Cardiac X syndrome: an overview of the literature and the local experience in Southern Switzerland

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Summary

In recent years, a particular emphasis from the European authorities was put on women's health. Different publications emerged in international journals dedicated to this topic. Several studies described the difficulties and the differences in diagnosis and treatment of heart diseases in women emphasising how even common cardiac conditions are often undertreated and misdiagnosed. The Swiss Society of Cardiology annual congress this year was also dedicated to the topic "Women and the Heart", underlying the nationwide relevance of the problem. These data demonstrate the need for more specific attention and research on female aspects of cardiovascular care.

Besides the typical manifestations of heart disease, such as acute coronary syndromes, angina or hypertension which have a similar prevalence in both genders, there is a syndrome mostly affecting perimenopausal women. It is defined as Cardiac syndrome X (CSX), and is a clinical condition usually characterised by anginal pain, positive exercise stress testing and negative coronary angiography. Although the prognosis according to previous studies was thought to be good, it is now appreciated that these women face significantly greater morbidity than once believed, with an uncertain treatment course and a substantial cost burden to the health care system. Thus, this particular syndrome deserves special attention from health care professionals.

Different pathophysiological mechanisms have been proposed to explain the nature of this syndrome. In this article we will review the literature data on CSX with a special focus on symptoms, pathophysiologic mechanisms, difficulties in management and prognosis in this particular group of patients, sharing the authors' experience in this field as well.

Key words: cardiac X syndrome; microvascular angina

Authors' contribution:
equal contribution
(JK and APP)

Funding / potential competing interests:
No financial support and no other potential conflict of interest relevant to this article were reported.

Introduction

The term Cardiac syndrome X (CSX) was introduced by Kemp in 1973 [1]. CSX is usually characterised by the presence of typical angina chest pain, pathological stress test results according to the standard criteria and the absence of coronary disease on the coronary angiography. The character and location for the chest pain, its triggering factors and the occurrence of the ST segment shifts during chest pain are similar to those seen in patients with coronary artery disease [2].

This is a classical definition of CSX. However, the broader definition based only on the presence of angina-like pain associated to normal epicardial arteries has also been used. The exclusion of extracardiac and known cardiac causes of chest pain, such as left ventricular hypertrophy, systemic hypertension, valvular heart disease, diabetes mellitus, and cardiomyopathy is usually required for the diagnosis of CSX. However, according to the review of Vermeltfoort et al. [2] in at least one-third of the studies concerning CSX, patients with over mentioned pathologies were not excluded from the analysis. Moreover, according to Lanza et al. patients with typical cardiovascular risk factors (diabetes, hypertension, smoking or obesity) should be included in the definition of the CSX as these risk factors contribute to the "microvascular dysfunction" typically involved in the pathogenesis of the syndrome [3]. According to these observations Lanza has proposed new definition of CSX (table 1).

Thus, the multiple definitions of this entity and the variations in inclusion and exclusion criteria contribute to the conflicting reports in literature regarding its frequency, risk factors, and treatment and make interpretation of the results of individual studies difficult. This shows the need for a generally accepted definition of CSX.

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Table 1
The proposed definition of the Cardiac X syndrome according to Lanza et al. [3].

1. Stable angina, exclusively or predominantly induced by effort.
2. Findings compatible with myocardial ischaemia/coronary microvascular dysfunction on diagnostic investigation
3. Normal (or near normal) coronary arteries at angiography
4. Absence of any other specific cardiac disease (for example, variant angina, cardiomyopathy, valvular disease)

Epidemiology

Demographic and clinical factors associated with CSX have been largely derived from smaller mechanistic and observational studies. Reports suggest that women with CSX are older and more frequently postmenopausal [4], but other larger studies, such as the Women's Ischaemia Syndrome Evaluation (WISE) cohort, describe these women to be younger and more commonly premenopausal than those with obstructive coronary artery disease (CAD) [5]. Clearly, methodological differences, such as selection bias and reference populations, impact these discrepant findings.

Up to 30% of women undergoing coronary angiography because of angina typical enough to suggest coronary artery disease may have normal arteries [6]. Data from the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO) and Thrombolysis in Myocardial Infarction (TIMI) trials demonstrated that 10–25% of women presenting with acute coronary syndrome and STEMI have normal arteries, compared with 6–10% of men [7]. Takotsubo cardiomyopathy, which represents another clinical entity of chest pain syndrome without obstructive coronary artery disease, affecting mostly postmenopausal women, surely contributes to these gender differences and represents an estimated 1% to 2% of patients who present with an acute coronary syndrome [8]. Applying these percent values to the amount of coronary angiographies performed in dedicated cardiac care centres, the potential number of patients with such a cardiac clinical condition is of significant importance with a strong impact on human and financial resources.

Pathophysiological mechanisms

In the last years, several studies focussed on the analysis of CSX pathophysiological mechanisms which have not yet been fully elucidated and are likely to be multiple. Most of the studies about the pathophysiology of CSX are mainly derived from pharmacological stress studies. Hereby we present an overview of the different mechanisms which have been implied in CSX puzzling pathogenesis.

Microvascular dysfunction

Since its first description, it was proposed that in CSX angina is caused by a dysfunction of small resistance coronary artery vessels not detectable on coronary angiography. For this reason, Cannon et al. referred to chest pain with angiographically normal coronary arteries with the name of "microvascular angina" [9]. Evidence of microvascular dysfunction in CSX patients derives from studies assessing coronary flow response to vasoactive stimuli. Several studies have indeed shown a reduction in both endothelium-dependent and endothelium-independent coronary vasodilation, using both invasive and noninvasive techniques for the measurement of coronary blood flow [10]. Consequently, a number of causal mechanisms have been proposed for microvascular dysfunction. Due to decreased coronary flow response to endothelium mediated vasodilator stimuli, the latest studies focussed on endothelial dysfunction as a leading explanation for microvascular dysfunction. On the other hand, since impairment of coronary microvascular dilation in response to endothelium-independent stimuli has been demonstrated, microcirculation abnormalities have been proposed including altered resting vascular smooth muscle tone, altered response to constrictor or dilator stimuli, reduced number of arterioles and capillaries (rarefaction), structural alterations that contribute to decreased lumen size, increased wall-to-lumen ratio and increased stiffness [3, 11]. Moreover, risk factors of CAD such as obesity, hypertension, hypercholesterolaemia and smoking, frequently present in CSX patients, may play a role [12], and other factors have also been recently identified such as homocysteine, O_2-free radicals, infections, inflammatory mechanisms, and oestrogen deficits [13]. Diffuse atherosclerosis has also been implied since even layers of fatty deposits which line the small coronary vessels could restrict blood flow without evidence on coronary angiography or may lead to remodelling of the arterial wall [7]. Indeed, several studies have demonstrated that patients with microvascular dysfunction frequently have atherosclerosis on intravascular coronary ultrasound [14] and face a 2.5% annual adverse rate, including myocardial infarction, stroke, hospitalisation for congestive heart failure, and sudden cardiac death [11]. The summary of the mechanisms responsible for microvascular dysfunction and predisposing clinical conditions are presented in table 2.

Based on all this evidence, Bairey Merz et al. [11] proposed a coronary reactivity testing for risk stratification and optimal management planning in appropriate at-risk subjects. This strategy includes intracoronary infusion of adenosine, acetylcholine, and nitroglycerin to assess microvascular and macrovascular endothelial and nonendothelial function. Although potentially serious complications such as coronary dissection can occur, coronary reactivity testing could

Table 2
Mechanisms of microvascular dysfunction and the predisposing clinical conditions.

Impaired coronary reactivity (altered response to constrictor or dilator stimuli)	Oestrogen deficiency, hypertension, LV hyperthrophy
Endothelial dysfunction	Hypertension, dyslipidaemia, Smoking, Diabetes mellitus, inflammation, oestrogen deficiency
Structural alterations (decrease lumen size, increased stiffness)	Hypertension, LV hypertrophy, Diabetes mellitus, chronic inflammation
Altered resting vascular smooth muscle tone	Oestrogen deficiency, hypertension
Reduced number of arterioles and capillaries	LV hyperthrophy

be performed in high-risk patients by experienced interventional cardiologists in order to guide the therapy.

Myocardial ischaemia

There has been substantial controversy about whether myocardial ischaemia is widely prevalent in CSX. Myocardial ischaemia is objectively documented in approximately 25% of patients affected by CSX [15]. Evidence of myocardial ischaemia in these patients derives from transient ST segment depression or reversible defects on myocardial perfusion studies and up to 20% of CSX patients also show metabolic evidence of myocardial ischaemia [16–17]. In contrast, other studies, especially those using stress echocardiography, have demonstrated normal global or regional contractile reserve despite the provocation of typical symptoms [18–20]. A lot of expectations were put on cardiac magnetic resonance as a noninvasive diagnostic tool that could help to evaluate the presence of abnormal myocardial perfusion. However, despite encouraging preliminary results [21] that demonstrated subendocardial hypoperfusion, the latest study by Karamitsos et al. [22] failed to confirm these findings. The authors came to the conclusion that patients with syndrome X have no evidence of transmural hypoperfusion or deoxygenation during vasodilatory stress but show greater sensitivity to chest pain compared with healthy controls.

Abnormal pain perception

Increased pain perception is common in patients with CSX, but the reason remains elusive. A potential link between microvascular dysfunction and abnormal cardiac pain perception has been suggested by Lanza et al. [23]. After demonstrating a coronary adrenergic hyperreactivity in CSX patients, they hypothesised an enhanced reactivity to usually innocuous stimuli due to functional alterations of cardiac nerve ending following repeated episodes of myocardial ischaemia. However, pain perception could not be explained only by the presence of ischaemia, as according to data in the literature not all patients with provoked chest pain have demonstrated reduced myocardial blood flow. Indeed, also in a recent study performed with cardiac magnetic resonance imaging (MRI), the majority of patients with CSX reported chest pain of moderate extent during adenosine stress although no myocardial perfusion defects were found compared to the control group [22]. In addition, chest pain can be provoked in some patients by movement of the catheter within the right atrium or right ventricle, which instead results from mechanical distortion of mechanoreceptors to catheter stimulation [24].

Oestrogen deficiency

Considering the high prevalence of peri- and postmenopausal women in most series of CSX, oestrogen deficiency has been suggested to play a role in the pathogenesis. Oestrogen deficiency can be associated with the vasomotor instability [25] and a link between reduced oestrogen and impaired endothelial dependant coronary vasomotion has been proposed [26]. Moreover, changes in women's oestrogen concentrations modulate the natural ability of brain to suppress pain. Thus, when concentrations are low, the neural system does not control pain as efficiently, therefore contributing to the increased nociception [27].

The role of inflammation

Previous studies showed that patients with CSX have higher serum high sensitivity C-reactive protein (hs-CRP) levels, increased common carotid artery intima-media thickness (CCA-IMT) and increased carotid artery stiffness than controls, suggesting the presence of an inflammatory background and an impaired arterial wall structure possibly due to atherosclerotic burden [12]. Increased hs-CRP levels in CSX patients in the present study support previous observations suggesting a role of inflammation in the pathogenesis of endothelial dysfunction. In fact, the presence of CRP is associated with enhanced levels of cellular adhesion molecules, increased endothelin-I expression and reduced bioavailability of nitric oxide [12]. Moreover, elevated CRP levels have been reported to correlate with electrocardiogram markers of myocardial ischaemia and clinical disease activity [28].

Autonomic dysfunction

Alterations of autonomic nervous control of cardiac function have been described in CSX. The hypothesis of

an autonomic imbalance in CSX patients was firstly proposed by Montorsi et al. [29] who demonstrated that a subgroup of CSX patients with abnormal electrocardiogram at rest showed coronary adrenergic hyperactivity during cold stress test. Abnormal cardiac adrenergic nerve function was also detected by [123 I] metaiodobenzylguanidine (MIBG) myocardial scintigraphy [23]. Improvement of the clinical symptoms was sometimes obtained with β-blocker treatment [30]. However, direct signs of coronary adrenergic hyper-reactivity had never been demonstrated since myocardial blood flow was not raised by α-blockade [31], and CSX patients did not show increased levels of plasma catecholamines [32, 33]. On the other hand, the indexes of parasympathetic tone were shown to be frequently impaired, at least in a subgroup of CSX patients. For this reason, Rosano et al. [34] suggested that the sympathetic predominance in CSX patients was caused by a leftward shift of the sympatho-vagal balance which seemed to precede ECG-detectable ischaemic episodes [35]. However, many authors cast some doubts on this interpretation and focussed their attention on the reduction of vagal tone, subsequently confirmed by Gulli et al. who demonstrated a reduced parasympathetic tone in about two-thirds of CSX patients [36]. Indeed, it is well known that vagal tone contributes to the regulation of baseline coronary vascular resistance and direct vagal stimulation produces vasodilatation across left ventricular wall. Moreover, parasympathetic impairment might also be related to the endothelial dysfunction in CSX patients since acetylcholine released at the parasympathetic endings increases the vasodilator effect of nitric oxide on the vascular endothelium [10].

These data show that the investigation of the actual neuro-vegetative impairment might be of primary importance in the therapeutic approach to the disease.

Diagnosis

According to the definition proposed by Lanza [3], the diagnosis of CSX would require, together with the presence of typical angina and normal coronary arteries at angiography, some findings compatible with myocardial ischaemia or coronary microvascular dysfunction, or both (table 3). Different diagnostic modalities have been studied in CSX populations. It is known that quantitative regional myocardial blood flow (MBF) can be measured noninvasively and accurately using positron emission tomography (PET) [37]. The results of PET studies aimed to assess the MBF in patients with CSX showed conflicting results. According to one study about one third of patients showed reduced coronary vasodilator reserve during an exercise test, but no correlation could be found between coronary vasodilator reserve and the presence or absence of chest pain and/or ST depression after dipyridamole infusion [38]. Another study by Camici et al. did not find differences in MBF either at rest or after dipyridamole, despite syndrome X patients experiencing chest pain after dipyridamole to the same extent as patients with CAD [39]. Both these studies cast further doubt on ischaemia as the basis of the chest pain, at least in the majority of syndrome X patients. MRI has a superior spatial resolution compared to nuclear studies. The previous studies with MRI have shown conflicting results regarding the presence of ischaemia [40, 41]. The overmentioned study by Karamitsos et al. [22] aimed for the first time to quantitatively evaluate the myocardial blood flow reserve and oxygenation as a marker of ischaemia in the patients with CSX. The study did not find the evidence of transmural hypoperfusion or deoxygenation during vasodilatory stress test. These results could be explained by the selection criteria of the patients. Indeed, only patients without conventional cardiovascular risk factors, that could contribute to microvascular dysfunction, were included. This could be a reasonable

Table 3
The findings compatible with myocardial ischaemia or coronary microvascular dysfunction mandatory for the diagnosis of CSX (modified according to Lanza [3] and Bairey Merz et al. [11]).

1. Positive exercise test results according to the standard criteria
or
2. Reversible perfusion defects on stress myocardial scintigraphy
or
3. Stress-induced coronary blood flow abnormalities by cardiac magnetic resonance / Doppler ultrasound
or
4. Myocardial blood flow reserve abnormalities by PET
or
5. Metabolic evidence of transient myocardial ischaemia (cardiac PET or magnetic resonance)
or
6. Coronary blood flow abnormalities in response to various vasoconstrictor and vasodilator stimuli during coronary angiography

explanation and might underline the presence of the mechanisms other than ischaemia potentially responsible for the symptoms in these patients.

Special tests such as the changes in oxygen saturation, pH, and the production of lactate in coronary sinus blood observed during stress test [26] can be used only for research purposes but not in daily clinical practice.

According to the current knowledge, we would say that there is no gold standard diagnostic test for CSX due to different reasons, such as heterogeneity of the CSX populations, different syndrome definitions and patients inclusion criteria. In our clinical practice we establish the diagnosis on the basis of the presence of the typical exertion chest pain, pathological exercise test results and normal coronary angiogram. We use other diagnostic modalities only if exercise test results are inconclusive. We suppose that invasive diagnostic strategy could indeed be proposed to a subset of patients with repetitive uncontrolled symptoms in order to guide the pharmacological treatment according to the predominant pathophysiological mechanism. However, the use of the invasive technique is not widely spread due to lack of standardisation and possible complications related to the invasive approach [11].

Treatment

Managing patients with CSX can be frustrating for both patients and physicians, as there is a lack of data regarding an optimal treatment algorithm. Most studies are observational or only involve a small sample size, yielding conflicting results. The treatment strategies can be subdivided according to the presumably predominant pathophysiology mechanism (table 4).

Table 4
Treatment strategies in patients with CSX.

Anti-ischaemic agents	Beta blocker
	Nitrates
	Calcium antagonists
	Xantine derivates
Abnormal endothelial function	ACE inhibitors
	Statins
	Metformin
	Life style modification: smoking cessation, weight control, physical training
	Enchanced external counterpulsation
Abnormal cardiac nociception	Imipramine
	Neurostimulation
	Oestrogens
Oestrogen deficiency	Hormone replacement therapy

Life style modification

Life style modification can improve the cardiovascular risk factor profile in patients with CSX, as most of them significantly contribute to the microvascular coronary dysfunction. Given the association of obesity [42] and smoking [43] with endothelial dysfunction, weight loss and smoking cessation are encouraged in patients with CSX. Moreover, as a small study by Eriksson et al. demonstrated, exercise training in patients with CSX results in increased exercise capacity with lesser angina pain [44].

Beta blockers

Multiple studies have demonstrated a central role for beta blockers in the management of CSX [45–47]. Although the response to beta blockers is variable in improving chest pain (19–60%), beta blockers work by lowering adrenergic tone and reducing myocardial oxygen demand, as well as enhancing endothelium-dependent vasodilation. Beta blockers undoubtedly are considered the first line therapy for CSX especially in patients with increased sympathetic activity and those with typical tachycardia-related chest pain [48].

Calcium channel blockers

Clinical results from the use of calcium channel blockers are highly variable. While some studies suggest clinical benefit in CSX [49], others found no improvement in ischaemic episodes [46]. The efficacy of calcium channel blockers has yet to be established but they can be used as combination therapy with beta blockers.

Nitrates

The use of nitrates in CSX is controversial, as therapy with these agents have a high treatment failure rate. Observational studies by Kaski et al. have suggested the efficacy of sublingual nitrates for treating CSX, though this was effective in only 42% of the patients [15]. In general sublingual nitrates may benefit symptomatic episodes, but long acting nitrates have proven disappointing as an initial treatment strategy and are best used as combination agents [45].

Xantine derivates

Some investigators have suggested a role for xanthine derivatives, such as oral aminophylline, which block the adenosine receptor and lead to a more favourable redistribution of coronary blood flow [50]. Adenosine can play a pathogenetic role in syndrome X both as an algogenic substance and a powerful arteriolar dilator able to contribute to microvascular 'steal' mechanisms that may lead to subendocardial ischaemia [51]. The treatment with aminophylline could be particularly useful for patients with syndrome X and reduced pain threshold and those who also have chronic obstructive airways disease, bronchial asthma and unexplained

shortness of breath as a major component of the syndrome [48].

Oestrogens

Oestrogens may have an effect on pain perception and can improve endothelium-dependent coronary vasodilation. Even though many patients with CSX are perior postmenopausal, studies regarding the efficacy of hormone replacement therapy using various preparations provide conflicting results [52, 53]. Moreover, the use of oestrogen therapy is not without problems at present [54], as shown by randomised control clinical trials. This therapy can increase the risk of cardiovascular disease, and of breast cancer [54]. In summary, oestrogen therapy may be considered for symptom management in postmenopausal women with CSX particularly in those with other well-defined indications for this therapy, balancing the slightly increased risk of CV events.

ACE inhibitors

Given the reported role of the renin-angiotensin system in promoting microvascular dysfunction, angiotensin converting enzyme (ACE) inhibitors have been proposed as potential therapies for CSX. The studies have shown improved total exercise duration and exercise capacity in CSX patients on treatment with ACE inhibitors [55, 56]. According to Kaski et al. [48] ACE inhibitors could be particularly useful in patients with borderline hypertension or a family history of essential hypertension and documented endothelial dysfunction.

Statins

Outside of their lipid lowering properties, statins have been shown to decrease inflammation and improve endothelial function [7, 57]. They could be efficacious agents for the management of CSX, especially in the patients with elevated C-reactive protein levels and other markers of the chronic inflammation. The combination of an ACE inhibitor and a statin may amplify the beneficial effects of both on microvascular function resulting in the improvement of the quality of life and exercise duration [58].

Analgesic therapy

Another way to improve symptoms experienced by patients with CSX is through pain modulation especially in those with clear evidence of altered somatic and visceral pain perception. Imipramine, typically used in chronic pain syndromes, has been shown to reduce episodes of chest pain in CSX patients, but no improvement of the overall quality of life was observed. The large incidence of side effects of imipramine in this study probably account for the latter [59]. Imipramine thus could be useful in selected patients, but with close monitoring of the possible side effects.

Novel therapies

Other therapies such as metformin, nicorandil, extracorporeal enchanced counterpulsation have shown some beneficial effects in the patients with CSX.

Our experience in the field of CSX

Giving the lack of a universal definition of CSX and clear inclusion and exclusion criteria together with the heterogeneous pathophysiological mechanisms, the number of patients involved in previous studies has been quite limited. The data regarding the prognosis are also lacking. Thus, the Department of cardiology and cardiovascular pathophysiology of the University of Perugia has launched the multicentre observational prospective registry of the CSX in order to obtain clinical and follow-up data of these patients on a large scale. The Cardiovascular Research Unit of Ospedale San Giovanni in Bellinzona has become a unique Swiss partner centre in the ongoing registry. This was one of the main reasons that revived our interest in the CSX.

We started to search for patients in the Canton Ticino that could fulfil the inclusion criteria and would give their informed consent for participation in the registry. With the help of the regional group of cardiologists from the Canton Ticino we have so far recruited 14 patients.

Entry criteria were recurrent typical chest pain at rest and on effort, a normal 12-lead ECG at rest, positive exercise tests for ischaemia-like ECG changes (horizontal or down-sloping ST-segment depression of >1.5 mm at 60 ms after the J point in ≥2 contiguous leads) or other pathological functional stress test in the presence of normal left and right ventricular function, absence of valvular heart disease or myocardial hypertrophy on echocardiography, and normal coronary angiogram without evidence of focal or diffuse coronary spasm.

Having collected the data of the Swiss Italian cohort of CSX we decided to describe the clinical characteristics of these patients as well as to look retrospectively on the follow-up data.

In our study the Swiss Italian cohort of patients affected by cardiac syndrome X was represented by 14 women (100%) with a mean age 57.9 ± 8.8 years and mean BMI 24.2 ± 3.9 kg/m^2. A total of 35.7% were smokers, 50% had hypertension, and 42.8% had dyslipidaemia. The patients were on treatment with various agents (aspirin 21.4%, clopidogrel 14.2%, beta blockers 57.1%, ACEI/ARB 28.5%, calcium antagonists 64.2%, nitrate 57.1%, statins 57.1%). Moreover, a substantial percentage of patients received either benzodiazepines (50%) or antidepressants (14%). Adverse events are shown in the table 5. There were two minor cerebral ischaemic events without precise aetiology.

Our data have shown that the Swiss Italian cohort of patients with CSX is represented by middle-aged,

Table 5
Adverse events of the CSX on the follow-up in the Swiss Italian cohort (n = 14).

Years of follow-up, average ± SD	7.7 ± 6.3
All cause mortality	0
Hospitalisation for angina	4 (28.5)
Residual angina	9 (64.2)
Acute coronary syndrome	0
Decompensated heart failure	0
Stroke/TIA	2 (14.2)
Recoronary angiography	3 (21.4)

mostly perimenopausal women with various cardiac risk factors. Anti-anginal treatment is not always efficacious although agents with different mechanism of action are employed. Some patients present adverse events during follow-up. Repetitive hospitalisations for recurrent and residual angina may influence the quality of life. The occurrence of two cerebral ischaemic events without overt aetiology, although potentially reliable to chance in our relatively small cohort of patients, deserves attention.

Further studies

Given the interest and experience of our group in atherosclerosis and endothelial function, we have also come to the idea to study the endothelial function in this particular group of patients by means of novel non-invasive technique for the evaluation of the endothelial function (EndoPat, Itamar medical, Israel).

Endothelial dysfunction has shown to be an established pathogenetic factor of the microvascular coronary dysfunction as we have already mentioned above. It is likely to be multifactorial in these patients, since it is conceivable that risk factors such as hypertension, hypercholesterolemia, diabetes mellitus and smoking can contribute to its development [12]. Moreover, it has been observed in previous studies that patients with endothelial dysfunction have a higher risk of adverse cardiovascular events on follow-up [11]. There is a substantial amount of data regarding coronary endothelial function in Cardiac syndrome X. However, the evaluation of systemic endothelial function in this rare disease is limited. Given the complexity and invasiveness in measuring coronary endothelial function and considering the data that have shown that endothelial dysfunction affects not only the epicardial coronary arteries, but also the microcirculation and peripheral circulation, the evaluation of endothelial function using reliable noninvasive methods could give an answer to several open questions. The evaluation of the endothelial functions could allow to identify a subgroup of patients with increased risk of adverse cardiovascular events on follow-up using a user-friendly non-invasive technique; as well as to investigate the effect of potentially interesting drug interventions in this rare disease.

We, therefore, plan to examine the systemic endothelial function using EndoPAT in 25 patients with classic cardiac Syndrome X enrolled from the Swiss cohort of the Italian Registry on CSX. The main endpoint will be the assessment of the endothelial function by EndoPAT, which is a well-validated tool to assess systemic endothelial function in humans [60].

A further intriguing and quite unexplored issue is the pathophysiological relationship between endothelial dysfunction and autonomic imbalance both implied in CSX pathogenesis. Very few data exist about it. An interesting previous study [61] suggested a possible link between these two different pathogenic hypotheses showing, in a higher risk group of the entire CSX population, a reduced coronary flow reserve in patients with parasympathetic dysfunction. Therefore, this result seemed to support the idea that parasympathetic impairment could probably be related to microvascular dysfunction through its influence on endothelial function, even if the relation between autonomic tone and a direct marker of endothelial dysfunction has never been assessed.

Therefore, in order to further explore this issue, we also plan to assess the presence of autonomic imbalance with the evaluation of the BaRoreflex Sensitivity (BRS), in the same cohort of patients undergoing EndoPat. Indeed BRS has proved to be one of the most reliable markers of cardiovascular autonomic control. The main endpoint will be the evaluation, for the first time, of the potential link between autonomic imbalance and a direct marker of endothelial dysfunction.

Conclusions

Cardiac X syndrome still represents a diagnostic and therapeutic challenge for health care professionals. Applying the novel definition criteria, the syndrome can be estimated to be widely under-diagnosed among women with chest pain and normal coronary arteries. This syndrome, therefore, should not be neglected despite of the quite good overall prognosis, mostly because some high-risk patients can present the adverse events on follow-up and face repetitive hospitalisations and diagnostic procedures. Specific treatment regimens should be applied according to the predominant pathogenetic mechanisms. Further large scale studies should be encouraged and consensus on the diagnostic and treatment strategies of this syndrome is required.

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