Dr Opie is a Director of the Cape Heart Centre and Director of the Medical Research Council Interuniversity Cape Heart Research Group at the University of Cape Town. He has been Visiting Professor (1984-1998) at the Division of Cardiovascular Medicine, Stanford University Medical Centre, Stanford University, California. After graduating from the University of Cape Town, he studied at Oxford as a Rhodes Scholar and was a Research Fellow at Harvard from 1959 to 1961. He became a Fellow of the Royal College of Physicians of London in 1974, and Life Fellow of the University of Cape Town in 1976. From 1976 to 1978, he was President of the International Society for Heart Research. From 1990 to 1993 he served as Chairman of the Committee on Cardiovascular Drugs of the International Society and Federation of Cardiology. During 1991 to 1995 he was Visiting Senior Fellow of the British Heart Foundation at St Thomas’ Hospital, London, and the Department of Biochemistry, University of Oxford, England. In 1997 he was Visiting Research Fellow, Merton College, Oxford, and the Department of Physiology, University of Oxford, England. In 2003 he was appointed Director of the Hatter Institute, Cape Heart Centre. In 1994 he was appointed Honorary Professor of Medicine, University College London. His major publications are Drugs for the Heart (6th edition), and his single-author book Heart, Physiology, from Cell to Circulation, 4th edition, LWW, 2004.

A senior clinical editor for Advanced Studies in Medicine (ASiM) interviewed Dr Opie to discuss the future of treating coronary heart disease.

Coronary heart disease (CHD) is a prevalent disease around the globe and is associated with significant morbidity and mortality. CHD is associated with a reduction in the blood supply to the heart resulting in inadequate oxygenation of the heart’s muscle. This myocardial ischemia may manifest as chronic stable angina. Traditional antianginal pharmacotherapy reduces myocardial oxygen demand via an increase in coronary blood flow and a reduction in hemodynamic properties such as heart rate, cardiac contractility, arterial blood pressure, and afterload on the left ventricle. A better understanding of cardiac metabolism during ischemia and reperfusion has led to the development of exciting novel antianginal agents that manipulate cardiac metabolism in order to provide relief from anginal symptoms.

What follows is an interview with Lionel Opie, MD, PhD, DSc, FRCP, in which he discusses the metabolic activities as well as theoretical strategies aimed towards improving the efficiency of energy use in the ischemic heart. He also provides insight into the imbalance between the production and expenditure of energy observed during ischemia.

ASiM: What is the nature of the imbalance between the supply and expenditure of energy during ischemia?

Dr Opie: The imbalance between supply and expenditure of energy during ischemia is based on the oxygen demand-supply hypothesis, first conceived in relation to the legs. The first reference to this was by a Scottish surgeon named Burns in 1809, who was intrigued by the loss of muscle power when the blood supply to the leg was compromised. He wrote: "If we call into vigorous action the limb around which we with a moderate degree of tightness applied a ligature,
we find then that the member can only support its action for a very short time, for now its supply of energy and its expenditure do not balance each other. To apply this concept to the heart was the work of the English physiologist, Erichsen, who in 1842 found that “arrest of the coronary circulation produces a speedy cessation of the heart’s contraction.” In modern terms, the supply of energy for contraction of the heart is basically dependent on oxidative metabolism and the synthesis of adenosine triphosphate (ATP). When the blood supply to the heart is impaired, the result is myocardial ischemia (which means the “holding back” of blood), so that the production of ATP must be lessened. Even when there is coronary artery disease, in a resting situation where the demand for energy (ie, the demand for ATP for contraction) is at a lower level, for example during rest, the potentially impaired supply of energy may not be noticed. But in a patient with effort angina when energy demand is increased, as during exercise, then the energy demand exceeds the supply. Thus, the high energy phosphates, ATP and phosphocreatine, get broken down. The force of contraction in the ischemic area diminishes and the pain fibers get stimulated, probably by formation of adenosine from ATP. When the burst of increased oxygen demand is over, at the end of exercise, then the ATP demand decreases, the ATP balance can be restored, and the anginal pain passes over.

**AS/iM**: What are the metabolic activities that require expenditure of energy in the heart?

**Dr Opie**: The metabolic activities requiring energy expenditure in the heart are not exactly known, the major problem being the vast amount of energy spent on heat production. Heat production consumes something like 60% to 70% of the energy. Thus, only a minor part of the total ATP expenditure is devoted to contraction and the associated ion movements, such as the calcium and sodium-potassium pumps required to maintain ion balance throughout the contraction cycle. In the normal heart there are lesser degrees of energy expenditure devoted to synthesis of various complex compounds and to futile metabolic cycles. Only small amounts of ATP are required to form cyclic adenosine monophosphate, an important regulator. Heat production is difficult to measure and, hence, usually ignored. Why heat production seems to waste energy and is apparently so nonproductive yet so energy consuming is not known and seldom studied.

**AS/iM**: What are theoretical strategies to improve the efficiency of energy use in the ischemic heart?

**Dr Opie**: Efficiency of energy use is a different concept from energy balance. The efficiency relates to the output of work, compared with the uptake of oxygen and the amount of ATP that should be produced. Normally, a certain amount of work needs a certain amount of ATP and a certain uptake of oxygen. Loss of efficiency can be expressed as diminished amount of cardiac work in relation to the simultaneously measured oxygen uptake. The prime problem lies in the conversion of the oxygen uptake to ATP. Our hypothesis is that abnormally increased rates of fatty acid metabolism “waste oxygen,” may enhance the activity of uncoupling proteins that break down ATP, and decrease the efficiency of conversion of oxygen-dependent synthesis of ATP. In our earlier studies, mechanical efficiency of the heart was only about 23% at the most. Of note, during ischemia efficiency fell by about one quarter. During the postischemic recovery phase, oxygen uptake rapidly rose, but mechanical efficiency stayed low, showing that there was stunning. Thus, both during ischemia and in the postischemic phase, there is marked mechanical inefficiency as shown by Lopaschuk et al. Likewise, the work of Stanley et al shows that loss of efficiency of contraction also occurs in heart failure.

**AS/iM**: During ischemia, how does the imbalance between energy production and expenditure impact the electrical and mechanical properties of the heart?

**Dr Opie**: The imbalance between energy production and expenditure during and just after ischemia impacts on both the mechanical and electrical properties of the heart. Myocardial contraction rapidly diminishes, an event that can be viewed as an energy-conserving maneuver even though there may be a fatal price to pay. The marked loss of contraction when a large artery is occluded can cause sudden cardiac death, an extreme case of what is good for the individual organ (the heart) being bad for the body taken as a whole. The electrical changes in ischemia are well described but not fully understood. There are typical changes in the ST segment, either depressed or elevated, depending on where the exploring electrode is placed; this is called the “current of injury,” which together with the shortening of the action potential duration is potentially proarrrhythmic. Lack of energy, and particularly the membrane-related ATP made by
glycolysis from glucose or glycogen, is required for continued activity of the sodium pump. An increase in intracellular acidosis and a fall in the pH limits the effects of insulin, otherwise known to be protective in the setting of ischemia. As glycolysis becomes inhibited by decreasing insulin action and increasing intracellular acidosis, the activity of the sodium pump falls, and the intracellular sodium rises. Speculatively, intracellular sodium might also rise through continued activity of the late sodium current, as in heart failure. If the rise of cytosolic sodium is not limited, then eventually the cell will die as a result of enhanced osmotic pressure.

Part of the compensatory events to maintain intracellular ionic balance during severe ischemia involves sodium/proton and sodium/calcium exchange. As sodium rises, so does calcium. The increased calcium is thought to underlie potentially fatal serious arrhythmias caused by afterdepolarizations. Thus, it is clear that a host of serious events running all the way from ATP and phosphocreatine depletion through to electrophysiological and ion changes occur during severe ischemia. If left unchecked, the result is cell death by energy starvation, that is by necrosis. Whether the ion changes and particularly the rise in intracellular calcium can also set off cell death by the alternative mechanism of apoptosis is not clear in the setting of ischemia. Of note, return of blood flow does not immediately restore the metabolic and electrical imbalances. Rather, there is postischemic stunning when these imbalances gradually become normalized. That means that a patient suffering from an attack of angina pectoris does not fully recover mechanical function upon cessation of pain. This aspect of angina, the postanginal recovery, deserves much more attention and further studies.

REFERENCES