What is new and significant must always be connected with old roots, the truly vital roots which are chosen with great care from the ones that merely survive.

Bela Bartok
I will begin my analysis of evidence in medical science where I myself began, and consider the mechanism of what is generally known as "heart attack" or, in medical terminology, acute myocardial infarction. These two terms are not necessarily interchangeable, and where there is doubt I shall use the former one.

ANATOMICAL DIAGNOSIS

We will go back to basics and consider the evidence in each of the four categories delineated in Chapter 2, first examining the anatomical site of the lesion. This is usually fairly straightforward, because the distribution of infarction or death of heart muscle tissue almost always occurs within the territory of supply of one of the two main epicardial coronary arteries or their major branches. But although this is not usually in dispute, it is something that should not be lost sight of, as it occasionally is by those who postulate that acute myocardial infarction may be caused by essentially small vessel disease.

PATHOLOGICAL DIAGNOSIS

I will approach this first from the viewpoint of the relevant clinical evidence. The suddenness of the onset of most heart attacks in this respect suggests a vascular event, on general grounds either an interruption of coronary blood flow, or coronary artery rupture. Now, we can readily dismiss the latter possibility from the lack of any pathological evidence for it at post-mortem, and from the clinical observation that heart attacks are frequently preceded by transient episodes of similar pain or “pre-infarction angina” in the weeks immediately beforehand suggesting a much more reversible process than rupture. It would therefore seem likely that the attacks are precipitated by some primarily ischaemic process, i.e. a relative lack of blood supply to the area of heart muscle concerned. In most organs, of course, this would imply a vascular obstruction to blood flow, but in the case of the heart we must ask whether we are dealing with true ischaemia related to an absolute reduction in blood supply, or a relative one determined by an increase in heart muscle work. This consideration arises because of the general belief that much angina of effort is due not to any change in the patency of the coronary arteries themselves with exercise, but to a relative ischaemia brought about by an increased metabolic demand on the part of the exercising heart muscle. Whether this is indeed the simple and sole cause of angina of effort is very dubious — a point I shall take up later — but such a mechanism is very unlikely to be important in precipitating acute myocardial infarction. In the first place, heart attacks usually begin during a period of rest, without any suspicion of increased activity, either emotional or physical, which might
increase heart work and therefore myocardial demand on blood flow. This old clinical observation has now been extended by Maseri and his colleagues by more direct studies. At least during the episodes of the rest angina that so often precedes myocardial infarction, these researchers were unable to detect any increase in the haemodynamic determinants of myocardial oxygen demand. Indeed the primary event seemed, rather, to be a fall in regional coronary blood flow. It seems likely, therefore, that the ischaemia occurring at the onset of myocardial infarction is due to an absolute decrease in blood supply, rather than one relative to a change in heart muscle work.

Having established the likely initial reduction in blood supply at the onset of heart attacks, we must next consider whether this, in turn, is related to a decrease in the general arterial systemic pressure perfusing the coronary arteries, or to a local obstruction of coronary blood flow. Reduced blood pressure in itself might not at first sight seem very likely to cause any event confined to the territory of distribution of one particular coronary artery or branch, but myocardial infarction usually occurs within the distribution of an artery already narrowed by atheroma, and under these circumstances a drop in pressure perfusing the coronary arteries might well cause some localisation of the ischaemic process. Nonetheless, except for occasional cases of sub-endocardial infarction, such a mechanism seems unlikely to be very important. Moreover, the evidence is against it in the usual patient. For example, there is no sign of any blood pressure fall at all that ‘unstable’ angina which so frequently precedes acute myocardial infarction. Also, ischaemic myocardial necrosis is sometimes found within the distribution of a normal coronary artery i.e. one without any pre-existing atheromatous narrowing at all that one might point to as a mechanism for localising a reduced blood flow.

By exclusion then, it would appear that myocardial infarction must be precipitated by an acute local obstruction to coronary artery blood flow. And indeed up to this point there is very little controversy. It is the nature of this obstruction that has been so elusive. Very often, there is a pre-existing narrowing from atherosclerosis in the arterial segment concerned, but this is not always the case and even when present is not in itself a sufficient explanation, as the discussion above and the extremely poor clinico-pathological correlation between the degree of coronary atherosclerosis and the severity of clinical symptoms attest. Whether on a background of pre-existing atheroma or not, the superimposed element of the acute coronary artery obstruction is traditionally thought to be thrombotic in nature and indeed there is good evidence for the occurrence of coronary thrombosis in patients with established myocardial infarction. In recent years, however, the primacy of this event in initiating heart attacks has been called increasingly into question. Despite the continued assertion by some pathologists of the traditional view that full-thickness myocardial infarction is almost always associated with coronary thrombosis some found occlusive thrombi in only about 50% of such patients, and almost all are agreed that coronary thrombi are distinctly uncommon in those with partial-thickness or sub-endocardial infarction. Initially, it seemed that the difference of opinion about coronary thrombi in full-thickness infarcts might be related to how soon the patient died after the onset of pain. Thus those claiming a high incidence of coronary thrombi were usually only studying cases where death had occurred 24 hours or more after admission to hospital, and other studies showed a much lower incidence in patients dying earlier than this.
Now, importantly, Erhardt and colleagues found, using radio-fibrinogen as a marker of in vivo thrombosis, that most of the coronary thrombi they were able to investigate at post-mortem appeared to have been laid down some time after the onset of the clinical attack. And whilst the timing and extent of this delay in coronary thrombosis was disputed, there seemed little doubt from these studies that at least some coronary thrombi did not begin to form until after the onset of pain.

In attempting to interpret these findings, several authors focused attention away from large coronary vessel changes to smaller ones, either to small vessel disease per se or to functional haemodynamic changes within the small collateral arteries supplying the ischaemic area. Apart from the fact that these suggestions raised as many questions as they answered, there was no evidence for either of these mechanisms, and because the large vessel distribution of myocardial infarction made them violate the principle of Occam's razor, they were difficult to accept.

Later work established that coronary thrombi actually occurred quite frequently, and quite early (within the first few hours) during the evolution of an acute full thickness myocardial infarction. Part of the evidence for this came from the increasing data on the efficacy of parenteral fibrinolytic agents in lysing coronary thrombi when used within a few hours after the onset of pain. But whether coronary thrombosis is actually the initiator of the sequence of events which leads to myocardial infarction is much less certain. Doubts on this point come from the clinical history of the extreme suddenness of onset of pain in most patients, because we usually think of thrombotic events as being of much more gradual onset, over a period of hours rather than minutes. And even if thrombi did begin to form, it is hard to see how, without postulating some additional factor, the haemodynamics of blood flow through the now-narrowed coronary artery segment would be conducive to the build-up to an occlusive thrombus. This is because, for any given moderate segmental narrowing of the by clot, there will be an increase in flow velocity at the narrowed point (approximately proportional to the square of the radius of narrowing), as anyone who has hose-watered a garden with finger as constricting nozzle would know (see also Chapter 4) - and, other things being equal, this would tend to disperse any newly-developing clot at the site. Moreover, it is difficult to see why coronary thrombosis should occur de novo as a 'spontaneous' event, particularly when it usually does so at the site of an atherosclerotic plaque that has been stable over long periods of time.

It is therefore hard to avoid the conclusion that myocardial infarction is precipitated by some non-thrombotic vascular event, with local thrombosis at the site being secondary to that, albeit sometimes quite soon. And because the heart muscle damage all occurs within the territory of distribution of a major coronary artery, I am lead to propose that this initiating event is acute focal coronary artery constriction or 'spasm' (increase in arterial tone), either precipitating coronary occlusion in its own right (see below) or, less directly in situations where there is an associated atherosclerotic plaque, doing so by cutting off the plaque's vasa vasorum blood supply so as to lead to ischaemic plaque necrosis (haemorrhage, ulceration, rupture, etc.) with (adherent) thrombosis being secondary to that (see below; also Chapter 4).

CORONARY ARTERY SPASM: HISTORY.
Morbid anatomists could only ever be in a position to recognise fixed arterial obstruction, so there is very little point in looking further in this field for evidence of coronary artery spasm. Any clue is more likely to be found in the various clinical aspects of myocardial ischaemia, to which we shall now turn. Being in a position to witness the sudden onset and rapid reversibility of much angina, including that which may precede acute myocardial infarction, clinicians over the years have been much more receptive to the idea of arterial spasm than pathologists. At least this was so in the first half of this century, particularly in its early years, when the concept of a vasospastic origin to angina was championed by such esteemed physicians as Sir William Osler in North America and Jakob Pal in Europe. But when the passing of the years saw no positive evidence emerge to confirm their view, their idea was, not unnaturally, challenged, particularly by Sir George Pickering. In his writings, Pickering pointed to the lack of positive evidence for coronary artery spasm, and turned the tide firmly against the whole concept by emphasising that many of the episodic clinical vascular events once thought to be caused by arterial spasm could now be accounted for on the basis of more observable arterial thrombo-embolic phenomena.

Though lack of evidence does not necessarily deny a concept, the idea of arterial spasm was impossible to test at that time, and in Popper's terms was therefore almost metaphysical. Given this, it is not surprising that other more concrete and testable propositions like thrombo-embolism were preferred, especially when positive evidence began to accumulate in their favour. Even the strong circumstantial evidence from Prinzmetal and his colleagues that one particular form of angina, 'variant' or Prinzmetal's angina, seemed likely to be due to coronary arterial spasm, went unheeded through lack of any direct evidence to confirm it. Prinzmetal's patients had severe (transmural) episodic myocardial ischaemia occurring independent of the sort of physical activity previously used to explain angina of effort, and therefore independent of any increase in metabolic demand by the heart muscle tissue. But the attacks were also readily and often rapidly reversible, and therefore not likely to be explained by coronary thrombosis.

The introduction of coronary angiography completely changed our ability to assess the role of coronary vasospasm in variant angina as well as other forms of myocardial ischaemia, and as a result it has now been conclusively shown that Prinzmetal's view was the correct one, i.e. that many attacks of variant angina are indeed due to localised or focal coronary arterial spasm. Having accepted the evidence for a vasospastic origin to variant angina, I became interested in the possible scope of localised vasospasm in explaining other aspects of the broad spectrum of ischaemic heart disease. A detailed analysis of the literature resulted in a strong circumstantial case that it might explain a great deal, and I subsequently published the results of this analysis. The evidence accumulated since then has continued to support that concept, and I should now like to examine the subsequent evidence, beginning with an enquiry into the mechanism of acute myocardial infarction, and parallels it might have with Prinzmetal's angina.

**VARIANT ANGINA AND MYOCARDIAL INFARCTION**

As it happens, Prinzmetal's angina is characterised by a number of features which are highly relevant to our discussion of the initiation of myocardial infarction. First, in variant angina, the ST segments in the electrocardiogram are elevated during attacks of pain (Prinzmetal et al., 1959), just as they are in full thickness myocardial infarction. Second, dysrhythmias and
conduction defects and even Q waves have all been observed during attacks of variant anginal pain, and again these are the classical hallmarks of an evolving myocardial infarct. From this, it is clear that the picture of variant angina during an attack of pain may be identical with that of transmural myocardial infarction, i.e. ST segment elevation, dysrhythmias, conduction defects and even Q waves on ECG. Of course Prinzmetal's angina distinguishes itself by being reversible, but when any patient is seen early during the course of an acute heart attack it would be impossible to say whether at that moment he was suffering from Prinzmetal's (vasospastic) angina or an evolving acute myocardial infarction. The early phase of both conditions being identical therefore allows us to ask, on the principle of Occam's razor: “What is the need to postulate anything other than focal coronary artery constriction as the initiating cause of acute myocardial infarction?” In my view, there is no need to look beyond this because, as discussed, any coronary artery thrombosis in acute myocardial infarction seems likely to be a secondary event in time. This is not to say that such coronary thrombosis is necessarily of secondary importance as a pathogenetic mechanism in acute myocardial infarction. Indeed, as I shall suggest, it may well be that secondary thrombus formation is often crucial in tipping the balance between what is severe myocardial ischaemia from spasm on the one hand, and actual death of heart muscle tissue from complete coronary occlusion on the other. Nor does the relegation of thrombosis to the status of a secondary event in time explain how it comes about, and this too will need to be taken up later. But the point I make here is that the sort of local coronary vasospasm that occurs in variant angina is also a reasonable and sufficient explanation for the initial phase of acute myocardial infarction. The studies of Maseri and his colleagues would strongly support this view.

Takotsubo cardiomyopathy

In recent years, the frequent appearance of the left ventricule as being like an octopus trap (tako-tsubo) has come to dominate the terminology of many acute reversible coronary syndromes, which are now often referred to as takotsubo cardiomyopathy. I think this is unhelpful. As far as I can tell, the condition is a mere variation on the theme of variant angina. Perhaps its most interesting aspect is that it was first described in Japan, where coronary artery spasm, extant or inducible is relatively common. But it unfortunately takes the focus away from the frequent coronary vasospastic nature of the episodes, so clearly documented in the original paper.

CORONARY SPASM AND MYOCARDIAL INFARCTION: THE EVIDENCE

What then is the evidence for the primacy of coronary artery spasm in myocardial infarction? When I first wrote on this topic in 1977, it was very indirect. Essentially it came from two sources. The first was the finding of normal coronary angiograms during follow-up of some patients after myocardial infarction. But the vaguaries of interpretation of the coronary angiogram and the possibility that coronary thrombi initially present might have been lysed or even recannalised in the interval before the follow-up angiogram made it difficult to advocate any strong argument for coronary artery spasm on this basis alone.
The next piece of evidence came from studies showing an apparent limitation of infarct size in patients infused intravenously with the coronary vasodilator drug nitroglycerin during the evolution of acute myocardial infarction.\textsuperscript{37,38} Unfortunately, here too there were difficulties in interpreting this data, due largely to the poor correlation of eventual infarct size with either ECG or enzyme release patterns.\textsuperscript{39,40} Perhaps that should not have surprised, since much of the initial ECG change and enzyme rise could have reflected ischaemia than infarction. Training athletes certainly develop muscle soreness and enzyme release without apparent ill effect, rather the contrary.

Since the time these arguments were first put forward,\textsuperscript{30,36,41} more evidence has accumulated that bears more strongly on the possible initiating role of coronary artery spasm in acute myocardial infarction. The first is again indirect and comes from the investigations of Maseri and colleagues in patients with ‘pre-infarction’ or ‘unstable’ angina.\textsuperscript{4,33} Their studies make it clear that events of this type are often due to coronary artery spasm, commonly focal, and because any episode which subsequently evolves into acute myocardial infarction is the same at onset in every other way as pre-infarction or unstable angina, there seems to me little reason to postulate a different initiating mechanism for it (see also Maseri et al., 1978a). Second, and more directly, Oliva and Breckinridge performed coronary angiography in patients presenting with acute evolving myocardial infarction within a few hours of the onset of their pain, and found (reversible) coronary vasospasm in at least 40% of patients.\textsuperscript{42} And as the authors themselves point out, their figures on the incidence of spasm in the left coronary artery system might well have been an underestimate, because they were unable to cannulate selectively the particular branch of the left coronary artery concerned. As a result, the injected nitroglycerin may have effectively bypassed the site of spasm, by now being channelled down the other (patent) branch of this artery. Be that as it may, this finding of focal coronary artery spasm by direct angiography at the time of acute myocardial ‘infarction’ provides strong and direct evidence for the present proposal. Its prime importance has certainly been recognised in Japanese patients.\textsuperscript{9}

A PERSPECTIVE ON VASOSPASM AND THE INITIATION OF ACUTE ACUTE CORONARY SYNDROMES

The epicardial arteries have a smooth muscle coat (media) richly supplied with sympathetic nerves right down to the large arteriolar level, almost to the extent of being a cellular extension of the nerves themselves.\textsuperscript{43} The sympathetic nervous system is activated by stress, either physiological or psychological, so I propose that such stress is the prime mover initiating coronary artery constriction that leads on to myocardial infarction.\textsuperscript{30,36,41} When I first put forward this view, the evidence for the relationship to psychological stress was sparse and inconclusive. Apart from anything else, one man’s meat being another’s poison, psychological stress is difficult to define\textsuperscript{1}, and any relationship of, for example ‘life events’ to heart attacks often very indirect. But a relationship there indeed seems to be,\textsuperscript{44-47} and sometimes a very dramatic one, as in the ‘broken heart’ syndrome\textsuperscript{48} and the closely related Takotsubo’s cardiomyopathy.\textsuperscript{34} One issue of controversy is how focal coronary arterial construction could reduce coronary blood flow enough to cause infarction, a point that puzzled that champion of coronary spasm, Atillio Maseri.\textsuperscript{49} But as we have found in the rat (see Cover photo) and others have also

\textsuperscript{1} I prefer to define stress, psychological or physiological, as that which activates the sympathetic nervous system in usual degree.
observed experimentally, vasoconstriction tends to occur irregularly along the arterial system.

I suggest that focal spasm often involves the larger resistance arterioles as well as the main coronary artery in heart attacks, and to a degree sufficient to reduce blood flow and cause myocardial infarction in the territory concerned.

**How might coronary arterial spasm cause thrombosis?**

One obvious way, postulated previously, is via a reduction in the *volume of blood flow*, with consequent stasis, in the arterial territory beyond the focally constricted point. However, I now hold that any such stasis alone is not sufficient. The *velocity* of blood flow at any focally constricted arterial point would likely be higher than that in the region immediately beyond, just as partial constriction of the outflow from a garden hose will increase the flow velocity of the locally issuing jet (see also chapter 4). For these reasons it now seems to me that any overall reduction in blood volume flow at a point of vasospasm would not normally be sufficient alone to account for secondary thrombosis following arterial spasm, unless that spasm was particularly severe.\(^9\) Maseri, who was largely responsible for the renewed interest in coronary vasospasm, also came to understand this point full well.\(^{49}\)

One factor that might predispose to focal coronary thrombosis would be arterial wall damage at the site of local coronary spasm.\(^{53}\) Such damage might come about in a number of ways. First, coronary artery blood flow is normally auto-regulated over a wide range,\(^{54}\) so that any tendency for a drop in regional blood flow to occur because of focal coronary *artery* constriction would be largely compensated by a decrease in the more peripheral coronary *arteriolar* resistance. And as blood volume flow under these circumstances would remain relatively constant this, from Bernoulli’s law, would mean a dramatic increase in blood flow velocity at the point of constriction itself (inversely proportional to the square of the radius of constriction at that point). Such a change in blood flow velocity, even perhaps to the point of turbulence, would place a high shear stress on the endothelial lining at that point. And once endothelial damage had exposed sub-endothelial collagen, local platelet deposition would likely ensue. This sequence of events is certainly more than just a theoretical possibility.\(^{56}\)

It is also possible that the release of vasoconstrictor substances such as thromboxane A2 (TXA2) from platelets in the coronary thrombi might add a further local vasoconstrictor drive, through a direct effect of TXA2 on the coronary artery itself\(^{56}\) perpetuating the coronary artery spasm.\(^{30}\)

**Coronary atherosclerosis and coronary spasm**

Of course, coronary thrombosis usually occurs within an arterial segment already affected by atherosclerosis and this could have additional effects predisposing to more complete and even to less reversible coronary occlusion.

First, most of these atherosclerotic lesions cause some structural narrowing of the involved coronary artery segment to begin with, so that little further superimposed functional vasospasm might be required to produce a complete occlusion at the site. Local stasis could also then become a more important factor tending to precipitate secondary coronary thrombosis.

A second effect could follow from the observation that these narrowed atherosclerotic arterial segments are often the site of focal coronary artery spasm.\(^{57}\) The emerging consensus view now is that this is likely due to a deficiency of endothelium derived relaxing factor (EDRF) at the site, so as to predispose the site to constriction as a secondary rather
Regardless of how any coronary artery constriction comes about, it could have important consequences not generally appreciated in the mainstream literature on the subject. My take on this is as follows:

As the atherosclerotic plaque increases in size, it develops a vasa vasorum blood supply at its base from adventitial layer of the coronary artery itself. This means that these vasa vasorum have to run through the media or muscle layer of the involved coronary artery on their way to the intima. As a result, any focal constriction of the coronary artery medial coat high enough to narrow the main coronary lumen must, almost by definition, also be high enough to also exceed the blood pressure prevailing within the vasa vasorum lumen, so throttling the blood supply to the overlying intimal plaque. And if sustained, this could lead to ischaemic plaque degeneration, osmotic swelling and necrosis and rupture; (see also Chapter 4). A sequence like this might well cause further structural narrowing of the coronary lumen, and also explain the acute haemorrhage/necrosis so often seen in atherosclerotic plaques at the time of acute clinical events like myocardial infarction and unstable angina. Because of associated damage to the overlying intima, it could also be another important factor contributing to coronary thrombosis at the site of vasospasm, relevant to both myocardial infarction and unstable angina.

Given this background evidence, we might well ask why there should still be such a barrier to the idea that coronary artery spasm could actually be the prime initiating cause of myocardial infarction. Partly, I think this is due to the long-held tradition that if arterial spasm occurs in man at all, it can only account for reversible events such as Raynaud’s phenomenon and migraine, and that any tendency for its persistence would somehow eventually be overcome by the body’s physiological methods of blood flow regulation. Second, there appears to be a difficulty in accepting that spasm might ever be complete enough in an artery of this size to totally abolish blood flow. Neither of these conditions is necessary, however. First, the view I present depends not so much on changes in total volume of luminal blood flow as an increased flow velocity at the point of spasm damaging the arterial wall. Second, the coronary artery constriction itself would seriously compromise the vasa vasorum blood flow. Both factors then predispose to the secondary changes of local arterial wall damage, platelet aggregation, thrombosis. These changes, together with any ischaemic plaque swelling and necrosis secondary to coronary artery constriction, could set in train a process of irreversible narrowing which would eventually becomes quite independent of its initiating cause. The degree of spasm need not even be great in most cases. First, as we have already seen, it appears to occur most often in areas already narrowed by atherosclerosis, where very little reduction in concentric arterial smooth muscle fibre length would be required to cause complete obliteration of the lumen, and/or seriously interfere with the plaque’s adventitial vasa vasorum blood supply. Second, even minimal coronary artery constriction, perhaps undetectable on coronary angiography, would tend to overcome vasa vasorum blood flow.

**MYOCARDIAL INFARCTION: THE HYPOTHESIS.**

My interpretation of the evidence, therefore, is that myocardial infarction is initiated by acute segmental focal coronary artery territory arteriolar spasm, most usually occurring in an area of artery already narrowed by atherosclerosis. This vasospasm, and the related ischaemic heart muscle damage in its territory of supply, are seen as being potentially reversible in the early phases, as evidenced by recovery from ‘variant’, unstable, and ‘pre-infarction’ forms of angina. But if spasm persists, a secondary and less reversible coronary narrowing ensues, due

---

2 Discussed in more detail in Chapter 4.
either to coronary thrombus formation on the site of ensuing damage to the arterial wall, or plaque swelling secondary to its ischaemic necrosis, or both.\textsuperscript{62} It is further suggested that this additional narrowing might frequently result in the complete cessation of a blood flow which had previously been adequate to support cardiac muscle cell viability, so tipping the balance from a potentially reversible ischaemic heart muscle damage to complete and irreversible myocardial cell death.

There is no conclusive proof of the sequence of events proposed, but the accumulating evidence is in its favour. For example, there is the evidence of an important role for coronary vasospasm in much of that angina which precedes acute myocardial infarction: 'unstable', 'accelerated' or 'pre-infarction' angina.\textsuperscript{4,33} There is also in vivo documentation of associated sub-intimal plaque haemorrhage and/or partial overlying coronary thrombosis in acute coronary syndromes.\textsuperscript{65} In keeping with our principle of Occam’s razor, we must therefore ask whether there is any need to postulate a different mechanism for the initiation of acute myocardial infarction from that occurring in the anginal episodes which may immediately precede it, and on occasion even cause it.\textsuperscript{9} In view of the potential such a vasospastic mechanism has for reversibility by \textit{early} therapeutic intervention, it is especially important that it be strongly borne in mind in future research in this field.

**FUNCTIONAL DIAGNOSIS**

According to our formal analysis of clinical data, we still have two more categories of question to consider. The first is, “What are the secondary or functional aspects of acute myocardial infarction, and in particular which of the apparent effects are worth re-examining for a possible feedback relationship to cause?” In this respect, sweating, tremor, pallor and agitation are common in patients with myocardial infarction, and all reflect increased sympathetic nervous activity, which we usually take to be secondary to pain. Whatever its cause, it could secondary contribute importantly to pathogenesis if the sympathetic nervous discharge included a component of the sympathetic vasoconstrictor fibres to the epicardial coronary artery bed concerned.\textsuperscript{52} Hyperventilation is also a frequent anxiety manifestation, and the alkalosis consequent upon that could well contribute further to coronary vasospasm and its consequences.\textsuperscript{56,67}

**AETIOLOGICAL DIAGNOSIS: MECHANISMS OF CORONARY VASOSPASM**

The last category of our diagnosis is the aetiological one. As discussed, the evidence here is increasingly in favour of coronary arterial vasospasm as the initiating cause of whole spectrum of myocardial ischaemia, spontaneous or inducible.\textsuperscript{9,68-71} Sympathetic mechanisms are frequently involved albeit through transmitter mechanisms not fully understood,\textsuperscript{4,72} but possibly including the co-release of neuropeptide Y with noradrenalin from sympathetic nerve terminals.\textsuperscript{73} Such a sympathetic mechanism would fit well with the increasing evidence for an important role of life events and stress — as perceived in one way or another\textsuperscript{47,74,75} — as factors predisposing to myocardial ischaemia, because we have long known that psychological stress can activate the sympathetic nervous system in considerable degree.\textsuperscript{76,77} Indeed, we are entitled to ask: “If not physiological or psychological stress, what else is there to activate the sympathetic nervous system?

Once initiated, it might seem folly for any coronary artery spasm to continue, and there are probably powerful negative feedback mechanisms tending to
overcome it. However, it often does continue and there may be other important factors operating to facilitate this; for example, the increased sympathetic drive associated with any secondary cardiac failure, with continuing pain, and/or with the stress resulting from the patient’s almost certain knowledge in these enlightened times that he has had a heart attack. Also, as discussed above, the release of thromboxane A2 from any secondary local platelet thrombi in the area of spasm could perhaps add some further vasoconstrictive drive tending to perpetuate any coronary constriction.

**What initiates coronary spasm?**

This is the root aetiological question. As discussed, there is more than a suspicion that stress is important in the background to myocardial infarction (see for review), but acceptance of its role has been hampered both by the difficulty of defining stress in a precise way, and by a failure to conceive of tangible mechanisms through which it might cause events in space and time. This temporal and spatial localisation of coronary events is no more difficult to understand here, though, than in conditions where a relation to psychological stress is much more accepted, such as migraine aura.

**ANGINA**

Even in angina, there is reason to suppose that increased coronary tone may be important. The traditional view that angina of effort is related to a relatively increased myocardial metabolic demand over coronary blood flow certainly leaves a number of features unexplained. First, many patients with angina show a great variation in the amount of effort needed to induce pain on different occasions. This variability of exertional angina has been best described in patients with variant angina — where coronary artery spasm has been clearly demonstrated during exercise — but it has also been noted in classical angina of effort. In particular, there is good evidence of sympathetically-mediated constriction of coronary artery segments narrowed by atherosclerosis in response to exercise and other sympathetic nervous system stimulants such as the cold pressor test, isometric hand grip, and mental arithmetic.

The main view that now prevails is that any coronary artery constriction is due to a deficiency of EDRF over sites of coronary atherosclerotic narrowing. This view has been given force by the quite striking effect of agents such as acetylcholine (which releases EDRF) to paradoxically constrict narrowed atherosclerotic coronary artery segments, in contrast to its effect to vasodilate normal ones.

Regardless of the potential contribution of this paradoxical effect, such EDRF deficiency is not enough to explain the initiation of acute coronary syndrome attacks. There must be some trigger to set the whole process in train, and the evidence that should not be lost sight of in this respect, is stress-induced sympathetically-mediated coronary artery constriction. Nowhere is that more shunned, it seems to me, than in the re-naming of conditions such as ‘broken heart syndrome’ with the term tako-tsubo cardiomyopathy, where the initial description clearly recognised the importance of coronary artery vasospasm.

The more angina and acute coronary syndromes are studied, the more the evidence accumulates for an initiating role of coronary vasospasm across the
whole spectrum. Such vasospasm seems highly likely to be evoked by sympathetically-mediated stress, either physiological or, more importantly, psychological. Those stress triggers may not always immediately apparent in the time, any more than they are in common migraine aura. It seems likely that coronary vasospasm is pathogenetically important across the whole range of myocardial ischaemic events, rather than being limited to the unusual few.

CONCLUSION

According to the present analysis, the sequence of events in the progression of myocardial ischaemia may well be as follows:

1. **ST segment depression on ECG with exercise in the presence of a normal coronary angiogram.** This may well represent the minimal form of ischaemic heart disease, where reflex sympathetically-mediated coronary arterial constriction occurs during exercise, but where the coronary artery and its branches appear normal during angiography performed at rest. If such is the case, the ST segment depression on ECG could be due to sub-endocardial ischaemia, this being the area of highest pressure within the myocardium and therefore the most liable to suffer ischaemia during any general reduction in coronary blood flow.

2. **Stable angina of effort** with ST depression would again indicate subendocardial ischaemia, but this time on a background of focal atherosclerosis in the vascular territory concerned.

3. **Subendocardial infarction** (‘non-STEMI’). More prolonged and/or more severe degrees of spasm may result in subendocardial necrosis with inversion of T waves on ECG.

4. **Transmural ischaemia** is probably the next most severe grade. This is can be observed in so-called variant angina and Takotsubo ‘cardiomyopathy’ where the spasm may involve small as well as larger coronary arteries, but where the attack usually subsides without sequelae - provided that irreversible ventricular fibrillation or other fatal dysrythmia does not ensue. [Such ventricular fibrillation of ischaemic origin may occur in the absence of any pain whatsoever, and could well account for much of the syndrome of so-called ‘primary’ ventricular fibrillation.]

5. **Acute transmural myocardial infarction.** If this above degree of spasm persists, the pattern of transmural ‘infarction’ will begin to evolve, with elevated enzymes etc. This may nonetheless be reversible up until the point at which haemodynamic damage occurs to the arterial wall at the point of constriction. At that stage, secondary coronary thrombosis may supervene to cause complete occlusion of the artery and total abolition of coronary blood flow, with myocardial cell death. These changes may take several hours to develop, and it is likely that a minimal blood flow may be all that is required for the maintenance of a viable myocardium right up until the point at which secondary thrombosis totally stops coronary blood flow and precipitates irreversible myocardial infarction. Indeed, we now know that intervention within this time frame may indeed allow myocardial salvage.
References


90. National Heart Foundation Of Australia Coronary Thrombolysis G. Coronary thrombolysis and myocardial salvage by tissue plasminogen activator given up to 4 hours after onset of myocardial infarction. The Lancet. 1988; 331:203-208.