BIOCHEMISTRY: INDEX OF THE FUNCTIONAL STATE OF THE HEART?

W. ISSELHARD

Twenty-five years ago, in an era when a large number of specific assays were being developed, it was believed that biochemical measurements could provide an index for the functional state of the heart. For example, it had been shown that the rapid deterioration in function in the asphyxiated animal was associated with the rapid breakdown of creatine phosphate (CrP) and a continuous decrease in ATP [8, 11]. The changes were assumed to be attributable to inadequate energy production in anaerobiosis, and it was known that the changes could be reversed providing that the limit of tolerance for anaerobiosis had not been exceeded. However, more recent work has suggested that the relationship between myocardial metabolism, in particular the myocardial status of energy-rich substrates and phosphates, and myocardial function, is not as clearly defined as had been thought.

"NORMAL" METABOLIC STATUS AND FUNCTION OF THE HEART

In the normally perfused and functioning heart, there is a pool of adenine nucleotides (5-7 µmol/g wet tissue) with ATP being by far the largest fraction. The energy charge potential (ECP = (ATP + 0.5 ADP)/(ATP + ADP + AMP)) has a high value of about 0.9. The tissue concentration of total creatine (TCr) is two to four times higher than that of the adenine nucleotides; between 35 and 50% of TCr is phosphorylated to creatine phosphate (CrP). In the unstressed myocardium of animals, the ratio CrP:ATP exceeds the value of 1. The human myocardium is usually reported to have smaller concentrations of tissue CrP and TCr, and of the ratios CrP:TCr and CrP:ATP, than those found in laboratory animals. The normal myocardium is rich in glycogen. The tissue concentrations of the intermediates of the glycolytic system and of lactate are low.

The tissue concentrations of many substrates, metabolites and enzyme activities vary in different regions of the heart. For example, there are differences between atrial and right or left ventricular myocardium, between epicardial and endomyocardial layers, and between basal and apical areas of the ventricles. There are also some quantitative variations between the hearts of different species. In addition, there are individual variations and concentrations vary with factors such as age, season of the year, special diet, withdrawal of food, stress, experimental or operative manipulations, and the method of tissue sampling and preparation, as well as the method of assay. Anaesthesia induces a variety of alterations, including those in metabolism. However, the myocardial status of energy-rich phosphates of otherwise unstressed hearts is only little affected by pentobarbitone, hexobarbitone, thiopentone (with or without nitrous oxide), ether, chloralose plus urethane, or halothane, during anaesthesia of up to 9 h duration in rabbits [1]. The analysis of metabolite patterns and their changes yields better information than a measurement of one or two single substances.

Steady state tissue concentrations of substrates and metabolites reflect an equilibrium between synthesis and supply on the one hand, and demand and utilization on the other. There is a high degree of coupling and a massive disturbance on either side will render steady states impossible. Under physiological conditions, and under certain pathological situations which have not progressed beyond a critical point, the steady state is not a fixed one, but changes with the loads on the cells of the heart. It is well established today that myocardial load and energy demand affect the myocardial metabolic status of the "normal" heart. For example, in the heart–lung preparation of guineapigs, Hochrein and Döring demon-
strated as early as 1960 [5] that left ventricular work load and CrP concentration are inversely correlated in a quasi-linear manner, and that the CrP concentration is influenced about 2.5 times more by changes in pressure load than by alterations in volume load. Changing the pressure-volume load by a factor of 10 by varying the volume load caused the concentration of CrP to vary between 6 and 12 μmol g⁻¹, while the ATP concentration changed by only 5%. In a compilation of data obtained in canine hearts by several research groups, Kübler [12] demonstrated a similar inverse relation between the myocardial status of energy-rich phosphates and myocardial oxygen consumption, which may be used as a criterion of the myocardial energy demand and which varied between 12 and 0.5 ml min⁻¹/100 g. The change in the CrP concentration averaged 6 μmol g⁻¹, and was related in a non-linear manner to the oxygen consumption. The ATP concentration changed by about 20 %. Clinical medicine takes advantage of this fact, for example in cardiac surgery, when hearts are arrested by means of cardioplegic perfusion of several minutes’ duration at low temperature under aerobic conditions. While the adenyllic acid system shows only a tendency towards an improvement, the CrP concentration is drastically increased with that of TCr remaining constant.

In the normal heart, high concentrations of CrP usually reflect a low energy demand of myocytes, but also result from a so-called “utilization insufficiency,” irrespective of the energy demand.

"ALTERED" METABOLIC STATUS AND FUNCTION OF THE HEART

In the search for relationships between metabolism and function, it is pertinent to enquire how myocardial function is affected by deviations from the regular metabolic status, and what are the consequences of a deterioration in metabolic status? Clinically, the most important situations are those resulting from an inadequate oxygen supply.

Critical hypoxia, asphyxia, and critical incomplete or complete ischaemia result in massive alterations in function, metabolism and morphology. Although there are certain differences in the consequences of these pathophysiologically different situations, the ultimate cause for the failing and finally the cessation of any kind of function, and for the structural derangements, is an inadequate energy production in anaerobiosis. The myocardium has a remarkable glycolytic energy capacity, but glycolytic energy production cannot substitute for aerobic energy supply. Depending on the situation, anaerobic energy production and distribution are limited by the availability of utilizable substrates, by a critical reduction of energy-rich phosphates, by an increasing tissue acidosis, or by the accumulation of inhibitory substances. Common to all situations is the drastic change in the metabolic status as compared with the regular pattern. It is characterized by a breakdown of CrP, a decrease in ATP and possibly a temporary increase in ADP, AMP and degradation products of the nucleotides, a continuous reduction of adenine nucleotides, a decrease in glycogen, and an accumulation of lactate. Heavy or long lasting deprivation causes a loss of TCr, which is possibly indicative of irreversible damage of myocytes.

There is some doubt concerning the functional capacity of the myocardium following anaerobic situations which result in persistent alterations of the metabolic pattern. The rate and extent of recovery of the metabolic status are in many cases a function of the degree of the ischaemia-induced alterations, but there may be prolonged recovery periods even though the loading had clearly been within the tolerance limits. The CrP concentration is usually restored rapidly, and often overshoots. Markedly depleted glycogen stores are replenished within a few hours, but the restoration of ATP and the pool of adenine nucleotides may take many days. This is especially true if the adenine nucleotides had been degraded beyond adenosine during anaerobiosis, and the degradation products have been washed out. After 30 or 60 min occlusion of the anterior descending branch of the coronary artery in canine hearts, with a reduction of the ATP concentration to 58% or 39%, and of the sum of the adenine nucleotides to 66% or 48% respectively, the restoration of normal values took about 14 days [9].

In the isolated working heart or the paced septal preparation, a large body of results show a linear relationship between the degree of alteration of the metabolic status and the extent of depression of various functional parameters. These include: aortic flow as a function of the tissue concentration of ATP plus CrP [4] and tissue ATP in relation to (a) ventricular power (calculated as the product
BIOCHEMISTRY: INDEX OF CARDIAC FUNCTION?

of the aortic flow times the difference between the aortic and left atrial pressure [15], (b) maximal rate of tension development [14], (c) coronary and aortic flow rate, heart rate and developed aortic pressure [7]. In one and the same experimental preparation the extent of depression of different functional parameters may vary considerably with a given tissue concentration of ATP [7]. As a rule, the hearts had been damaged globally by ischaemia, anoxia or special perfusion techniques.

A relationship between metabolic acidosis and function has also been described in the heart in vivo. For example, Hayashi and colleagues [3] have shown a relationship between reduction in coronary blood flow produced by graded coronary artery constriction, regional myocardial contraction, and the local tissue concentration of ATP. Similarly, it has been shown that there is a correlation between the rate of recovery of ATP and the adenine nucleotide pool, and the restoration of functional parameters after regional myocardial ischaemia [15, 16].

In summary, it is not surprising that some people interpret the statistical correlation between myocardial metabolic status and functions as a cause-and-effect relationship. However, the significance of such a relationship should be considered critically for several reasons. First, individual variations between metabolic parameters such as ATP, ATP + CrP, CrP, adenine nucleotide pool, and the functional parameters are large. The linear relationships are only derived by mathematical handling of data, and the correlation coefficients are not always convincing. Second, functional performance does not depend on energy supply alone, but is influenced by a large variety of factors such as electrolyte milieu, pH, hormones, substrate supply, etc. Third, tissue concentrations do not reflect the turn-over of substrates and metabolites and thus the availability of biologically utilizable energy. Fourth, the myocardial cell must be seen as a compartmentalized entity in terms of its functional performances and energy-generating systems. Fifth, an increasing body of evidence has shown that there is not necessarily a correlation between the status of energy-rich phosphates and functional performance.

During post-asphyxial recovery, hearts may perform normal or increased pressure-volume work, although the tissue concentrations of ATP and adenine nucleotides are below the normal ranges and the CrP concentration is increased above the normal value [8]. After induced cardiac arrest, post-ischaemic functional recovery improves progressively within a short time without concomitant changes in the over-all metabolite pattern [10]. After cardiac arrest, induced by various methods, post-ischaemic functional recovery may be different despite an identical myocardial metabolic status [10]. Recovery of function after cardiac arrest may be influenced independently of the tissue concentration of ATP by a variety of factors, such as the use of normal blood or substrate-enriched blood or perfusate, reduction of Ca++-activity in the perfusate, secondary cardioplegia, or reduction of the after-load in the early recovery phase [17]. During regional ischaemia or post-ischaemic reperfusion, an individual correlation between ATP concentration and segmental function of the myocardium could not be demonstrated [19]. Data are available which show that there is no close relationship between the post-ischaemic ATP concentration and the degree of dysfunction on the one hand, and the rate of recovery of both function and nucleotide pool on the other hand [6]. Although a close correlation existed in the heart between the rate of ultrastructural, functional and metabolic deterioration at the end of an ischaemic period, during reperfusion the restoration of cardiac function and of high energy phosphate metabolism occurred at a slower rate than the reconstitution of cellular structures [18].

"CRITICAL DETERIORATION" IN METABOLIC STATUS AND FUNCTION OF THE HEART

When considering the potential relationship between function and metabolism or metabolic status, it is important to consider whether there is a critical metabolic status beyond which there is no return of function. It is generally agreed that the post-an aerobic recovery of many or possibly all aspects of cellular performance is an exponential function of the duration, extent, or both, of the anaerobiosis-induced alterations. This implies that, beyond a "borderline" situation, the recovery period will be infinite. Since life support devices can only take over organ function for a limited period of time, it is important to restrict the alteration of organ function to such a degree that a reasonably short recovery period is possible.

Bretschneider [2] suggested that canine myocardial tissue concentrations of ATP and CrP of about 4 and 2 µmol g⁻¹ wet weight were the limit
beyond which the myocardial metabolic status should not be altered. It might be considered helpful to define a certain metabolic pattern when comparing various experimental loads under otherwise similar conditions in one species, but it is not possible to generalize concerning absolute values. First, the metabolic status differs qualitatively in various species under normal conditions and, second, CrP is usually restored rapidly and a reduction to zero values during anaerobiosis does not preclude rapid restoration within a few minutes. Third, data have been published which show that hearts in situ have resumed and maintained circulatory performance with a heavily altered metabolic pattern. A 30–40% reduction in tissue ATP and total adenine nucleotide concentrations seems to be tolerable during the early post-ischaemic recovery phase [13]. Complete post-ischaemic restoration of cardiac function has been described in hearts with a tissue concentration of ATP at the end of ischaemia and post-ischaemic reperfusion of about 1.2 and 2 µmol g⁻¹, respectively, if appropriate measures were taken in the early recovery phase. However, hearts with ATP concentrations of about 2.1 and 2.8 µmol g⁻¹ recovered poorly if blood was used for reperfusion [17].

There is certainly a critical tissue concentration of ATP or a critical ATP concentration at the sites of various functions within the cell. However, these critical concentrations will vary with the method used, with the skill of the investigator, and with the increase in knowledge of the pathophysiological processes in the anaerobic and post-anaerobic heart. It is, therefore, probably better to characterize the potential for return of function according to the possibility of rapidly normalizing the ECP, restoring a normal tissue concentration of CrP, and rapidly eliminating tissue acidosis in situations in which the tissue concentration of TCr has not been reduced massively.

SUMMARY

The description of metabolic patterns during well defined conditions has been, and will be, a very helpful tool in characterizing reactions of cells, tissues and organs to physiological and pathophysiological situations. As a rule, the measurements yield global values. Discrimination between the integrity of different cellular compartments and individual cell functions is difficult and possible only in particular circumstances. Metabolism is not a static, but a dynamic cellular activity. Status analyses are like stills from a movie. With the present state of the art, however, it seems neither possible nor justified to describe or predict functional performance of the heart using analyses of metabolism, which can be performed simply, rapidly, reliably and with general validity. The best way to assess functional performance is to measure function!

Metabolism and metabolites are the fuel and constituent parts of structure and its functions. Because of this, there must be a link between function, structure and metabolic activities and metabolite patterns. The successful symptomatic therapy of myoadenylate deaminase deficiency in patients by administration of ribose [20, 21] is just one good example of the relation between metabolism and function, and of the value of subtle studies of metabolism and analyses of metabolic patterns in animals and in man.

REFERENCES


