Special Article*

Treatment of Heart Failure from the Standpoint of Myocardial Metabolism

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The normal function of the heart, continuous contraction-relaxation, is maintained on the basis of a chain of biochemical reactions in the myocardium. A disturbance somewhere in this metabolic process leads to the functional disturbance of the heart.

Although the fact that digitalis therapy is the most typical and most effective treatment of heart failure has been remained unchanged since the old time of Withering, the consideration on myocardial metabolism would make the effect of digitalis more certain and more pronounced. The treatment aiming at the improvement of myocardial metabolism has recently been introduced in clinical practice.

In the present paper, in order to understand the significance of metabolic therapy in the treatment of heart failure, the myocardial metabolism under various pathological conditions was observed, and the effects of so-called metabolic remedies were investigated experimentally and clinically. Furthermore, the future of metabolic therapy will be inferred.

I. Myocardial metabolism under pathological conditions

The pathological conditions which are frequently encountered in clinical practice are discussed in the below.

1. Ischemic heart disease

Since the heart is an extremely aerobic organ, hypoxia causes a disturbance in energy production.

When the cardiac metabolism was studied by the use of the coronary sinus catheterization technique following the inhalation of gas with low oxygen tension¹⁾ or coronary occlusion²⁾, the coronary arteriovenous differences of lactic acid, pyruvic acid, fatty acids and ketone bodies decreased. In some cases these substrates were released from the cardiac muscle. These results indicate the disturbance in the myocardial utilization of carbohydrates and fats.

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This is apparently attributed to the inhibition of TCA cycle due to oxygen deficiency, nevertheless it cannot be neglected that the muscle ammonia, which is produced by the degradation of adenylic acid and increased with hypoxia, further inhibits the TCA cycle³⁾.

For the treatment of ischemic heart disease, the improvement of blood supply to the myocardium naturally comes first. For this purpose many kinds of coronary vasodilators are used. However, coronary sclerosis obscures the effect in many cases. The site of disturbance in myocardial intermediary metabolism due to hypoxia is known to be the level of coenzyme. Since all the coenzymes active in TCA cycle require vitamins as the material, overall supplement of these vitamins is also necessary from the metabolic point of view.

2. Undernutrition

Hypoproteinemia or malnutrition is known to be one of the causes of unresponsiveness to digitalis in chronic heart failure. In chronic heart failure, undernutrition might be frequently induced by anorexia due to congestion of the digestive organs, disturbance of liver function and administration of the cardiotonics and/or diuretics with an irritating effect on the stomach.

The observations on the myocardial metabolism during starvation and hypoproteinemia in experimental animals, using the coronary sinus catheterization method, revealed a decrease in the extraction of lactic acid and pyruvic acid and an increase in that of fatty acids and ketone bodies⁴⁾. In starvation and hypoproteinemia, a disturbance in myocardial energy metabolism through the TCA cycle seems to be present from the result of the disorder in carbohydrate metabolism despite the compensation due to the increased utilization of fat. Upon determination of phosphate compounds in the myocardium of starved rats and of those fed with low protein diet, the contents of ATP and creatine phosphate were decreased and ATP-ase activity was also lowered⁵⁾.

Since the undernutrition such as starvation and hypoproteinemia thus disturbs energy production by the myocardium, aggravating the preexisting disturbance in cardiac function, all attempts should be made to improve the undernutrition in chronic heart failure.

3. Valvular heart disease

No agreement has been reached as yet among various investigators whether there is a disturbance in myocardial energy production in heart failure due to valvular disease. Studies in patients with chronic congestive heart failure revealed no disturbance, while some experimental studies using the failing heart of animals showed the presence of disturbance.

In the author's study on myocardial energy metabolism in dogs with aortic valvular lesion, a decrease in the myocardial extraction of lactic and pyruvic acid was noted in the group with heart failure¹⁾, suggesting the presence of disturbance in energy production in the failing heart.

Although it cannot be excluded that this is a secondary phenomenon based on

heart failure, at least it may be considered that a disturbance in energy production may secondarily develop as its severity advances. The need for treatment of heart failure with consideration to metabolic therapy thus arises. Although digitalis alone frequently improves the myocardial metabolism, unresponsiveness to digitalis necessitates to improve the myocardial metabolism.

In order to study the mechanism of development of valvular heart failure, changes in myocardial metabolism were assessed through alterations in the protein contents of functional fractions of the myocardium in dogs with aortic valvular lesion⁶⁾. Increases in the mitochondrial and microsomal protein in the initial stage of valvular injury suggest augmentation in the activity of energy production and protein synthesis. As the contractile protein increased, energy production and protein synthesis were normalized. Such increases in energy production and protein synthesis in the initial stage of valvular injury might indicate the metabolic response to the increase in cardiac work. In the "impending myocardial failure" which was produced by overloading of infusion of a large amount of fluid to the heart in established hypertrophy, no increase in the activity of protein synthetic enzymes, such as observed with the increase in cardiac work in the initial stage, was noted. This indicates a decrease in responsiveness of the protein synthetic activity to a load. The increase in mitochondrial protein per unit contractile protein was also slight, suggesting a relative decrease in energy production. Thus the disturbance in both energy production and protein synthesis appears to participate in the mechanism of development of heart failure.

Muscular contraction is accompanied by the degradation of adenylic acid and formation of ammonia. A dynamic equilibrium is kept between the degradation and synthesis of adenylic acid under normal condition. However, a decrease in total nucleotides and an increase in ammonia are noted under an excessive loading⁷⁾. Since ammonia inhibits the TCA cycle, the mechanism of metabolizing ammonia appears to play an important role in the maintenance of cardiac function. The metabolism of these amide-nitrogen is probably connected closely with the mechanism of development of heart failure.

II. Metabolic remedies from the standpoint of energy production

Among metabolic remedies aiming at the improvement of energy production, caloric source such as glucose, vitamins such as thiamin, riboflavin, nicotinic acid and pantothenic acid, hormones such as adrenocortical hormone and sex hormone, and enzyme preparations such as cytochrome C are found.

The necessity of caloric source and vitamins was stated above. Hormones playing an important role in the regulation of metabolism are usually used under specific circumstances. Basic and clinical results⁸⁾⁹⁾¹⁰⁾ for each preparation will not be explained in detail.

III. Metabolic remedies from the standpoint of energy utilization

Metabolic therapy aiming at the improvement of energy utilization is on the way of its development at present and many problems are still open.

1. Digitalis and electrolytes

The electrolytes occupy an important position in the process of energy production as activators of enzymatic reaction. Moreover, adequate ionic milieu is an important factor in the mechanism of muscular contraction.

There are many conflicts in the studies on the mechanism of the inotropic action of digitalis from the standpoint of myocardial metabolism or mechanism of muscular contraction, and it will require some time to solve these problems. At all events, when the effect of digitalis is observed on the myocardial metabolism, the action on the transfer of intra- and extracellular electrolytes should be regarded as most important.

When the effect of digitalis on electrolytes was observed through the myocardial balance study¹¹⁾, alterations were found in each of potassium, sodium and calcium, suggesting that digitalis changes the ionic milieu of muscle cells. However, no information was obtained on the relationship between the ion transfer and the inotropic action. Among these electrolytes, potassium showed a different direction of changes between administration of a therapeutic dose and a large dose causing sagging depression of ST or atrioventricular block. The release of potassium coincided with the toxic findings in ECG. In clinical practice, hypokalemia readily precipitates digitalis intoxication. These facts allow to infer that the movement of potassium is apparently related with digitalis intoxication. Since the decrease of potassium in the failing myocardium is known, supply of potassium should be remembered during digitalis therapy.

2. Amino acid metabolism in the myocardium

To keep the contractile protein normal is one of the important factors in respect to energy utilization of the myocardium. Furthermore, the protein and amino acid metabolism of the myocardium plays an important role in respect to energy production by maintaining the various enzyme proteins. In spite of the importance, many things still remain unknown concerning myocardial amino acid metabolism due to the complexity of the intermediary metabolism. Elucidation of these points may open a new way of metabolic therapy. The informations on the myocardial amino acid metabolism obtained by the author and coworkers will be introduced below in outline.

According to the experimental study by the use of ^{14}C labelled amino acids¹²⁾¹³⁾, amino acids are utilized as the energy source of the myocardium. However, its proportion is minor, while the major use of amino acids is probably found in protein synthesis. This is supported by the fact that amino acids were utilized better when the glucose level in the perfusate of the heart-lung preparation was maintained normal than during deficiency of glucose in the perfusate¹²⁾.

When the composition of free amino acid in the myocardium was compared with that in the skeletal muscle, the former was rich in most of the amino acids except

for glycine, and the activity of transaminase was also distinctly higher in the myocardium¹²⁾, suggesting the importance of amino acid in the myocardial metabolism.

In the study on the arteriovenous balances of amino acids in the normal myocardium by the method of the coronary sinus catheterization¹⁴⁾, active metabolism of individual amino acid associated with a dynamic equilibrium of total amino-nitrogen was demonstrated. Among these amino acids, release of glutamic acid and extraction of alanine were noticed under normal condition.

Under various pathological conditions the changes in myocardial free amino acids were characterized by a decrease of glutamic acid¹²⁾. Aspartic acid was also frequently decreased. In view of the decrease of glutamic acid and aspartic acid under pathological conditions, these amino acids were administered to observe the effect on free amino acids in the myocardium¹²⁾. Glutamic acid administration increased the myocardial concentrations of most of the amino acids. Aspartic acid administration also increased the concentrations of aspartic acid, glutamic acid, taurine and alanine. Tracer experiments using ¹⁴C-labelled glutamic and aspartic acid also demonstrated the incorporation of the isotope into various amino acids.

Amino acids have to be transferred into the myocardium to be utilized. Since the intracellular concentration of amino acids is higher than that in blood, active transport is required. The increase in the concentrations of various amino acids in the myocardium with the administration of glutamic and aspartic acid, therefore, appears to be favorable for the utilization of amino acids by the myocardium.

3. Amino acid preparations

Based on the above mentioned reasons, glutamic acid and aspartic acid salt were used clinically. The latter is already used in clinical practice as potassium and magnesium aspartate. Although the emphasis has been laid on the action as electrolyte, the action as amino acid may also be expected. From these clinical results¹⁵⁾¹⁶⁾, they appear to be useful as the supporting drug for digitalis.

4. Anabolic hormone

Experimental observation on the action of anabolic hormone, which is used for the improvement of protein synthesis, on the contents of myocardial proteins revealed a tendency of increase in soluble protein, mitochondrial protein, microsomal protein and contractile protein. There was, however, no statistical significance.

In the results of clinical use, no remarkable effect was obtained in valvular heart disease, but some improvement of subjective symptoms and objective signs was obtained in ischemic heart disease.

5. Nucleotides and its analogues

The decrease in the activity of myocardial protein synthesis is one of the factors participating in the mechanism of development of heart failure. Synthesis of nucleic acid is required before protein synthesis.

In experimental observation⁷⁾, the total content of nucleotides as the precursor of nucleic acid showed a reversed correlation with the ratio of heart weight to body weight, showing to decrease with the progress of cardiac hypertrophy. The total

nucleotide content decreased also upon myocardial fatigue due to forced loading. Such decrease in nucleotide probably represents one of the causes of the decrease in protein synthesis. Adenosine nucleotides especially play an important role in energy production as the material for ATP.

Substances used clinically as the precursors of nucleic acids include ATP, adenosine, nucleic acid hydrolysates and inosine. However, all of these are used on account of their direct pharmacological action, i.e., coronary dilating or inotropic action. Due to the above mentioned reasons, however, the long term use of these nucleic acid precursors is of interest from the viewpoint of prevention of the development of heart failure.

Reports on the experimental studies are also available on the preventive effect of the combined use of various nucleic acid precursors and digitalis against the development of heart failure. Clinical evaluation of these is left for future study.

Energy is continuously produced and used in the heart without rest, myocardial proteins are likewise being repaired after fulfilling its function, and these two are closely and ingeniously connected. This may be said for each heart cell and for the heart as a whole. Furthermore, the heart is also connected with the vascular system, respiratory system, endocrine system and all other organs. Although only the myocardial factor in the heart failure was discussed in this paper, general and overall understanding is necessary besides the observation on the heart itself.

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