Enzymes in Cardiology

Diagnosis and Research

Edited by
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Foreword

P. Y. Hatt

Enzyme release and myocardial cell damage are both closely related to the deterioration of the myocardial cell membrane and its permeability characteristics. The cell membrane is an efficient diffusion barrier which ensures the maintenance of the cellular integrity by insulating the intracellular milieu from the noxious components of its environment and by preventing the outward diffusion of intracellular macromolecules such as enzymes. The loss of the semi-permeability properties of the cell membrane is one of the earliest manifestations of cellular damage and it is this myocardial lesion which will be extensively discussed in many chapters of this book.

The word 'lesion' is derived from the latin verb '*laedere*' meaning to wound or to do an injury. When applied to the cell this damage would be evidenced by changes in morphology, biochemistry, electrophysiology, etc. Until recently myocardial cell damage has been classified morphologically on the basis of structural changes revealed by light microscopy. These rather descriptive changes included 'coagulation necrosis', 'contraction bands', 'hyalinization', etc. The advent of electron microscopy has permitted far more specific ultrastructural changes to be described. Furthermore, it is now possible to correlate structural and functional changes within sub-cellular organelles such as mitochondria, myofibrils, tubular systems and sarcolemma, to differing facets of myocardial damage. Thus, for example, the observation of disappearing glycogen granules and increasing lipid deposits in the cell during ischaemia may be specifically related to ischaemia-induced changes in the metabolic pathways of glycolysis, glycogenolysis and lipolysis. Similarly the observation of cell swelling can be attributed to intracellular oedema resulting from the ischaemia-induced impairment of pumps which are located in the sarcolemma and which control water and ion movements.

Other ultrastructural characteristics of myocardial cell damage are less easily related to specific biochemical changes. Ischaemia-induced changes in mitochondria include for example: loss of dense intracristal granules, swelling, disruption of cristae and the appearance of dense calcium-rich deposits. The molecular mechanisms underlying these structural alterations are complex but may include changes in ATPase activity, changes in the chemo-osmotic properties of various mitochondrial membranes and decreased

availability of cellular high energy phosphates. Ischaemia-induced myofibrillar lesions, such as the lysis of the myofilaments, are also complex and inadequately understood but might be related to proteolysis secondary to lysosomal disruption or to inadequate supplies of energy necessary for the maintenance of highly organized macromolecular structures such as the myofibrils.

Clearly, much remains to be learned about myocardial cell damage, for example, the nature of reversible and irreversible damage and the critical point of transition between these states; the effects of transient ischaemia and reperfusion; the relationship between myocardial ischaemia and other lesions with closely related mechanisms such as acute heart overload. The investigation of these molecular mechanisms will undoubtedly be advanced by a better understanding of the phenomena of myocardial enzyme release and its relationship to myocardial cell injury.

Preface

The phenomenon of enzyme leakage has been recognized since the beginning of this century and for over 50 years it has been used for the detection and assessment of tissue injury. From its early empirical nature diagnostic enzymology has developed into a highly sophisticated and precise science which has been exploited for the benefit of mankind, particularly in the sphere of cardiac disease.

Despite its established history, diagnostic enzymology as a methodology has grown faster than our knowledge of the principles upon which it is based. Despite our ability to use enzyme leakage to pinpoint an exact disease process in a specific tissue or group of cells, to measure the mass of tissue involved, and maybe even predict the ultimate extent of injury we still remain ignorant about many of the fundamental cellular processes which lead to, and support, the phenomenon. It is the objective of this book to discuss and define the principles underlying these complex processes.

The book commences with a consideration of the biochemical changes which predispose to cellular injury and in particular the changes which occur during ischaemia and evolving myocardial infarction. The ischaemia-induced loss of intracellular enzymes is related to changes in cellular ultrastructure. The complex problems associated with the translocation of enzyme macromolecules from the cytoplasm to the extracellular space is discussed as is the movement of these molecules from the interstitial fluid to the circulating blood. These latter processes require a consideration of the respective roles of coronary and lymphatic drainage, the distribution of the enzymes in various fluid compartments and the mechanisms responsible for the clearance of the enzyme from the blood.

Having defined some of the basic principles governing enzyme leakage we have directed the emphasis of the book towards the concept of tissue specificity and the way in which the leakage of specific enzymes, groups of enzymes or isoenzymes can be used to detect and assess tissue damage. The meaningful measurement and interpretation of enzyme release profiles necessitates a full understanding of the complexities of the measurement of enzyme activity and the instrumentation required to accomplish it. These topics are covered in the early chapters of this book.

The cell contains many hundreds or thousands of enzymes and the

practical considerations which determine which of these enzymes are best suited to the detection of myocardial damage are discussed as is the application of enzyme release to routine diagnosis.

From the relatively straightforward and well established use of enzyme leakage for the detection of damage has grown the concept that the phenomenon may be used to accurately quantitate and possibly even predict tissue damage. This important and controversial aspect of myocardial enzyme leakage is given major consideration in this volume.

While enzyme leakage is a proven and indispensible diagnostic tool its value is by no means limited to the practicing clinician and is utilized by many investigators as a research tool for probing the molecular complexities of disease processes and cellular damage. We have therefore attempted in the concluding chapters of this book to give an insight into enzyme leakage as an instrument of study and show how it may further extend our knowledge of the workings of the cell in both health and disease.

We would like to take this opportunity to thank the many eminent scientists who have contributed to this volume. We would also like to record with deep regret the death of Professor Henry Wilkinson who has contributed so enormously to the understanding of enzymes and isoenzymes. At the time of his death Professor Wilkinson had partly written Chapter 7 of this book and we are indebted to Dr. Alistair Smith for completing, at very short notice, this valuable contribution. Finally, we would like to thank those whose names are not appended to chapters: Mrs. Christine Boles for secretarial help and endless patience and Dr. Howard Jones of John Wiley for making the book possible.

DAVID J. HEARSE

1978 JOËL DE LEIRIS

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CHAPTER 1

Cellular damage during myocardial ischaemia: metabolic changes leading to enzyme leakage

D. J. Hearse

INTRODUCTION

This book deals with the detection and assessment of cardiac injury through the measurement of myocardial enzyme leakage. Before we are able to exploit fully the diagnostic or research potential of enzyme leakage, it is necessary to understand the mechanisms controlling leakage and the origins of the leakage itself. While a number of pathological conditions result in the loss of myocardial enzymes, the one which will dominate this book is myocardial ischaemia. The aim of this first chapter is to describe in general terms the cellular conditions which characterize the process of myocardial ischaemia and which eventually lead to the leakage of cytoplasmic constituents from the intracellular to the extracellular space.

The broad overview presented in this introductory chapter has, by necessity, been assembled from a multitude of studies using different models, different species, and different conditions of oxygen deprivation. Caution must therefore be exercised in extrapolating many of the findings to the clinical situation. In particular, in this and subsequent chapters, it is most important to distinguish between ischaemia and anoxia or hypoxia.

Ischaemia, which is the more frequently encountered clinical condition is conventionally defined as a lack of blood in a particular tissue. However, a more broadly based definition which accounts for the dynamic nature of the

condition and accounts for the removal as well as the supply of compounds to the myocardium is more appropriate. Essentially, ischaemia represents an imbalance between the myocardial demand for, and the vascular supply of, coronary blood. Not only does this create a deficit of oxygen, substrates, and energy in the tissue, but also, and of considerable importance, it results in an insufficient capacity for the removal of potentially toxic metabolites such as lactate, carbon dioxide, and protons. The total cessation of coronary flow is not a prerequisite of myocardial ischaemia, it rarely occurs clinically and even under experimental conditions with multiple coronary artery ligations, the collateral circulation may provide substantial perfusion in the ischaemic zone. Indeed, myocardial ischaemia could arise without a reduction in coronary flow under circumstances where there was an inadequate vascular response to an increased work or energy demand on the heart.

Anoxia and hypoxia are totally different[74] to ischaemia in both their origins and consequences and are conditions which are less frequently observed clinically. In anoxia or hypoxia the oxygen delivery to the myocardium is reduced by removing all or some of the oxygen in the coronary supply. Thus while the Po_2 is reduced, coronary flow may be normal or even elevated, and substrate delivery and metabolite removal may also be normal.

In considering ischaemic or hypoxic damage it is important to appreciate that they are not static conditions, but dynamic processes. Thus as discussed in Chapter 2, ischaemic tissue evolves[37,38] through reversible to irreversible damage, cell death and tissue necrosis; the whole process representing myocardial infarction. The rate at which these processes occur and the nature of the processes themselves are influenced by a number of factors including the severity of ischaemia or hypoxia, the age, sex, and species of the tissue under investigation, the hormonal, nutritional and metabolic status of the tissue and the coexistence of other disease processes.

A striking and important characteristic of ischaemia and to a lesser extent hypoxia, is its macroscopic and microscopic heterogeneity.[35,37] Varying conditions of work load and tissue perfusion may create a transient or patchy ischaemia. In the latter instance islands of severely ischaemic tissue may be interspersed with, or lie adjacent to, areas of normal tissue. Within a single ischaemic area, regional differences may exist with concentric zones of decreasing ischaemia radiating outwards from the core of the ischaemic area. This situation may create border zones[12,27,68] of marginally damaged tissue which separate severely ischaemic from normal tissue. Within these border zones gradients of metabolism, electrophysiology and flow may exist. Some investigators[1,9,54] believe these gradients to be very sharp such that within a single cell one may find two adjacent mitochondria one being aerobic and fully functional, the other being anaerobic and non-functional. Other investigators[27] believe that the gradients may be less abrupt with a

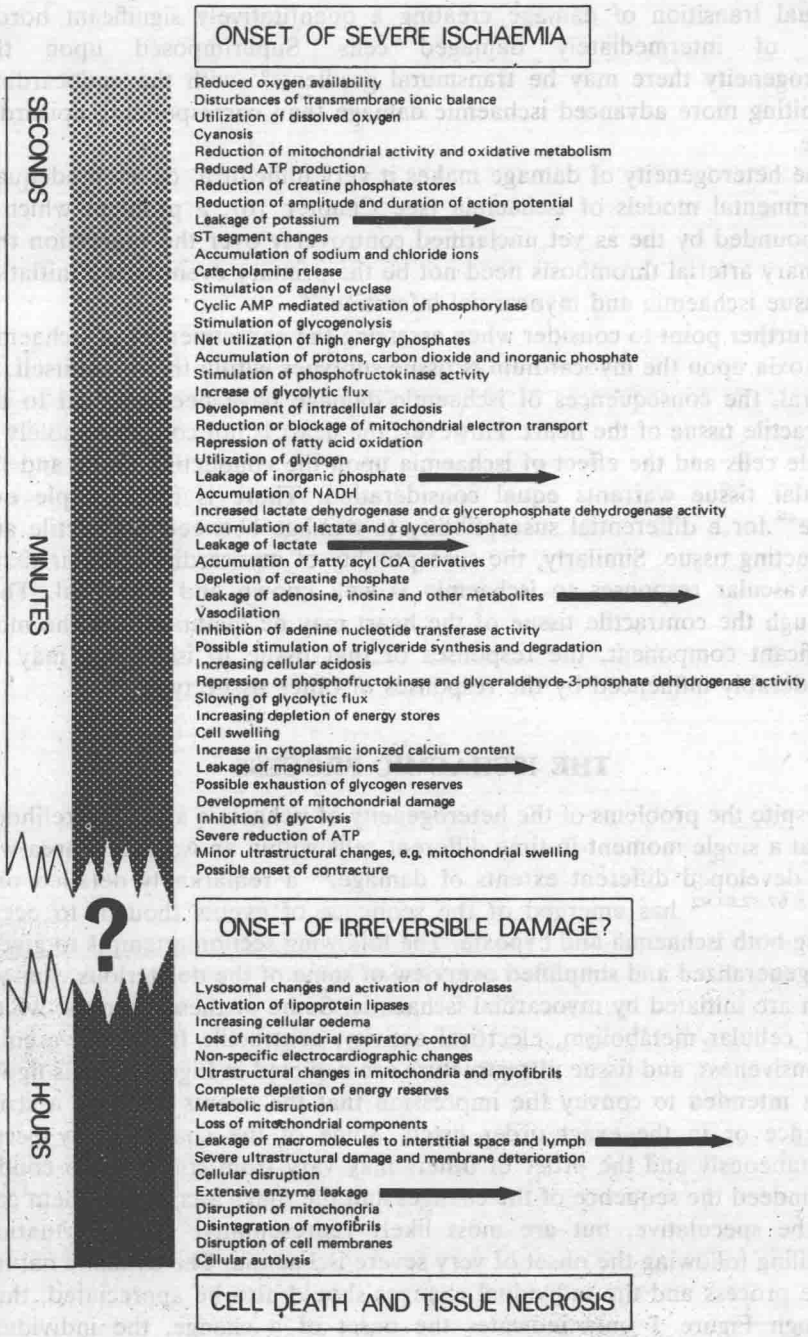
gradual transition of damage creating a quantitatively significant border zone of intermediately damaged cells. Superimposed upon this heterogeneity there may be transmural gradients[67] with the endocardium exhibiting more advanced ischaemic damage than corresponding epicardial tissue.

The heterogeneity of damage makes it very difficult to develop adequate experimental models of ischaemia (see Chapter 16); a problem which is compounded by the as yet unclarified controversy over the suggestion that coronary arterial thrombosis need not be the primary event in the initiation of tissue ischaemia and myocardial infarction.[22]

A further point to consider when assessing the consequences of ischaemia or anoxia upon the myocardium is tissue subtypes within the organ itself. In general, the consequences of ischaemic damage have been applied to the contractile tissue of the heart. However, the heart is not composed solely of muscle cells and the effect of ischaemia upon the conducting tissue and the vascular tissue warrants equal consideration. There is for example evidence[49] for a differential susceptibility to damage between contractile and conducting tissue. Similarly, the susceptibility of myocardial vascular tissue and vascular responses to ischaemia is well known and is critical. Thus although the contractile tissue of the heart may be quantitatively the most significant component, the responses of that tissue to ischaemia may be considerably influenced by the responses of other tissue types.

THE ISCHAEMIC PROCESS

Despite the problems of the heterogeneity of ischaemia and the likelihood that at a single moment in time different cells within an ischaemic area will have developed different extents of damage,[38] a remarkably detailed picture[4,6,67,82,84,92] has emerged of the sequence of events thought to occur during both ischaemia and hypoxia. The following section attempts to give a very generalized and simplified overview of some of the deleterious changes which are initiated by myocardial ischaemia. Some of these changes, which affect cellular metabolism, electrical activity, contractile function, vascular responsiveness, and tissue ultrastructure are depicted in Figure 1. This figure is not intended to convey the impression that the events occur in a strict sequence or in the exact order listed. Some of the changes may occur simultaneously and the order of others may vary from condition to condition, indeed the sequence of the changes and the times ascribed to them can only be speculative, but are most likely representative of the situation prevailing following the onset of very severe ischaemia. The dynamic nature of the process and the individual changes should also be appreciated, thus although Figure 1 only indicates the onset of a change, the individual changes may continue for some time.



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