NONOBSTRUCTIVE CORONARY ARTERY DISEASE – CLINICAL RELEVANCE, DIAGNOSIS, MANAGEMENT AND PROPOSAL OF NEW PATHOPHYSIOLOGICAL CLASSIFICATION

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SUMMARY – New data gathered from large clinical trials indicate that nonobstructive coronary artery disease (non-CAD) is a clinical entity that should not be ignored. It is estimated that 50% of female population undergoing coronarography are diagnosed with non-CAD. There is also an increase in the prevalence of non-CAD in both genders, which is probably due to gradual expanding of clinical indications for angiography in patients with angina. Furthermore, considering the increased mortality risk established recently, a prognosis of non-CAD is not benign as previously thought. However, the concept and definition of non-CAD remains elusive causing difficulties in diagnosis and treatment. One of the major shortcomings is the exclusion-based diagnosis of non-CAD. Furthermore, treatment of non-CAD still presents a great challenge and optimal therapy is yet to be determined. There are two major hypotheses explaining the pathophysiological mechanisms of non-CAD, i.e. ischemic hypothesis based on abnormal microvascular dysfunction and non-ischemic one based on altered pain perception. This review encompasses a broader spectrum of pathophysiological mechanisms of non-CAD, and proposes a new way of classification based on the major disorder involved: type I (ischemic mechanisms) and type II (non-ischemic mechanisms), depending on which mechanism predominates. Hopefully, this would provide new insights in the understanding of this disorder, thus leading to accurate and early diagnosis and successful treatment, especially considering the increased mortality risk in these patients.

Key words: Coronary artery disease; Classification; Diagnosis; Angiography

Introduction

The concept of coronary syndrome X (CSX) was introduced in clinical practice in 1973 by Kemp et al. to describe patients with angina during physical exercise and normal coronarography¹-³. Over time, this term has encompassed a broader spectrum of patients including those with angina regardless of the cause and absence of significant changes on coronary vessels. Patients with other cardiac pathology such as cardiomyopathies, left ventricular hypertrophy or significant valvular disease are usually, although not always, excluded from this definition⁴. Many authors recommend associating this syndrome with angina and microvascular dysfunction⁵. On the other hand, some authors suggest exclusion of certain diseases, such as hypertension or diabetes, which can lead to microvascular dysfunction⁶.
Classic definition of CSX is: angina during physical exertion, significant changes of ST segment during exercise test, and angiographically smooth coronary arteries in the absence of other cardiac or systemic diseases (e.g., hypertension and diabetes), which can lead to vascular dysfunction. This definition is presently inappropriate for research and clinical purpose, the main objection being the impossibility of including all patients with microvascular dysfunction. Hence, new, more appropriate definitions have recently been introduced by scientific community.

Lanza has proposed that CSX consists of chest pain predominantly during physical exertion, established ischemia or diminished coronary reserve, using noninvasive provocation tests, normal (or almost normal) coronary arteries at angiography with stenosis less than <20%, and exclusion of other specific diseases such as Prinzmetal's angina, cardiomyopathies and valvular heart disease. Accordingly, the CSX now includes not only conditions with diminished coronary reserve that can be established with modern diagnostic procedures of ergometry, stress induced myocardial scintigraphy, pharmacological stress tests or ECG Holter monitor test, but also other diseases such as hypertension or diabetes, which are common causes of microvascular dysfunction.

Owing to the new understandings, Cannon and Epstein introduced a new concept of microvascular angina in 1985. This concept defines CSX as chest pain with normal coronary angiography associated with enhanced sensitivity of microcirculation to vasoconstrictive influences or abnormal vasodilatory response due to endothelial dysfunction. The level of endothelin (vasoconstrictor) in plasma of these patients is significantly increased. This was an attempt to unite pathophysiology of the clinical condition, accentuate significant role of endothelial dysfunction, and achieve a more homogeneous group of patients. However, this approach is not fully satisfying since it becomes more obvious that endothelial dysfunction is only part of the pathophysiological cascade.

In 2011, Kothawade et al. suggested a new term of microvascular coronary dysfunction (MCD). The CSX is defined as diminished coronary reserve and/or coronary endothelial dysfunction, and is clinically presented with a triad of symptoms: persistent chest pain, nonobstructive coronary disease (coronary artery stenosis <50% on coronaryography), and ischemia established with noninvasive methods. The gold standard for MCD diagnosis is invasive coronary reactivity testing (CRT).

Regardless of definition and terminology, it is necessary to emphasize that obstructive coronary disease (CAD) indicates stenosis of coronary vessel ≥50% on coronaryography, while nonobstructive coronary disease (non-CAD) indicates stenosis of coronary artery <50%. That criterion is common to all definitions and understandings of this complex clinical syndrome.

However, there are still some differences in understanding non-CAD that cause discrepancies in results and observations. Therefore, new definitions should be considered to enable unique and accurate defining of this clinical entity with all its diversities.

Nonobstructive Coronary Artery Disease – Pathophysiological Mechanisms

There are two major hypotheses explaining the pathophysiological mechanisms of non-CAD, i.e. ischemic and non-ischemic hypotheses. Ischemic theory is based on abnormal microvascular dysfunction, whereas non-ischemic theory is grounded on altered pain perception.

Ischemic hypothesis

Since the time when CSX was recognized as a specific clinical entity, it was assumed that chest pain was caused by dysfunction of small coronary arteries (<500 μm), not seen during coronaryography, hence naming the whole syndrome microvascular angina. Myocardial ischemia in these patients can be established by ST segment changes at rest or exertion and by perfusion redistribution on scintigraphy. Moreover, there is some metabolic evidence for ischemia during exercise, e.g., increased lactate production, decreased oxygen saturation in coronary sinus, decreased pH and increased phosphate consumption on nuclear magnetic resonance (NMR), which can be confirmed in 20% of patients.

However, not all studies managed to demonstrate the presence of ischemia since disturbance of regional contractility was not confirmed by echocardiography. In 1991, Maseri et al. tried to explain this contradictory observation with the following hypothesis. Microvascular dysfunction encompasses small prearterio-
lar vessels (100-500 μm), while their inadequate vaso-
dilative response during exercise or pharmacological
stress tests leads to localized ischemia surrounded by
areas with functioning arteriolar vessels. This induces
compensatory response by increasing contractility,
thus preventing diagnosis of regional or global con-
tractility disturbance by echocardiography.

Coronary flow is regulated by endothelial depen-
dent and non-endothelial dependent factors, which
regulate macro- and microvascular blood vessel tone. Endothelial dependent factors regulate coronary re-
serve modulating vasomotor tone by releasing vasoac-
tive factors. The most important vasodilator is nitric
oxide (NO), a factor released by endothelial cells.
Non-endothelial dependent factors encompass aortal
pressure, myocardial contractility output, neurohu-
moral mechanisms and myocardial metabolism17. En-
dothelial dysfunction leads to vasodilatory imbalance
between NO and vasoconstrictor endothelin-1 and
reduced release of anti-inflammatory and antithrom-
botic factors17.

Since microvascular dysfunction cannot be estab-
lished by classic coronary angiography (coronarogra-
phy) and there are no other available methods at pre-
sent for visualizing vasculature smaller than 500 μm,
other diagnostic methods are needed to indirectly
demonstrate microvascular dysfunction. These tests
can be invasive (thermodilution and invasive evalua-
tion of coronary flow) or noninvasive (myocardial
scintigraphy-radionuclide perfusion, positron emis-
tion tomography (PET), NMR)17.

The gold standard in the diagnosis of vascular dys-
function is invasive evaluation of coronary flow reserve.
Coronary flow reserve is an increase in blood flow in
response to metabolic or pharmacological stimuli19.
Diminished coronary reserve is an indicator of possi-
ble ischemia, which could be provoked by increase in
myocardial oxygen demand. Results of the above men-
tioned test indicate that microvascular dysfunction is a
plausible cause of CSX. Novel studies using magnetic
resonance (MR) confirm decreased subendocardial
perfusion in patients with CSX compared to healthy
control group19. PET demonstrated diminished coro-
mary reserve in 50% to 60% of female patients with
non-CAD, and MRI in 25% of the same population19.
However, the prevalence of ischemia is probably un-
derestimated with MR considering the limited ability
to induce stress or exertion during MR20.

Obviously, microvascular dysfunction is a very im-
portant mechanism in the development of non-CAD.
Primary disorder in microvascular dysfunction is al-
ter (decreased) vasodilative response to adequate stimuli, but in a specific group of patients enhanced
vasoconstrictory response can be present21.

Decreased endothelial dependent vasodilation (en-
dothelial dysfunction) is diagnosed with provocation
tests using acetylcholine or with direct electrostimula-
tion of the right atrium, while non-endothelial depen-
dent dysfunction can be established by adenosine,
pyridamole or papaverine provocation tests21,22. Ab-
normal vasoconstriction can be confirmed by provoca-
tion with ergonovine, cold, hyperventilation, hand-
shake test and acetylcholine23. After performing one of
these provocation tests, diminished coronary reserve
should be diagnosed with one of the previously men-
tioned methods (indirectly invasive – coronary flow
reserve test or noninvasive tests – PET, MR).

Based on the results of our recently published re-
search24, we propose a new mechanism that could be
added to endothelial independent mechanisms within
the ischemic hypothesis on the development of non-
CAD. Alongside the known endothelial independent
pathophysiological mechanisms such as aortic pres-
sure, myocardial contractility, myocardial metabolism
and neurohumoral factors25, another possible contrib-
utor would be the type of coronary supply, specifically
the left type of dominance (particularly in women),
and absence of mixed type in men24.

Non-ischemic hypothesis

Non-ischemic hypothesis explains the CSX phe-
omenon and non-CAD because of altered pain per-
ception25. Previous studies demonstrated that patients
with angina and normal coronary arteries had en-
hanced pain perception to heat and electrical stimuli26.
There is evidence supporting the absence of habitua-
tion to frequent pain stimuli in these patients (habituu-
al theory)27. Furthermore, it is well known that estro-
gen has analgesic properties, which are mediated
through opioid system, thus explaining the presence of
chest pain in postmenopausal women with normal coronarography. It is possible that the lack of estrogen
in females participates in altered chest pain percep-
tion28.

In 1988, Shapiro et al. demonstrated that intracar-
dial stimulation by infusion of saline to the right atri-
um induced chest pain in patients with angina and normal coronary arteries. It was the first paper published that explained this phenomenon using altered pain perception. Although results of previous studies indicated generally diminished tolerance to all pain stimuli in these patients, the study by Iannetti et al. denied such notion. Earlier studies were poorly controlled and badly designed, whereas new studies with laser pain stimuli on the skin surface established unaltered general pain perception. In addition, local electrostimulation of the right ventricle with higher frequencies demonstrated altered pain perception in the heart.

Rosen et al. demonstrated that activation of the right frontal insula of the brain cortex in patients with CSX and ST changed during dobutamine stress test, suggesting cortical origin of this disorder. Afferent (sympathetic) and efferent (nociceptive) fibers can be affected as well. Enrolment of the sympathetic heart system (afferent component) can be clinically diagnosed by metaiodobenzylguanidine (MIBG) scintigraphy. In patients with CSX, radionuclide I- MIBG uptake is completely absent, although the liver and lung are clearly visible. This implicates significant abnormality in sympathetic heart innervation in patients with non-CAD. Involvement of efferent (nociceptive) fibers is established directly with electrostimulation of the right heart or pharmacologically with dobutamine or adenosine delivered locally as intracardial infusion.

Integrated ischemic and non-ischemic hypothesis

It is currently presumed that the pathophysiological relationship between ischemic and non-ischemic hypothesis exists. Microvascular dysfunction and repeated subclinical episodes of ischemia could lead to structural changes in heart innervation through fibrosis or prolonged mild inflammation. This is presented as an enhanced pain perception to harmless local stimuli (efferent innervation) or as a decreased uptake of MIBG in sympathetic heart fibers, which implicates involvement of efferent fibers.

Traditional risk factors such as hypertension, hypercholesterolemia and diabetes have a significant role in the development of microvascular dysfunction through endothelial dependent vasodilatation (endothelial dysfunction) and are part of ischemic hypothesis. Insulin resistance and glucose intolerance are also
associated with endothelial dysfunction\textsuperscript{34}. The lack of estrogen in females and hysterectomy are part of the non-ischemic hypothesis based on analgesic properties of estrogen\textsuperscript{35}, while mild inflammation with increased concentration of C-reactive protein and interleukin-1 receptor antagonists is a possible risk factor in non-ischemic and ischemic hypothesis causing structural changes of neural fibers\textsuperscript{36} (Fig. 1).

Diagnosis of Nonobstructive Coronary Artery Disease

Diagnosis of non-CAD is based on clinical presentation and diagnostic procedures. Clinical presentation of angina can be more or less typical. Diagnostic tests in non-CAD can be invasive and noninvasive (Table 1).

Table 1. Diagnostic tests (invasive and noninvasive) in nonobstructive coronary artery disease (non-CAD)

| Clinical presentation | Stress test positive | Coronary angiography | Non-CAD |
|----------------------|----------------------|----------------------|---------|
| ↓                    | ↓                    | ↓                    | →       |
| Chest pain (anginal) | Exclusion of other conditions | Stress test | Possible acetylcholine or ergonovine test (vasospasm) |
| Exclusion of other conditions | Stress test | Coronary angiography | MSCT |
| Coronary angiography | Myocardial scintigraphy | MSCT |  |
| <50% stenosis | | | |
| Non-CAD | | | |

MSCT = multi-slice computed tomography

It is very important to emphasize that non-CAD is diagnosed by exclusion\textsuperscript{6}. Exclusion of all other non-cardiac causes of angina such as musculoskeletal pain, gastrointestinal disorders, pulmonary causes and various psychiatric disorders is necessary. In patients with probable angina, noninvasive diagnostic tests are performed trying to confirm ischemia through significant ST-T changes (based on established standardized diagnostic criteria) mostly during exertion. The basic test of physical activity is ergometry or exercise myocardial perfusion scintigraphy\textsuperscript{37}.

Currently, there are no defined criteria for differentiating obstructive from nonobstructive disease in patients with positive stress test\textsuperscript{38}. However, some authors suggest several criteria such as increased pressure and pulse pressure product during stress needed to cause ST changes in patients with non-CAD\textsuperscript{39}.

Therefore, patients with positive stress test are candidates for further invasive diagnostic work-up to confirm or exclude obstructive changes of coronary arteries. Usually, direct catheterization of arteries (coronarography) is performed, although there are other noninvasive methods such as multi-slice computerized tomography (MSCT)\textsuperscript{6}.

Some authors suggest acetylcholine or ergonovine test (intracoronary or intravenously) in patients with normal coronaryography to exclude spasm of major arteries. Unfortunately, this procedure is highly risky due to the possibility of strong vasospasm and hypotension, thus it is not part of routine clinical work-up\textsuperscript{6}.

After exclusion of all non-cardiac causes, diagnosis of CAD is based on clinical presentation of chest pain and diagnostic procedures. First procedure is noninvasive test of physical activity (ergometry, or rarely myocardial stress scintigraphy). In patients with positive stress test, coronarography is performed to definitely confirm or exclude obstructive stenosis (≥50%) of epicardial arteries. Spasm of major arteries can be diagnosed with ergonovine or acetylcholine test but due to the considerable risk it is not part of routine clinical work-up\textsuperscript{37}.

Routine clinical work-up ends at this point. Additional tests for more accurate diagnosis of non-CAD are used only for research purposes\textsuperscript{6}. In patients with suspected ischemic etiology (microvascular dysfunction), some pharmacological tests can be performed to confirm altered vasodilatation or enhanced vasoconstriction. The most commonly performed tests are acetylcholine test or electrostimulation to establish endothelial dependent dysfunction and adenosine, pyridamole or papaverine tests to establish non-endothelial dependent dysfunction. Vasoconstriction can be diagnosed with ergonovine test or cold pressure test\textsuperscript{23}.

After implementation of one of these tests, establishing induced ischemia in the microvasculature area (<500 μm) is necessary\textsuperscript{8}.

Since small blood vessels cannot be displayed on coronaryography, ischemia is indirectly visualized with invasive methods such as the test of coronary flow reserve (CFR) or with noninvasive methods such as myocardial scintigraphy, MR or PET\textsuperscript{19,20}.

To confirm non-ischemic origin of the disorder (altered pain perception), MIBG scintigraphy of sym-
pathetic heart innervation for visualizing afferent dysfunction and direct heart stimulation with dobutamine or electrostimulator for demonstrating efferent dysfunction can be performed. Additional tests are also available such as insufficiently standardized psychological tests for establishing habitual component of disorder, as well as absence of adaptation to repeated pain stimuli. All additional diagnostic tests are summarized in Table 2.

### Table 2. Additional tests for exact identification of the extent of non-obstructive coronary artery disease

| Clinical condition                  | Diagnostic tests                  |
|------------------------------------|-----------------------------------|
| Ischemic mechanisms                |                                    |
| Reduced vasodilation               | Endothelium dependent             |
|                                    | Endothelium independent            |
|                                    | • Acetylcholine                    |
|                                    | • Electrostimulation               |
|                                    | • Adenosine                        |
|                                    | • Pyridamole                       |
|                                    | • Papaverine                       |
| Increased vasoconstriction         | • Ergonovine                       |
|                                    | • Acetylcholine                    |
|                                    | • Exposure to cold                 |
| Non-ischemic mechanisms            |                                    |
| Neurogenic disorder                | Afferent (adrenergic)              |
|                                    | MIBG myocardial scintigraphy       |
|                                    | Efferent (nociceptive)             |
|                                    | Pharmacological                    |
|                                    | Mechanical                         |
|                                    | Dobutamine                         |
| Habitual disorder                  | Psychological testing              |
| Decreased coronary reserve (<500 μm) | Invasive                          |
|                                    | Noninvasive                        |
|                                    | CFR                               |
|                                    | • Myocardial scintigraphy          |
|                                    | • MR                              |
|                                    | • PET                             |

MIBG = 123I-methaiodobenzylguanidine; CFR = coronary flow reserve; MR = magnetic resonance; PET = positron emission tomography

Prognosis of Nonobstructive Coronary Artery Disease and Prevalence of Major Cardiovascular Outcomes

Unlike former opinions, current studies have verified that patients with non-CAD have an increased risk of cardiac mortality. Prognosis of non-CAD is not benign considering 2% risk of cardiac death or myocardial infarction within 30 days of disease manifestation. Several studies demonstrated that advanced coronary atheroma could be present despite normal or almost normal coronary arteries, thus increasing the risk of adverse acute events. The Women's Ischemia Syndrome Evaluation (WISE) trial, which included women with non-CAD, demonstrated that different symptom profiles were associated with different long-term outcomes. An increase in adverse cardiac events was observed in patients with non-CAD. These findings suggest that normal or almost normal coronary arteries on coronaryography do not imply benign prognosis.

Furthermore, classic definition of coronary disease symptoms encompasses retrosternal chest pain or discomfort (which can irradiate into the neck, arm, jaw and back), with pain quality described as dull, sharp, crushing or burning, lasting for 2-20 minutes and worsened with physical activity, while alleviated with rest or nitroglycerin. On the other hand, the majority of patients (around 70%) in the study performed by Johnson et al. presented with atypical symptoms regardless of verified nonobstructive or obstructive coronary disease on coronaryography. As a consequence of this symptom variability, patients with atypical presentation and an increased risk of adverse cardiac events can be easily overlooked. Previous studies performed in patients with angina and normal coronaryography in the 1960s did not demonstrate an increased prevalence of adverse clinical events, or increased mortality. Those studies were performed in a small number of patients with short follow-up; therefore, the increased risk in those patients was not determined. The WISE trial was the first study that demonstrated completely
opposite results in females with CSX. Those patients had a three-fold higher prevalence of adverse cardiovascular events (including heart failure and stroke) compared to healthy controls during the 5-year follow-up (2.4% vs. 7.9%; p=0.002)\(^4^4\). These results were confirmed by the British Columbia registry, which established a 4 times higher probability of hospital readmission in females with angina and nonobstructive changes on coronaryography presenting as acute coronary syndrome compared to males during early follow-up\(^4^8\).

However, the WISE trial was not successful in establishing statistically higher prevalence of myocardial infarction or cardiac death compared to healthy population, despite numerical differences. Nevertheless, the total mortality rate was significantly higher compared to the control group (2.1% vs. 3.0%; p=0.04)\(^4^4\). This observation is extremely important since a high mortality rate was established for the first time in women with non-CAD. It is considered that prognosis in females with non-CAD depends on microvascular dysfunction\(^4^9\). Several studies demonstrated that patients with CSX and established microvascular dysfunction had a higher probability of developing CAD in the future and higher prevalence of adverse cardiovascular events\(^5^0\). Moreover, investigators in the WISE trial additionally stratified patients with nonobstructive disease in two groups. First group consisted of patients with confirmed ischemia using MR spectroscopy (indirect proof of microvascular dysfunction), whereas in the second group of patients diagnosis of ischemia with that method was not possible. In the group of patients with confirmed ischemia and microvascular dysfunction, a higher prevalence of adverse cardiovascular events was observed even when considering all traditional risk factors\(^4^4\). The WISE trial included only women, thus it is still unclear whether the same observations apply to male population.

In 2012, Jespersen \(et \ al\).\(^{5^1}\) published results from the Copenhagen City Heart trial including 11,233 patients that underwent coronaryography due to the symptoms of stable angina and were compared to healthy individuals without cardiovascular events. Significantly more females (65%) compared to males (32%) had non-CAD among patients with stable coronary disease. This is consistent with the observations from the WISE trial that 62% of patients who underwent coronaryography due to chest pain had non-CAD. The Danish trial was designed as a retrospective cohort study including all patients from eastern Denmark that underwent coronaryography due to angina from 1998 to 2009\(^5^1\). This trial demonstrated that both males and females with anginal symptoms and normal or nonobstructive changes of coronary arteries had an increased risk of adverse cardiovascular events compared to healthy population without ischemic events. That specific group of patients with normal coronary arteries or nonobstructive changes of coronary arteries had 52% and 85% increased risk of major adverse cardiac events (MACE) including cardiac death, hospitalization due to myocardial infarction and heart failure or stroke, and 29% and 52% had an increased mortality risk regardless of the cause. There was no statistically significant difference for MACE or mortality rate between men and women\(^5^1\).

### Treatment of Nonobstructive Coronary Artery Disease

Treatment of non-CAD presents a great challenge. Unfortunately, therapy is often unsuccessful because symptoms persist at 5-year follow-up in almost 50% of treated women\(^5^4\). There are few medications and procedures that are undoubtedly efficient in CSX treatment. Experiences gathered from large clinical trials are lacking. Most of observations and conclusions are based on smaller and observational studies that included only a few dozens of patients or less. Results of those trials are mostly contradictory or lacking well defined control groups for comparison. The Effects of Allopurinol on Coronary and Peripheral Endothelial Function in Patients with Cardiac Syndrome X (APEX) trial is one of the few clinically controlled pending trials (started in 2008) that is trying to evaluate specific drug efficacy, in this case allopurinol, in treating CSX\(^5^5\). However, based on the current knowledge, it is safe to say that beta-blockers and lifestyle changes modifying cardiovascular risk factors have a central role in non-CAD treatment\(^5^5\). All therapeutic measures in non-CAD treatment can be divided into medicamentous and non-medicamentous measures that are summarized in Table 3.

#### Medicamentous measures

There are numerous small trials demonstrating atenolol efficacy in CSX treatment\(^5^6-5^8\). Atenolol
decreases pain, improves coronary reserve, and decreases ST depression during exertion test\(^6\). The calcium channel blockers verapamil and amlodipine were not efficient compared to atenolol, although there are some reports indicating beneficial effect of atenolol and amlodipine combination\(^6\). Unfortunately, controlled experiences with other beta-blockers are lacking. Nebivolol is the only drug investigated in patients with non-CAD. Nebivolol is a highly selective beta-1-blocker with beneficial effect on endothelial function, which increases bioavailability of the most potent endogenous vasodilator NO\(^55\). Upon intracoronary infusion, it increases coronary reserve in patients with and without obstructive changes in the epicardial arteries. However, intracoronary application of this drug is not clinically possible, while experiences with oral usage are still lacking.

Investigators generally agree that beta-blockers have beneficial effect, although there is a response variability of 19\%–60\%\(^59\). However, based on current research, beta-blockers (especially atenolol) should be the first line treatment in patients with CSX\(^60\).

Although expected, efficacy of nitrates in CSX treatment is still questionable. In small observational studies, efficacy was present in only 42\% of patients. Moreover, there are some reports indicating decreased tolerance during the test of physical activity in those patients when treated with nitrates\(^61\). Therefore, nitrates are recommended exclusively in combination with other efficient drugs\(^66\).

The xanthine derivatives aminophylline and theophylline are blocking adenosine receptors, thus enabling more favorable redistribution of coronary flow and probably blocking adenosine effect in pain provocation (intracoronary infusion of adenosine elicits chest pain in patients with CSX)\(^6,55\). Intravenous or oral administration of aminophylline during the test of physical activity increases exercise tolerance, diminishes pain perception, and decreases ST changes\(^62,63\). Therefore, these medications can be recommended, especially in patients treated for asthma or chronic obstructive pulmonary disease\(^55\).

In small observational and placebo controlled trials, some angiotensin-converting enzyme (ACE) inhibitors had certain beneficial effect\(^64\), this referring to cilazapril\(^65\), enalapril\(^66\) and a combination of ramipril and statin (atorvastatin)\(^55\). Antagonists of angiotensin receptors (ARB), despite expectations, did not demonstrate any favorable effects in a trial investigating irbesartan\(^67\). For other members of this group, efficacy was neither investigated nor established.

In several studies, statins showed some efficacy in treating CSX, probably due to their anti-inflammatory effect. The effect was present regardless of the plasma lipid profile baseline value\(^68,69\). Furthermore, additional synergic effect was established with some ACE inhibitors, especially for atorvastatin and ramipril\(^6,55,68\).

Of all other medications utilized in CSX treatment that had certain success, we should mention estrogen in postmenopausal women\(^55,70\), L-arginine (precursor
of vasodilator NO)71,72, metformin in patients with glucose intolerance23, and imipramine that is used in the treatment of chronic pain74,75.

The efficacy of α-antagonists (doxazosin and clonidine) has not yet been established in the treatment of non-CAD symptoms76.

There are several new drugs with probable therapeutic effect in CSX based on their mechanism of action. However, currently there is no strong evidence to confirm their efficacy and justify their application. Some of these drugs are bosentan (ET-1 inhibitor), cariporid (Na-H+ exchanger), fasudil (rho-kinase inhibitor) and trimetazidine (metabolic antianginal drug)55. Only nicorandil, activator of vascular potassium channels with vasodilatory abilities, is effective in the treatment of microvascular coronary disease77,78.

Non-medicamentous measures

Besides the above mentioned pharmacological measures in the treatment of CSX symptoms, there are also non-medicamentous procedures that exhibited favorable effect in some patients. Spinal cord stimulation (SCS) with low voltage electric impulses affects pain modulation and diminishes pain sensation in patients with angina79. This method is approved in the treatment of refractory angina in patients with CAD unsuitable for revascularization, and has class IIb recommendation according to the American College of Cardiology/American Heart Association (AHA/ACC) guidelines80. There are several reports indicating efficacy of this method in long-term control of symptoms in patients with CSX79,81.

Similar procedure is transdermal electric nerve stimulation (TENS). This procedure improves coronary flow without altering microvasculature diameter and has beneficial effect in eliminating symptoms82-84.

Extracorporeal enhanced counter pulsation (EECP) consists of periodical inflating and deflating pressure cuffs on lower extremities that proved efficient in recovering endothelial function and in some small studies led to diminishing anginal symptoms85.

Lifestyle modifications and affecting cardiovascular risk factors are basic recommendations for patients with non-CAD55. Physical exercise improves coronary reserve and exercise tolerance, and diminishes symptoms in both CAD and non-CAD86. Additional improvement of exercise tolerance, quality of life, and beneficial effect on anginal symptoms can be achieved through rehabilitation87,88. Recommendations are weight reduction89, smoking cessation90 and low fat or Mediterranean diet91, which improves endothelial dysfunction55.

New Classification of Nonobstructive Coronary Artery Disease Suggested

We propose here a new classification of non-CAD, separating the whole syndrome in type I (ischemic disease) and type II (non-ischemic disease), based on which clinical syndrome predominates. Each of these is further divided based on the existing mechanism and is marked by letters A, B or C, as shown in Table 4.

Disorder 1A represents endothelial dependent reduced vasodilatation, which clinically corresponds to

| Type of non-CAD disorder | Underlying mechanism | Clinical presentation |
|--------------------------|----------------------|----------------------|
| Type I: Ischemic mechanisms | 1A | Endothelium dependent reduced vasodilation | Endothelial dysfunction |
|                           | 1B | Endothelium independent reduced vasodilation |
|                           | 1C | Vasconstriction |
| Type II: Non-ischemic mechanisms | 2A | Neurogenic afferent |
|                               | 2B | Neurogenic efferent |
|                               | 2C | Habitual |

| Type | Underlying mechanism | Clinical presentation |
|------|----------------------|----------------------|
| I    | Ischemic mechanisms  | Endothelial dysfunction |
|      | 1A                   | Endothelium dependent reduced vasodilation |
|      | 1B                   | Endothelium independent reduced vasodilation |
|      | 1C                   | Vasconstriction |
| II   | Non-ischemic mechanisms | Neurogenic afferent |
|      | 2A                   | Neurogenic efferent |
|      | 2B                   | Habitual |

Table 4. Suggested classification of pathophysiological mechanisms in nonobstructive coronary artery disease (non-CAD)
endothelial dysfunction. Established cardiovascular risk factors such as smoking, dyslipidemia, diabetes mellitus or hypertension are involved in the pathophysiology of this mechanism, as well as NO, endothelin-1, and other anti-inflammatory and antithrombotic factors. Disorder 1B represents endothelial independent mechanisms. Clinically, this includes aortic pressure, myocardial contractility, myocardial metabolism, neurohumoral factors, and type of coronary artery supply. As previously highlighted, left dominance in women is more frequent in non-CAD, as well as the absence of mixed dominance in men. Disorder 1C represents increased vasoconstriction. This mechanism contains both microvascular and macrovascular (vasospastic) vasoconstriction, but without permanent obstruction of coronary arteries >50%. In a broader sense, this refers to the bridging of coronary arteries as well, which represents dynamic stenosis in the location where major coronary artery is running intramyocardially. This is mostly seen in the left anterior descending artery, but may be seen in other coronary arteries as well.

Non-ischemic mechanisms may also be divided into three basic groups, and are marked by letters A, B and C: 2A is a neurogenic afferent mechanism, which clinically represents adrenergic disorder of heart innervation; 2B is neurogenic efferent mechanism that clinically represents nociceptive disorder; and 2C is habitual mechanism that represents behavioral disorder.

In clinical practice, the same patient may have more of less combined induced mechanisms. However, there is always one predominant mechanism in clinical presentation of non-CAD, and the disorder can be classified by that predominant mechanism.

Certainly, microvascular dysfunction plays a significant role in the development of non-CAD, but other mechanisms should not remain unattended. These pathophysiological mechanisms are well defined and lead to anginal symptoms, and affect major coronary arteries, not the microvasculature. This especially refers to vasospastic, Prinzmetal’s angina, and phenomenon of myocardial bridging. Both affect major coronary arteries and should be placed among the mechanisms of non-CAD.

With this new classification, the aim is to include all the known pathophysiological mechanisms and align classification to current diagnostic testing, thus hopefully contributing to better understanding, timely diagnosis and comprehensive management of non-CAD.

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Sažetak

NEOPSTRUKTIVNA KORONARNA BOLEST – KLINIČKA VAŽNOST, DIJAGNOSTIKA, LIJEČENJE I PRIJEDLOG NOVE PATOFIZIJOLOŠKE KLASIFIKACIJE

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Novi podaci prikupljeni iz velikih kliničkih ispitivanja pokazuju da je neopstruktivna koronarna bolest (ne-OKB) klinički entitet koji se ne smije zanemariti. Procjenjuje se da se u 50% ženske populacije koja se podvrgava koronarografiji dijagnosticira ne-OKB. Također postoji povećanje rizika od smrtenosti koji je nedavno ustanovljen, što se razlikuje u oba spola, što je vjerojatno posljedica postupnog širenja kliničkih indikacija za koronarografiju u bolesnika s anginom pektoris. Nadalje, s obzirom na povećani rizik od smrtenosti koji je dobio u 20% bolesnika, postoje postupci koji upravljaju rizikom od smrtenosti kod bolesnika s ne-OKB. Međutim, koncept i definicija ne-OKB ostaje nedovoljno definiran, što uzrokuje poteškoće kako u dijagnozi tako i u liječenju. Jedan od glavnih nedostataka je dijagnostika ne-OKB koja se temelji na dijagnostici isključivanja. Nadalje, u liječenju ne-OKB i dalje predstavlja velik izazov, a optimalnu terapiju tek treba odrediti. Postoje dvije glavne hipoteze koje objašnjavaju patofiziološke mehanizme ne-OKB. Ishemijska hipoteza temelji se na mikrovaskularnoj disfunkciji, a neishemijska hipoteza na promijenjenoj percepciji bolesti. Ovaj pregledni članak obuhvata širok spektar patofizioloških mehanizama ne-OKB i predlaže novi način klasifikacije temeljen na glavnom poremećaju koji je uključen u patofiziologiju: tip I. (ishemijski mehanizam) i tip II. (ne-ismijski mehanizam), ovisno o tome koji mehanizam prevladava. Nadamo se da će to omogućiti nove spoznaje u razumijevanju ovog poremećaja, što dovede do točne i rane dijagnoze i uspješnog liječenja, osobito s obzirom na povećani rizik smrtnosti kod ovih bolesnika.

Ključne riječi: Koronarne arterije, bolesti; Klasifikacija; Dijagnostika; Angiografija