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Coronary Occlusion and Metabolic Heart Infarcts - Mg, Se, Si and Other Antioxidants

Timo Töysä*

Licentiate of Medicine, Specialty General Practice, Retired, Student of Eastern Finland, Finland

***Corresponding author:** Töysa T, Licentiate of Medicine, Specialty General Practice, Finland

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ABSTRACT

Etiology of heart infarct can be divided in two categories: occlusion of the coronary arteries and metabolic factors. This article is assessing atherosclerosis, pure calcification is excluded. Metabolic and mechanical factors can cause irritation, inflammation, collection of fat in monocytes, atheroma formation and occlusion, which can cause infarction. Characteristics of medial and outer layers of coronaries can have role in vascular changes. The main aim of this survey is to discuss on the development of heart necrosis without coronary occlusion.

Keywords: CHD; Infarct; Inflammation; Atherosclerosis; Mg; ROS; Se; Si; Lactate; GAG

Abbreviations: AtSO: Atherosclerosis; BP: Blood Pressure; LCAT: Lecithin- Cholesterol Acyltransferase; Si: Silicon; ROS: Reactive Oxygen Species; GSH: Glutathione; SOD: Superoxide Dismutase; Cu: copper; Zn: zinc; Mn: Manganese; Fe: Iron; FA: Fatty Acids; Se: Selenium; MAP: Microangiopathy; GAG: Glycosaminoglycans

Introduction

Infarction is tissue death (necrosis) due to inadequate blood supply to the affected area. It may be caused by artery blockages, rupture, mechanical compression, or vasoconstriction [1]. It is not uncommon that human cardiac death happens without coronary occlusion: Professor of cardiology in Helsinki University taught in 1973, that heart infarct is a "necrosis of myocardium", and divided its etiology in two groups [2]:

a) Ischaemic (stoppage of blood flow [3]) and

b) An unknown metabolic factor.

He told, that if a patient dies from a heart infarct immediately, no infarcts are seen, if within 1-2 days thrombi are seen by 20 %, but after 2 weeks thrombi are detected in 90 % of cases. He even concluded, that thrombi are obviously secondary [2]. In 1986 Vikhert published that he had found acute coronary thrombosis in about 20 percent of the CHD patients who died suddenly and according of the literature survey, frequencies of acute coronary thrombosis were between 4-93%, without consistent time dependence [4]. A similar grade of atherosclerosis was discovered in patients with ischaemic heart disease not dying suddenly [4].

As early as 1969 Robbins Pathology wrote: "In the series of patients studied at the Boston City Hospital, roughly 40 % of the coronary occlusions were found in the right coronary artery, 40 % in the left anterior descending artery and the remainder in the left circumflex", but independently "whichever the artery occluded, over 95 % of infarcts occur in the left ventricle or in the interventricular septum" [5]. The discrepancy between locality of coronary occlusions and myocardial infarcts was explained unsatisfactorily [5]. Even "the exact mechanism producing paroxysmal hypoxia (e.g. angina pectoris without strain) is poorly understood" [5]. It has been explained e.g. by arterial spasms and compensatory mechanisms via anastomotic supply. According to Blumgart et al. (1940, 1941) hearts of angina pectoris patients invariably revealed occlusions of small arterial branches (in [5]) Stress ECG could not predict the grade of angiographic atherosclerosis [6].

Development of Coronary Occlusion

Atherosclerosis (AtSO) is narrowing arteries and can cause arterial occlusion [5]. The generally known/accepted risk factors of (coronary) atherosclerosis are age, gender, smoking, blood pressure (BP) and (total cholesterol/HDL cholesterol) ratio (Tot/HDL) [7]. Seelig has published a compilation with 237 references [8], which presents

e.g. how magnesium deficiency can be a cause and its correction a treatment for atherosclerosis, diastolic and systolic BP, hypokalemia, hyponatremia, Tot/HDL ratio and cardiac arrhythmias and nervous irritability and how high fat diet can promote loss of divalent cations via feces and urine [8]. Mg is controlling cholesterol synthesis (about like statins) [9] and increasing cholesterol esterification by Lecithin-Cholesterol Acyltransferase (LCAT) [9,10] with decreasing effect on Tot/HDL ratio [9,11]. Mechanical factors can increase vascular wall irritation and atheroma formation [12], partially associated with Mg and silicon (Si) supply [13]. AtSO changes are highest at the first third part (with the largest mechanical load) of arterial branches [13]. Oxidation of LDL cholesterol causes inflammation, which promotes AtSO [14]. Inflammation marker hsCRP and vasospastic marker endothelin-1 have been suggested for (negative) indicators of body Mg content [15]. Mg can protect against coronary occlusion by antagonizing calcium, promoting fibrinolysis, and stabilizing fibrinogen and blood platelets [16,17].

Myocardial Infarct as a Consequence of Metabolic Factors – Observations

Myocardial infarct without coronary occlusion has not been satisfactorily explained [5]. Elevated lactate production associated with sympathicotonia (hyperirritability) and low Mg:Ca ratio and decreased ATP production is one explanation [18]. Mg deficiency is known to increase body temperature, decrease pH and cause muscle lesions [19]. By swine rapid glycolysis, low pH and temperature are known to change muscle structure to pale, soft and exudative meat (PSE meat) [20]. The change can occur rapidly during waiting slaughter or transportation [20]. Correction of Mg deficiency can increase ATP synthesis (Mg dependent ATP synthase activity) [18], which could prevent lactate accumulation and pH drop. Glycolysis produces stoichiometrically [H+] and lactate ions [21]. Normally (monocarboxylase) lactic acid transporter removes excess lactate from cells [21]. If this does not work properly, cell function can be paralyzed in hyperacidity [21]. "The pKa of lactic acid is 3.86 at at 20 degrees C, and the pH of a 1 mMolar solution of lactic acid in water is about 3.5" [22]. That's why it is not a surprise that low pH predicted best mortality in cases of Metformin overdose [18,23]. A failure of serum lactate to rise with exercise (reported in skeletal muscles) could be a sign of overloading of lactic acid transporter capacity, i.e. "invisible lactic acidosis", in myocardium (?) or deficiency in glycolysis (because of deficiency of substrate?) [24].

Reactive oxygen species (ROS) can cause tissue injuries [15,25]. These can be counteracted by antioxidative defense mechanisms [26] (examples: Glutathione (GSH), glutathione peroxidase (GPx-1) (selenium compound), superoxide dismutase(s) (SOD), catalase, vit A, C, E [26]). SOD enzymes need proper amounts of copper (Cu), zinc (Zn), manganese (Mn) or iron (Fe) [26]. Mg is needed for GSH synthesis (with potassium) [27]. This can partially explain why Mg deficiency reduces cellular capacity to defy ROS [H2O2] [28]. Approximately 70% to 90% of cardiac ATP is produced by the oxidation of fatty acids (FA) [29]. Possibly this increases the susceptibility of myocardium to ROS. Anyhow neutralizing of ROS is energy consuming, e.g. decomposition of H2O2 needs 18,000 cal./mole without catalyst, with catalase < 2,000 cal./mole [30]. Obviously even the synthesis of catalase is energy consuming.

Plain muscle spasm produced pharmacologically with diazinon [31] can cause lactic acid production. Human experiment (in which reduction of diameter of coronary lumen before experiment was less than 50 %) revealed, that acetylcholine, which caused spasms in visible coronary arteries, without heart symptoms and without lactate production, caused lactate production in coronary veins and ECG changes in patients with "microvascular spasm" [32]. This "microvascular spasm" [32] seems to be quite different to (partially experimental produced) dietary microangiopathy of pigs [33], which is divided in two groups (simplified presentation): "MAP is the term applied particular lesions in the capillaries and small muscular vessels of the myocardium (cardiac MAP) and sometimes other tissues (extracardiac MAP). MAP may follow an episodic pattern; if a pig survives an episode, the lesions recognized as initial-phase MAP can then give way to changes aiming at restoration of vascular structure, "restitution-phase MAP" ([33], p. 98).

The usual appearance of MAP pigs is dominated by changes in myocardium (vivid red mottling – "mulberry heart", [33], p.6), transudation to the major serous cavities, and signs of acute circulatory failure. Myocardial changes, however, vary greatly from pig to pig and need not to be grossly evident. Secondary effects of extracardiac MAP are sometimes manifest as local oedema or, in the skin, as distinct macules… Affected segments of capillaries, precapillary arterioles and arterioles are wholly or partially obstructed by PAS-positive material, compatible with neutral glycoprotein… Within the myocardium initial-phase MAP is mainly a capillary lesion and is found in conjunction with varying degrees of local vascular engorgement, haemorrhage, degeneration of myocardial fibers, and sometimes an exudative inflammatory reaction. These changes are spatially and quantitatively subordinate to MAP and have been interpreted as secondary and dependent phenomena. The presence of restitution-phase MAP associated with focal myocardial scarring has been taken as a sign of the potentially episodic nature of MAP [33]. These changes were commonly prevented by vitamin E and/or selenium (Se). Grant discovered that "yellow fat" pigments, caused by fish oil (before refrigerator transportation) were not prevented by Se. Mg deficiency can produce "sterile inflammation" evaluabled by cytokines [34].

Discussion

Ischaemia, stoppage of blood flow [3] means stoppage of input (e.g. oxygen and glucose) and output of CO2 and lactate. Metabolism of cells is predestined by reservoirs of energy and protective substrates, their half-time can variate greatly. Closer discussion concerning roles of Se, Si, Cu, Zn, Mn, Fe and other micro- or macroelements are excluded from this assessment. Evaluation of intracellular contents of

protective nutrients via extracellular measurements can be misleading. Atherosclerosis is generally defined by the changes in the first 1/3 part of the arteries. Changes in the distal parts of the arteries and capillaries, e.g. microangiopathy (MAP) of young, non-smoking pigs with low-fat diet can be included in metabolic diseases, with periodic character and uneven distribution by locality ("mulberry disease") [33]. The pig MAP [33] seems to be quite different phenomenon to microvascular spasm [32], where word "vasospasm" is used without measurable changes in vascular diameters [32].

Even Robbins [5] discussed on the "paroxysmal myocardial hypoxia poorly understood" and small occlusions of small arterial branches, (which could explain the myocardial scarring in ASHD) [5]. "Degeneration of myocardial fibers, (sometimes) an exudative inflammatory reaction" [33] seems to be in common with pig MAP and occurrences preceding SPE meat [20], as obviously in [19], too. SPE meat formation can be preceded by malignant hyperthermia (cf delirium tremens [18]) or (some kind) porcine stress syndrome as described earlier. The role of glycosaminoglycans (GAG) is discussable [35]. It is suggested that GAG's work in vascular wall like in tenosynovitis (anti-inflammatory, in proper amounts in proper phase and with proper GAG). One effect of magnesium is relaxation of muscles. [19]. If this occurs in myocardium, it suggests on higher ejection fraction, which could save heart from exhaustion and production of lactate and ketone bodies [19].

There are a plenty of single studies, which support the protective effects of Mg against heart infarction, e.g. [36,37], but not [38], in which oral 15 mmol daily dose (MgO) was not beneficial. Remarkable is, that S-Mg in the study group (vs placebo group) was at the baseline 0.85 (0.84) and after 12 months 0.85 (0.86) mmol/L, which suggests that half of the experimentees in the study and placebo group suffered of Mg deficiency at the baseline and at the end of the study (S-Mg below 0.85 mmol/L [39]). This suggests on unproper randomization and high need on proper total or tissue Mg determination, which could be made through muscle [37] or bone (via trochanter) biopsy [39] instead of inconvenient Mg load tests, during waiting new methods and instruments [39].

Inflammation is a metabolic phenomenon, which can recurrently influence on well-being of arteries and myocardium (or muscles) [12-15,28,29,33-35]. Mg can protect against inflammation by eliminating reactive oxygen species [28] and preventing cytokine production [34]. Acethylcholine can be included in dynamic metabolic factors. Its effects on vessels are primarily vasodilative [40,41]. Magnesium deficiency promotes excretion of inflammatory cytokines and endothelin [39], which obviously explain the "vasospasm" in [32]. On the other side Mg can counteract vasospastic effects of endothelin-1 [42]. The process producing PSE meat is very intensive, promoted by acidity and temperature. In humans visible tissue changes of begin after 18 hours of the heart attack and yellow fatty degeneration is visible after 2-5 days of the attack [5]. Anyhow in both cases the metabolic susceptibility was builded up from the birth (genetic structure) or during preceding months (the half-time of Mg is 1 000 hours [39]).

The production of ATP [43] is a very rapid phenomenon, why the follow-up of lactate production in vivo seems to be very difficult (Glancy & al., 2021 in [18]). Anyhow lactate production in "vasospam" [32] (obviously via Mg dependent ATP deficiency and lactate production) could be about the same in hypoxia and prolonged muscle contraction [18,31], which could be recurrent and produce tissue injury in arterial wall and myocardium (cf. ASHD [5]). Lactate burst in exhausted myocardium can cause spasm and tissue injury of myocardium, if serious enough, metabolic infarct, heart necrosis.

Conclusion

Heart infarcts can be explained by metabolic and mechanistic phenomena. Rapid change in local lactate metabolism associated with decreased ATP production and deficiency of Mg and microelements can be the metabolic factors, which can initiate the myocardial metabolic infarction without coronary occlusion.

PS

It seems plausible that the common CHD risk factors [7], even partially dependent on the above described metabolic factors, cannot fully explain the low rural male CHD mortality [44] in 1951-57 (Figure 1), when people especially in the countryside consumed raw milk, with fat content 4.5-5 % [45], (before the era of statin medication).

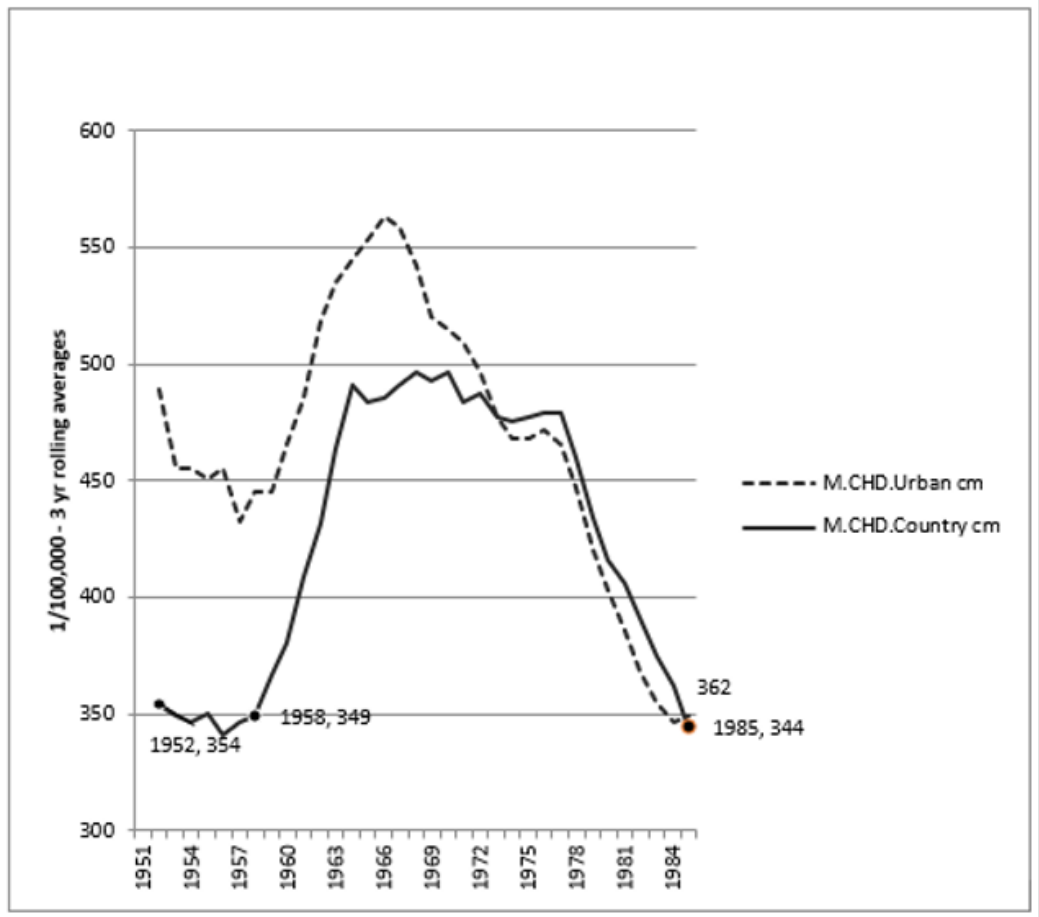

Figure 1: Age adjusted male CHD mortality, 35-64yrs, in urban and rural Finland

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