Syndrome X defines a group of patients who present with typical, usually exertional angina pectoris and a normal coronary arteriogram. They often have a positive exercise test, but direct signs of ischemia are detectable in only a minority of patients. A reduced coronary vasodilative response to dipyridamole or pacing is observed in such patients with or without a positive electrocardiographic exercise test. It is proposed that patients with syndrome X have a patchily distributed abnormal constriction of coronary prearteriolar vessels not involved in metabolic autoregulation of flow. An increased resistance of prearteriolar vessels can explain the reduced coronary vasodilative response observed in these patients, even when arterioles dilate maximally. Distal to the most constricted arterioles a localized compensatory increase of adenosine concentration can cause angina even in the absence of ischemia because adenosine is an algogenic substance. Ischemia can develop when myocardial metabolic demand exceeds blood supply or when metabolic or pharmacologic arteriolar vasodilation causes excessive reduction of pressure at the origin of the arterioles and possibly prearteriolar collapse.

The more severe and confluent is the patchy prearteriolar constriction, the more detectable become the signs of myocardial ischemia. The proposed abnormal prearteriolar constriction could be caused by lack of endothelium-derived relaxing factor flow-mediated vasodilation, by abnormal nervous stimuli or by a combination of these two mechanisms. However, the causes of abnormal coronary prearteriolar constriction are not necessarily the same in all patients.

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disease, a large proportion of these transient episodes are not preceded by changes of heart rate or occur at heart rates lower than those observed during exercise (15).

Symptoms, a positive exercise test and episodes of transient ST segment depression during Holter monitoring may persist over a period of several years (17-20). However, even using strict inclusion criteria, recent careful studies failed to show myocardial lactate production during pacing (21), increases in pulmonary pressure during spontaneous episodes of transient ST segment depression (16), abnormalities of left ventricular wall motion as assessed by two-dimensional echocardiography during dipyridamole testing (22) or decreases in coronary sinus blood oxygen saturation during atrial pacing (in 8 of 10 patients) (8). Conversely, the majority of patients with syndrome X with and without ischemic ECG changes during exercise testing seem to exhibit an abnormally small increase in coronary flow in response to dipyridamole or pacing (5,7,14,23), particularly after ergonovine administration (23). In one study (24) of patients with syndrome X, most without ischemic ECG changes during exercise testing, an abnormal vasomotor response in the forearm was also observed. Therefore, although the adoption of stricter inclusion criteria such as transient ischemic ST segment shifts during anginal pain should considerably narrow the diagnostic field, the absence of ECG changes during pain does not necessarily exclude a cardiac origin of symptoms.

**Distinguishing clinical features.** The uncertainties about the causes of the syndrome make the diagnosis of a cardiac or noncardiac origin of the pain difficult. Patients with syndrome X with or without ischemic ECG changes often present some distinguishing clinical features not usually observed in patients with critical epicardial coronary stenoses or spasm. To date, these features have not received adequate consideration.

Even those patients who demonstrate transient ischemic-like ECG changes exhibit a substantial discrepancy between the presence of anginal pain, usually severe, and signs of left ventricular dysfunction during pain, which are usually mild or undetectable (16,22). This is in sharp contrast with the frequent absence of pain despite the profound alterations of left ventricular function consistently associated with transient ischemic ECG changes in patients with epicardial coronary artery stenoses or spasm (25-27). Additionally, patients with syndrome X often report a prolonged duration of pain continuing for >30 min after effort or emotion. In our experience, occasional episodes of pain induced by effort or emotion lasting >30 min were reported by 40% of 42 patients with angina, a normal coronary arteriogram, no evidence of epicardial coronary artery spasm and ischemic-like ECG changes during exercise testing. The discrepancy between the presence of anginal pain and the lack or scarcity of objectively detectable myocardial ischemia suggests that predominantly algogenic rather than ischemic stimuli operate in this syndrome. Thus, any pathogenetic hypothesis that attempts to explain the reduced coronary flow response to vasodilatory stimuli and the possible development of ischemia and angina in these patients should explain: 1) the occurrence of angina and ischemic ST changes during efforts of variable intensity and occasionally also at rest, as well as the occurrence of angina after dipyridamole; and 2) the presence and long duration of anginal pain with minimal or no detectable ECG abnormalities and normal left ventricular function.

**Pathogenetic Hypothesis**

**Role of small vessel disease.** In the absence of both atherosclerotic obstruction and demonstrable epicardial coronary artery spasm, the reduced coronary blood flow in response to vasodilatory stimuli and the occasional development of objective signs of ischemia are very likely caused by small vessel disease. The subjective report of a wide variability of effort tolerance with occasional occurrence of apparently spontaneous episodes and the objective finding of variable levels of heart rate at the onset of ST segment depression during Holter ECG monitoring (15,20) suggest that the flow-limiting abnormality of small vessels is functional rather than organic. Thus, we believe that the morphologic abnormalities of small vessels observed in some studies (28,29) represent an associated or secondary phenomenon rather than the actual cause of the disease. Epstein and Cannon (30) proposed that “the impediment to flow may be located in the small intramural prearteriolar vessels” before they give off subepicardial and subendocardial branches. In their view, the localization of the flow impediment in intramyocardial vessels before the branching point of subepicardial vessels is necessary to account for dipyridamole-induced coronary transmural blood flow steal, which they assume is the cause of myocardial ischemia in their patients with “microvascular angina” (30).

**Abnormal coronary vascular resistance.** Although we do concur with Epstein and Cannon (30) that a prearteriolar alteration is the most likely cause of abnormal coronary vascular behavior, we propose a more general model in which the abnormality resides in a well identified functional segment of resistive vessels. In our model, the alteration can involve any site or the whole segment of the arterial vascular bed, with appreciable resistance to flow proximal to the segment directly involved in the metabolic regulation of coronary blood flow (Fig. 1). We also propose that focal, sustained, compensatory release of adenosine distal to the most severely constricted prearterioles may cause persistent chest pain, possibly even in the absence of myocardial ischemia.

**Distribution of Resistance in the Coronary Vascular Bed**

**Functional components of coronary artery bed.** The coronary artery bed is usually considered to be composed of two
functional components: 1) conductive vessels that offer a negligible resistance to blood flow, functioning as a bellows by storing blood during systole (31) and dilating when flow increases by a flow-dependent local release of endothelium-derived relaxing factor to reduce intimal shear stress forces (32); and 2) resistive vessels responsible for the regulation of myocardial perfusion. However, considering resistive vessels as a single functional vascular segment appears rather simplistic. Coronary vascular resistance is distributed from small epicardial coronary branches to capillaries, as indicated by the gradual continuous pressure decrease between these two extremes (33,34). Yet, within this resistive segment, vessels of different caliber may exhibit opposite responses to the same vasoactive stimulus (35).

Resistive vessels and metabolic regulation of myocardial blood flow. We believe that a functional separation of those resistive vessels not directly involved in the metabolic regulation of myocardial blood flow from those directly exposed to the effects of myocardial metabolites is important to understand the principles that regulate coronary blood flow. Although it is certain that epicardial coronary vessels as well as the larger intramural branches are not directly involved in the process of metabolic autoregulation of flow, the type and size of vessels involved in the metabolic regulation of flow cannot be defined histologically (36,37). If the findings obtained in subepicardial vessels by direct visualization can be extrapolated across the whole wall thickness, metabolic regulation of flow appears to be confined to arterioles <100 μm in diameter (38). Thus, about

Figure 1. Schematic representation of a conduit coronary artery and prearteriolar and arteriolar vessels with patchily distributed prearteriolar constriction in control conditions (A, upper panel) and during arteriolar vasodilation (B, upper panel). In this functional classification, conduit coronary arteries do not have appreciable flow resistance. arteriolar vessels are responsible for the metabolic autoregulation of coronary blood flow and prearteriolar vessels are those segments interposed between conductive arteriolar vessels with appreciable coronary flow resistance that are responsible for maintaining perfusion pressure at the origin of arterioles within optimal levels. The vasodilatory reserve of arterioles distal to constricted prearteriolar vessels is reduced because they are already dilated to preserve rest flow.

In conduit coronary arteries, the pressure remains similar to aortic pressure, but decreases progressively across prearteriolar vessels in proportion to their degree of constriction (A, lower panel). During metabolic or pharmacologic arteriolar vasodilation, the pressure drop increases only slightly distal to some prearteriolar vessels (a1, a2, b2) because vasodilation related to flow-mediated release of endothelium derived relaxing factor compensates nearly completely for the increased flow. The pressure drop increases markedly across more constricted prearteriolar vessels (b1, c1, c2) (B, lower panel). Steal can develop when an increase in flow through c2 causes a pressure decrease at the branching point distal to the constricted segment c1, so that the driving pressure becomes insufficient to perfuse adequately the most constricted branch c1 and blood flow (as indicated by arrows) can become lower than during rest conditions. The possibility of flow steal is greatly enhanced if branch c2 perfuses subepicardial layers of the ventricular wall with a greater flow reserve and if branch c1 perfuses the subendocardial layers with a smaller flow reserve. At the end of the prearteriolar vessels with the most marked increase in tone (b1), intravascular pressure may become insufficient to maintain lumen patency, resulting in vessel collapse.
50% of total coronary vascular resistance would reside proximal to this site (36). In the absence of precise anatomic criteria, we propose a functional definition of arteriolar and prearteriolar vessels.

**Functional definition of arteriolar and prearteriolar vessels.** *Arteriolar vessels* are those vessels responsible for the continuous physiologic matching of coronary blood flow to myocardial oxygen consumption. The function of arteriolar vessels is to regulate flow to maintain the composition of intracellular myocardial fluid within optimal limits for its contractile function. This regulatory mechanism seems to be largely the result of the dynamic equilibrium between diffusible vasodilatory metabolites produced by myocytes and their washout by blood flow, perhaps with the contribution of tissue oxygen and carbon dioxide tension (31). Adenosine seems to be an important physiologic mediator of this autoregulatory mechanism (39). Within each layer of the myocardium, flow through arterioles depends on their tone, extravascular resistance and, when they are maximally dilated, the perfusion pressure at their origin. In turn, the maintenance of this pressure within an optimal operational range depends on prearteriolar resistance.

*Prearteriolar vessels* are those vessels with significant resistance to flow interposed between conductive coronary arteries and arteriolar vessels. The function of prearteriolar vessels is to maintain pressure at the origin of arteriolar vessels within an optimal operational range. This is achieved by 1) constricting when aortic pressure increases and dilating when it decreases; and 2) dilating when coronary flow increases above rest levels. The physiologic changes in tone of prearteriolar vessels when aortic pressure varies are likely to be primarily maintained by the myogenic regulation of smooth muscle tone (40). Only when aortic pressure decreases to very low levels does dilation of arterioles (38) intervene to compensate for the inevitable decrease in perfusion pressure and maintain normal flow. The dilation of prearteriolar vessels during metabolic autoregulation of flow is likely to be primarily related to flow-mediated local release of endothelial-derived resistance factor (32). Both myogenic and metabolic autoregulation can be modulated by neural and humoral stimuli, which appear to have remarkably different effects in successive segments of the arterial bed, even on the microvascular level (35).

**Hemodynamic Consequences of Abnormal Prearteriolar Constriction**

Even a small amount of constriction of prearteriolar vessels, or the failure to dilate when flow increases, would require a considerable compensatory arteriolar vasodilation to maintain adequate myocardial perfusion. Although adequately compensated by distal arteriolar vasodilation, an increase in prearteriolar resistance would have three important interrelated consequences: 1) A reduction of coronary flow reserve, as a fraction of the available arteriolar dilating capacity, must already be utilized at rest. 2) A reduction in pressure at the origin of arteriolar vessels, because according to the general relation: flow = pressure gradient/resistance, an approximately linear increase in the pressure gradient is necessary to compensate for the increased prearteriolar resistance to maintain rest flow. Therefore, the pressure gradient between the aorta and the origin of arteriolar vessels must approximately double if resistance across prearteriolar vessels doubles and flow remains constant. 3) A sustained increase in interstitial adenosine concentration (which may in turn be responsible for the occurrence of anginal pain).

**Mechanisms of Impaired Coronary Blood Flow**

The only consistent finding in syndrome X seems to be an impaired coronary vasodilator response, which was observed by different investigators using different techniques (5,7,14,23). In contrast myocardial ischemia was convincingly documented in only a minority of patients (6–14).

**Prearteriolar constriction.** We propose that the vascular abnormality responsible for these findings is located in prearteriolar vessels as just defined (Fig. 1). The abnormal constriction of prearteriolar vessels is likely to be patchily distributed and impair arteriolar blood flow more in the inner than in the outer layers of the ventricular wall; a higher extravascular pressure is present in the inner myocardial layers, thus requiring a higher pressure to oppose extramural compressive forces and cause prompt diastolic reopening of the vessels (31). The inner myocardial layers are also more likely to develop ischemia because they have a higher myocardial oxygen consumption than the outer layers.

**Distal to the most intensely constricted prearterioles,** ischemia may develop either at rest or when myocardial oxygen consumption increases. During effort, ischemia may develop as a result of two factors that can operate in combination: 1) increase in myocardial oxygen consumption not matched by an adequate increase in coronary blood flow because of the reduced arteriolar vasodilatory reserve; and 2) arteriolar vasodilation with consequent reduction in intraluminal distending pressure, which may become insufficient to oppose extramural pressure.

**Transmural blood flow steal.** In our model, as in the model proposed by Epstein and Cannon (30), transmural myocardial blood flow steal can develop during metabolic or pharmacologic arteriolar dilation if a substantial fraction of prearteriolar resistance is located proximal to the origin of arterioles in the subepicardial layers and would be enhanced by an increase in the resistance interposed between the origins of subepicardial and subendocardial arterioles. In our model, however, steal could occur even in the same myocardial layer if a marked pressure decrease occurs proximal to the branching point of two branches with a markedly different degree of constriction. Moreover, metabolic or
pharmacologic arteriolar vasodilation could impair flow through a different mechanism, namely a reduction in luminal diameter and even total occlusion in the terminal portion of the most constricted prearterioles as a result of the luminal instability created by the combination of increased vasomotor tone and decreased distending pressure (41,42). Thus, arteriolar vasodilation could initiate a vicious cycle that would prolong the impairment of flow and duration of myocardial ischemia.

Mechanisms of Anginal Pain

Adenosine as a mediator of anginal pain. We recently demonstrated (43) that in patients with angina, intracoronary infusion of adenosine causes anginal pain similar to that experienced by these patients during daily life. We also observed that theophylline, an adenosine antagonist, reduces the intensity of spontaneous anginal pain. These findings lend objective support to the hypothesis proposed by Sylven et al. (44) that adenosine is a mediator of anginal pain, which is also supported by the observation that application of adenosine to human skin blisters causes severe pain (45). Because our results (43) showed that only adenosine concentrations greater than those required to produce maximal coronary vasodilation are algogenic, a constriction that elicits maximal compensatory dilation seems necessary to cause an adequate algogenic stimulus.

Adenosine and anginal pain in syndrome X. The demonstration that adenosine can be a chemical mediator of anginal pain could explain the discrepancy between the severity of angina and the scarcity of objective ischemic signs in patients with syndrome X compared with those with epicardial coronary artery obstructions. In the latter, the resistance created by epicardial coronary stenoses is compensated for by a decrease in vascular resistance shared by all distal arterioles. When coronary flow reserve is exhausted, widespread myocardial ischemia develops in the whole region supplied by the stenotic vessel. Thus, major impairment of cardiac function causes an unstable hemodynamic situation that either regresses or evolves rapidly as a result of a vicious cycle related to increased wall stiffness and diastolic pressure. Conversely, in the presence of a patchily distributed and sparse prearteriolar constriction, the local concentration of adenosine may become sufficient to stimulate cardiac afferent nerves in the absence of impairment of overall cardiac function. The potential positive feedback mechanisms triggered by arteriolar vasodilation and a decrease in distending pressure, leading to further constriction at the distal end of prearterioles and a further compensatory increase in adenosine concentration, could explain the prolonged pain experienced by patients with syndrome X.

Chest pain in absence of ischemia: role of adenosine. It is possible that in syndrome X, chest pain might occur in the absence of ischemia, just as during intracoronary infusion of adenosine. The possibility that a local increase in adenosine concentration distal to the most severely constricted arterioles might cause pain in the absence of ischemia is suggested by observations in open chest dogs. L’Abbate et al. (46) showed that the effects of a steady-state adenosine infusion are time-dependent, so that coronary flow values 100% greater than those produced by peak reactive hyperemia can be attained after 30 min of adenosine infusion. It would be conceivable, therefore, that in the absence of impaired cardiac function, a sustained focal release of adenosine could result in sufficient prearteriolar dilatation to prevent myocardial ischemia.

Enhanced perception of painful stimuli. The patchy distribution of markedly elevated adenosine concentrations caused by the most constricted prearteriolar vessels might also contribute to making the algogenic stimulation supraliminal, if the perception of pain depends on a spatially inhomogeneous stimulation of cardiac afferent polimodal receptors (47). Finally, another possible component of the discrepancy between the severity of pain and the minimal objective alteration of cardiac function in patients with syndrome X seems related to an enhanced perception of potentially painful stimuli (48–50).

Possible Causes of Abnormal Prearteriolar Constriction

Insufficient vasodilation or inappropriate vasoconstriction. The cause of prearteriolar coronary constriction may be related to a local deficit of flow-mediated endothelium-derived relaxing factor production (32) so that prearterioles do not dilate when arterioles dilate and cause flow to increase, resulting in a large pressure decrease at the end of prearteriolar vessels. Alternatively, it could be related to a primary inappropriate constriction of the smooth muscle that could result from either a very specific powerful neural stimulus or a nonspecific hyperreactivity to a variety of constrictor stimuli (51) similar to that responsible for segmental epicardial coronary artery spasm (52,53). Our observations that neuropeptide Y (54) and endothelin (55) can cause massive transmural myocardial ischemia in the absence of detectable epicardial coronary artery constriction provide evidence that distal coronary vessels have the potential to constrict to such an extent as to completely overpower metabolic autoregulation. Alpha-adrenergic stimulation was also shown (56) to cause hypoperfusion resulting in ischemia, but only in the presence of a critical coronary stenosis.

Resetting of myogenic control of prearteriolar tone. Alternatively, the abnormality might be related to a resetting of the myogenic control (40) of tone in prearteriolar vessels, which, superimposed on the marked physiologic spatial microheterogeneity of myocardial perfusion (31), could result in patchily distributed hypoperfusion. There is no precise evidence for this mechanism, but impaired coronary flow reserve has been reported (57,58) in hypertensive
patients in the absence of myocardial hypertrophy in association with angina and normal coronary arteries.

**Segmental versus generalized distribution of prearteriolar abnormalities.** It is still unknown whether the alteration of prearteriolar vessels in syndrome X is distributed uniformly in the ventricular walls or whether it is regional. A segmental abnormality corresponding to the territory of a major coronary artery branch would be compatible with a segmental neural abnormality because the efferent sympathetic innervation of the heart has a segmental distribution that parallels that of major arterial branches (59). Conversely, distribution of the abnormality to the entire coronary arterial bed would suggest a generalized alteration.

**Clinical implications.** The causes of prearteriolar coronary constriction need not be the same in all patients; thus, the evolution of the disease may vary despite a similar clinical presentation. However, in most cases these causes must be stable because the disease tends to remain stable for years. Understanding the causes of the abnormal prearteriolar constriction is important because the beneficial effects of traditional antianginal drugs in patients with syndrome X are small and difficult to demonstrate in controlled trials. Beta-adrenergic blockers are much less effective in patients with syndrome X than in those with chronic stable angina and coronary artery disease (4,60–62), suggesting that a reduction in myocardial oxygen consumption is not an effective means of preventing or compensating for the underlying vasomotor abnormality. Calcium channel antagonists and nitrates produce inconsistent responses (20), suggesting that at the doses currently used, drugs that reduce vascular smooth muscle tone nonspecifically are ineffective in preventing the abnormal segmental constriction of those prearteriolar vessels most severely involved. Clonidine and prazosin are also ineffective in improving symptoms or ischemic ST segment changes (63). In contrast, the fact that aminophylline was found (64) to be effective in improving symptoms and ST segment ischemic changes is compatible with an important role of excessive myocardial adenosine release.

**Conclusions**

On the basis of available information, it would seem reasonable to postulate that a dynamic inappropriate constriction of prearteriolar vessels can cause a limitation of coronary flow reserve, anginal pain and possibly myocardial ischemia. Prearteriolar constriction need not be segmentally localized in intramyocardial vessels proximal to the origin of subepicardial arterioles and is likely to be nonuniform, with only a minority of prearteriolar vessels very intensely constricted. During increased cardiac activity, focal myocardial ischemia can result from the reduction in coronary flow reserve because some flow reserve is utilized during rest conditions to compensate for the prearteriolar constriction. During increased myocardial blood flow, focal myocardial ischemia can also result from the decrease in pressure at the terminal end of the most intensely constricted prearterioles because distending pressure may become insufficient to adequately oppose extravascular compressive forces and maintain subendocardial myocardial perfusion and lumen stability. Because prearteriolar coronary constriction stimulates the local release of adenosine, a focal increase in myocardial adenosine concentration, if intense and prolonged, could cause anginal pain, even in the absence of detectable signs of myocardial ischemia since adenosine appears to be an adequate chemical stimulus for cardiac pain.

This hypothesis could explain the wide spectrum of clinical presentations of patients with syndrome X. At one end of the spectrum, the involvement of a large number of prearteriolar vessels would explain the reduced coronary flow reserve and the presence of myocardial ischemia observed in some patients. At the other, the involvement of a very limited number of prearterioles could explain the occurrence of pain in the absence of detectable signs of ischemia and perhaps even in the absence of a detectable reduction in total coronary flow reserve. The difference in response to treatment and in evolution may be related to different underlying causes of the prearteriolar vasoconstriction. The evolution in some patients to dilated cardiomyopathy (65) could be related to intense forms of small vessel spasm, similar to that observed in the Syrian hamster model (66).

The study of the mechanisms of inappropriate constriction of coronary prearteriolar vessels in syndrome X may also be relevant to the understanding of distal coronary vessel constriction in acute (67) and chronic (68) ischemic syndromes associated with epicardial coronary artery disease.

Our hypothesis is intended to explain the clinical features of the syndrome and stimulate further research into the mechanisms of this common clinical syndrome to develop diagnostic criteria that would allow a positive identification of the cardiac origin of the pain and effective treatment. Meanwhile the term syndrome X should remain to remind us of our ignorance.

**References**


