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Pharmacological Management of Cardiac Syndrome Y: A Focused Review

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Abstract

The Coronary slow flow phenomenon or cardiac syndrome Y is a relatively newly described microvascular coronary artery disorder that is still not fully understood. It is thought to be caused by increased flow resistance in the microvascular coronary artery beds. Patients affected by the CSY are typically young patients who suffer from myocardial ischemia at rest. Ischemia is often recurrent and as a result, patients suffer from a poor quality of life. The management of patients diagnosed with CSY is especially challenging, owing to its poorly understood pathophysiology, relatively recent recognition as a separate microvascular coronary artery disorder and most importantly the lack of large, homogenous, randomized controlled trials that compares the efficacy of various pharmacological agents. In this review, we touch briefly on the clinical presentation and the pathophysiology of the CSY and then we examine, in depth, the currently available evidence for the management of patients affected by this disorder.

Introduction

Myocardial ischemia in patients with normal epicardial coronary arteries still pose a diagnostic challenge to the treating cardiologist [1]. Although atherosclerotic coronary artery diseases account for the majority of ischemic cardiomyopathies, the significance of non-atherosclerotic coronary artery diseases as a cause of myocardial ischemia, is being only recently appreciated [2]. Several non-atherosclerotic coronary artery disorders have been so far described. Based on the caliber of the coronary arteries affected, they can be broadly classified into two major groups : A-Macrovascular coronary artery diseases affecting epicardial coronary arteries, a well described disorder that falls into this category is "Variant" or "Prinzmetal angina", B-Microvascular coronary artery diseases, which include a heterogeneous group of disorders that can be further sub-classified based on the etiology, examples include: cardiac syndrome X, microvascular angina and cardiac syndrome Y [1,2].

Microvascular Coronary Artery Diseases

Arbogast et al. in 1973 were the first to report on a microvascular coronary artery disease, when they reported a group of patients suffering exertional chest pain, yet having angiographically normal epicardial coronary arteries, due to the unclear etiology of the disorder it was subsequently named cardiac syndrome X [3]. The diagnosis of cardiac syndrome X, required the presence of exertional chest pain episodes, a positive exercise stress test, normal coronary arteries on angiography and exclusion of an epicardial coronary artery spasm as a cause of the anginal pain [1,4]. Subsequently, many patients were later diagnosed as having syndrome X yet not fulfilling the clinical diagnostic criteria, and therefore available data prompted the call for a further sub-classification of microvascular coronary artery disorders. Microvascular coronary artery disorders represent a heterogeneous group of disorders, all causing dysfunction at the microvascular level [5], they can be further sub-classified into 4 main subtypes: Cardiac syndrome X, microvascular spasm, microvascular angina and cardiac

syndrome Y. The diagnostic criteria for cardiac Syndrome X requires the presence of typical anginal-type chest pain (often in association with positive stress test and objective evidence of ischemia) with normal epicardial coronary arteries in angiography, where the diagnosis of variant angina has been excluded [6]. Syndrome X patients who have an impaired coronary flow reserve meets the criteria for the diagnosis of microvascular angina [7]. On the other hand, microvascular spasm warranted a separate classification within the microvascular coronary vasomotor disorders, as its name implies microvascular spasm is caused by a pathologic spasm of coronary microvasculature, it is diagnosed when spasm is noted after the administration of acetylcholine leading to chest pain, ischemic ECG changes and lactate production [8]. Table 1 summarizes the major differences between microvascular coronary artery disorders. The Coronary slow flow phenomenon or cardiac syndrome Y will be the focus of this review.

The Coronary Slow Flow Phenomenon or Cardiac Syndrome Y

The coronary slow flow phenomenon, remains up to date a poorly understood microvascular coronary artery disorder [9]. Tambe et al. were the first to report the coronary slow flow phenomena [10]. Clinically, it is defined as the slow passage of contrast material in epicardial coronary arteries in the absence of atherosclerotic lesions, spasm of the epicardial coronary arteries or any secondary etiology that may explain the slow flow [10,11]. An increased resistance to blood flow at the level of the microvascular coronary artery beds is thought to account for the myocardial ischemia occurring mostly at rest in these patients [11,12]. Inappropriate release and increased levels of the vasoconstrictor alkaloids neuropeptide Y [13], endothelin-1 [14], thromboxane A2 [15] and platelet aggregation [16] have been reported to play a role in the pathophysiology of this disorder. Moreover, endothelial cell dysfunction have been proposed based on studies reporting histological evidence of swelling and degeneration of endothelial cells, along with narrowing of the vascular lamina and

fibromuscular hyperplasia [17-19]. Controversy still exist however, for an endothelial cell dysfunction as the cause of the CSFP, since other reports observed intact endothelial cell function in patients with CSY [20]. The unique clinical characteristics of the CSFP warranted the call for a separate classification within the microvascular coronary artery disorders [5, 9, 12, 21-27], the name cardiac syndrome Y has been suggested due to the possible role of Neuropeptide Y in the pathophysiology of the CSFP [24,26]. The corrected TIMI frame count has been adopted as a standard method to quantify the slow flow, a TIMI frame count of 27 or more has been considered an acceptable angiographic definition of slow flow [28], which in the setting of a typical history and clinical presentation, strongly favors a diagnosis of CSY. Patients affected by the CSFP are typically young males who are smokers and presenting with a clinical picture of an acute coronary syndrome [29]. Only Yilmaz et al., found an association with the metabolic syndrome while Hawkins et al found an association with obesity [30]. It is very prudent, before diagnosing a patient as having the CSY, to rule out secondary causes of angiographic slow flow, examples include: Coronary ectasia, coronary spasm, coronary stenosis, inadvertent air embolism, residual infarct related stenosis and left ventricular hypertrophy causing microvascular dysfunction [9,12, 31]. Currently, the sensitivity and specificity of the angiographic slow flow as it relates to the CSY is still undetermined.

Management

Repurposing of the currently available pharmacological armamentarium has been attempted to treat CSY patients, yet no consensus exists so far on the optimal pharmacological management, mainly due to the lack of a thorough understanding of the pathophysiology and the lack of a large, randomized clinical trials assessing optimal pharmacological therapy. As a result, currently available data derives from small trials that often used heterogeneous inclusion criteria [32, 33]. The treatment of the CSFP should be therefore individualized and tailored for each patient, taking in account coexisting medical illnesses.

Mibefradil

Mibefradil is a selective inhibitor of T-type calcium channels that preferentially dilates the coronary vasculature [34]. A lack of negative inotropy and ability to cause reflex tachycardia was among the best marketed assets of Mibefradil [34], however due to reported lethal drug-drug interaction with many drugs, Mibefradil was subsequently withdrawn from the market. Mibefradil, was one of earliest pharmacological therapies that were examined for the treatment of patients affected by the CSFP. Beltrame et al. examined the direct angiographic effects of Mibefradil injection on the coronary circulation of patients with the CSFP [35], whereby patients were evaluated via angiography before and 30 min after 50 mg Mibefradil injection. Angiographically, Mibefradil reduced the number of vessels exhibiting a TIMI-2 flow from a total number of 18 to 5, at the same time lowering the TIMI frame count in remaining vessels exhibiting a TIMI-2 flow [35]. Clinically, Mibefradil was shown to reduce the anginal episodes frequency by 56%, episodes of prolonged angina by 74% and sublingual nitrate consumption by 59%. These results although interesting were not confirmed by a subsequent larger study and were therefore limited by the small sample size of 20 patients.

Nebivolol

Nebivolol, is a highly selective β1 receptor blocker that also have NO potentiating effects and therefore vasodilator properties [36] in addition, Nebivolol has anti-oxidative effects. These properties of Nebivolol have led to investigating it as a possible therapeutic option for the treatment of CSY. In total, 4 studies investigated the use of Nebivolol in patients with CSF [37-40]. Akcay et al., investigated the effect of Nebivolol treatment on the oxidative stress markers in Patients with CSF [37], a treatment regimen consisting of Nebivolol 5 mg per day for 6 months caused a significant decrease in the levels of MDA, NO and SOD level in patients with CSFP as compared to the control group [37]. Furthermore, the effect of Nebivolol on Endothelial function was explored by Albayrak et al. [38] whereby it was shown that 5 mg per day for 12 Weeks was able to improve endothelial function in patients with the CSFP. Albayrak et al., reported chest pain relief in 90% of treated patients [38]. Moreover, parameters measured included systolic, diastolic blood pressure and CRP all of which significantly decreased with Nebivolol therapy, in addition Brachial artery dilation variables including basal resistive index, post flow mediated RI and post nitrate mediated dilation RI were all significantly decreased after therapy with Nebivolol [38]. Gunes et al., explored Nebivolol vasodilator property to assess the regional functions of the left ventricle in patients with the CSF, the study included 27 Patients and showed improvement in angina, exercise capacity and LV functions as assessed using myocardial tissue Doppler velocities, assessment was done after 12 weeks of Nebivolol 5 mg per day.

Other Pharmacologic Therapies

Another agent that was investigated in the treatment of the CSF is Nicorandil [41,42]. Nicorandil is an anti-anginal medication that mediates its vasodilator effects by increasing the second messenger cGMP [43]. A comparison of the effect of Nicorandil and Isosorbide dinitrate on the TIMI frame count in patients affected with the CSFP showed that intracoronary injection of Nicorandil was superior to Isosorbide dinitrate, leading to a more significant reduction in the TIMI frame count [44]. Moreover, administration of Nicorandil 5 mg three times daily has been reported to decrease chest pain episodes and improve LV function in a small study consisting of 36 patients, possibly via an increase in NO release and decrease in endothelin-1 levels [41]. Another single-center, single-blind, randomized clinical trial by Sani et al., confirmed the superiority of Nicorandil to Nitroglycerin, in providing symptomatic relief from anginal chest pain in patients suffering from the CSFP [42]. Trimetazidine, is another anti-anginal drug that has been assessed for the treatment of patients with CSFP [45]. Trimetazidine, inhibit fatty acid beta oxidation leading enhancement of glucose oxidation and therefore optimization of energy utilization [46]. Short term use of Trimetazidine lead to decrease in anginal symptoms along with significant reduction in NO and ET-1 Levels [45] and improvement of heart rate variability parameters [45]. Finally, it is of importance to note that, in Patients with established infarcts, the use of the standard pharmacological armamentarium (Aspirin, Beta Blockers, and Statins) for secondary prevention is recommended.

Summary

The Coronary slow flow phenomenon or cardiac syndrome Y, remains a poorly understood microvascular coronary artery disorder. It's a diagnosis by exclusion, patients are typically young males,

smokers presenting with chest pain at rest. Unfortunately, there is no established therapy for the treatment of CSY, mainly due to the lack of homogenous large, randomized clinical trials. Based on the small number of studies conducted it appears that drugs that have antioxidant effects or drugs that have vasodilator effect, may be of benefit in the treatment of CSY patients. It remains up to the discretion of the treating physician to select the appropriate therapy. It should also be taken into account other coexisting medical conditions. In Patients with established infarcts, the use of the standard pharmacological armamentarium (Aspirin, Beta Blockers, and Statins) for secondary prevention is recommended. Future research direction should be more directed toward establishing standardized diagnostic criteria to diagnose patients with CSY, moreover a close look into the exact pathophysiology may also be of help in developing a targeted therapy. Finally, novel use of biomarkers may be of great benefits, microRNA for example, as this has never been studied.

	Microvascular Coronary artery Diseases			
	Cardiac Syndrome X	**Microvascular Angina**	**Coronary Slow Flow**	**Microvascular Spasm**
Chest Pain	Prolonged pain – with exertion	Variable, but often at rest	Prolonged- at Rest	Rest chest pain
Angiography	Normal	Normal	Normal with delayed opacification	Normal
Pathophysiology	Unclear/ microvascular dysfunction	Unclear/ Smooth muscle disorder	Unclear/ Increased microvascular resistance	Spasm of the micro coronary arteries
Risk Factors	Peri/ Post menopausal status	Unknown	Male gender, Obesity	Female gender and positive family history
Coronary flow reserve	Normal	Impaired	Normal/ debatable	debatable
Nitrates response	Usually not responsive	Usually not responsive	variable	variable
Exercise stress test	Positive	Usually negative	Usually Negative / debatable	Usually Negative
Diagnostic test	None	None/ abnormal coronary blood flow response in CSX	None	Acetylcholine induced ischemia in absence of epicardial spasm
Management	Beta Blockers, CCB, low dose Imipramine? others: of limited benefit	CCB, low dose Imipramine?	Mibefradil, Nicorandil, Nebivolol, others are investigative	Not clear but a combination of CCB and ACEI is proposed
Patient Population most affected	Menopausal females	Females	Young Males	Females

Table1: Coronary artery vasomotor disorders-a summary.

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