ACE inhibitors in acute and chronic ischaemia: current status and future promise

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1 Myocyte loss, reactive hypertrophy, dynamic ischaemia with 'stunning', and ventricular wall remodelling are all involved in the initiation and progression of myocardial failure which is ischaemic in origin.

2 The effects of ACE inhibitors to reduce preload and afterload has potentially salutary effects in these settings. Moreover, sulphyl containing ACE inhibitors may have further actions in reducing free radicals and their damage in the acute phases of these events.

3 These promising initial studies warrant further exploration.

Keywords heart failure myocyte loss stunned myocardium ventricular remodelling

Introduction

Myocardial ischaemia produces a range of effects on contractile behaviour and ventricular geometry. These effects are both acute and chronic, as well as reversible and irreversible. They range from the abnormalities of contractile activity that occur abruptly with acute transient ischaemia and disappear rapidly as the process abates to more sustained loss of contractile behaviour from more prolonged and severe periods of acute ischaemia. With persistent ischaemia, myocardial infarction ultimately ensues. Transient ischaemia as well as infarction are further complicated in that they occur not only segmentally, but transmurally. When coronary blood flow is reduced in a region of the ventricular wall, contractile activity falls initially in the endocardium and progresses toward the epicardium as it becomes more severe (Kirk *et al.*, 1972). Overall transmural contractile activity reflects the sum of activity generated within the ventricular wall. Variations in the time course and duration of contraction of fibres in the wall are occurring as well. Thus a wide variety of segmental changes in contractility may be seen producing variable dyskinesia and

akinesia which may change with time. Follow-up recovery from transient ischaemia, contractile activity may only recover after a prolonged period of time ('stunning') (Braunwald & Kloner, 1982; Ellis *et al.*, 1983). Further persistence of ischaemia results in necrosis and with the subsequent healing producing focal fibrosis. Here too the process has an acute phase as well as a more sustained phase, characterized by compensatory ventricular wall expansion and myocardial hypertrophy in the non-ischaemic region. (Anversa *et al.*, 1985a; McKay *et al.*, 1986; Roberts *et al.*, 1984). These latter changes are evident especially in the presence of a large area of tissue loss. In these many pathophysiological settings of acute ischaemia and myocardial infarction, angiotensin converting enzyme (ACE) inhibitors may play a useful role. Current acute therapeutic opportunities exist in intermittent ischaemia with 'stunning', in acute myocardial infarction in both its early and late stages, perhaps in cardiomyopathies with microvascular stenosis and focal ischaemia (Factor & Sonnenblick, 1987).

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Transient myocardial ischaemia

During episodes of transient myocardial ischaemia, especially when prolonged or repetitive, contractile activity declines quite rapidly in the area involved and this may result in significant reduction of overall ventricular performance if the area of myocardium affected is substantial, i.e. more than about 20% of the ventricular mass. With restoration of coronary blood flow and adequate oxygenation to this acutely ischaemic area, the recovery of contractile activity in the region may be delayed for hours and even days. This sustained reduction of contractility following reperfusion and relief of ischaemia has been termed 'stunning' (Braunwald & Kloner, 1982). If the period of ischaemia is not too prolonged, 'stunning' occurs without necrosis of myocardium. Commonly some sub-endocardial necrosis occurs with 'stunning' in the surviving transmural layers of the ventricular wall. The phenomenon of 'stunning' may actually reflect a number of ischaemia-induced abnormalities that may require significant time for reversal. These abnormalities may also differ depending on duration and severity of ischaemia as well as conditions under which reperfusion occurs. In our particular studies (Zhao *et al.*, 1987), ventricular 'stunning' has been produced in the anterior wall of a dog left ventricle by occluding the left anterior descending coronary artery for 5 min with subsequent 10 min periods of reperfusion. This procedure was repeated 12 times and the consequences to the ventricle in terms of contractile behaviour, tissue compliance, and ultimately structural alteration have been investigated. When the anterior aspect of the ventricle is made acutely ischaemic, contractile activity declines very rapidly until bulging of the area occurs in systole. This is demonstrated with sono-micrometer clips which provide pressure-length curves in the area made ischaemic (Zhao *et al.*, 1987). With severe ischaemia, this bulging occurs along the anticipated diastolic pressure-length curve for the region. However, if the ischaemia persists, systolic contraction stretches the region progressively so that the pressure-length curve moves to the right. Recovery to the left is only partial during reperfusion. Thus, not only is there a loss of contractile activity but changes in the diastolic properties of the ischaemic area of the heart occurs. Structurally, despite total preservation of the myocardial cells with no damage to their interior components, as best could be perceived by transmission electron microscopy, scanning electron microscopy revealed major disruption of the connective tissue that interconnects one myocardial cell to another

(Zhao *et al.*, 1987). The extracellular collagen matrix of struts and coils between myocytes were disrupted to a variable degree, and in the most notable cases there was complete loss of these intercellular connections (Zhao *et al.*, 1987). These coils and struts between cells have been shown to be major sites of resting tension in the myocardium and may also contribute to diastolic recoil during ventricular filling (Caulfield & Borg, 1972; Robinson *et al.*, 1988). These intercellular connections are probably the major mechanism by which systolic force is transmitted as well (Robinson *et al.*, 1988). Thus, although contractile activity may be restored with reperfusion of the myocardium, a major persistent lesion may be the loss of intercellular connective tissue that allows the delivery of contractile force from one cell to another. Moreover, with the destruction of intercellular connections, remodelling with slippage of myocardial cells may occur so that an augmented volume is created for a given filling pressure. This would help explain how a region of myocardium can expand without a proportional increase in sarcomere length, as has been observed in chronic volume overloads in dogs (Ross *et al.*, 1971). Moreover, a natural consequence of such 'slippage' of myocytes would be a decrease in the number of cells across the ventricular wall. On this basis, repeated episodes of acute ischaemia could potentially produce an area of aneurysm formation in the involved region despite the preservation of structurally normal myocardial cells.

The mechanisms by which dissociation of intercellular connective tissue occurs during 'stunning' remains a matter of speculation. Nevertheless it is intriguing to note that collagenases are present in the myocardium (Caulfield & Wolkowicz, 1988), and oxygen derived free radicals produced during reperfusion (Bolli, 1988; Hammond & Hess, 1985; Mullane, 1989), may activate collagenase (Greenwald & Moy, 1979; Kako, 1987). From the present studies it is unknown whether the disruption of the collagen matrix results from the ischaemia or the reperfusion, and whether a comparable phenomenon would occur with lesser amounts of ischaemia. In addition, it is unknown whether inhibition of free radicals will inhibit these connective tissue changes, and whether recovery requires resynthesis of intercellular connections. With these considerations in mind, the studies of Westlin & Mullane (1988) are particularly noteworthy since they demonstrate that captopril can attenuate the duration and extent of the depression of contractility following 15 min of transient ischaemia. Sulphydryl-containing compounds were found to be more effective than non-

sulphydryl ACE inhibitors such as enalapril. This is of interest since the former compounds may help to scavenge free radicals (Mullane, 1989). It is also possible that the acute unloading produced by ACE inhibition could contribute to these effects by reducing systolic bulging during ischaemia. Moreover, rapid recovery may reduce the diastolic damage to this acutely ischaemic myocardium when connective tissue is seriously compromised. That this latter effect may not be the dominant one is shown by the lack of benefit derived from nitroprusside (Przyklenk & Kloner, 1987).

Acute myocardial infarction

The role of ACE inhibitors in acute myocardial infarction and its sequelae is an intriguing and evolving story. These effects may be separated into those related to acute events and those that are involved in more long-term or chronic changes associated with myocardial infarction.

Consequent to an acute myocardial infarction, there is a rapid decline in ventricular ejection fraction which occurs in approximate proportion to the amount of myocardium that is lost (Fletcher *et al.*, 1981; Pfeffer *et al.*, 1985a). The immediate result of this loss of contractile behaviour in the infarcting area is to shift the load to the remaining myocardium which compensates for this by an increase in filling pressure that allows the heart to work on a higher portion of a Frank Starling curve. With this increase in diastolic distension, there is an effect on the infarcted portion of the heart as well as the degree of diastolic stretch of the surviving tissue (Weisman *et al.*, 1988). The evolution of the infarction acutely is thus affecting the tissue that is being lost and also the remaining myocardium. The adaptations of the remaining non-ischaemic myocardium are very rapid in onset. In rats sustaining an acute myocardial infarction, 29% enlargement of myocytes was evident by 3 days. Similarly, remodelling of cells in the region of infarction is evident at the same time (Anversa *et al.*, 1985b). Accordingly, early intervention would appear most appropriate if the longer term changes in the infarcted and remaining non-ischaemic tissue (Pfeffer *et al.*, 1979) are to be avoided. Given the considerations noted above and the effects of captopril during 'stunning', it is reasonable to expect that ACE inhibitors could play an important role immediately after an acute infarction because of their unloading actions on both the venous and arterial side of the circulation. This ought to permit the damaged pump to function on a more advantageous portion of its Frank Starling curve

relative to the surviving tissue and without as much diastolic stress to the necrotic region of the heart. The role of ACE inhibitors in this setting is now being explored in man. Following the acute phase of an infarction, the longer term evolution of distension of scar tissue as well as the deterioration of left ventricular function appears to be ameliorated by the unloading effects of ACE inhibitors. This has been amply demonstrated by Pfeffer and his associates wherein captopril has reduced mortality and improved survival in rats (Pfeffer *et al.*, 1985b). This was most apparent in moderate sized infarctions. Similar results have been noted in man over a period of 1 year (Pfeffer *et al.*, 1988; Sharpe *et al.*, 1988).

The longer term consequences of a large myocardial infarction are determined to a large degree by time related changes in ventricular performance. Once healing of the infarcted area has occurred, the remaining part of the myocardium continues to hypertrophy in relation to the amount of myocardium that is lost (Anversa *et al.*, 1985a). Over several weeks, this hypertrophy in the remaining non-ischaemic myocardium can be quite substantial, in response to a complex load created not only from the tissue lost, but also from the load produced by the increase in volume. We have been interested in the contractile behaviour of the non-ischaemic portion of the ventricle that remains after an acute myocardial infarction. Accordingly, we have ligated to left anterior coronary artery in rats, producing infarction of the anterior ventricular wall (Anversa *et al.*, 1985a). The posterior wall hypertrophies while ventricular dilatation occurs. Ten weeks later, we have removed the posterior papillary muscles from these hearts and studied their mechanics (unpublished observations). We have found that contractile behaviour is altered in a manner that parallels that which is seen with pressure over-load hypertrophy as produced experimentally with renal hypertension (Capasso *et al.*, 1981). Thus, in this ostensibly normal non-ischaemic myocardium, the rate of contraction is slowed, the time to peak tension is prolonged, and the rate of relaxation delayed, although peak tension may still be sustained (unpublished observations). A parallel reduction in the actomyosin ATPase activity of the myocardium has also been shown in hypertrophied myocardium remaining after an infarction (Michel *et al.*, 1988) as well as in pressure overload hypertrophy (Capasso *et al.*, 1986).

When captopril has been administered to rats 1 week following an acute infarction, less deterioration in ventricular function ensued (Pfeffer *et al.*, 1985a) along with an improve-

ment in long-term survival (Pfeffer *et al.*, 1985b). In a recent study, similar treatment with captopril resulted in a lesser increase in heart size with less ventricular hypertrophy as well as a reversion of the slower actomyosin ATPase to normal (Michel *et al.*, 1988). The mechanical results that we have observed in terms of contractile activity are parallel to these biochemical findings (unpublished observations) and would indicate that the treatment with captopril results in less contractile abnormalities consequent to a pressure overload than would be anticipated in the untreated infarction.

Ischaemic cardiomyopathy

One may attribute the ischaemic cardiomyopathy to both wall remodelling due to ventricular distension interacting with non-contractile fibrotic zones which augments wall tension in systole, and also to intrinsic depression of contractile activity in the hypertrophied region due to the hypertrophy itself. Any residual ischaemia can only add to these detriments. The above studies would commend the use of ACE inhibitors in patients that have sustained a large myocardial infarction in the hopes of reducing ventricular wall remodelling and thus the long-term development of an ischaemic cardiomyopathy.

The present discussion would support the use of ACE inhibitors relatively late after an acute infarction (i.e. 1 week) when a good deal of the damage has already ensued and the majority of the adaptive responses of dilatation in hypertrophy have occurred, but also in the acute episode when the process of necrosis is evolving.

Experimental dilated cardiomyopathy

Given the effects of captopril in acute intermittent ischaemia that results in 'stunning', as well as the longer term effects to reduce ventricular wall remodelling and failure after infarction, there are intriguing findings in experimental cardiomyopathies that may find a parallel use for these agents. In the hereditary cardiomyopathy that occurs in the Syrian hamster, myocytolytic focal lesions occur early in the disease process with scarring in these areas and resultant reactive hypertrophy that ultimately leads to ventricular dilatation and death (Factor & Sonnenblick, 1985, 1987). These focal lesions appear to be due to microvascular spasm that is superimposed on tissue that cannot sustain acute ischaemic events normally (Factor *et al.*, 1982).

Thus, microvascular spasm may indeed cause focal ischaemia that ultimately leads to cell loss. The loss of cells may not be adequate to explain the failure of contractile activity that subsequently occurs. Reactive hypertrophy of a pressure overload nature does eventually occur and may explain some of the reduction in contractile activity, but once again this does not appear to be entirely adequate. An intriguing finding is that surrounding the acute myocytolytic lesion and the identifiable loss of cells is a halo or ring surrounding the obvious lesion where connective tissue is lost (Cohen-Gould *et al.*, 1987). This would suggest that the acute ischaemic episode that leads to myocyte loss may also be associated with a further loss of connective tissue beyond the area that actually goes on to necrosis. Thus, the acute ischaemic episode of microvascular spasm may be causing focal 'stunning' in addition to myocyte loss. Given the influence of captopril in the setting of 'stunning', its effects on cardiomyopathy would be of great interest. In addition, to the degree that captopril reduces both preload and afterload, the extent of reactive hypertrophy in ventricular wall should be lessened and the degree of ventricular dilatation should be somewhat reduced. Both of these effects should be beneficial in a given cardiomyopathy and this may be one of the reasons why ACE inhibitors are of such value in chronic cardiomyopathies in general. Thus, in addition to reduction of load, both preload and afterload, a reduction of connective tissue loss that might amplify wall remodelling could be an added factor. Whether these findings in animals can be generalized upon will require further studies. Moreover, there are other types of experimental cardiomyopathies such as the one that develops in the hypertensive diabetic rat (Fein *et al.*, 1988). Here too, microvascular spasm occurs with myocyte loss and the effects of ACE inhibitors on these lesions and the course of this disease process warrants study. Long-term influences of ACE inhibitors may well be derived in the peripheral vasculature too (Levy *et al.*, 1988). These may be manifested by lesser changes in the peripheral microvasculature when central pump dysfunction is present. This would explain some of the long-term effects of captopril that are manifest at a much later time than the improvement in ventricular performance that is seen with the acute effects of the drug (Mancini *et al.*, 1987). Improvements in the peripheral circulation may involve remodelling of this system as well towards a more beneficial setting.

In summary, myocyte loss, reactive hypertrophy, dynamic ischaemia with 'stunning', and ventricular wall remodelling are all involved in

the initiation and progression of myocardial failure, ischaemic in origin (Sonnenblick *et al.*, 1989). The effects of ACE inhibitors to reduce preload and afterload has salutary effects in these settings. Moreover, sulphyl containing ACE inhibitors may have further influences in

reducing free radicals and their damage in the acute phases of these events.

Accordingly, these promising initial studies warrant further exploration.

This work was supported in part by grants: HL37412 (EHS).

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Discussion

Peter S. Sever (London): Since the animal data appear so persuasive, and the haemodynamic studies in man are so encouraging, do you think that the time has come for a major intervention trial with these drugs, after uncomplicated myocardial infarction?

Edmund H. Sonnenblick (New York): There is one under way at present involving captopril called the SAVE Study. This deals with infarction that has primarily healed with the aim to reduce progression to cardiac dilatation and heart failure over a period of time. There is also the SOLVD Study which is studying the clinical course of asymptomatic patients with reduced ejection fractions of whatever cause, and whether progressive ventricular dilatation can be reduced or prevented by ACE inhibition. What is not currently being done, but is in the early stages of planning, is to see how one can treat the early events in ischaemia and infarction to prevent further immediate destruction and/or remodelling of tissue; for example, some ventricular wall remodelling, which leads to the pressure/volume alterations, may occur during the first week. Further safety data on the use of ACE inhibitors early in MI are required so that the drugs can potentially be used to good effect earlier after infarction.

Giuseppe Licata (Palermo): By what mechanisms do ACE inhibitors increase ejection fraction in myocardial infarction?

Edmund H. Sonnenblick (New York): If you maintain stroke volume, and the end-diastolic volume does not enlarge over a period of time, you will tend to preserve or increase the ejection fraction. To the degree that you have better contractile activity and less reactive hypertrophy occurring from smaller heart size, an improving ejection fraction could result. It depends what happens to the diastolic volume of the heart; a heart that is not enlarging is ultimately a better heart at less risk.

John G. F. Cleland (London): Could left ventricular dilatation be beneficial in some patients after MI, as this will help maintain cardiac output in the face of a reduced ejection fraction?

Edmund H. Sonnenblick (New York): The heart is not a very good volume pump in the face of ventricular dilatation. As the heart becomes larger, the tension in the wall increases for any given degree of pressure in line with the LaPlace relation. This leads to a limited compensation, and I believe that cardiac dilatation in fact produces heart failure. It produces mitral insufficiency, and a dilating heart may ultimately die,