Coronary artery vasospasm: the likely immediate cause of acute myocardial infarction

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SUMMARY Features of infarction can be divided into two types—the spasmodic and the mechanical. The former (pre-infarct angina and emotional factors in infarction) seem readily explainable by spasm, and are similar to the findings in angina which prompted Heberden to consider angina as spasmodic. The mechanical features of infarction (association with thrombosis and arteriosclerosis, and severe and unremitting chest pain) seem to be the antithesis of spasm and probably account for the reluctance to consider spasm seriously in infarction.

The injury-vasospasm hypothesis of acute myocardial infarction explains both spasmodic and mechanical features. Spasm represents a dominance of vasoconstricting over vasodilating forces. Coronary sclerosis can result in both ischaemia (vasodilating) and ischaemic injury-spasm (vasoconstricting). The fight-flight component of the autonomic nervous system is considered to be vasodilating, and the conservation-withdrawal portion to be vasoconstricting. Once spasm occurs, a new balance of forces obtains which can lead either to vasodilatation and relief of symptoms or to infarction.

Although there is growing interest in coronary artery vasospasm in acute myocardial infarction (Lange *et al.*, 1972; Cheng *et al.*, 1972; Hellstrom, 1973; King *et al.*, 1973; Khan and Haywood, 1974; Ciraulo, 1975; Chahine and Luchi, 1976; Engel *et al.*, 1976; Wiener *et al.*, 1976; Oliva and Breckinridge, 1977), the spastic origin of this disorder is not well accepted. In this discussion it will be proposed that vasospasm very likely initiates infarction.

There appears to be more evidence for spasm, albeit mostly circumstantial, than is generally realised. It will be argued that there has been a preconceived view that spasm is incapable of causing infarction and this has resulted in the neglect of readily accessible clinical evidence in favour of spasm, and in a disregard of inconsistencies in conventional pathogenetic concepts.

Angiographic evidence of spasm in infarction

Recently, in a few cases of infarction coronary artery spasm has been demonstrated angiographically (Cheng *et al.*, 1972; King *et al.*, 1973; Engel *et al.*, 1976; Wiener *et al.*, 1976). Such observations have not evoked strong support that spasm is the major

cause of this disorder. Even though these are isolated cases, they seem important, as they associate spasm directly with muscle necrosis. As angiograms are taken only rarely during infarction, the few cases where spasm was shown provide little information as to the overall incidence of spasm with infarction. Importantly, spasm was recognised in 40 per cent of a recent series (Oliva and Breckinridge, 1977).

In addition, there are multiple observations of spasm in angina pectoris (Maseri *et al.*, 1977). This is accepted as indirect evidence for spasm in infarction, as infarction and angina are considered as one disorder, with myocardial necrosis representing an arbitrary division relating to the intensity and duration of spasm.

Spasmodic features of infarction—pre-infarct angina and emotional factors

Some attributes of infarction are similar to the findings in angina pectoris which prompted Heberden, who first described angina, to consider it as spasmodic. In his *Commentaries* (1802), he emphasised the character of the attack, the relation to emotional factors, and the occurrence of chest pain at rest. '... the access and recess of the fit is sudden . . . , it is increased by disturbances of the

mind . . . (and) its attacks are often after the first sleep.'

This description resembles pre-infarct angina with features suggesting spasm. Pre-infarct angina often occurs at rest; this is also the major feature of variant angina for which a spastic origin is well documented (Higgins *et al.*, 1976; Maseri *et al.*, 1977). It seems reasonable that emotional factors and stress induce spasm by operating through the autonomic nervous system (Hellstrom, 1973, 1977).

The spasmodic features of myocardial infarction were recognised relatively recently. Emotional factors (Jenkins, 1976) were either minimised or totally neglected until 15 years ago (Russek, 1962), and while pre-infarct angina was described as early as 1937, it has been emphasised only in the past decade (Solomon *et al.*, 1969; Feinleib *et al.*, 1975). It was not until 1960 that Prinzmetal rediscovered that angina could occur at rest, and predicted a spastic origin.

In the mid-twentieth century, when spasm was unfashionable and spasmodic clinical features were not appreciated, those clinical characteristics of ischaemic heart disease were emphasised that matched the then accepted pathogenetic mechanisms. Descriptions of infarcts were confined to a discussion of the rapid onset of crushing, unremitting chest pain, a finding highly consistent with a sudden coronary thrombosis. Angina was described as occurring only with exertion, compatible with an origin from arteriosclerosis and relative vascular insufficiency. It might now be regarded as cautionary that spasm could have been considered an 'extravagant and improbable hypothesis' (Pickering, 1951).

Today, while spasmodic features of infarction are well described, they are usually ignored by those who believe exclusively in mechanical obstruction of coronary arteries. In addition, when discussed, it is only rarely that they are attributed directly to spasm (Burch and Giles, 1973; Hellstrom, 1973; Maseri *et al.*, 1977), probably because spasm had been declared irrelevant in infarction.

Deficiencies of nonspastic pathogenetic mechanisms of infarction

CORONARY ARTERY THROMBOSIS

The evidence that thromboses are secondary is convincing, especially the observation that their incidence is higher in the presence of infarcts which are one or more days old (Spain and Bradess, 1960). Some thrombi resemble postmortem clots (Hellstrom, 1971), suggesting a secondary development, and occur in vessels so constricted that their obstruction does not seem capable of causing

infarction (Horn, 1963). Further, pre-infarct angina and the emotional component of infarction are not explained by thrombotic occlusions. However, a recent study group favoured the primacy of thrombosis (Chandler *et al.*, 1974). In any event, there is sufficient doubt to preclude belief in a primary role for thrombosis being used as convincing evidence against a vasospastic cause.

PLATELET AGGREGATION

This mechanism has been applied mainly to sudden coronary death (Schwartz and Gerrity, 1975), where platelet aggregates in intramyocardial arteries have been shown at necropsy (Haerem, 1972). However, experimentally, myocardial infarcts have followed adenosine diphosphate induced platelet aggregation (Mustard, 1972) and there is evidence of increased platelet stickiness in ischaemic heart disease (Frishman *et al.*, 1976). Platelet aggregates provide at least a theoretical explanation for spasmodic features of infarction, considering that stress causes intramyocardial platelet agglutination in rats (Haft and Fani, 1973) and pre-infarct angina might be explained by reversible platelet clumping.

The evidence for significant platelet clumping is not substantial, and there is little necropsy evidence for it in infarction. Moreover, platelet aggregates might be secondary events resulting from spasm itself, as coronary artery platelet aggregates have been found in dogs soon after experimental sudden partial coronary artery occlusion (Folts *et al.*, 1976). In addition, vascular injury (as would occur with spasm) itself probably induces platelet clumping (Mason *et al.*, 1977). Platelet aggregates might be secondary to infarction, as catecholamines and free fatty acids, which increase platelet stickiness (Taggart and Carruthers, 1971), are increased in infarction (Opie, 1975). The possibility of release of vasoconstrictive agents from aggregated platelets is discussed below.

DIRECT ARTERIOSCLEROTIC CAUSE OF INFARCTION

This concept assumes that the blood supply to the myocardium is limited by arteriosclerotic stenosis and myocardial necrosis is the result of relative ischaemia (Braunwald and Maroko, 1974).

The direct arteriosclerotic cause of infarction came into prominence shortly after the primacy of coronary thrombosis was questioned, and represents a significant modification of the classic cause of infarction. Previously, it was assumed that most infarcts were the result of coronary thrombosis, and only a minority resulted directly from coronary sclerosis, and then *only* in combination with shock, haemorrhage, etc. (Friedberg, 1967). The logic of a

direct arteriosclerotic cause is not convincing. Many with severe coronary disease do not develop myocardial necrosis, and infarction can occur with patent arteries. If infarction is due directly to stenotic disease, how could an individual be capable of strenuous exercise immediately before an attack? And why do infarcts occur at rest? In addition, pre-infarct angina and the importance of emotional factors are inadequately explained by a direct arteriosclerotic cause.

The arteriosclerotic cause of infarction is associated closely with the concept of preservation of ischaemic myocardium. That pharmacological manipulation can improve survival of ischaemic myocardium in the dog after coronary artery ligation (Braunwald and Maroko, 1974) should not imply that infarction is caused by a fixed obstruction of coronary arteries.

Rebuttal to arguments that spasm cannot cause infarction

SCLEROTIC ARTERIES CANNOT UNDERGO SPASM

This concept was applied originally to angina (Keefer and Resnik, 1928; Blumgart *et al.*, 1940) and was a substantial reason for abandoning the notion of spasm in this disorder. While epicardial arterial spasm now is a recognised occurrence, most apparently consider that severely sclerotic arteries, as found in infarction and effort angina, cannot constrict. However, there is angiographic evidence that spasm occurs in infarction, in arteriosclerotic arteries in angina (Gensini, 1975; Maseri *et al.*, 1977), and even in effort angina (Chahine and Luchi, 1976). Though some sclerotic segments are probably too rigid to contract, it seems reasonable that spasm can involve vessels with significant disease. Rupture of coronary artery plaques implies violent vascular contractions (Leary, 1934; Hellstrom, 1977).

SPASM IS TOO MILD AND EVANESCENT TO CAUSE INFARCTION

Spasm in infarction has been rejected because of the lack of direct proof that it can cause myocardial necrosis (Arnett and Roberts, 1976). Further, in angina, spasm is a relatively mild and short lived event. These facts cannot preclude the possibility of spasm being severe or persistent enough to induce myocardial necrosis. The angiographic evidence of the association of spasm with infarction is at least suggestive that spasm can *cause* myocardial necrosis.

THERE IS LITTLE OR NO EXPERIMENTAL EVIDENCE FOR SPASM IN INFARCTION

One reason for the reluctance to accept an aetiological role for spasm in infarction is the sparsity of experimental data. This should not be taken as evidence against the hypothesis. There has been a lack of interest in pursuing spasm experimentally, and in recent years research workers have been preoccupied with the preservation of ischaemic myocardium.

SPASM CANNOT EXPLAIN ALL OF THE FEATURES OF INFARCTION (AND ANGINA)

Features of infarction can be divided into two types—the spasmodic and the mechanical. While the former (pre-infarct angina and emotional features) appear to be consistent with spasm, the mechanical attributes of infarction seem to be the antithesis of spasm. These include the association of infarction with arteriosclerosis and thrombosis, the severe and unremitting chest pain, and the persistence of the ischaemia during the early course of infarction. In addition, in effort angina, the onset of chest pain is related to the degree of exertion. Possibly intuitively, it has been felt that these mechanical aspects ruled out spasm, and this might be a major reason for the retention of current pathogenetic principles, no matter what their deficiencies.

Usually, those who stress the mechanical cause of infarction ignore the spasmodic features, and those who subscribe to spasm have not reconciled spasm with the mechanical features. A credible concept for the aetiology of infarction and effort angina should include an explanation for both types of features. Such an explanation might require viewing ischaemic heart disease from a different perspective.

The injury-vasospasm hypothesis of ischaemic heart disease

This concept explains both mechanical and spastic features of infarction and has been described elsewhere (Hellstrom, 1973, 1975, 1977). This abridged discussion will represent spasm as a dominance of vasoconstricting over vasodilating forces (Fig.).

The two major factors involved with infarction are arteriosclerosis and emotional stress. Arteriosclerosis is considered to cause chronic myocardial injury, which, in turn, incites injury-vasospasm. Conversely, arteriosclerosis induces ischaemia, which, via the anoxic-feedback mechanism of coronary autoregulation, is a potent vasodilator. If the injury reaction overwhelms the anoxic-feedback mechanism, spasm occurs.

Fig. Diagram of major forces involved in ischaemic heart disease. Alpha-adrenergic dominance probably also is vasoconstricting. When vasoconstriction is dominant, spasm occurs. Spasm causes a new dynamic balance, with higher levels of ischaemic injury and ischaemia. If, at these new levels, vasodilatation does not supervene, infarction occurs.

Emotional stress is related to the autonomic nervous system, which can effect coronary artery dilatation or constriction, and which might function in concert with the anoxic-feedback mechanism through neural reflexes. The anoxic-feedback mechanism is based in intramyocardial arteries, and the autonomic nervous system innervates both large and small coronary arteries. There is evidence that stress can induce an inappropriate parasympathetic response (Engel, 1971), and coronary artery constriction probably is caused by parasympathetic (Endo *et al.*, 1976) or alpha-adrenergic (Levene and Freeman, 1976) activity.

There are, undoubtedly, additional factors involved in the coronary vasodilative/vasoconstrictive balance. Irregular blood flow through a stenotic coronary segment might cause local injury-spasm. Prostaglandins cause both dilatation and constriction (Ogletree and Lefter, 1977), are involved in coronary autoregulation (Alexander *et al.*, 1975), and might influence the cardiac response to ischaemia (Berger *et al.*, 1976).

The hypothesis can be illustrated by applying it to clinical situations. In effort angina, the attack is the result of a combination of chronic ischaemic myocardial injury (arteriosclerosis) and acute ischaemic injury (effort), with the latter triggering the attack. A given amount of exertion usually is necessary to cause sufficient ischaemic injury to reach the threshold at which spasm is triggered.

In all types of angina, once spasm occurs a new balance of forces obtains, because spasm causes higher levels of both ischaemia and ischaemic injury (Fig.). If, at the new levels, vasodilatation continues to overbalance vasoconstriction, infarction develops. However, the anoxic-feedback mechanism responds in proportion to the level of ischaemia, and it is likely that spasm usually results in the generation of sufficient vasodilative metabolites for self-correction. This is in keeping with the small fraction of attacks of angina which proceed to infarction. If spasm continues long enough for severe muscle injury and injury-spasm to develop, a different dynamic balance obtains, which favours the continuance of spasm and the development of infarction. Occasionally, effort angina is improved by further exertion (Lown, 1977). This apparent paradox is ascribed to an ascendancy of vasodilative forces at the higher levels of ischaemia induced by effort, possibly abetted by a fight-flight autonomic nervous system response.

Coronary artery spasm caused by aggregated platelets

Instead of aggregated platelets directly causing intracoronary obstruction, it has been proposed recently that they cause coronary spasm by the release of vasoconstrictors such as the prostaglandin related thromboxane A₂ (Oliva and Breckinridge,

1977). This approach to coronary spasm differs from the injury-vasospasm concept, where importance is placed on the injured myocardium and the direct coronary artery effect of the autonomic nervous system. In any event, the availability of more than one possible model for spasm should be advantageous.

The apparent reduction in sudden cardiac deaths with sulphinpyrazone, a prostaglandin inhibitor (Sherry, 1978), has been a major stimulus to the current interest in aggregated platelets. However, it is possible that the beneficial effects of sulphinpyrazone is not related to platelets and coronary arteries. The incidence of infarction in this study did not appear to be decreased significantly, and Frishman *et al.* reported in 1976 that reduction of platelet aggregability by prostaglandin inhibition did not affect angina. The reduced incidence of sudden cardiac death following treatment with sulphinpyrazone might be related to a decrease in ventricular fibrillation, and this arrhythmia occurs less frequently during experimental myocardial ischaemia after pretreatment with aspirin, one of whose actions is prostaglandin inhibition (Moschos *et al.*, 1978).

Therapeutic possibilities with a vasospastic cause of infarction

If, indeed, spasm initiates infarction, there are therapeutic possibilities beyond simple preservation of ischaemic myocardium. Vasodilators might abort the attack and during the acute stage of infarction might relieve spasm and reduce myocardial ischaemia (Hellstrom, 1975). The greatest potential might be in preventing infarcts. In addition to the obvious benefits in avoiding the acute attack and its complications, a major consideration is that acute coronary seizures may result in sudden death.

The adoption of fresh concepts of infarction may be useful in order to help prevent the attacks. Engel in 1977 suggested that, in medicine, the current biomedical model 'leaves no room within its framework for the social, psychological, and behavioral dimensions of illness' and should be replaced by a biopsychosocial model. While there are many published reports which detail the emotional side of infarction (Jenkins, 1976), this area is fairly isolated from the biomedical mainstream and overall receives inadequate attention, probably because of the lack of any notion of an integrating pathogenetic mechanism.

Proper attention should be paid to the early warnings of impending infarction and sudden coronary death. The high incidence of prodromata is well known (Feinleib *et al.*, 1975), but it is likely

Table Levels of acceptance of coronary artery spasm

Coronary artery spasm does not exist
Spasm occurs only with catheter injury during angiograms
Spasm is real but associated only with variant angina
Variant angina is caused by spasm
Spasm is rarely shown in infarction
Spasm is more common than generally appreciated in infarction
Spasm is observed rarely in effort angina
Pre-infarct angina and infarction are caused by spasm
Effort angina is due to spasm

that the lack of a satisfactory explanation for their occurrence has inhibited a thoroughgoing approach to use recognition of these phenomena to prevent infarction. Relating tension and prodromata to spasm might encourage a more rational handling of the pre-infarct phase of myocardial infarction.

Acceptance of coronary artery spasm

Each year there has been an increased acceptance of coronary artery spasm (Vaisrub, 1976), and possible stages in this process are depicted in the Table. The current awareness varies from person to person, but the spastic cause of variant angina seems to be generally accepted. There is some interest in the possibility of spasm in infarction, but little for effort angina.

The possibility, or even probability, that spasm initiates infarction is now a tenable concept.

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