Coronary Circulation and Energetics of the Myocardium

International Symposium held at the Istituto di Cardiologia Sperimentale della Simes S. p. A.
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Coronary Circulation and Energetics of the Myocardium

Edited by G. MARCHETTI and B. TACCARDI

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Opening Address

G. E. Ghirardi

In my capacity as president of the ‘Istituto di Cardiologia Sperimentale’ I feel it my duty to thank the Rector Magnificus of the University of Milan and Professor Villa, President of the ‘Società Italiana di Medicina Interna’, who is representing the Rector Magnificus here today. Through them it has been possible to hold the opening ceremony of the Symposium on the Coronary Circulation and Energetics of the Myocardium within the trine-honoured walls of this University.

I would also like to thank those distinguished members of the Italian academic world who have been good enough to come here today in the guise of sponsors of the Symposium.

I am most honoured to be able to welcome Dr. Donald E. Gregg, Chief of the Department of Cardiorespiratory Diseases at the Walter Reed Army Institute in Washington, who has most kindly consented to act as Chairman of this Symposium. To him I extend my heartfelt thanks for thus endowing the meeting with the prestige, standing and skill of a lifetime’s devotion to the investigation of the arduous problems of coronary physiology.

I would also like to welcome all those who have come to Milan this week from America, Belgium, France, West Germany, East Germany, Great Britain, Nigeria, Norway, Poland, Sweden and Switzerland, as well as Italy, who will each be making a valuable contribution to coordinated progress in the field of cardiology.

I hope you will allow me also to extend a special welcome to Professor Pierre Rijlant, who is with us today. Professor Rijlant is the director of the Solvay Institute of Physiology at the University of Brussels, and is an old friend of mine and of many Italian students of cardiology. He was the distinguished Chairman of the International Symposium on the Electrophysiology of the Heart which was organized by our Institute in 1963, and it was exactly three years ago this month that meeting was inaugurated within these same walls. To all of us it is a source of particular pride and satisfaction that meetings organized by my Institute should thus be opened in the

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University, as this is a sign of active cooperation between research
centres run by public bodies and those run by private enterprise. The ‘Istituto di Cardiologia Sperimentale’ is, in fact, part of the Simes group, a specialised company founded by myself to carry out research and production of drugs used in cardiotherapy.

In the last fifty years, scientific research has come on in leaps and bounds, and breakthroughs and new contributions have been the order of the day. These have been made possible for two reasons. First, there has been a very high rate of technical progress in all sectors of human knowledge, and secondly, there has been increasing awareness of the role played by scientific progress in competition on an international scale.

There is no country today which is unaware that the stimulus to carry out scientific research is an essential basis for the development of the national heritage as a whole.

The ‘Istituto di Cardiologia Sperimentale’ is an organisation set up to promote basic and applied research in the field of cardiovascular physiology and pathology. Its aims are twofold: first to carry out a large-scale research programme and, secondly to foster scientific exchanges between investigators the world over, and it is with this in mind that the International Symposium on the Coronary Circulation and Energetics of the Myocardium has been set in hand. Faced with the dramatic inroads made by cardiovascular disease and coronary disturbances in particular, this Symposium aims to combat these diseases by gathering and coordinating all the new discoveries relating to the physiology and pathology of the heart, and the biochemical aspects of myocardial energetics.

Public opinion has been deeply disturbed by the high incidence and serious implications of heart disease, and in the last few decades, this has led increasing numbers of investigators to believe in the absolute necessity of organizing the body of knowledge resulting from the neverending investigation of the mysterious mechanism which gives life to the heart and thus to man.

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This necessity is felt all the more deeply in that the use of complex, highly sensitive investigation procedures and the comparison and discussion of theoretical and experimental results have only recently enabled science to achieve breakthroughs of unprecedented significance. I am confident that this Symposium will provide a valuable contribution to progress in this highly specialised and fundamental sector of cardiological research and I wish those taking part all
success in their work. Buon Lavoro!

Foreword

Alongside research carried out in its laboratories, The Institute of Experimental Cardiology of Simes S.p.A. also organizes international meetings on specific aspects of cardiovascular physiology and pathophysiology. In 1963 an International Symposium on the Electrophysiology of the Heart was held in Milan at the Institute of Experimental Cardiology under the chairmanship of Pierre Rijlant. A number of investigators of the highest standing took part in this Symposium, whose object was to examine in detail the problems of anatomy, biochemistry, physics and physical chemistry related to cardiac electrophysics.

The very favourable results of this Symposium encouraged the scientific staff of the Institute of Experimental Cardiology to organize a further Symposium. Against a backdrop of the dramatic increase in heart disease, this new international Symposium was held with the object of assembling and co-ordinating all the new knowledge about the pathophysiological aspects of the coronary circulation and the energetic metabolism of the myocardium with a view to making a positive contribution towards the solution of problems of a clinical and therapeutic nature involved in coronary insufficiency.

This was answer to a need which had been expressed by investigators of the highest standing who had been in contact with the research staff of the Institute of Experimental Cardiology at Simes S.p.A. for some time, all the more so as there had never been an international meeting of this kind previously, dealing with the specific subject of the coronary circulation and energetics of the myocardium. The scientific programmes were prepared in the course of preliminary discussions held with Dr. D. E. Gregg, Chairman-designate of the Symposium. These discussions enabled a choice of subjects and speakers to be made. The Symposium was thus divided into five sessions, covering papers and discussions on the regulation of the coronary circulation, the effects of the catecholamines on the coronary circulation, the energetic metabolism of the heart, and finally on the coronary insufficiency.

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The interest shown by Italian and foreign investigators was clearly shown by the number of those attending the sessions held in
the ‘Aula Magna’ of Milan University and in the Lecture Halls of the Institute of Experimental Cardiology, and not least by the lively and fruitful discussions which followed each communication. Our warmest thanks are extended to Dr. D. E. Gregg for his very valued and generous advice, which he so gladly gave throughout the whole year which was required to plan the Symposium, and also during the subsequent preparation of this publication. We should also like to thank all the speakers and the members of the Italian and foreign medical profession who assisted in bringing this Symposium about, and by their presence and lively participation in the discussions, made a decisive contribution towards the success of the venture.

G. Marchetti and
B. Taccardi
Editors

Introduction to the Symposium

D. E. Gregg

Conference Chairman

Department of Cardiorespiratory Diseases, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C.

This meeting is designed to consider new data and the creative ideas that they generate regarding the myocardium and the circulation of blood through its walls. In some selected areas, it has also seemed appropriate to take inventory of information previously available so that it can be determined how best to direct future investigative efforts. Progress although seemingly very slow has actually been rapid in recent years. As late as 1930-40, the coronary arteries were regarded as end arteries, hence, investigation of this system was regarded as futile. It was as late as 1939 that the first continuous measurements were made of coronary flow with the heart in the chest, albeit in the presence of much anesthesia and trauma. I can still remember the enthusiasm with which we stayed up all night to make these observations, crude as they were. Despite the inadequacies of the ‘earlier’ methodologies on crude animal preparations as well as some later developments applicable
to man, their use has led to many isolated and seemingly important observations. I should like to allude briefly to a few of these as examples only and without regard as to whether they necessarily apply to your heart and mine. Some of the characteristics of the heart thus revealed would appear to be of unknown or doubtful value. In both ventricles, ventricular contraction impeded or throttled coronary flow. Although about 85% of right and left coronary inflow drained through the corresponding superficial coronary veins, up to 15% (left coronary flow) drained directly into the right ventricular and left atrial cavity. A myocardial tissue pressure gradient was believed to exist across the myocardium but with an unknown order of magnitude. The systolic component of left coronary inflow was essentially zero, and with increasing heart rate, stroke coronary flow decreased largely; therefore, heart rate was the supreme controller of coronary flow. The myocardium was primarily dependent on coronary flow for its oxygen requirements since the oxygen extraction was near maximum.

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and quite constant. Hence, this circuit operated with very little reserve. The empty heart, beating or quiescent and doing no external work used a large amount of oxygen. Despite the implication of some of the preceding that the coronary circulation had very little reserve to meet emergencies, it did appear to have certain built-in safety factors. Its almost invariable pattern of response to most stress states, including hormone and drug injections and cardiac sympathetic nerve stimulation was vasodilatation which could, at times, be quite massive. This was especially exemplified by its reactive hyperemia. Following release of a temporary coronary artery occlusion, the increase in coronary blood flow and oxygen usage far exceeded the flow and oxygen consumption which would have occurred during the period of flow stoppage. This response was regarded as the most characteristic and important hemodynamic response of the coronary bed to myocardial hypoxia. The underlying mechanism was unknown. Presumably, it occurred with every heart beat following ventricular contraction; it could be decreased or eliminated by massive coronary bed dilatation or by inducing coronary insufficiency (reduced coronary flow) through coronary artery constriction. I believe we might all agree that the input disturbances that alter the coronary circulation and which we are most concerned with
are those associated with everyday activity, i.e. physical exertion, emotional stimuli, and, possibly, hypoxia. If we consider the coronary flow as the output or the response of interest, then we know in a rather vague sort of way that this depends upon a combination of the geometry, structure and properties of the coronary blood vessels and the heart rate and blood pressure. We also know from the examples given and many others that there are multiple systemic and local control elements that influence the coronary flow. These include vascular receptors, the nervous system, endocrines, water, electrolytes, blood borne constituents, parenchymal activity and local metabolic products, autoregulators, and many others. But we do not know their proper weighting or significance or, indeed, that many of them actually obtain in the normal coronary circulation. We do not know what is the mechanism or the measuring device used to sense the need for flow and/or oxygen, nor how this is set, nor how information is transmitted to monitor the myriad of controlled elements.

In light of this we have for these sessions tried to pick certain research areas in which the methodologies and approaches might partially illuminate some of the ‘black boxes.’ As the sessions of this symposium indicate, these include the ultrastructure and mechanics of myocardial contraction versus myocardial energetics, the state of pressure and flow in the epicardial and endocardial shells, transcapillary exchange, the state of the coronary circulation in normal dogs with everyday stress, and, especially, the possible role of catecholamines and alpha and beta receptors in regulating this circuit, adjustments of the coronary collateral circulation in man and chronic animals in the presence of coronary insufficiency, and, finally and most important, the energetic metabolism of the heart upon which all the preceding depends.

It is our hope that we are sufficiently intelligent and knowledgeable to interchange ideas and views so that we leave not with the fixed views with which we came but with some new vistas and an eagerness to return to the laboratory where the answers are.