Use of Nitrates in the Treatment of Unstable and Variant Angina

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Summary

Unstable angina is a clinical syndrome that includes patients with new onset of angina, a change in a previous stable pattern, or the development of chest pain at rest. Generally, more than 90% of patients with this syndrome have significant fixed atherosclerotic coronary artery disease. Other complex, interacting pathophysiological mechanisms may include coronary vasoconstriction, plaque rupture and thrombosis.

Therapeutic strategies aim at either reduction of myocardial oxygen demand or restoration of coronary blood flow. Both alternatives have been suggested as treatment of choice. However, as long as the pathophysiological mechanism(s) is unknown in the individual case, the treatment will mainly be empirical or based on results from clinical trials of heterogeneous groups of patients with unstable angina with probably varying aetiology. The results from such studies indicate that some strategies may be of value, but others may even be harmful in treatment of patients with this unstable syndrome. In this situation nitrates seem to be a safe drug which may be used in most forms of angina irrespective of the underlying pathophysiological mechanism(s).

Unstable angina pectoris is a clinical syndrome which encompasses a wide variety of clinical presentations with different pathogenic mechanisms.

1. Definition

The definition of unstable angina varies, and different definitions have been used by various authors. However, many have now adopted the definition proposed by Conti et al. (1973), who suggested three categories:
1. Angina on effort of recent onset.
2. Angina on effort with a change in a previously stable pattern, with increased frequency or severity; this change is sometimes termed accelerated or crescendo angina.
3. Development of chest pain at rest, which typically requires no stress to provoke the episodes of ischaemic pain.

These three subgroups overlap each other to a considerable extent. Sometimes, patients who develop angina during the recovery phase after a myocardial infarction are included in the definition of unstable angina.

2. Pathophysiology

As the appropriate selection of therapy for the individual patient depends on the pathophysiological mechanism behind the symptoms, it is important to consider possible mechanisms in every individual case. Several conditions either alone or
in combination with each other may be responsible (Conti 1985). These conditions include
• extracardiac or aggravating factors
• progressive coronary atherosclerosis
• rapid decrease in coronary lumen size secondary to haemorrhage into or rupture of atherosclerotic plaque
• transient platelet aggregation in vessels with very narrow lumen
• transient coronary artery thrombosis
• abnormal coronary artery vasoconstriction in normal or diseased vessels.

Extracardiac or aggravating factors such as arrhythmias, hypertension or anaemia should always be considered in cases of unstable angina. Elevated plasma viscosity has also been suggested as a contributing factor in this syndrome (Fuchs et al. 1984).

The vast majority of patients with unstable angina have significant atherosclerotic coronary artery disease. The distribution and severity of the coronary stenosis are of the same magnitude as seen in patients with stable angina pectoris (Allison et al. 1978). Thus, normal coronary angiograms are seen in approximately 10% of patients with unstable angina, single-vessel disease in approximately 20%, two-vessel disease in 30% and three-vessel disease in 40%. Significant left main disease is found in 10 to 15% of patients with this syndrome.

However, a progressive narrowing of coronary stenoses has been found in 75% of patients with unstable angina compared with 30% in a comparable group with stable angina (Moise et al. 1983).

The importance of platelet aggregation, thrombus formation and abnormal vasoconstriction as main pathogenetic factors in unstable angina is being increasingly considered (Born 1979). The important question is what triggers these mechanisms in patients with moderately severe coronary atherosclerosis and changes their clinical course into that of unstable angina.

Intramural haemorrhage into an atherosclerotic plaque with damage of the endothelial surface has been suggested as a possible triggering mechanism. In the clinical situation it is impossible to tell if this mechanism is responsible in an individual case. However, from autopsy studies it is known that plaque fissures, often with coexisting coronary thrombi, are frequently seen in patients who die suddenly of ischaemic heart disease (Davies & Thomas 1984). It is also known from experimental studies that endothelial damage may change the coronary artery response to endogenous vasoactive substances (Furchgott 1983).

One possible mechanism for coronary artery vasoconstriction and thrombus formation could be endothelial damage or some local defect in the synthesis, or release, of endothelial-derived relaxing factor (EDRF) and/or of vasodilator prostaglandins. This might lead to smooth muscle hyperreactivity by removing the 'brake' effect of EDRF release. In addition, loss of prostacyclin could lead to localised platelet adherence, to the release of platelet-derived vasoconstrictors (thromboxane A, serotonin) and proaggregatory agents (thromboxane A, ADP, serotonin), to platelet aggregation and to transient coronary artery thrombosis. Some clinical findings support this hypothesis.

Angiographic evidence of coronary artery thrombosis is seen with increasing frequency in coronary angiograms performed shortly after the onset of symptoms of unstable angina (table I). In a study by Cowley et al. (1985) intraluminal filling defects were seen in 45% and thrombotic occlusion in 13% of 69 patients with unstable angina investigated within 24 hours after onset of symptoms. The corresponding numbers in 20 patients with stable angina were 5% and 0%, respectively. In a study of 9 patients with unstable angina, intracoronary glyceryl trinitrate (nitroglycerin) was administered. Only one totally occluded vessel was opened in response to this treatment, but the patient was left with a major vascular obstruction that was eliminated by the administration of streptokinase. Four of the 9 patients responded to streptokinase infusion with opening of an occluded vessel, a decrease in coronary stenosis, dissolution of an intracoronary filling defect or a combination of these effects (Mandelkorn et al. 1983).