Immunoglobulin E and Matrix Metalloproteinase-9 in Patients with Different Stages of Coronary Artery Diseases

Gwo-Ping Jong[1,2], Yuh-Feng Wang [3], Fuu-Jen Tsai[4], Chang-Hai Tsai[5], Ching-Lin Wu[6], Rosa Huang Liu[7], Dennis Jine-Yuan Hsieh[8], Fu-Yang Ko[9], Chih-Yang Huang[9,10,11,*], and Shin-Da Lee[12,*]

[1]*Division of Cardiology*
Armed Force Taichung General Hospital, Taichung
[2]*Community Medical Research Center and Institute of Public Health*
National Yang-Ming University, Taipei
[3]*Department of Nuclear Medicine*
Buddhist Dalin Tzu Chi General Hospital, Chia-Yi
[4]*Department of Pediatrics, Medical Research and Medical Genetics*
China Medical College Hospital, Taichung
[5]*Department of Healthcare Administration*
Asia University, Taichung
[6]*Department of Exercise and Health Science*
National Taiwan College of Physical Education, Taichung
[7]*School of Nutrition, Chung-Shan Medical University, Taichung*
[8]*School of Medical Technology*
Chung-Shan Medical University, Taichung
[9]*Graduate Institute of Chinese Medical Science,*
[10]*Institute of Medical Science*
China Medical University, Taichung
[11]*Department of Health and Nutrition Biotechnology*
Asia University, Taichung
and
[12]*Department of Physical Therapy, China Medical University*
Taichung, Taiwan, ROC

Abstract

The aims of this study were to identify levels of total immunoglobulin E (IgE) and matrix metalloproteinase (MMP)-9 in patients with different stages of coronary artery diseases. IgE, MMP-9, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL) and triglyceride (TG) were measured by fluorescence enzyme immunoassay, gelatin zymography, and autoanalyzer in normal subjects (n = 40), patients with stable angina pectoris (SAP, n = 40), patients with unstable angina pectoris (UAP, n = 40), patients with acute myocardial infarction (AMI, n = 40), or post-CABG-surgery of those acute myocardial infarction (P-CABG, n = 40). Compared with normal subjects, increased IgE but unchanged MMP-9, CPK, LDH were found in SAP group and UAP group, whereas IgE, MMP-9, CPK and LDH levels were all significantly increased in AMI group. IgE, MMP-9, CPK and LDH levels in P-CABG group were significantly reduced, compared with AMI group, and were similar to those in normal subjects. Cholesterol, LDL, HDL and TG were not significantly changed in all groups. We suggest that serum total IgE can be an early marker of coronary artery disease and MMP-9 is a marker of acute myocardial infarction.

Key Words: IgE, MMP, ischemic heart disease, coronary artery bypass grafts

Corresponding author: Dr. Shin-Da Lee, Department of Physical Therapy, China Medical University, 91 Hsueh-Shih Road, Taichung, 40202, Taiwan, ROC. Tel: 886-4-22353366 ext. 7300, Fax: 886-422065051, E-mail: shinda@mail.cmu.edu.tw
*Share equal contribution
Received: September 20, 2006; Revised: December 20, 2006; Accepted: April 17, 2007.
 ISSN : 0304-4920. http://www.cps.org.tw

Introduction

Biochemical testing for the diagnosis of acute myocardial infarction and other coronary artery diseases included in the wide spectrum of the so-called "acute coronary syndrome" (AMI) is rapidly changing from the traditional enzymatic assays to mass measurement of more specific and sensitive markers (17). Acute myocardial infarction can be diagnosed on the basis of clinical history, electrocardiographic findings, abnormalities in glutamic oxaloacetic transaminase (GOT), creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) enzyme levels to confirm or exclude the diagnosis (18). After the onset of AMI, the amount of CPK appearing in blood is directly related to the number of myocytes that become necrotic; but CPK values do not increase in patients with stable or unstable angina without infarction (5). Cardiac markers of "minor myocardial damages" in patients with stable angina pectoris (SAP) or unstable angina pectoris (UAP) are not confirmed and the early marker of acute coronary syndrome is not well-established.

The matrix metalloproteases (MMPs) play an important role in myocardial or vascular tissue remodeling associated with various pathological processes in cardiovascular diseases (9, 14). The increase of MMP-9 levels and activity may be used as a new marker to diagnose the development of heart failure in patients with post myocardial infarction (10). The MMP-2 were markedly increased in dilated cardiomyopathy in an animal model (10). Synthesis of MMPs has been reported in coronary atherosclerotic lesions in patients with UAP, suggesting a pathogenic role of MMPs in the development of acute coronary syndromes (11). Peripheral blood levels of MMP-2 and -9 appear to be elevated or unchanged in patients with acute coronary syndromes in different periods of time (11). The role of MMP in acute coronary syndromes appears to be controversial.

Immunoglobulin E (IgE), known primarily as a mediator of allergy, can cause platelet activation (22), and arterial smooth muscle hyperplasia (13). IgE-mediated histamine release may influence vascular autoregulatory responses and may induce coronary artery spasm concerning pathogenesis of variant angina pectoris (7). Thus, IgE has a plausible physiologic role in the etiology of cardiovascular diseases and the elevated IgE is an independent factor of prospective risk for myocardial infarction in men (13). Besides, IgE may play a role in the pathogenesis of unstable angina pectoris and acute myocardial infarction (12) or during the acute phase of acute coronary syndromes (4). However, the role of IgE and MMPs in SAP, UAP, AMI or AMI patients with post-coronary artery bypass grafts (CABG) surgery (P-CABG), to our knowledge, is not totally understood.

The aims of this study were to identify IgE levels, MMPs, and other markers (lipid profile, GOT, CPK, LDH) in patients with different stages of coronary artery diseases including SAP, UAP, and AMI, and in AMI patients with post-CABG surgery.

Materials and Methods

Subjects

All patients at Armed Forces Taichung General Hospital underwent angiography for evaluation of clinically-defined SAP (n = 40), UAP (n = 40), AMI (n = 40) or those AMI patients with P-CABG (n = 40). The exclusion criteria in the current study were other known diagnosed diseases, body mass index larger than 30 kg/m^2 and acute phase of fever. Exclusion criteria for patients with post-CABG surgery were complications in the postoperative course, defined as postoperative myocardial infarction diagnosed by electrocardiogram abnormalities in association with abnormal wall motion and hemodynamic instability. The control group consisted of normal age range-matched normal subjects (normal, n = 40) who had normal coronary artery angiograms collected within the same interval as the patient group. All subjects gave written informed consent for examinations and participation in the study.

Diagnostic Definitions

All patients were diagnosed with coronary artery diseases. SAP generally occurs during exercise or under stress and is relieved by a nitrate spray or tablet (e.g. amyl nitrate). UAP defined by clinical history and minor electrocardiographic findings, generally occurs at rest and is unrelieved with the usual medication. The diagnosis of SAP or UAP was determined by cardiologist, and all such patients had normal CPK levels. The diagnosis of AMI was established by the presence of chest pain lasting > 20 min associated with electrocardiographic changes (ST-segment elevation ≥ 1 mm in ≥ 2 extremity electrocardiographic leads, ≥ 2 mm in ≥ 2 contiguous precordial leads, or new-onset left bundle branch block) or increased activity of serum CPK to ≥ 2 times, the upper limit of normal. The AMI patients with P-CABG all received isolated CABG with the use of cardiopulmonary bypass.

Blood Sampling

Overnight fasting blood samples were drawn from 7:00 to 9:00 am by a trained phlebotomist *via* a venipuncture of an antecubital vein from the patients

in a supine position. The blood samples of AMI patients with Post-CABG were drawn after 7~14 days from surgery. The blood samples drawn were immediately used for biochemical autoanalyzer. The serum samples were separated by refrigerated centrifuge at 3000 rpm for 15 min at 4°C, and within 1 h of drawing blood. The serum samples were subsequently frozen at -80°C until fluorescence enzyme immunoassay (FEIA) analysis and gelatin zymography.

Autoanalyzer with Enzymatic Methods

Total cholesterol (CHOL), triglyceride (TG) concentrations and high density lipoprotein (HDL) concentration were measured by a Hitachi 7170 Autoanalyzer (Hitachi Instrument, Tokyo, Japan) with enzymatic methods. Low density lipoprotein (LDL) was calculated by Friedewald's equation (6). Enzymatic methods with commercial kits such as Cica liquid GOT, Cica liquid CPK (KANTO Chemical Co., Inc, Tokyo, Japan), LDH II-HA test WAKO (Wako Pure Chemical Wako, Japan) were used to determine GOT, CPK and LDH with a Hitachi 7170 automated analyzer (Hitachi Instrument).

Gelatin Zymography Protease Assay

The proteins extracts (20 μg) from 16 μl sample were mixed thoroughly with a suitable volume of PBS buffer and 4 μl of dye. Gelatin zymography analysis was carried out by loading 20 μl of the serum 0.1% gelatin and 8% SDS-PAGE, and run by electrophoresis at 140 V for 2.5 h. The gels were washed in a 2.5% Triton X-100 solution with shaking for 30 min and then incubated in 50 ml reaction buffer (40 mM Tris-HCl, pH 8.0; 10 mM $CaCl_2$, 0.01% NaN_3) at 37°C for 12 h before staining with 0.25% Coomassie brilliant blue R-250 in 50% methanol and 10% acetic acid for 1 h. Quantitative analysis was performed after discoloring the stain in a destaining solution (10% acetic acid, 20% methanol) twice for 30 min.

Pharmacia CAP System FEIA

Total serum IgE levels were quantified by Pharmacia CAP system FEIA (Pharmacia and UpJohn Diagnostics, Uppsala, Sweden), using UNICAP 100, according to the manufacturer's instruction. Total serum IgE values were expressed in KU/l.

Protocol

Serum CHOL, LDL, HDL, TG, GOT, CPK, LDH, MMPs and total IgE were measured by Autoanalyzer with enzymatic methods, gelatin zymography and CAP system FEIA. All tests were performed by experienced technicians in a blinded design. All parameters were analyzed and divided into five groups, *i.e*. normal subjects (Normal, n = 40), patients with SAP (n = 40), UAP (n = 40), AMI (n = 40), and AMI patients with P-CABG (n = 40).

Statistical Analysis

All parameters (CHOL, LDL, HDL, TG, GOT, CPK, LDH, MMPs and total IgE) were analyzed by an analysis of variance using the general linear model (GLM) in a one way ANOVA with pre-planned comparison with normal healthy subjects and comparison between AMI and P-CABG. In all cases, a difference at $P < 0.05$ was considered statistically significant. All data presented in the text, tables, and figures are means ± SD.

Results

Lipid Profiles

CHOL, LD, HDL and TG were not significantly changed in patients with SAP, UAP, AMI, or AMI patients with P-CABG, compared with normal health subjects (Table 1).

GOT, CPK and LDH

Compared with age range-matched normal subjects, GOT, CPK and LDH significantly increased in AMI group (22.3 ±1.5 *vs*. 50.6 ±11.7 mg/dl, $P < 0.05$; 103.2 ±20.3 *vs*. 461.2 ±110.2 IU/l, $P < 0.01$; 357.5 ±12.9 *vs*. 726.5 ±96.3 IU/l, $P < 0.01$) but did not increase in SAP and UAP groups (Table 1, Fig 2, Fig 3). CPK and LDH significantly ($P < 0.01$) decreased, but GOT did not change in P-CABG group, compared with AMI group (Table 1, Fig 1, Fig 2).

MMP-9

Compared with age range-matched normal subjects, MMP-9 and MMP-2 did not change in SAP, UAP and P-CABG groups. MMP-9 significantly increased in AMI group whereas MMP-2 did not change in AMI group. Compared with AMI group, MMP-9 significantly decreased in P-CABG group (Table 1 and Fig 3).

IgE

Compared with age range-matched normal subjects, serum IgE significantly ($P < 0.01$) increased in patients with SAP, UAP and AMI (31.7 ±4.4 *vs*. 117.2 ±38.2, 149.9 ±51.6, 106.6 ±19.0 KU/l) (Table

Table 1. Serum levels of lipids, enzymes, and IgE in patients

Groups	Normal	SAP	UAP	AMI	P-CABG
Number of subjects	n = 40	n = 40	n = 40	n = 40	n = 40
Male/Female	M(18)/F(22)	M(22)/F(18)	M(22)/F(18)	M(20)/F(20)	M(24)/F(16)
Age (years old)	63 ± 10	65 ± 11	64 ± 11	66 ± 15	59 ± 11
CHOL (< 200 mg/dl)	187.6 ± 8.7	184.8 ± 8.6	177.2 ± 13.0	193.3 ± 10.4	186.8 ± 8.8
LDL (< 130 mg/dl)	100.6 ± 8.3	110.2 ± 7.4	107.7 ± 10.4	126.3 ± 9.3	108.4 ± 9.8
HDL (35-60 mg/dl)	49.0 ± 3.0	35.9 ± 2.5	28.7 ± 2.3	38.3 ± 2.1	38.8 ± 2.4
TG (50-200 mg/dl)	193.8 ± 19.7	195.2 ± 41.5	209.1 ± 44.8	144.9 ± 20.9	193.5 ± 29.6
GOT (8-38 mg/dl)	22.3 ± 1.5	24.1 ± 5.7	23.7 ± 3.7	50.6 ± 11.7*	39.1 ± 8.9
CPK (20-190 IU/l)	103.2 ± 20.3	72.5 ± 12.4	57.6 ± 9.9	461.2 ± 110.2 **	119.3 ±17.6$^{\#\#}$
LDH (200-410 IU/l)	357.7 ± 12.9	350.9 ± 24.9	375.0 ± 27.8	726.5 ± 96.3*	432.3 ± 35.7$^{\#\#}$
IgE (< 100 KU/l)	31.7 ± 4.4	117.2 ± 38.2**	149.9 ± 51.6**	106.6 ± 19.0**	34.5 ± 5.9$^{\#\#}$

Values are mean ± SD. Definition of abbreviations: CHOL = cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein; TG = triglyceride; GOT = glutamic oxaloacetic transaminase; CPK = creatine phosphokinase; LDH = lactate dehydrogenase; MMP = matrix metalloproteinase; IgE = total immunoglobulin E. Normal = normal health subjects; SAP = stable angina pectoris; UAP = unstable angina pectoris; AMI = acute myocardial infarction; P-CABG = AMI patients with post-CABG surgery. n = numbers of subjects; M/F = numbers of male subjects/ numbers of female subjects. *$P < 0.05$. **$P < 0.01$ Significant difference between normal and patients with coronary diseases. $^{\#\#}P < 0.01$ Significant difference between AMI and P-CABG.

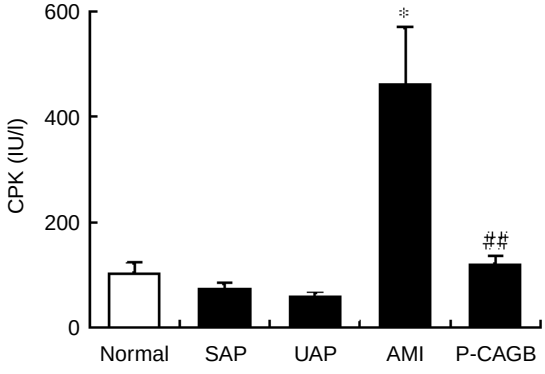

Fig. 1 Serum creatine phosphokinase (CPK) measured in age range-matched patients with stable angina pectoris (SAP, n = 40), unstable angina pectoris (UAP, n = 40), acute myocardial infarction (AMI, n = 40), or AMI patients with post-CABG surgery (P-CABG, n = 40), compared with normal health subjects (normal, n = 40). *$P < 0.05$ significant different between patients and normal subjects, or $^{\#\#}P < 0.01$ significant difference between AMI and P-CABG. Values represent mean ± SD.

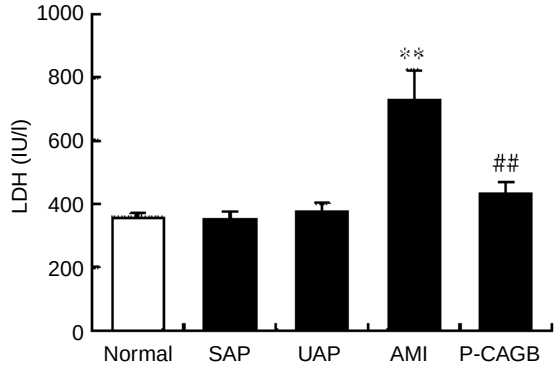

Fig. 2 Serum lactate dehydrogenase (LDH) measured in age range-matched patients with stable angina pectoris (SAP, n = 40), unstable angina pectoris (UAP, n = 40), acute myocardial infarction (AMI, n = 40), or AMI patients with post-CABG surgery (P-CABG, n = 40), compared with normal health subjects (normal, n = 40). **$P < 0.01$ significant different between patients and normal subjects, or $^{\#\#}P < 0.01$ significant difference between AMI and P-CABG. Values represent mean ± SD.

1, Fig 4). Compared with AMI group, IgE significantly decreased in P-CABG group (Table 1 and Fig 4)

Discussion

Our major findings can be summarized as follows: [1] IgE increased but MMP-9, CPK, LDH remained unchanged in SAP group and UAP group, compared with normal subjects; [2] IgE, MMP-9, CPK and LDH levels were significantly increased in AMI group; [3] IgE, MMP-9, CPK and LDH levels in P-CABG group returned to normal levels, compared with AMI group; [4] Lipid profile such as CHOL, LDL, HDL and TG were not significantly changed in all coronary artery syndromes groups and P-CABG group.

Cardiac enzymes of coronary artery diseases cannot be excluded by a single “normal” value nor established by a single “abnormal elevated” value (19). Angina pectoris (Latin for “chest constriction”) is the result of a lack of oxygen supply to the heart muscle,

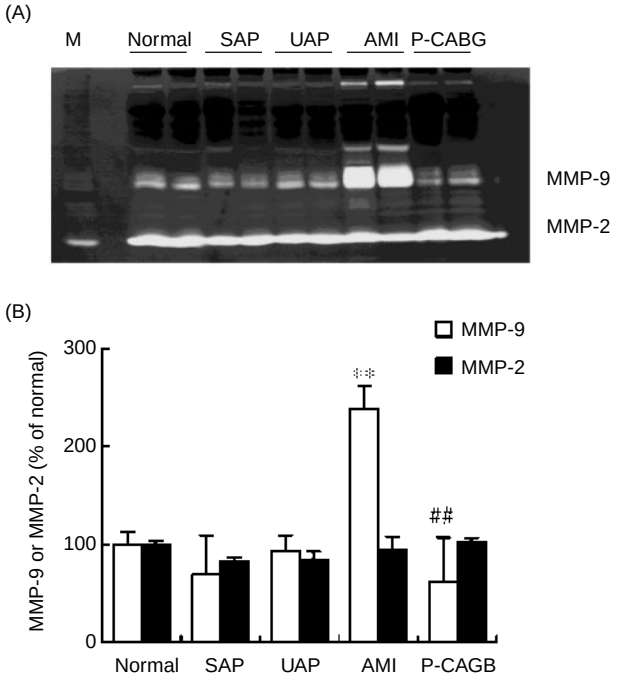

Fig. 3 Serum MMP-9 and MMP-2 measured in patients with stable angina pectoris (SAP, n = 40), unstable angina pectoris (UAP, n = 40), acute myocardial infarction (AMI, n = 40), or AMI patients with post-CABG surgery (P-CABG, n = 40), compared with normal health subjects (normal, n = 40). Bars indicate the amount of MMPs expressed in percentage of normal level. $^{**}P < 0.01$ significant different between patients and normal subjects, or $^{\#\#}P < 0.01$ significant difference between AMI and P-CABG. Values represent mean ± SD.

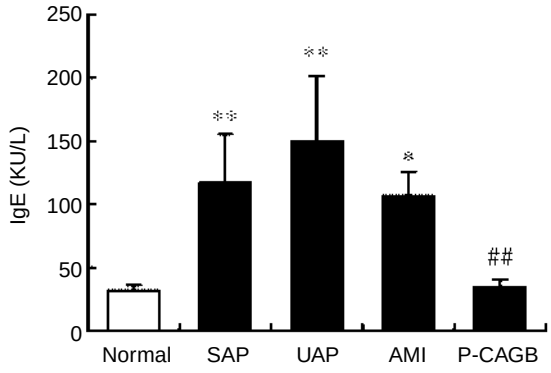

Fig. 4 Serum total-immunoglobulin E (IgE) measured in age range-matched patients with stable angina pectoris (SAP, n = 40), unstable angina pectoris (UAP, n = 40), acute myocardial infarction (AMI, n = 40), or AMI patients with post-CABG surgery (P-CABG, n = 40), compared with normal health subjects (normal, n = 40). $^{*}P < 0.05$, $^{**}P < 0.01$ significant difference between patients and normal subjects, or $^{\#\#}P < 0.01$ significant difference between AMI and P-CABG. Values represent mean ± SD.

due to a reduced blood flow around the heart's blood vessels. This lack of oxygen to the heart is known as myocardial ischemia or coronary artery syndromes. Angina, caused by stimulation of nerve endings in the heart muscle and its blood vessels, is the most common symptom of myocardial ischemia, especially in the early stage.

The use of biochemical markers to diagnose AMI can be dated back to 1954 when aspartate aminotransferase [AST (GOT)] was first used. CPK replaced AST in late 1960's and LDH started to be used as a late marker in 1970's. GOT, CPK and LDH were considered as biochemical markers for AMI (1, 3, 16), whereas biochemical markers for micro-infarction, minor cardiac damage or non-ischemic cardiac damage seemed to be much less reported. Creatine kinase (CK), also known as CPK, functions as the catalysis of the conversion of creatine to phosphocreatine, consuming adenosine triphosphate (ATP) and generating adenosine diphosphate (ADP). Measurements of CK, isoenzyme CK-MB mass or CK isoform in emergency rooms were often used to rule out AMI. However, within the first 3 to 4 h from chest pain onset, their sensitivities are too low to contribute to micro myocardial damage or coronary vascular during this period (15). Previous study suggested that the severity of myocardial infarct or reperfusion cannot be estimated by serum CPK level alone (8). LDH found in skeletal muscle and heart is responsible for the inter-conversion of pyruvate and lactate during glycolysis. The major limitation of CK or LDH is their comparatively late release after about 4 to 6 hours following myocardial infarction (24).

It is now becoming increasingly clear that extracellular matrix degradation by MMPs is also involved in the pathogenesis of cardiovascular disease, including atherosclerosis, restenosis, post-infarction left ventricular remodeling and dilated cardiomyopathy (2). Our findings showed that MMP-9 activities in AMI group were higher than those in SAP group, UAP group, P-CABG group and normal group whereas MMP-2 levels in all groups were similar. Part of our findings are consistent with previous reports, in which MMP-9 increased in AMI group and returned to normal level after therapeutic intervention (11, 23). Inconsistently, higher serum MMP-2 and MMP-9 concentration in patients with UAP reported in the previous study were not found in the current study (11). It is unclear why our findings at UAP were differ from those of Kai *et al.* (11), but our findings may be related to race difference, methodological difference of MMP measurement, minor difference in disease classification, or differences in MMP activity instead of MMP concentration.

The role of inflammation and mast cell activation

has been implicated in atherosclerotic plaque destabilization and rupture (4). IgE levels were found to be significantly higher in the patients with unstable angina and acute myocardial infarction, compared to the patients with stable angina pectoris and controls. (12). After infarction, patients with high initial IgE levels (greater than 200 IU/ml) had a greater increase in IgE and less frequent severe complications than those whose initial IgE levels were below 200 IU/ml (21), which suggested that patients with high IgE levels might be protected against complications of infarction because of a favorable ratio of locally released mediators and because of decreased platelet function. Furthermore, high serum IgE levels were associated with delayed thrombin generation in the clotting blood of survivors of myocardial infarction (20). Early determination of serum IgE levels might help to detect patients at risk of sudden cardiac arrest during myocardial infarction (20). In the current study, IgE appeared to be an early marker, compared with other markers of coronary artery diseases, such as GOT, CPK and LDH. Besides, after CABG, IgE levels were back to normal.

Adequate "early diagnostic sensitivity" can prevent unnecessary damage and reduce unnecessary costly admissions. Early cardiac markers for identifying coronary artery disease can assist clinicians. Since our findings show that IgE may be an earlier marker of coronary artery disease than MMP-9, CPK and LDH, we may suggest that measurement of serum total IgE could be a helpful marker of coronary artery disease as well as MMP-9 could be a marker of AMI.

Acknowledgment

The paper is supported by grant CMU95-278 from the China Medical University, Taiwan, Republic of China.

References

1. Akyol, O., Sencan, O., Buyukberber, S., Canbolat, O. and Durak, I. Glutathione peroxidase activity in serum during acute myocardial infarction and unstable angina pectoris. *Jpn. Heart J.* 34: 551-555, 1993.
2. Benjamin, I.J. Matrix metalloproteinases: from biology to therapeutic strategies in cardiovascular disease. *J. Investig. Med*. 49: 381-397, 2001.
3. Blatterlein, I., Lehmann, I. and Wagenknecht, C. Pre-, intra- and postoperative behavior of LDH and GOT isoenzymes in the plasma of patients with chronic ischemic heart disease. *Z. Gesamte Inn. Med*. 32: suppl: 307-309, 1977.
4. Erdogan, O., Gul, C., Altun, A. and Ozbay, G. Increased immunoglobulin E response in acute coronary syndromes. *Angiology* 54: 73-79, 2003.
5. Ezaki, H., Matsushita, S., Ohkawa, S. and Kuramoto, K. Comparison of enzymatic, anatomic and electrocardiographic estimates of myocardial infarct size in man. *Jpn. Circ. J*. 51: 374-382, 1987.
6. Friedewald, W.T., Levy, R.I. and Fredrickson, D.S. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin. Chem*. 18: 499-502, 1972.
7. Ginsburg, R., Bristow, M.R., Kantrowitz, N., Baim, D.S. and Harrison, D.C. Histamine provocation of clinical coronary artery spasm: implications concerning pathogenesis of variant angina pectoris. *Am. Heart J*. 102: 819-822, 1981.
8. Horie, M., Yasue, H., Omote, S., Takizawa, A., Nagao, M., Nishida, S. and Kubota, J. The effects of reperfusion of infarct-related coronary artery on serum creatine phosphokinase and left ventricular function. *Jpn. Circ. J*. 48: 539-545, 1984.
9. Janicki, J.S., Brower, G.L., Gardner, J.D., Chancey, A.L. and Stewart, J.A., Jr. The dynamic interaction between matrix metalloproteinase activity and adverse myocardial remodeling. *Heart Fail. Rev*. 9: 33-42, 2004.
10. Jong, G.P., Ma, T., Chou, P., Chang, M.H., Wu, C.H., Lis, P.C., Lee, S.D., Liu, J.Y., Kuo, W.W. and Huang, C.Y. Serum MMP-9 activity as a diagnosing marker for the developing heart failure of post MI patients. *Chinese J. Physiol.* 49: 104-109, 2006.
11. Kai, H., Ikeda, H., Yasukawa, H., Kai, M., Seki, Y., Kuwahara, F., Ueno, T., Sugi, K. and Imaizumi, T. Peripheral blood levels of matrix metalloproteases-2 and -9 are elevated in patients with acute coronary syndromes. *J. Am. Coll. Cardiol*. 32: 368-372, 1998.
12. Korkmaz, M.E., Oto, A., Saraclar, Y., Oram, E., Oram, A., Ugurlu, S., Karamehmetoglu, A. and Karaagaoglu, E. Levels of IgE in the serum of patients with coronary arterial disease. *Int. J. Cardiol*. 31: 199-204, 1991.
13. Langer, R.D., Criqui, M.H., Feigelson, H.S., McCann, T.J. and Hamburger, R.N. IgE predicts future nonfatal myocardial infarction in men. *J. Clin. Epidemiol*. 49: 203-209, 1996.
14. Lee, S.D., Chen, L.M., Kuo, W.W., Shu, W.T., Kuo, W.H., Huang, E.J., Tsai, C.C., Li, P.C., Liu, J.Y., Chen, T.H. and Huang, C.Y. Serum insulin-like growth factor-axis and matrix metalloproteinases in patients with rheumatic arthritis or rheumatic heart disease. *Clin. Chim. Acta* 367: 62-68, 2006.
15. Mair, J. Progress in myocardial damage detection: new biochemical markers for clinicians. *Crit. Rev. Clin. Lab. Sci.* 34: 1-66, 1997.
16. Phillips, J.E. CPK and LDH isoenzymes in the diagnosis of myocardial infarctions. *J. Med. Assoc. Ga*. 63: 382-383, 1974.
17. Plebani, M. Biochemical markers of cardiac damage: from efficiency to effectiveness. *Clin. Chim. Acta* 311: 3-7, 2001.
18. Ruzich, R.S. Cardiac enzymes. How to use serial determinations to confirm acute myocardial infarction. *Postgrad. Med*. 92: 85-92, 1992.
19. Sobel, B.E. and LeWinter, M.M. Ingenuous interpretation of elevated blood levels of macromolecular markers of myocardial injury: a recipe for confusion. *J. Am. Coll. Cardiol*. 35: 1355-1358, 2000.
20. Szczeklik, A., Dropinski, J. and Gora, P.F. Serum immunoglobulin E and sudden cardiac arrest during myocardial infarction. *Coron. Artery Dis*. 4: 1029-1032, 1993.
21. Szczeklik, A., Sladek, K., Szczerba, A. and Dropinski, J. Serum immunoglobulin E response to myocardial infarction. *Circulation* 77: 1245-1249, 1988.
22. Tsicopoulos, A., Tonnel, A.B., Wallaert, B., Joseph, M., Ramon, P. and Capron, A. A circulating suppressive factor of platelet cytotoxic functions after rush immunotherapy in Hymenoptera venom hypersensitivity. *J. Immunol.* 142: 2683-2688, 1989.
23. Tziakas, D.N., Chalikias, G.K., Parissis, J.T., Hatzinikolaou, E.I., Papadopoulos, E.D., Tripsiannis, G.A., Papadopoulou, E.G., Tentes, I.K., Karas, S.M. and Chatseras, D.I. Serum profiles of matrix metalloproteinases and their tissue inhibitor in patients with acute coronary syndromes. The effects of short-term atorvastatin administration. *Int. J. Cardiol*. 94: 269-277, 2004.
24. Walter, S., Carlsson, J., Schroder, R., Neuhaus, K.L., Sorges, E. and Tebbe, U. Enzymatic markers of reperfusion in acute myocardial infarct. With data from the ISAM study. *Herz* 24: 430-439, 1999.