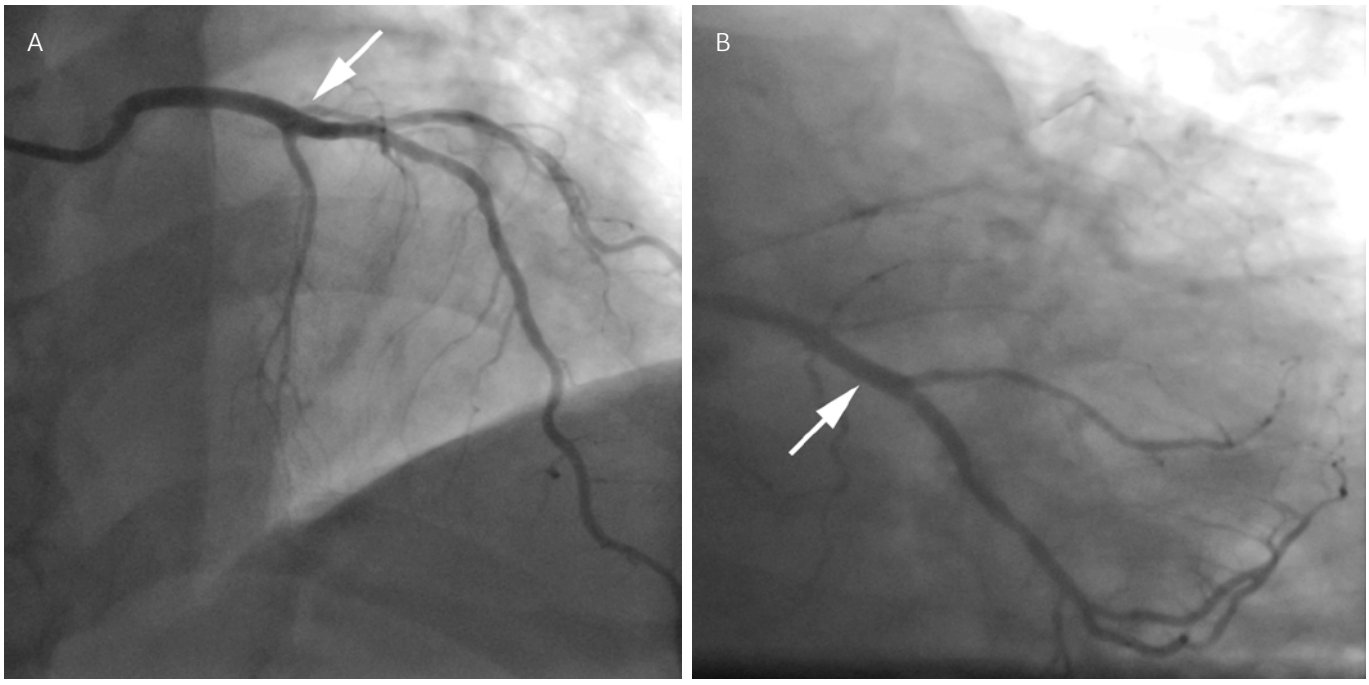

FIGURE 3. Case 3. Separate origin of the LAD and LCX from two different coronary ostia located in the left side of the Valsalva sinus. **A** – origin of LAD from a separate ostium (arrow); **B** – origin of the LCX from a separate ostium (arrow)

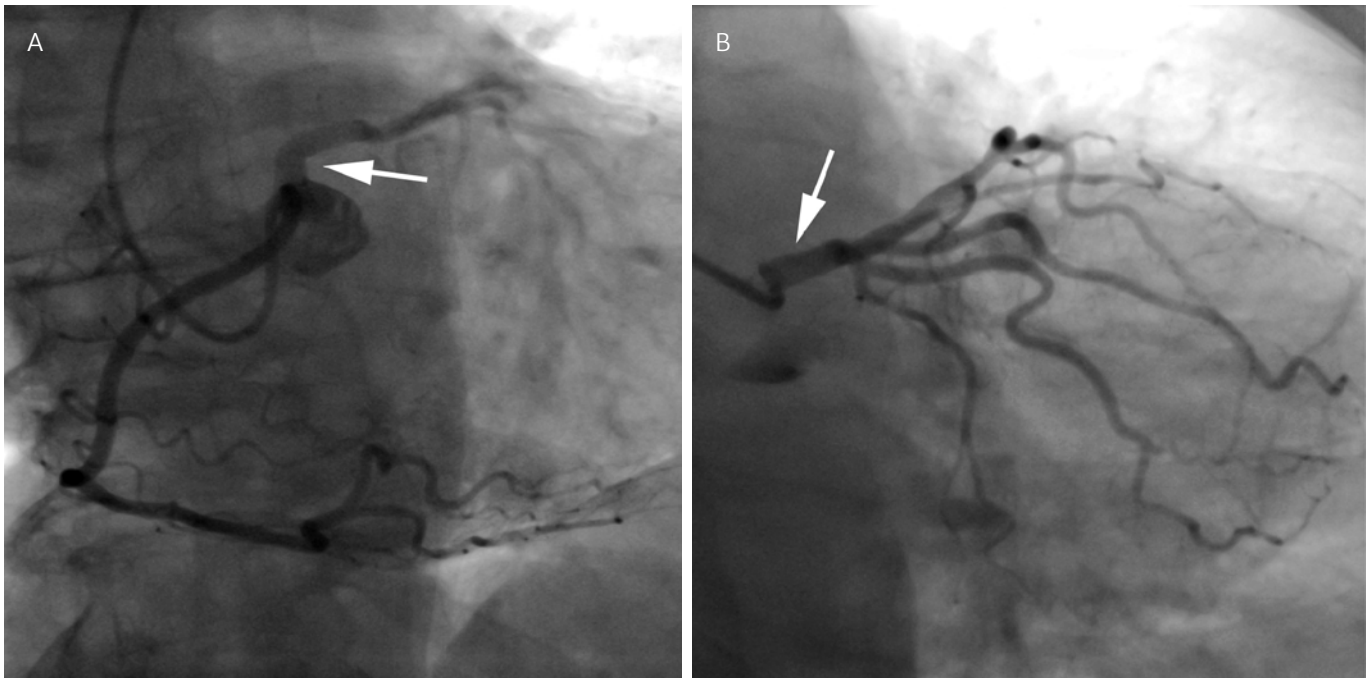

FIGURE 4. Case 4. **A** – Ectopic origin of the RCA from the left aortic sinus (arrow); **B** – No significant lesions on the LAD

(Figure 3A and 3B). Treatment consisted in beta-blockers and statins, and the patient presented a favorable evolution during regular medical follow-up.

CASE 4

The fourth case involves a 66-year-old, obese, smoker female patient, who presented at the emergency department with an intense retrosternal chest pain, started 7 hours prior to presentation. The electrocardiogram was not modified, and there were no elevations in serum levels of cardiac enzymes. Coronary angiography detected an ectopic origin of the RCA from the left aortic Valsalva sinus (Figure 4A) and no lesions on the LAD (Figure 4B). The patient received medical therapy and entered a rigorous follow-up program.

DISCUSSIONS

Coronary artery anomalies are rare forms of cardiac malformations that refer to the origin or the course of the artery.[6] In most cases, they are underdiagnosed due to the lack of symptoms, and the detection occurs incidentally, in 0.3–0.6% of the cases during coronary angiography examination and about 1% on routine autopsy.[2] The most frequent symptoms that can occur are thoracic chest pain due to myocardial hypoxia, myocardial ischemia, syncope, or malignant arrhythmias. This condition can be associated with other cardiac diseases such as coronary artery lesions or heart valve disorders.[3] Myocardial necrosis, congestive heart failure, or sudden cardiac death represent the most severe complications that can occur in this type of diseases.[7]

In certain cases, the diagnosis of this particular form can represent a challenge due to the fact that most patients are asymptomatic. This type of abnormality is usual associated with a poor tissular perfusion that can be responsible for hypoxia and myocardial ischemia.[3] In these cases, hypoxia is related to intramural hypoplasia or to the external compression of the vessel.[8] Whenever a coronary abnormality is diagnosed, it is extremely important to identify the exact origin of the abnormality and its relationships with other cardiac structures. The gold standard method for the diagnosis of these particular forms remains coronary angiography. Coronary CT offers the finest spatial resolution for the assessment of these lesions, being able to reveal the localization of the malformations and to assess their complexity.[2,9] Magnetic resonance imaging also provides safe information; however, the small size of the vessels, the impact of breathing, or the rapid motion of the coronaries can represent limiting factors for this examination.[10]

In some cases of coronary anomalies that involve the right side, percutaneous interventions and stenting can be recommended in the presence of the following criteria: high risk for sudden death, significant intramural

hypoplasia, documented reversible ischemia. The use of intravascular ultrasound before and during angioplasty is highly recommended in this type of cases.[11]

According to the literature, severe forms of coronary anomalies located in the left side of the heart might require surgical correction, consisting in re-implantation of the ectopic coronary in the aortic sinus, or osteoplasty, which creates a new ostium at the end of the intramural segment.[12]

All four patients presented in this case series were asymptomatic in their history and accused intense chest pain at presentation in the emergency room. Coronary angiography, indicated by the symptoms suggestive for acute myocardial infarction, identified the etiology of the chest pain and led to appropriate therapy in each case.

CONCLUSIONS

Coronary artery malformations are extremely rare abnormalities that are frequently underdiagnosed. Depending on the type of malformation and the associated lesions, the clinical presentation may vary from asymptomatic conditions to sudden cardiac death. As a consequence of the non-specific symptoms, the diagnosis can be challenging in many cases. Coronary angiography, as the gold standard imaging diagnostic technique, is able to reveal the type of malformation and its complexity, and can guide therapy in these rare diseases.

CONFLICT OF INTEREST

Nothing to declare.

ABBREVIATIONS

LAD left anterior descending artery
LCX left circumflex artery
RCA right coronary artery
PCI percutaneous coronary intervention

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CASE REPORT

Symptomatic Coronary-Pulmonary Fistula Revealed with Coronary CT Angiography

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ABSTRACT

Introduction: Coronary artery fistulas are usually incidental findings and rarely cause any clinical symptoms. **Case presentation:** In this case a coronary pulmonary fistula was revealed by coronary CT angiography and as it was considered responsible for the patients' symptoms, its' closure was performed during percutaneous coronary intervention. **Conclusion:** The noninvasive coronary CT angiography is a valuable examination in the diagnosis of coronary anomalies.

Keywords: coronary CTA, invasive coronary angiography, coronary artery fistula, atypical chest pain

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INTRODUCTION

Coronary artery fistulas (CAF) are abnormal connections between the coronary artery system and cardiac chambers or thoracic vascular structures. Most patients with CAF are asymptomatic, and fistulas are typically found incidentally during imaging studies. However, in some cases CAFs may cause serious conditions for the patient, such as myocardial ischemia, right heart failure, arrhythmias, or even sudden death, therefore is important to make the correct diagnosis.

CASE PRESENTATION

A 64-year-old man was scheduled for coronary CT angiography (CTA) due to atypical chest pain and intermediate cardiovascular risk. Coronary CTA identified a partially calcified plaque with high-risk features (low attenuation, positive remodeling, and napkin-ring sign) causing severe (70%) luminal stenosis in the mid segment of the left anterior descending (LAD) coronary artery. Additionally, several small tortuous branches were visualized connecting the septal branch of the LAD with the pulmonary artery (Figure 1).

The patient underwent invasive coronary angiography (ICA), which confirmed a coronary fistula between the LAD-septal branch and the pulmonary trunk (Figure 2). Fractional flow reserve (FFR) measurement was performed, which verified the significant stenosis in the mid LAD segment. Accordingly, percutaneous coronary intervention (PCI) was performed with a drug-eluting stent. Post-PCI FFR value was normal; however, after nitroglycerine administration, a significant decrease in the FFR

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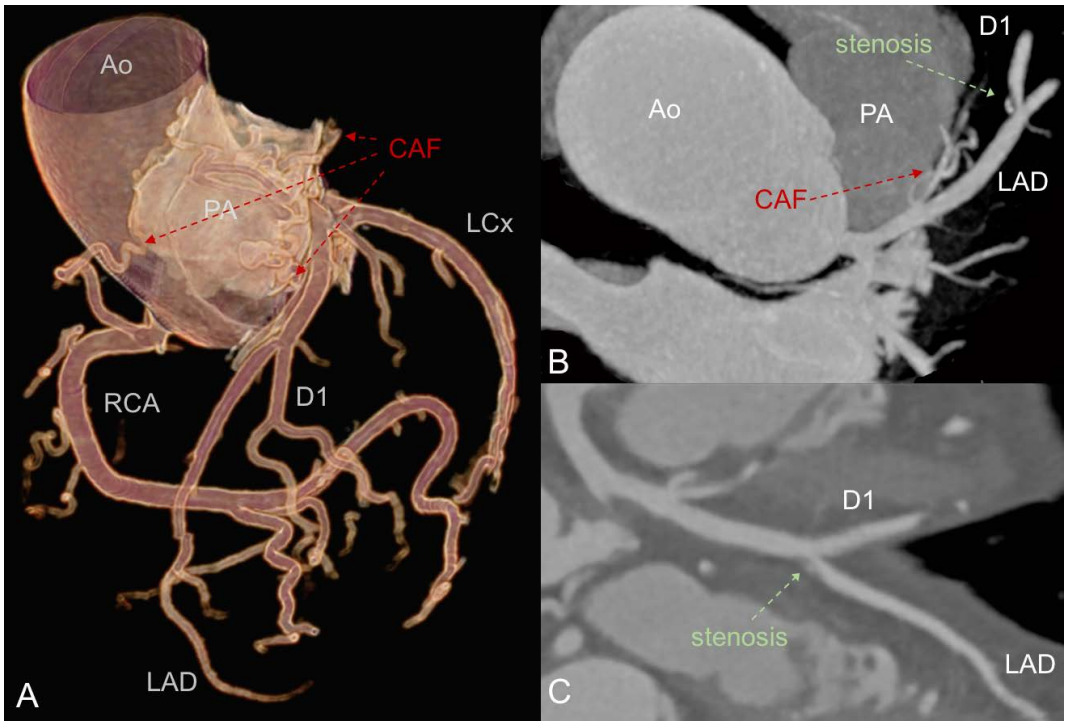

FIGURE 1. Coronary CT angiography. **A** – 3D volume rendered image of the coronary tree. Red arrows indicate the coronary artery fistula connecting the first septal branch of the LAD to the pulmonary trunk. **B, C** – Coronary CTA images with multiplanar reconstruction. On Panel **B** small branches, susceptible for coronary fistula can be seen (red arrow). Panel **C** illustrates a high-grade stenotic, partially calcified plaque in the mid LAD segment (green arrow).

value was observed, presumably associated with the dilatation of the fistula. Therefore, coil embolization of the fistula was performed (Figure 3). The FFR value normalized, and the patient became asymptomatic.

Twelve months later, due to the reoccurrence of his symptoms, the patient underwent control ICA, which excluded any significant restenosis in the mid LAD stent. However, the complete reopening of the coronary fistula was detected. A second attempt for the coil embolization was made; however, due to embolization of the coil during deployment in the LAD-septal branch, it partially shifted into the LAD. Consequently, a coronary artery stent was

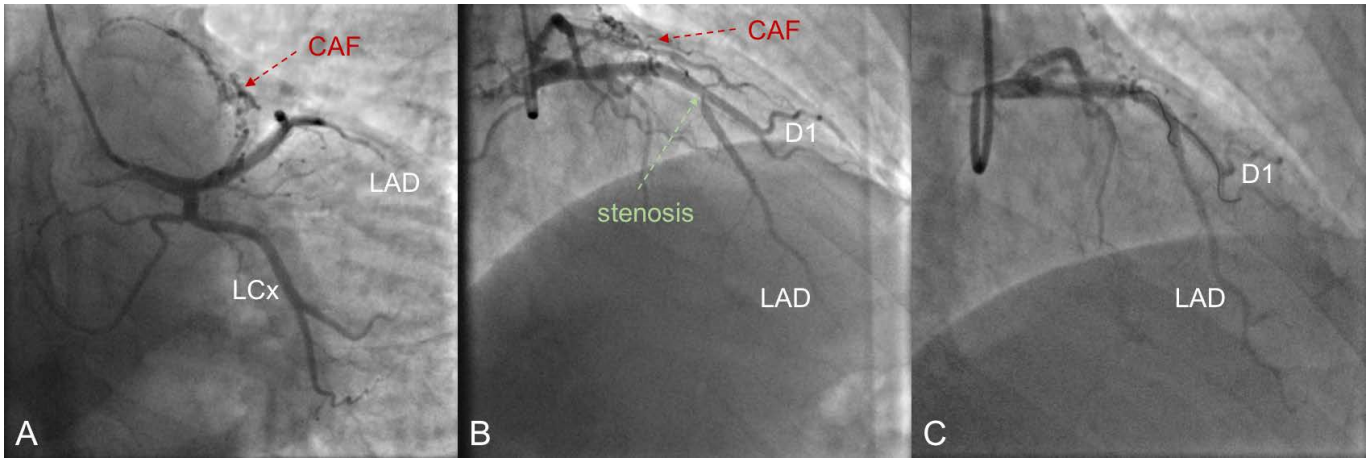

FIGURE 2. Invasive coronary angiography and percutaneous coronary intervention. **A** shows the coronary artery fistula (red arrow) originating from the first septal branch of the LAD. **B** illustrates the significant stenosis in the LAD-diagonal branch bifurcation (green arrow). **C** – Restored lumen of the LAD after stent implantation.

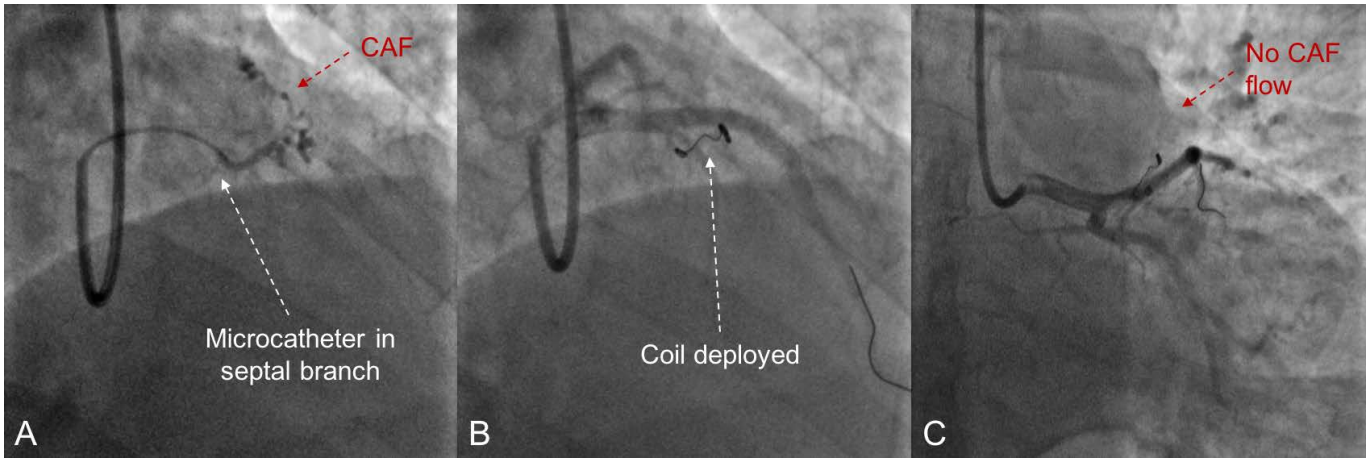

FIGURE 3. Coil embolization of the coronary fistula. **A** – Microcatheter placement in the septal branch of the LAD; **B** – Coil placement in the coronary fistula; **C** – No flow is present in the coronary-pulmonary fistula after successful coil embolization.

placed in the LAD to fix the coil position and prevent the occlusion of the LAD lumen. The stent deposition was successful, and no refill of the CAF was observed. Optical coherence tomography (OCT) imaging was performed, which confirmed the good positioning of the LAD stent (Figure 4). The patient was discharged symptomless after the procedure.

The patient agreed to the publication of his data, and the institution where the patient had been admitted approved the publication of the case.

DISCUSSION

Coronary artery fistulas (CAF) are direct precapillary communications between the coronary arteries, cardiac chambers, or other vessels.[1–4] CAFs can originate from the left and right coronary system, and the most common termination sites are the right ventricle, right atrium, and the pulmonary artery.[2,3] CAFs usually have small calibers and do not have any hemodynamic impact.[2,3] Rarely, large fistulas may cause symptoms and serious conditions for the patient.[3] Invasive coronary angiography is the method of choice to identify coronary fistulas. However, due to the increasing number of coronary CT angiography used on patients with chest pain, CAFs and other coronary anomalies are more frequently diagnosed.[2] Spontaneous closure of these fistulas may happen, but surgical or transcatheter closure of the CAF may also be indicated in symptomatic patients with large, hemodynamically significant fistulas.[4,5]

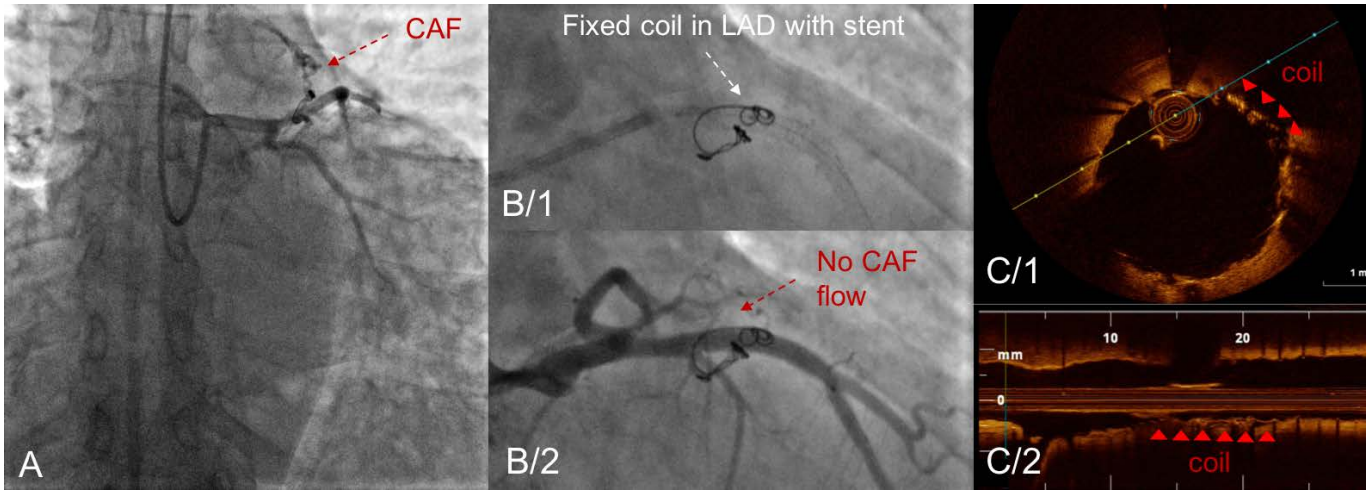

FIGURE 4. Second coronary angiography due to reoccurrence of patients' symptoms. **A** – Reopened coronary fistula (red arrow). **B/1** – Coil stabilization with a coronary stent in the LAD; **B/2** – Complete coronary flow in the LAD with no refill of the fistula after coil embolization; **C/1** –Cross-sectional OCT image of the coil in the LAD (red arrows); **C/2** –Longitudinal OCT image of the LAD (red arrows indicate the coil).

CONCLUSION

Our case underlines the potential of noninvasive coronary CTA to detect not only significant coronary luminal stenosis, but also extracoronary findings, such as fistulas as an underlying cause for patients' chest pain.

CONFLICT OF INTEREST

None declared.

ABBREVIATIONS

CAF coronary artery fistula
CTA computed tomography angiography
FFR fractional flow reserve
ICA invasive coronary angiography
LAD left anterior descending coronary artery
LCx left circumflex coronary artery
OCT optical coherence tomography
PCI percutaneous coronary intervention
RCA right coronary artery

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INSTRUCTIUNI ABREVIATE DE PRESCRIERE

Denumirea comercială a medicamentului: Brilique 90 mg comprimate filmate. **Compoziția calitativă și cantitativă:** ticagrelor 90 mg. **Forma farmaceutică:** Comprimat filmat (comprimat). Comprimate rotunde, biconvexe, de culoare galbenă, marcate cu '90' deasupra "T"pe una dintre fețe și plane pe cealaltă față. **Date Clinice: Indicații terapeutice:** administrat în asociere cu acid acetilsalicilic (AAS), este indicat pentru prevenția evenimentelor aterotrombotice la pacienții adulți cu sindrom coronarian acut (SCA) sau istoric de infarct miocardic (IM) și risc crescut de apariție a unui eveniment aterotrombotic. **Doze și mod de administrare:** Doze: Pacienții care utilizează Brilique trebuie să utilizeze zilnic și AAS în doză mică 75-150 mg, ca tratament de întreținere, cu excepția cazurilor în care există contraindicații specifice. *Sindrom coronarian acut:* Tratamentul se inițiaza cu o doză unică de încărcare de 180 mg (două comprimate de 90 mg) și se continua cu 90 mg de două ori pe zi, tratamentul este recomandat pe o perioadă de 12 luni la pacienții cu SCA, cu excepția cazului în care întreruperea administrării este indicată clinic. *Istoric de infarct miocardic:* Brilique 60 mg de două ori pe zi este doza recomandată când este necesară continuarea tratamentului la pacienți cu istoric de IM de cel puțin un an și risc crescut de apariție a unui eveniment aterotrombotic. Tratamentul poate fi început, fără perioadă de întrerupere, în continuarea tratamentului inițial de un an cu Brilique 90 mg sau cu alt inhibitor al receptorilor de adenozin difosfat (ADP) la pacienții cu SCA cu risc crescut de apariție a unui eveniment aterotrombotic. De asemenea, tratamentul poate fi inițiat într-o perioadă de până la 2 ani după IM sau de în cursul unui an după oprirea tratamentului anterior cu un inhibitor al receptorilor ADP. Există date limitate privind eficacitatea și siguranța Brilique după 3 ani de tratament extins. Dacă este necesară schimbarea tratamentului, prima doză de Brilique trebuie administrată în decurs de 24 de ore după utilizarea ultimei doze din celălalt medicament antiplachetar. *Omiterea dozei:* Trebuie evitată omisiunea administrării dozelor. *Grupe speciale de pacienți: Vârstnici:* Nu este necesară ajustarea dozei la vârstnici. *Insuficiență renală:* Nu este necesară ajustarea Pacienților care efectuează ședințe de dializă renală nu le este recomandat. *Insuficiență hepatică:* Ticagrelor este contraindicat. La pacienții cu insuficiență hepatică moderată trebuie utilizat cu prudență. Nu este necesară ajustarea dozei la pacienții cu insuficiență hepatică ușoară. *Copii și adolescenți:* Siguranța și eficacitatea ticagrelor la copiii cu vârsta sub 18 ani nu au fost stabilite. Nu există date disponibile. Mod de administrare: Pentru administrare orală. Brilique poate fi administrat cu sau fără alimente. Pentru pacienții care nu pot înghiți comprimatul/comprimatele în întregime, comprimatele pot fi zdrobite până la o pulbere fină, dispersate în jumătate de pahar cu apă, care se bea imediat. Paharul trebuie clătit cu o cantitate de apă corespunzătoare unei jumătăți de pahar, iar conținutul trebuie băut. Amestecul poate fi administrat, de asemenea printr-un tub nazogastric (CH8 sau mai mare). **Atenționări și precauții speciale pentru utilizare:** Risc hemoragic: Utilizarea ticagrelor la pacienți cunoscuți cu risc crescut de hemoragie trebuie evaluată în raport cu beneficiul legat de prevenirea evenimentelor aterotrombotice. Ticagrelor trebuie utilizat cu precauție la următoarele categorii de pacienți: 1. cu predispoziție la sângerări (de exemplu ca urmare a unui traumatism recent, intervenție chirurgicală recentă, tulburări de coagulare, sângerare intracraniană sau gastrointestinală activă sau recentă). Utilizarea este contraindicată la pacienți cu hemoragii patologice active, la cei cu antecedente de hemoragie intracraniană și la pacienții cu insuficiență hepatică severă. 2. Carora li se administrează concomitent medicamente care pot crește riscul de sângerare (de exemplu medicamente antiinflamatoare nesteroidiene (AINS), anticoagulante orale și/sau fibrinolitice) în următoarele 24 de ore de la administrarea ticagrelor). Este puțin probabil ca desmopresina să fie eficace în tratamentul evenimentelor hemoragice simptomatice. Tratamentul antifibrinolitic (acid aminocaproic sau acid tranexamic) și/sau factorul recombinant VIIa pot accentua hemostaza. Administrarea ticagrelor poate fi reluată după identificarea și controlarea cauzei sângerării. Intervenții chirurgicale: Pacienții trebuie sfătuiți să informeze medicii și dentiștii că utilizează ticagrelor înainte de programarea oricărei intervenții chirurgicale și înainte de administrarea oricărui medicament nou. Dacă un pacient urmează să fie supus unei intervenții chirurgicale elective și nu este dorit efectul antiplachetar, administrarea ticagrelor trebuie întreruptă cu 7 zile înainte de intervenție. Pacienți cu accident vascular cerebral (AVC) ischemic în antecedente: pot fi tratați cu Brilique pe o perioadă de până la 12 luni (studiul PLATO) dar nu mai mare. Insuficiență hepatică: Utilizarea este contraindicată la pacienții cu insuficiență hepatică severă. La pacienți cu insuficiență hepatică moderată se recomandă prudență în administrare. Pacienți cu risc de evenimente bradicardice: Având în vedere experiența clinică limitată, ticagrelor trebuie utilizat cu prudență la acești pacienți. În plus, trebuie manifestată prudență când se administrează ticagrelor concomitent cu medicamente cunoscute că produc bradicardie. În timpul substudiului Holter din PLATO, mai mulți pacienți tratați cu ticagrelor au avut pauze ventriculare >3 secunde în faza acută a SCA comparativ cu clopidogrel. Creșterea frecvenței pauzelor ventriculare depistate prin Holter sub tratament cu ticagrelor a fost mai mare la pacienții cu insuficiență cardiacă cronică (ICC) comparativ cu populația generală a studiului în faza acută a SCA, dar nu și la o lună de tratament cu ticagrelor sau comparativ cu clopidogrel. Nu au existat consecințe clinice negative asociate cu acest dezechilibru (incluzând sincopă sau implantare de pacemaker) în această grupă de pacienți. Dispnee: Dispneea a fost raportată la pacienții tratați cu ticagrelor. De regulă, intensitatea dispneei este ușoară până la moderată și frecvent dispare fără să fie necesară întreruperea tratamentului. Pacienții cu astm bronșic/bronhopneumopatie obstructivă cronică (BPOC) pot prezenta un risc absolut de dispnee crescut sub tratament cu ticagrelor. Ticagrelor trebuie utilizat cu prudență la pacienții cu antecedente de astm bronșic și/sau BPOC. Creșteri ale creatininemiei: Concentrațiile de creatinină pot crește în timpul tratamentului cu ticagrelor. Mecanismul nu a fost elucidat. Funcția renală trebuie verificată conform practicii medicale curente. De asemenea, la pacienții cu SCA se recomandă ca funcția renală să fie verificată la o lună după inițierea tratamentului, acordându-se atenție specială pacienților cu vârsta ≥ 75 de ani, pacienților cu insuficiență renală moderată/severă și celor cărora li se administrează concomitent tratament cu un blocant al receptorilor angiotensinei (BRA). Creșterea acidului uric. Se recomandă prudență la pacienții cu antecedente de hiperuricemie sau artrită gutoasă. Ca măsură de precauție, utilizarea ticagrelor la pacienții cu nefropatie urică este descurajată. Altele: Administrarea concomitentă a ticagrelor și doze de menținere crescute de AAS (>300 mg) nu este recomandată. *Întreruperea prematură:* Trebuie evitată întreruperea prematură a tratamentului. **Fertilitatea, sarcina și alăptarea:** Femei aflate la vârsta fertilă: Sarcina: Nu este recomandată administrarea ticagrelor în timpul sarcinii. Alăptarea: Nu poate fi exclus un risc pentru nou-născuți/sugari. Decizia de a întrerupe alăptarea sau de a întrerupe/nu administra ticagrelor trebuie luată ținând cont de beneficiul alăptării pentru copil și beneficiul tratamentului pentru femeie **Reacții adverse:** Rezumatul profilului de siguranță: Cele mai frecvent raportate reacții adverse la pacienții tratați cu ticagrelor au fost sângerare și dispnee. **Foarte frecvente:** Tulburări sanguine induse de sângerări, Hiperuricemie, Dispnee. **Frecvente:** Gută/artrită gutoasă, Amețeli, sincopă, cefalee, Vertij, Hipotensiune arterială, Hemoragii la nivelul sistemului respirator, Hemoragie gastrointestinală, Diaree, Greață, Dispepsie, Constipație, Hemoragii subcutanate sau dermice, Erupție cutanată tranzitorie, Prurit, Hemoragii la nivelul tractului urinar, Creșterea concentrației plasmatice a creatininei, Hemoragii post-procedurale, hemoragii traumatice. **Mai puțin frecvente:** Hemoragii tumorale, Hipersensibilitate, inclusiv angioedem, Confuzie, Hemoragie intracraniană, Hemoragie oculară Hemoragie otică, Hemoragie retroperitoneală. Hemoragii musculare Hemoragii la nivelul aparatului genital. Raportarea reacțiilor adverse suspectate: Raportarea reacțiilor adverse suspectate după autorizarea medicamentului este importantă. Acest lucru permite monitorizarea continuă a raportului beneficiu/risc al medicamentului. Profesioniștii din domeniul sănătății sunt rugați să raporteze orice reacție adversă suspectată la: Agenția Națională a Medicamentului și a Dispozitivelor Medicale Str. Aviator Sănătescu nr. 48, sector 1, București 011478- RO, Tel: + 4 0757 117 259, Fax: +4 0213 163 497, e-mail: adr@anm.ro. **Deținătorul autorizației de punere pe piață**: AstraZeneca AB, S-151 85, Södertälje, Suedia; **Data revizuirii textului: Februarie 2016. Se eliberează numai pe bază de prescripție medicală PRF. Pentru informații complete de prescriere vă rugăm contactați: AstraZeneca Pharma SRL, Bucharest Business Park corp D, et.1, str. Menuetului nr.12, 013713, București. Tel. +40 21 317 60 41; Fax: +40 21 317 60 53.**

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CASE REPORT

Intracoronary Imaging in the Management of a Complex and Recurrent Acute Coronary Syndrome Associated With Multiple Comorbidities. A Case Report

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ABSTRACT

Coronary artery disease represents a major cause of morbidity and mortality around the world. Unstable angina pectoris is a serious manifestation of ischemic heart disease and represents an acute condition caused by the narrowing of the coronary lumen as the result of an atheromatous plaque formation. In most cases the trigger of this process is represented by the rupture of a plaque that has become vulnerable or unstable. The first-line intracoronary imaging technique for the evaluation of plaque vulnerability is optical coherence tomography, which can measure the thickness of the fibrous cap (a significant predictor of plaque vulnerability) and can also assess other characteristics of plaque vulnerability (macrophage infiltration, lipid pool, intracoronary thrombus, or neointimal rupture). We present the case of a 67-year-old male with symptoms suggestive of unstable angina pectoris, caused by the presence of a vulnerable plaque on the left main coronary artery, where optical coherence tomography had a significant contribution in identifying the etiology of chest pain.

Keywords: acute coronary syndrome, vulnerable plaque, optical coherence tomography, coronary stenosis, angiography

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INTRODUCTION

Coronary artery disease (CAD) represents a major cause of morbidity and mortality around the world, contributing to the death of an estimated 13% of the global population.[1,2] Unstable angina pectoris (UA) is a serious manifestation of ischemic heart disease and represents an acute condition produced by the narrowing of the coronary lumen as the result of an atheromatous plaque formation. The majority of UA cases are triggered by the rupture of a previously stable coronary plaque that has become vulnerable or unstable. Coronary plaques have often been studied in relation to their location, severity, and functional impact. At present, all modifications in the structure of a plaque can be analyzed using newly developed imaging techniques.[3,4] Over the past decades, several major advances in the diagnosis and treatment of ischemic heart disease have been encountered; nevertheless, invasive coronary angiography remains the gold standard for diagnosing a coronary

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artery stenosis. Since its outset more than 40 years ago, several adjunctive techniques have been initiated in order to optimize the overall diagnostic accuracy and also to prevent the inter- and intra-observer variability related to the estimation of lesion severity. A novel invasive technology dedicated either to evaluate the physiological significance or the anatomical and morphological features of coronary lesions, optical coherence tomography (OCT), enriches the arsenal of diagnostic tools available to an interventional cardiologist. As an alternative to these invasive methods, noninvasive imaging techniques, such as multi-detector-row computed tomography (MDCT) or magnetic resonance imaging (MRI), have been developed, currently serving as the most promising noninvasive imaging tests for the diagnosis of coronary artery disease.[5]

In this paper, we present the case of a patient with multiple associated comorbidities, admitted to the cardiology clinic several times for multiple recurrent acute episodes of ischemic coronary artery disease, where modern imaging technologies allowed the establishment of a complex diagnosis and the initiation of appropriate therapeutic procedures.

CASE REPORT

A 67-year-old male, with a history of multivessel coronary artery disease associated with type 2 non-insulin-dependent diabetes mellitus and stage 3 chronic kidney disease, was admitted to the Cardio Med Medical Center in Tîrgu Mureș, Romania, presenting constrictive chest pain with sudden onset, lasting more than 20 minutes, radiating in the left upper limb, and associated with rest dyspnea and one episode of Adam-Stokes syncope.

Seven years prior to this presentation, the patient underwent a coronary angiography, which revealed an acute thrombotic stenosis on the anterior descending coronary artery (Figure 1A), treated successfully by the implantation of a drug-eluting stent with optimal results and TIMI III post-procedural flow (Figure 1B).

The patient gave informed consent allowing the publication of his data, and the institution where the patient had been admitted approved the publication of the case.

In addition to the typical signs and symptoms of acute coronary syndrome (ACS) mentioned above, physical examination revealed stage 2 arterial hypertension (blood pressure value 160/100 mmHg) and chronic heart failure.

Laboratory investigations showed elevated levels of serum biomarkers characterizing hepatic, renal, and pancreatic function such as: ALAT: 56 IU/L, ASAT: 123 IU/L, eGFR: 48.8–54.6 mL/min/1.73 m2 (Cockroft-Gault formula), blood glucose: 220 mg/dL. The electrocardiogram showed sinus rhythm, intermediate QRS axis, a heart frequency of 64 beats/minute, and the presence of a major right bundle branch block.

Coronary angiography revealed a minimal in-stent restenosis in the previously implanted stent and the development of new lesions in all three major coronary arteries: a 70% stenosis in the distal part of the left main coronary

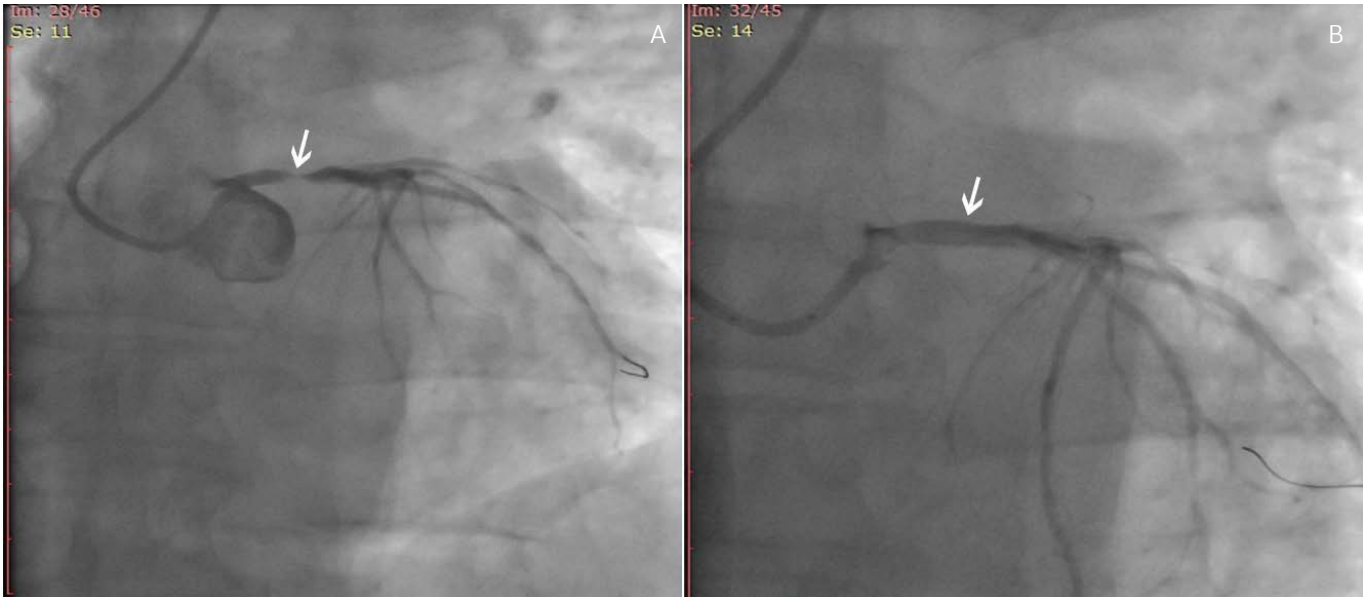

FIGURE 1. Coronary angiography. **A** – significant stenosis in the left coronary artery (arrow); **B** – post-intervention aspect, with no residual stenosis (arrow)

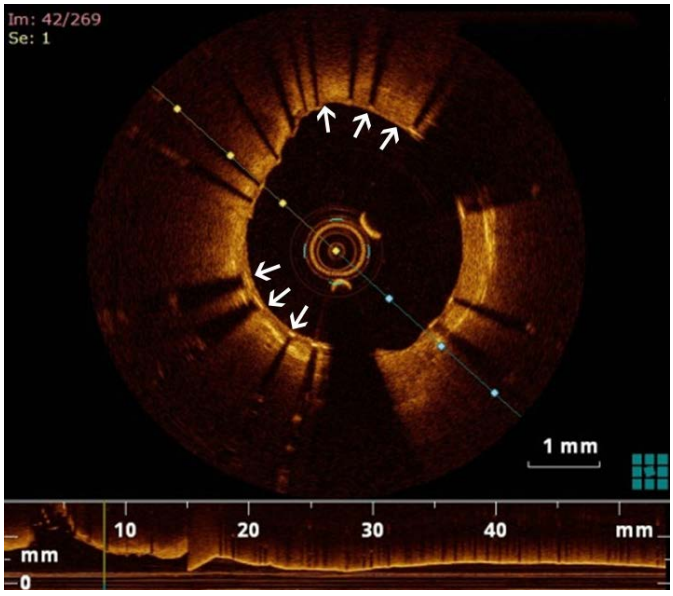

FIGURE 2. Optical coherence imaging showing a coronary stent well apposed to the arterial wall, with no signs of in-stent restenosis (arrows)

artery (Figure 1A), a 50% stenosis on the left anterior descending coronary (LAD), an ostial stenosis of the intermediary branch and a 70% long stenosis of the proximal right coronary artery.

The patient received interventional treatment consisting in the implantation of a 3.5 × 12 mm drug-eluting stent in the left main coronary artery (Figure 1B), a 2.75 × 15 mm drug-eluting stent in the intermediary branch, and a 3 × 23 mm drug-eluting stent in the right coronary artery, with optimal results and TIMI III flow in all territories. The lesion in the LAD remained untreated as it was not hemodynamically significant.

Following the interventional treatment, the patient was treated with anti-ischemic drugs, lipid-lowering drugs, diuretics, and antiarrhythmic drugs, with a favorable evolution.

At the 1-year follow-up, the patient reported the onset of a new chest pain for which he underwent an MRI study, an echocardiographic assessment, and a new coronary angiography. Despite several myocardial ischemic events, MRI showed no evidence of myocardial fibrosis of the left ventricle, and all structural and functional parameters of the myocardium were within normal range. Echocardiography revealed a calcified posterior mitral ring, a stage I/II mitral regurgitation, a stage I aortic regurgitation, lowered contractility of the left ventricle, decreased motility of the lateral wall of the left ventricle, and increased echogenicity of the posterior part of the pericardium. Coronary angiography identified new lesions in the coronary tree, however not significant, namely a 50% stenosis in the third segment of the anterior descending coronary artery and a minimal in-stent restenosis, without any indication for revascularization.

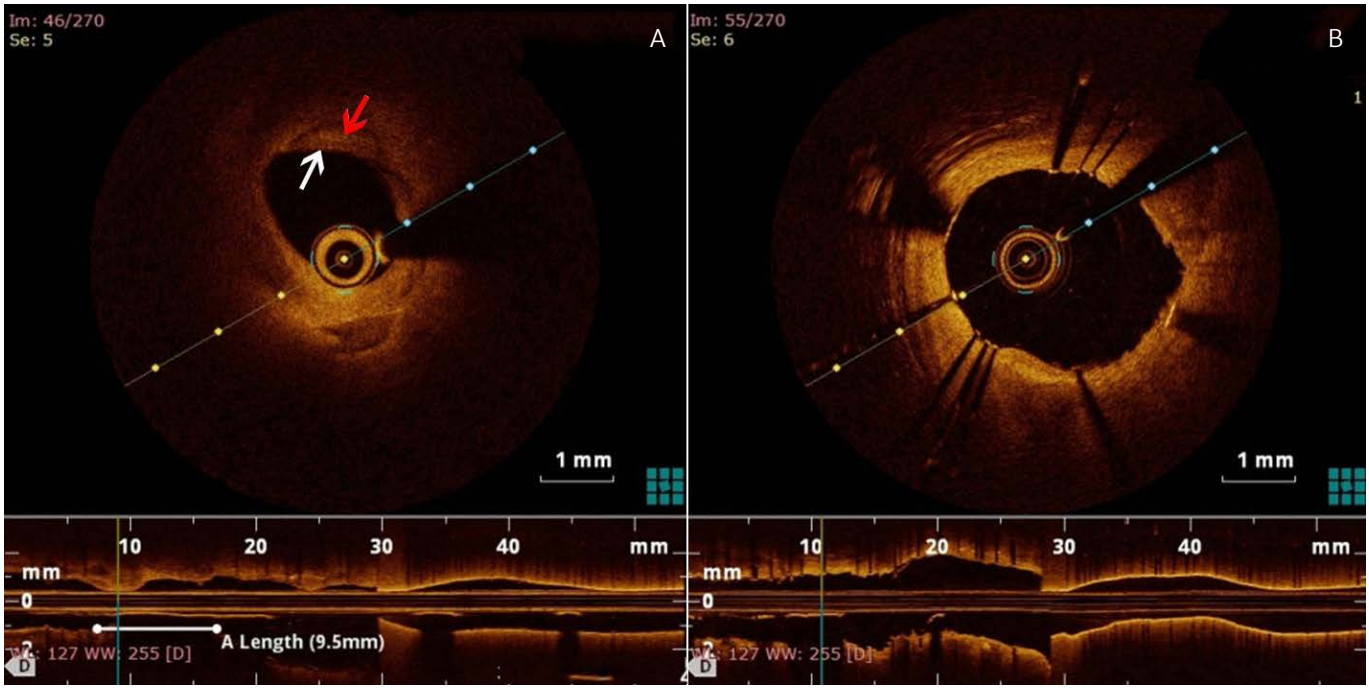

FIGURE 3. Optical coherence tomography distal to the stent implanted in the LAD. **A** – significant vulnerable coronary plaque (arrow); **B** – plaque treated by implantation of a coronary stent (arrow), well apposed to the vessel wall and with no plaque protrusion

After 3 weeks, the patient returned with acute chest pain, therefore a new coronary angiography was performed in emergency, which did not reveal any significant difference compared to the previous examination from an angiographic point of view. Therefore, an OCT examination was performed in order to evaluate in detail all new coronary lesions and to detect a possible vulnerable plaque responsible for the symptomatology. OCT showed a left main stent with well-apposed struts and good intimal coverage, without neointimal hyperplasia or neoatherosclerotic plaque inside the stented segment (Figure 2). At the same time, OCT visualized an atherosclerotic plaque in the proximal LAD, characterized by a large lipid pool and a thin fibrous cap of 18 microns, being therefore classified as a vulnerable plaque (Figure 3A).

As the plaque was characterized as unstable based on the OCT aspect and was highly symptomatic at the same time, the lesion was treated by implanting a new, 3 × 15 mm drug-eluting stent, preceded by balloon dilatation. Control OCT following stent placement showed good results, with compression of the plaque against the vessel wall, without luminal protrusion or edge dissections (Figure 3B).

At this stage, all therapeutic decisions were guided through OCT adjunctive imaging, leading to an optimal final outcome, with TIMI III flow in the entire coronary tree.

DISCUSSION

Acute coronary syndromes represent a major cause of cardiovascular morbidity and mortality, due to the significant reduction of myocardial perfusion, caused by the alteration in blood supply.[6] The vast majority of ACSs result from the progression of an atherosclerotic process, a chronic condition that leads to plaque formation.[7] The gold standard for emergency diagnosis in all ACSs is represented by coronary angiography, an invasive imaging technique that provides important information about the location and severity of the lesions, at the same time offering the possibility to perform the therapeutic intervention consisting in stent implantation immediately.

Besides coronary angiography, novel intracoronary imaging methods are able to provide a more accurate visualization of the lesion. OCT and intravascular ultrasound (IVUS) are two of the most widely used invasive imaging techniques, being useful in characterizing the vulnerability degree of coronary plaques, especially in patients who are considered to be at high risk of cardiovascular events.[8] As the patients continue to be exposed to the risk of cardiovascular events due to stent thrombosis, stent restenosis, or the development of new stenoses in the coronary tree even after treating the acute condition, the careful follow-up of all patients with a history of stent implantation is of extreme importance.[6] These new events can occur especially due to the dynamic nature of atheromatous plaque progression that can develop even faster after a stenting procedure.

OCT is an invasive imaging method that allows the interventionist to analyze the micromorphology of coronary arteries and the characteristics of restenotic tissue within the implanted stent.[6,9,10] At the same time, OCT presents a high resolution and numerous advantages for the study of coronary stents such as the possibility of quantifying the stent diameter and area, or detecting coronary artery dissections or stent malposition. Also, OCT is the first-choice technique to measure the thickness of the fibrous cap (a significant predictor of coronary plaque vulnerability), and to assess other characteristics of plaque vulnerability such as macrophage infiltration, lipid accretion, intracoronary thrombus, or neointimal rupture. Compared to IVUS, OCT can also recognize calcium deposited in the coronary artery wall. However, its main impediment is poor axial penetration, which precludes a precise estimation of the vascular remodeling process.[1,9,11]

Furthermore, OCT is frequently used as a guide during coronary angiography and in the assessment of vascular response following a percutaneous coronary implantation. The association of OCT to standard angiography can help to detect the vulnerable plaques, providing vital information about the therapeutic strategy to follow, balloon selection, or stent dimensions. In bifurcation lesions, the reconstruction of OCT data into 3D images can determine the location of the main artery and the position of the side artery, guiding the wire progression across a side branch over the stent insertion in the main artery.[10,11] In addition, OCT can appreciate several complications that can occur in the post-stenting period, such as incomplete stent strut coverage, in-stent restenosis, stent thrombosis, or neoatherosclerosis, providing relevant insights into the process of progression or endothelial healing over the stented area, incomplete stent apposition or stent strut coverage.[11,12]

However, OCT has some limitations in the assessment of coronary plaque vulnerability. The major limitation, which results from the limited penetration, is the inability to recognize the necrotic cores of the vulnerable coronary plaque. Moreover, OCT may require supplementary contrast use due to the fact that blood flow may influence OCT images.[11]

In our case, OCT was extremely useful for differentiating a possible intra-stent thrombosis or restenosis from a vulnerable plaque, as a cause for angina symptoms. The coronary angiography aspect remained unchanged

from the previous examination and showed no severe lesions, therefore the etiology of the new-onset angina remained unclear. OCT was able to identify the presence of a vulnerable plaque inside the coronary tree, which was responsible for the symptomatology, despite being hemodynamically non-significant. The entire revascularization procedure was guided by OCT, which was also useful for the evaluation of the previously implanted stents and their endothelial coverage, as well as the complete apposition of the newly implanted stent. This intracoronary imaging technique revealed permeable stents, without any signs of neointimal hyperplasia or neoatherosclerotic plaque formation inside the previously implanted stents, at the same time being able to identify the target lesion. The vulnerable plaque identified by OCT, with a large lipid pool and a thin fibrous cap, was the lesion responsible for the new onset of angina symptoms.

The case reported here represented a complex condition of a patient with severe recurrent angina pectoris and multiple cardiovascular comorbidities (type 2 diabetes mellitus and stage III chronic kidney disease). The particularity of this case consists in the fact that the patient presented at seven years after the implantation of a coronary stent with the same symptomatology, and the complex coronary artery imaging techniques demonstrated the progression of the disease with the development of multiple serial new stenoses, which required the implantation of new coronary stents. Moreover, after 1 year, the patient returned with severe chest pain caused by the development of a new vulnerable plaque. In this case, we faced an accelerated and progressive atherosclerotic process, probably augmented by the significant comorbidities.

CONCLUSION

This case accentuates the importance of the new intracoronary imaging techniques in monitoring the evolution of patients with implanted coronary stents. Cardiovascular comorbidities may have a direct influence on the atherosclerotic process, leading to the occurrence of new events, years after the acute episode. Invasive imaging techniques are currently considered extremely useful in achieving a personalized therapy in patients with coronary artery disease and high cardiovascular risk. One of the most important imaging techniques of this kind is OCT, which can provide relevant information on plaque vulnerability and intra-stent plaque formation.

CONFLICT OF INTEREST

Nothing to declare.

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