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Angina pectoris in patients without flow-limiting coronary artery disease (cardiac syndrome X). A forest of a variety of trees

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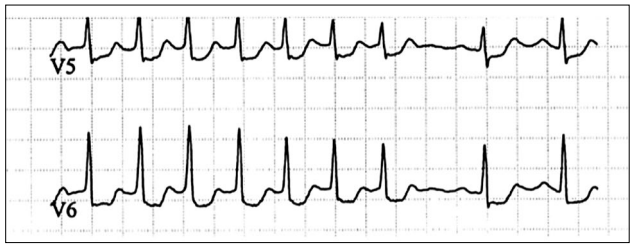
Sometimes, truth may be stranger than fiction



Abstract

Coronary heart disease (CHD) represents an important problem worldwide. At present, more women than men are evaluated for CHD and it has been recognized that the prevalence of this pathology in women is at least the same as in men. We have learned that cardiac syndrome X (CSX) is frequent because worldwide each year millions of people (mostly women) with angina pectoris without flow-limiting epicardial pathology are identified. Data from large myocardial infarction registries suggest a 5% to 25% prevalence of cases without flow-limiting coronary pathology. It must, however, be considered that these people are said to have normal coronary arteries by visual analysis of biplane coronarography. On the other hand, as demonstrated from autopsy, and in vivo by ultrasound intravascular studies, it would be more appropriate to say that in the majority of these cases no obstructive or flow-limiting coronary pathology was detected by coronarography. In CSX, endothelial dysfunction and microvascular dysfunction, sometimes with coronary microvascular spams and epicardial coronary artery spasm, have been recognized as pathophysiologic mechanisms. In CSX, symptoms and pathologic signs are the same in patients with flow-limiting coronary pathology. The difference lies in the fact that the mechanisms of myocardial ischemia are microvascular and flow-limiting epicardial coronary pathology is absent. By interplay, the pathologic entities at work in CSX are linked with poor long-term outcome. The prevalence of these outcomes is probably smaller than in patients with flow-limiting coronary pathology but we lack precise values. Nonetheless, severe cardiovascular complications are frequent in CSX and it is thus the pathology is not benign. Drugs used in coronary ischemic disease are empirically prescribed to treat CSX, but we lack data from specific trials. It seems that statins and ranolazine might exert positive effects. However, specific research to target interventions in CSX would be necessary. (Cardiol J 2015; 22, 6: 605–612)

Key words: cardiac syndrome X, coronary ischemic disease

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Introduction

Coronary heart disease (CHD) represents an important medical problem worldwide, whose prevalence is augmenting, especially due to the growingly ageing populations in the western countries and to the increasing changes in smoking and diet in the developing countries. As a result, the number of cardiac interventions is expected to increase further over the coming decades, reaching more than a million of annual procedures worldwide in the next years. In the past there was a strong bias in evaluating women with angina pectoris (AP). However, at present coronarography (CAG) is rapidly performed in women with suspected CHD and it is proven that CHD is at least as frequent in women as in men. Typical AP is a cardinal symptom of CHD and meets all of the following criteria: retrosternal chest discomfort of characteristic quality and duration; provoked by exertional or emotional stress; relieved by rest and/or nitrates within minutes [1, 2]. In 1940, it was stated [3] that no patients with AP failed to show occlusion in at least one of the major coronary arteries and flow-limiting coronary stenosis causing ischemia was accepted as the etiologic cause of AP and CHD. However, it was soon realized that this assumption was not unconditional because AP may also occur in other diseases, such as e.g. hypertrophic cardiomyopathy, severe aortic stenosis, profound anemia, and carboxyhemoglobin intoxication. In 1967, 2 papers [4, 5] described patients with typical AP, sometimes dyspnea and other neuro-vegetative symptoms (e.g. perspiration, tachycardia and dizziness) without epicardial coronary artery pathology. This pathology is not rare and is often termed 'cardiac syndrome X' (CSX) [6–10].

A typical patient with CSX

A 53-year-old Caucasian woman with a weight of 65 kg had stable typical AP, which was questionably relieved by sublingual nitroglycerin. Her father died at the age of 55 years because of myocardial infarction. The patient had no other cardiovascular risk factors. The resting electrocardiogram (ECG) showed ischemic changes (Fig. 1). Plasma levels of troponin, measured during and several hours after episodes of AP, were not increased. Echocardiography detected that left ventricular relaxation phase was moderately impaired, but there were no other pathologies, e.g. no hypertrophy, normal regional motility, normal systolic ejection (left ventricular ejection fraction — LVEF 58%); no significant valvular pathology, normal right heart and systolic pulmonary pressure, no pericardial effusion. A stress-test was interrupted at 80 W/min because of moderate AP with corresponding ischemic ECG changes (Fig. 2) at a heart rate of 125/min with sometimes undetectable P waves and ST-down-sloping (up to 2.5 mV) in I, II, II, aVF, V_5 and V_6 with mild mirror ST-up-sloping in aVR and V_1. Echocardiography did not detect dyskinesia, the left ventricular systolic ejection fraction increased from 62% to 73% and the ventricular volume remained unchanged. AP lasted up to 6 min and was not relieved by 0.8 mg sublingual nitroglycerin. The

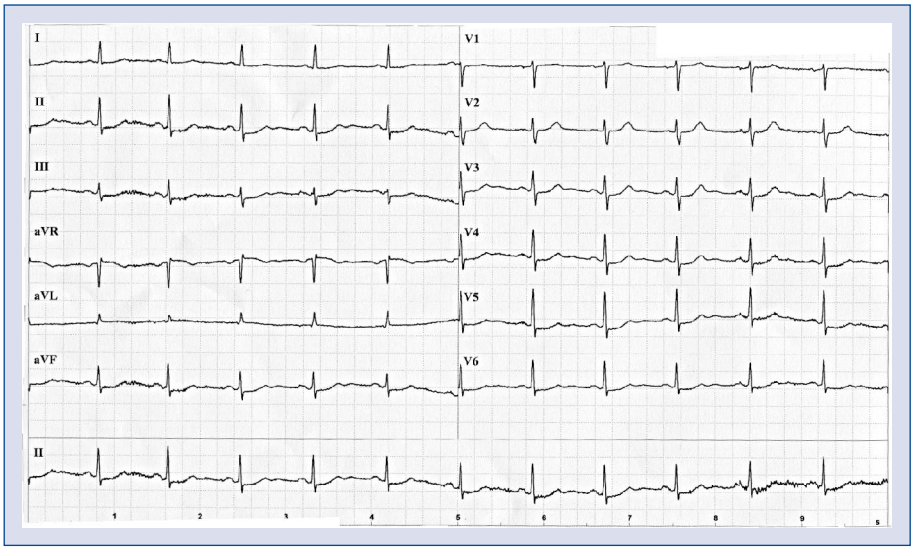

Figure 1. The resting electrocardiogram shows ischemic ST-changes, in V_{4-6} and inferior leads.

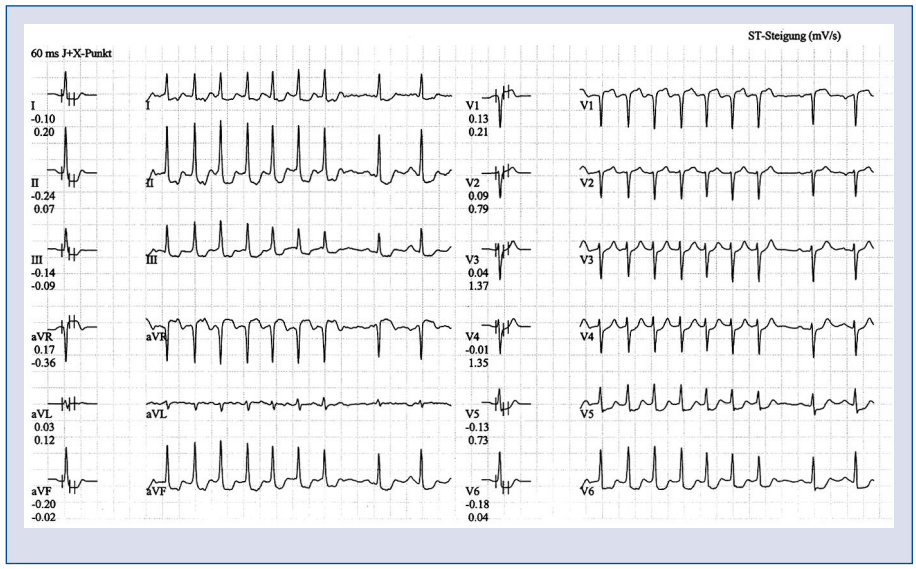

Figure 2. A stress-test was interrupted at 80 W/min because of moderate angina pectoris with corresponding ischemic changes. The electrocardiogram showed a heart rate of 125/min with sometimes missing P waves and ischemic ST-down-sloping (maximal –2.5 mV) in I, II, II, aVF, V_5 and V_6 with mirror ST-up-sloping in aVR and V_1. The echocardiography did not detect any pathologic changes.

woman had typical AP and ischemic ECG changes without left dyskinesia and we thought that the patient had CSX. Because of the positive family history for CHD and the stress-induced ischemic ECG changes, the referring physician required a ventriculo-coronarography: left ventricular anatomy and function were normal, no flow-liming coronary pathology was detected. The patient was treated with ranolazine (375 mg b.i.d for 2 weeks and afterwards 500 mg b.i.d.) and rosuvastatin 5 mg/day. After 3 weeks AP was significantly reduced (fewer episodes and less intensity of chest pain). After 3 months the repolarization changes were no longer detectable in the resting ECG. A stress-test under therapy with ranolazine was interrupted at 150 W because of mild AP at a heart rate of 145/min; the ECG showed a –0.2 mV ST-down-sloping in $V_{4–5}$ with ascending morphology. In comparison to the first stress-test the patient could exercise 3 min longer before mild AP occurred and the work load increased by 50 W.

Pathophysiology of ischemia and AP in CSX

Etiological heterogeneity and prominent contribution of co-morbidities make understanding the pathophysiology of CSX particularly challenging [6, 7, 9–16]. It has been, however, established that the interplay of multifactorial mechanisms (Table 1) may cause myocardial ischemia and AP in patients without flow-limiting coronary stenosis, i.e. with the so-called normal or non-significant CHD. As shown in Table 1, the most important mechanisms are endothelial dysfunction (ED), microvascular dysfunction (MVD) sometimes with coronary microvascular spasm, and epicardial coronary artery spasm (CAS).

Table 1. Mechanisms of ischemia and angina pectoris in cardiac syndrome X.

Endothelial dysfunction is present in the overwhelming majority of cases.
Microvascular dysfunction, in some cases with coronary microvascular spasm is also present in nearly 50% of cases.
Epicardial coronary artery spam is present in about 4% of cases.
All these mechanisms interplay, contribute to microcoronary ischemia, reduce collateral perfusion and, in the occurrence of a severe coronary flow reduction, such after a thrombotic event, limit the reperfusion.

Endothelial dysfunction is a systemic disorder which is present in patients with AP with/ /without epicardial coronary artery pathology. ED results from vascular injury due to arteriosclerotic inducing factors, anticipates the angiographic documentation of anatomical lesions and has been linked with adverse outcomes in many conditions

Table 2. Mechanisms involved in endothelial dysfunction.

Oxidative stress has several negative effects:
• Increases intracellular superoxide
• Inactivates nitric oxide and formation of peroxynitrite
• Induces nitric oxide synthase uncoupling
• Reduces nitric oxide signaling
• Inhibits prostacyclin formation
• Stimulates endothelin expression
• Inhibits the activity of soluble guanylate cyclase
Increases sympathetic activation and apocrine neurohormonal mechanisms:
• Increases production of norepinephrine (also called noradrenalin or levarterenol)
• Increases production of angiotensin II

[16–19]. Known pathophysiologic mechanisms related to ED are shown in Table 2. ED is present in large majority of CSX-patients, in nearly 50% of cases combined with MVD. MVD is defined by low coronary reserve, i.e. a dysregulation of coronary blood flow, which is not attributable to flow-limiting epicardial coronary artery pathology. MVD results from either structural or functional mechanisms in the microvasculature and induces an inappropriate vasodilatation of the coronary microcirculation [9, 16–22]. MVD has also been linked with adverse outcomes in an increasing number of pathologies [19–23]. Coronary microvascular spasm is a dangerous pathophysiologic mechanism which has been found in CSX-patients with MVD and is linked with poor outcomes [24]. In the WISE study, nearly 50% of the women with AP without flow-limiting epicardial coronary pathology were tested with adenosine and were found to have MVD, which was an independent predictor of adverse outcomes [20]. ED and MVD independently predict adverse cardiovascular events, such as after 5.4-year follow-up occurrence of death, acute coronary syndrome (ACS), myocardial infarction, stroke, and hospitalization for heart failure [17, 21–23]. These adverse outcomes are consistent with the cardiovascular continuum expected from a disorder involving the microvasculature [13, 16, 17, 21–23]. Many pathologic mechanisms may induce CAS which is a proven cause of myocardial ischemia and AP [13, 21, 24–30] and is the 3rd etiologic mechanism in CSX [13]. CAS is linked with some genetic background [9, 10, 23, 24]. In CSX-patients CAS has been linked with an ACS in > 50% of cases [26, 29, 30] and was thought to be the cause of myocardial infarction in some cases [24, 30, 31]. In CSX-patients, CAS has been induced with acetylcholine (i.e. the parasympathetic system) [27], adenosine [22], serotonin, ergonovine, histamine and many other less frequently causative agents, all of which cause vasodilation when the endothelium is intact by releasing nitric oxide [28]. Indeed, in the WISE study, CAS could be detected in nearly 4% of women without flow-limiting epicardial coronary pathology who were tested with acetylcholine [13]. This is the same frequency that is found in patients with AP and obstructive epicardial coronary artery pathology [26, 27, 29].

Left ventricular wall motion in CSX

In the WISE study, ventriculography data showed that resting left ventricular wall motion was preserved in CSX-patients [13–15]. Cardiac magnetic resonance imaging provides superior resolution to evaluate perfusion, and detected that CSX-patients had a relative failure to increase subendocardial perfusion [13, 14, 27, 28]. In the late seventies, our group [32, 33] used pharmacologic stress-testing with either isoproterenol or dopamine to assess the effects on left ventricular motility in patients with AP with/without flow-limiting coronary artery pathology. Kinetocardiography showed that left ventricular dyskinesia was induced in nearly 30% of patients without flow-limiting coronary pathology, and that the dyskinetic changes were similar to those detected in patients with epicardial coronary pathology [32, 33]. Isoproterenol and dobutamine may worsen ED and MVD, both frequent in CSX-patients. It is thus understandable that CSX-patients report AP with concomitant ischemic ECG changes and, if the cardiac ischemia is sufficient, dyskinesia may occur, as in patients with ischemic due to epicardial coronary pathology. Briefly, in CSX symptoms and signs of cardiac pathology are the same as those of patients with ischemia related to epicardial coronary pathology. The difference lies in the fact that in CSX the mechanisms of ischemia are microvascular and flow-limiting epicardial coronary pathology is absent.

Defining normal coronary arteries

By visual analysis of biplane CAG coronary arteries are often defined normal. However, pathologic studies indicate that visual analysis of angiographically normal coronary artery segments

underestimates the extent of coronary atherosclerosis. Intravascular ultrasound allows high quality cross-sectional imaging of the coronary arteries in vivo [11, 12] and was used to study angiographically normal coronary reference segments in 884 patients evaluated for transcatheter therapy for symptomatic native epicardial coronary artery pathology: only 60 (6.8%) of these angiographically normal reference segments were normal [12]. Reference segments contained less calcific and dense fibrotic plaque and proportionately more soft plaque elements. Independent predictors of reference segment percent cross-sectional narrowing were male gender, patient age, diabetes mellitus, hypercholesterolemia and presence of multivessel disease. Independent predictors of reference segment calcification were patient age and serum creatinine levels. Reference segment percent cross-sectional narrowing in 723 patients undergoing transcatheter therapy was similar to that in patients studied for diagnostic purposes. However, reference segment calcification was greater in treated patients. Interestingly, reference segment disease was not an independent predictor of subsequent angiographic restenosis or clinical events within 12 months of follow-up. In the WISE study, 100 consecutive women with normal coronary arteries were studied by intravascular ultrasound and about 80% had atherosclerotic plaques [12]. Extrapolating these findings, most of 48% women in WISE studied who were classified as having normal coronary arteries, would probably have some coronary plaques [13]. Therefore, when using visual analysis of biplane CAG, it would be better to speak about non-obstructive epicardial coronary pathology rather than saying that coronary arteries are normal.

Epidemiology of CSX

Most CSX-patients are women [4–10, 13–15]. There was a strong bias in evaluating women with CHD, however, at present coronary angiography is rapidly performed in women with suspected CHD. It has been now seen that nearly 75% of women with typical AP have no flow-limiting epicardial coronary pathology [11–15] and depending on different registry data this cardiac situation is also found in 5% to 15% of men [10, 13, 16, 21]. It must thus be accepted that millions of people (mostly women) with AP without flow-limiting coronary pathology will probably be identified each year.

Long-term outcomes in CSX

Cardiac syndrome X encompasses different pathophysiologic substrates. In spite of an extensive knowledge, we are still uncertain about the real outcomes of CSX-patients with stable AP. In 1940 it was stated that CSX-patients did not have an increased high cardiovascular risk, did not require cardiologic care [3], and to a certain extent, that they did not require a general medical care [13]. This is not true. As in most diseases, in CSX complications are associated with the progression of pathology. CXS-patients are not only disabled because of persisting symptoms, especially AP, but also have serious adverse cardiovascular outcomes [8–10, 13, 17, 22–25, 34–36]. It has been suggested that in CSX-patients, the prevalence of long-term outcomes may be similar to that of asymptomatic patients with flow-limiting coronary pathology [13, 37] but we lack precise data on long-term complications. A statistical method 'composite outcome measures' is often used to collect data on outcomes, but it is proven that the findings may obfuscate the data and lead to inaccurate conclusions [38]. To improve the validity of the analysis of long-term complications and poor outcomes in ACS the 'weighted composite endpoints' have been used [39]. Unfortunately, up to now, this approach has not been used to assess outcomes in CSX and in other clinical aspects of CHD. Thus, at present we know that CSX is not a benign condition as previously believed but we ignore the exact frequency of long-term complications in this pathology. Also, we cannot accurately compare the prevalence of cardiovascular outcomes between CSX-patients and patients with flow-limiting epicardial coronary artery pathology.

Causes of severe outcomes in CSX

By definition, in CSX myocardial ischemia and AP are not due to flow-limiting coronary pathology. As shown in Table 3, different complex microcoronary pathophysiologic substrates are present in CSX and are linked with adverse long-term cardiovascular complications [8–10, 13, 17, 22, 24, 34–36]. In CSX, most serious adverse events result from coronary thrombosis, which is usually associated with rupture or erosion of vulnerable plaques, usually not detected by conventional CAG [11–13, 40]. Gender and age are important in patients with ACS or myocardial infarction without

Table 3. Pathophysiology of serious cardiac outcomes in cardiac syndrome X.

Most adverse serious events, such as acute coronary syndrome and myocardial infarction result from coronary thrombosis. These events are usually associated with rupture or erosion of vulnerable plaques, usually not detected by conventional coronarography.
In patients with sudden coronary death, the most frequent cause (in a third of cases) is plaque rupture due to erosion. In the rest of cases, several causes were detected, such as calcified nodules.
Patient gender and age are important. Plaque rupture was the cause of death in about one third of women, but in less than one sixth of men. Acute cardiac thrombi were the predominant cause in women < 50-year; on the other hand, plaque rupture was the predominant cause in > 50-year-old women. In men, age did not play any role in the occurrence of plaque rupture.
In nearly 95% of cases, the pathophysiologic mechanisms are endothelial dysfunction, microvascular dysfunction (sometimes with coronary microvascular spasm). Epicardial coronary artery spasm occurs in nearly 4% of cases.
These mechanisms interplay with the plaque erosion or rupture and induce cardiovascular poor outcomes. As in other arteriosclerotic conditions, plaque rupture or erosion, coagulation dysfunction, several products of inflammation etc. may cause acute thrombosis and severe cardiac events.

flow-limiting coronary pathology. Female sex and younger age are independent predictors. These complications are detected in 10–25% of women and only in 6–10% of men [13, 31]. In CXS-patients with sudden coronary death, the most frequent cause was plaque rupture, in a third of cases erosion and in the rest several causes were detected, such as calcified nodules [13, 37]. Patient gender and age are important, because plaque rupture was the cause of death in nearly one third of women, but in less than one sixth of men. Acute cardiac thrombi were the predominant cause in women < 50-year but plaque rupture was the predominant cause in > 50-year-old women. In men, age did not play any role in the occurrence of plaque rupture. Of course, in CSX the presence of ED, MVD and sometimes CAS interplays with the plaque erosion or rupture and worsens the outcomes [13, 37, 40]. In CSX, most serious adverse events result from coronary thrombosis which is usually associated with rupture or erosion of vulnerable plaques, an event which commonly is not detected by conventional CAG [23–25, 37, 40]. In CXS-patients with sudden death plaque, rupture was the most frequent cause (in more than 30% of cases) while in the rest several causes, e.g. calcified nodules, were detected and there is a patient *gender difference*, because plaque rupture was the cause of death in about one third of women, but in less than one sixth of men [11, 36–38]. *Patient age* is also relevant in CSX. Indeed, in < 50-year-old women acute cardiac thrombi were the predominant cause. On the other hand, in > 50-year-old women plaque rupture was the predominant cause. Interestingly, age did not play any role in the occurrence of plaque rupture in men [11, 24, 36–38]. Of course, in CSX the presence of ED, MVD and sometimes CAS interplays with the plaque erosion or rupture and worsens the outcomes.

Therapy of CSX

Obviously, cardiac revascularization is not a therapeutic option in CSX. We lack specific drugs for treating CSX. Therapy is empirical and drugs used in CHD are also used in CSX. Low-dose aspirin is largely used, even if there is no evidence that long-term aspirin should be given to patients even with known cardiovascular disease: theoretical arguments that aspirin can prevent cardiovascular events by reducing the propagation of thrombus are countered by evidence that plaque hemorrhage from vasa vasorum may also cause plaque growth instability; aspirin may also detract from the benefits of angiotensin-converting enzyme inhibitors [41]. We lack controlled studies on statins (or HMG-CoA reductase inhibitors) in the therapy of CSX but these drugs are used to treat endothelial dysfunction. An experimental study [42] has proven that pravastatin reverses obesity-induced dysfunction of pluripotent stem-cells derived from endothelial cells via a nitric oxide-dependent mechanism. Similar data are not available for other statins. It is possible that statins may improve ED also in CSX. Short-acting sublingual or spray aspirin or isosorbide nitrates are largely used to treat AP in CSX, but in this pathology this therapy is less effective than in patients with CHD. Beta-blockers, calcium antagonists, and long-acting nitrates or nicorandil are often used to treat AP in CSX. However, beta--blockers are usually less effective than in CHD. Nitrates and nicorandil are also less effective and induce more adverse effects than in CHD. A study in patients with stable vasospastic angina has shown that, when compared with calcium antagonists, nitrates did not improve prognosis, and on the contrary, the combined therapy increased the risk for cardiac adverse events, especially when transdermal nitroglycerin and nicorandil were used [43].

Ranolazine is frequently off-label used in CSX [44, 45]. We lack controlled studies in CSX but many cardiologists report a better efficacy in reducing AP than with beta-blockers, calcium antagonists, and long-acting nitrates or nicorandil.

Conclusions

Coronary heart disease represents an important clinical problem worldwide. The number of cardiac interventions is expected to increase over the coming decades. In the past, there was a strong bias in evaluating women with CHD. However, at present, more women than men are evaluated for CHD and it has been recognized that the prevalence of CHD in women is at least the same as in men. We have learned that CSX is frequent because worldwide each year millions of people (mostly women) with AP without flow-limiting epicardial coronary pathology are identified. Indeed, in nearly 75% of women and in up to 15% of men with typical AP coronary angiography does not detect flow-limiting epicardial coronary pathology. Also, data from large myocardial infarction registries suggest a 5% to 25% prevalence of cases without flow-limiting coronary pathology [23]. It must be considered that these people are said to have normal coronary arteries by visual analysis of biplane CAG. However, as demonstrated from autopsy and in vivo by ultrasound intravascular studies it would be more appropriate to say that in the majority of cases CAG does not detect obstructive or flow-limiting coronary pathology. ED and MVD (sometimes also coronary microvascular spasm and epicardial CAS) are established coronary pathophysiologic substrates in CSX. Symptoms and signs of cardiac pathology are the same as those of patients with flow-limiting coronary pathology. The difference lies in the fact that in CSX the mechanisms of myocardial ischemia are microvascular and flow-limiting epicardial coronary pathology is absent. The pathologic entities at work in CSX by interplay are linked with poor long-term outcomes, specifically hospitalization, ACS, myocardial infarction, coronary revascularization and sudden death. The prevalence of these outcomes is probably smaller than in patients with CHD but we lack precise data. Given the association between CSX and consequent downstream morbidity, it seems logical to assess long-term outcomes by appropriate analysis, e.g. by the 'weighted composite endpoints' approach. Nonetheless, severe cardiovascular complications are frequent in CSX and thus CSX is not a benign condition. Drugs used in CHD are prescribed in the therapy of CSX, but we lack data from specific double-blind randomized trials. It seems that statins and ranolazine might exert positive effects. However, specific research to target interventions in CSX would be necessary.

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Conflict of interest: None declared

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