HOURLY CHANGES IN SERUM ENZYMES IN OPEN HEART SURGERY

Thesis Submitted in Partial Fulfilment for the Requirement of Master Degree in Clinical Pathology

BY

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C O N T E N T S

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INTRODUCTION

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Cardiac enzymology was initiated with findings by Karmen La Due and Wroblewski (1955), who first recognised that myocardial injury could be detected by elevated serum enzyme activity. Initially, increased serum glutamic oxalacetic transaminase (SGOT), also , called "Aspartate transaminase", in patients with acute myocardial infarction was noted, and subsequently changes in serum lactate dehydrogenase (LDH) activity were associated with this condition as well,(Wroblewski, F., Ruegsegger, P., and La Due, I.S., 1956). A few years later, Wroblewski (1963) reported that serum creatine phosphokinase (CPK) activity increased after acute myocardial infarction. Within a relatively brief interval after pioneering observations by Nissen and his co-workers (1965), it became clear that elevated activity of SGOT, LDH and CPK were hallmarks of acute myocardial infarction.

Determination of activity of serum isoenzymes, different molecular species with similar enzymatic properties, has improved the diagnostic sensitivity and specificity of serum enzyme deferminations,(Roberts, R., and Sobel, B.E., 1973). The profile of a certain isoenzyme in the serum reflects its profile in the injuried organ responsible for enzyme release into the blood, (Cohen, L., Djordjevich, J., and Ormiste, V.,

1964). Both electrophoresis and chemical methods have been used to differentiate isoenzymes from each other, (Lubran, M., and Jensen, W.E., 1968). Isoenzyme analyses have been particularly useful in identifying the organ responsible for serum enzyme elevations in specific instances. They also may shed light on the subcellular locus of injury by which we suspect the extent of injury sustained. An example of this is the transaminase which exists in at least two isoenzyme forms, one associated with mitochondria and the other with cytoplasmic compartment, (Bodansky, O., Schwartz, M.K., and Nisselbaum, J.S., 1966).

After coronary insufficiency, release of mitochondrial transaminase into serum may imply that injury to mitochondria has occured. Since mitochondrial damage has been associated with irreversible ischemic injury, serum isoenzyme analysis may be useful in differentiating reversible from irreversible ischemic insults, (Bodansky, et al., 1966.).

Several isoenzymes of creatine phosphokinase(CPK) are well recognised, (Rosalki, 1965). Each CPK isoenzyme is a dimer comprised of M (named for muscle) or B (named for brain) subunits. Human cardiac muscle cont-

ains approximately ten to thirty percent of one isoenzyme (MB-CPK) which is virtually abscent from extracts from skeletal muscle, brain, the gastrointestinal tract, lung, and Kidney, (Vanderveen, K.J., and Willebrands, A.F., 1966). Under physiological conditions, serum CPK activity is due almost to activity of the MM isoenzyme. After myocardial infarction, total serum CPK activity rises and MB-CPK begins to contribute substantially to total activity in serum samples, (Roberts, et al., 1973).

The Origin of Elevated Serum Enzyme Activity Associated With Myocardial Infarction :-

Enzymes are proteins capable of accelerating the rate of biochemical reactions. Eneymz assays do not measure the concentration of the protein molecule directly, but rather asse s the enzyme activity it exhibits, (Wilkinson, 1970). The absolute level of specific enzymes in individual subjects are determined by the rate of release of enzyme into the blood, often linked to physiological turnover of cellular elements and constituents and to the prevailing factors affecting disappearance rate of the same enzyme for each individual,

(Wilkinson, 1970). There is a remarkable consistency from day to day in serum enzyme activity in the same individual under comparable conditions. Enzyme values within a population vary with age and sex as well as physical activity, (Karemen, et al., 1955).

Increasing serum enzyme activity associated with myocardial infarction results from release of enzyme from myocardium itself. This release of enzyme from the heart is associated with irreversible ischemic injury. (Jennings, R.B., Herdson, P.B., and Sommers, H.M., 1969).

Enzymes can be released from organs such as skeletal muscle after intramuscular injections(Meltzer, 1968). Release of transaminase from liver accompanies passive hepatic congestion and can interfere with the interpretation of increased serum glutamic oxalacetic transaminase (SGOT) in patients with myocardial infarction exhibiting congestive heart failure, (Killip.,T., and Payne, M.A., 1960). Injured myocardium is the major source of serum enzyme elevations after acute myocardial infarction. Following coronary occlusion,activity of several myocardial enzymes decreases and is paralled by increased activity of the same enzymes in serum.

However, elevated activity of some enzymes in serum after myocardial infarction may reflect release from non myocardial components of the heart or organs other than the heart itself, (Wilkinson, 1970). Wroblewski (1956), concluded that the lactate dehydrogenase enzyme (LDH) content of fresh ventricular myocardium was insufficient to account for the prolonged elevation of serum LDH after myocardial infarction. Leukocytes and other components of the inflammatory and exudative reaction in the heart that accompanies infarction contain large amounts of LDH likely to be liberated when they themselves undergo necrosis.Thus, enzymes represented in nonmyocardial components as well as in myocardium may exhibit elevated activity in serum and may mask otherwise apparent depletion of enzyme activity from the heart (Hedmorth-Whitty, R.B., Whitfield, J.B. and Richardson, R.W., 1967).

Serum creatine phosphokinase (CPK) and CPK isoenzyme activity have consistently demonstrated a quantitative relationship between the magnitude and duration of their elevations after myocardial infarction.Increased activity of serum glutamic oxalacetic transminase (SGOT) and LDH in serum may correlate poorly

with changes of activity of these enzymes in the heart because of contributions from non-myocardial constituents, other organs or both. Accordingly, analysis of serum CPK or serum CPK isoenzyme changes appear to offer considerable advantages in the quantitative assessment of myocardial damage. (Sobel, B.E.,Roberts, R., and Larson, K.B., 1976). Loss of enzyme activity from myocardium with parallel elevations of serum enzyme activity reflect myocardial necrosis resulting from an ischemic injury. It seems difficult to determine whether enzyme is released into serum from cells reversibly injured but still capable of resuming normal function or from cells already irreversibly damaged, (Sobel,B.E., and Shell, W.E., 1973).

Determinants of Levels of Serum Enzyme Activity :-

The level of activity of any given enzyme in serum represents, under steady-state physiological conditions, a balance between appearance and disappearance of the enzyme. Normal subjects exhibit relatively constant levels of serum enzyme activity. After acute myocardial infarction, the rate of appearance of enzyme in blood exceeds the disappearance rate and serum enzyme activity increases, (Wilkinson, 1970).

Proteins in general and enzymes in particular appear to be removed from serum according to first order kinetics, i.e. the amount of enzyme disappearing from serum at a given moment in time is dependent upon the amount of activity present at that instant, (Fleisher, G.A., and Wakim, K.G. 1963). In other words, activity declines as a constant percentage of instantaneous activity, rather than as a constant amount of enzyme activity per unit time. After reaching a peak, enzyme activity disappears at a relatively constant rate (K_d) in a monoexponential fashion. This fractional disappearance constant (K_d) appears to be characteristic of each enzyme and to depend also on species (Shell, W.E., Kjekshus, J.K., and Sobel, B.E., 1971).

These general properties of disappearance have been demonstrated with cytoplasmic transaminase, LDH, SGPT, isocitric dehydrogenase (ICD) and aldolase. Fractional disappearance rate appears to remain relatively constant in the face of hemodynamic or metabolic changes, (Roberts, 1974).

Creatine phosphokinase (CPK) disappearance rate remains virtually constant despite changes in cardiac

output or renal blood flow, (Sobel, 1972). Decline of serum enzyme activity reflects removal of enzyme protein from the circulation and that enzyme clearance is not dependent primarily upon renal, hepatic or splenic function. Zymosan, an agent which inhibits the reticulo endothelial system, also inhibits the rate of enzyme disappearance. Other agents, such as barbiturate anaesthesia, diminish the rate of enzyme disappearance as well, (Shell, et al., 1971). When tissue containing CPK or CPK in solution is incubated in blood under sterile conditions, activity declines although not as rapidly as it does in the intact organism.

Other body fluids, such as lymph, may play an important role in deactivating enzyme and in transporting enzyme released from myocardium, (Duma, R.J., and Siegel, A.L., 1965). So, disappearance rates of activity of serum enzymes seem to depend to a large extent upon the lability of enzymes in body fluids and the activity of the reticuloendothelial system rather than on the function of a particular organ such as liver or kidney This may explain the relative constancy of fractional disappearance rates of individual enzymes among different members of the same species, (Wakim, K.G., and Fleisher, G.A., 1963).

Increased Serum Enzyme Activity After Myocardial Infarction :-

The triad of elevated activity of serum glutamic oxalacetic transaminase (SGOT), lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) in serum have become diagnostic standards of infarction because of their sensitivity and relative specificity, (Agress, C.M., and Kim, J.H.C., 1960). Although activity of numerous other enzymes may increase (including pyruvate kinase, glyceraldehyde phosphate dehydrogenase, myokinase, isocitric dehydrogenase, acid phosphatase and others), elevated SGOT, LDH and CPK have become hallmarks of myocardial infarction in the clinical setting. Serum samples showed elevations of one or more of these enzymes in all cases which proved later on to be myocardial infarction at autopsy, (Sobel, 1972). Thus, the absence of increased serum enzyme activity in serial samples obtained over twenty four to fourty eight hours is indeed an excellent criterion for the exclusion of infarction, (Goldberg, D.M., and Winfield, D.A., 1972). Elevated creatine phosphokinase (CPK) activity appears to be the most sensitive of the three conventionally used serum enzyme criteria of acute myocardial infarction. With any serum enzyme criterion of myocardial