INTERNATIONAL JOURNAL OF ADVANCED BIOLOGICAL RESEARCH

www.scienceandnature.org

# ECHOCARDIOGRAPHIC EVALUATION OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN DIABETIC PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION

[a]Radhwan Readh Alhmaidat, [b]Saad Merza Al-Araji & [c]Ala Hussain Abbase
[a] Karbala Health Directorate, Primary Health Care
[b] College of Medicine, Department of Medical Physiology, Babylon/Iraq
[c] College of Medicine, Department of Internal Medicine, Babylon/Iraq

**ABSTRACT**
Cardiovascular autonomic neuropathy (CAN) is a serious and common complication of type 2 diabetes mellitus (DM) and it is encompasses a damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics. The study was designated to estimate the prevalence of CAN in patients with type 2 DM and evaluate the effect of CAN in type 2 DM on the response to the thrombolytic therapy (Actilyse). The study extends from 3rd/November/2012 to 31th/May/2013 at Merjan Teaching Hospital in Babylon Province and Al- Zahraa center of internal medicine in Al- Hussain teaching hospital in Karbala Province. The total number of subjects involved in this study was 111, all of them were newly diagnosed ST-elevation myocardial infarction in the Coronary Care Unit. Patients were classified according to the presence of type 2 diabetes mellitus or not into 2 groups, and patients with the type 2 DM divided into 3 groups according to the presence of CAN in order to study the difference in the response to the thrombolytic therapy ( Actilyse ) between these groups. All patients enrolled in this study had undergone clinical assessment by history and examination, Echocardiographic study and serum cardiac troponin titer had been done for each one of them at admission and after 24 hours, Haematological assessment and biochemical assessment. The study revealed that there were an extremely significant difference between STEMI and type 2 DM ($p< 0.0001$). The echocardiographic examination revealed that there were an extremely significant association between the response of regional wall motion abnormality to Actilyse in STEMI and: the presence of type 2 DM ($p< 0.0001$), admission hyperglycemia ($p< 0.0001$), hypertension ($p< 0.001$) and a highly significant association with the duration of type 2 DM in years ($p< 0.01$) and a significant association with CAN ($p< 0.05$), The presence of Type 2 DM in STEMI patients lower the response of global left ventricle systolic function (EF%) to Actilyse ($p<0.01$) and ($p<0.05$). There was an extremely significant relation ($p< 0.0001$) between type 2 DM and decrease serum Troponin titer after 24 hours of Actilyse. In view of the changes summarized, history of type 2 diabetes mellitus in patient with ST-elevation myocardial infarction affect the response (successfulness ) of the thrombolytic therapy ( Actilyse ) that is seen by echocardiography and the level of troponin titer after the treatment, either by the effect of uncontrolled ( high blood sugar ) type 2 DM or the development of CAN.

**KEYWORDS:** autonomic nerve fibers, ST-elevation, STEMI patients, serum Troponin titer, Actilyse.

## INTRODUCTION

Coronary artery disease (CAD) is the most frequent single cause of death worldwide. Over seven million people all over the world every year die from CAD, accounting for 12.8% of all deaths [43]. Acute coronary syndrome (ACS) is a common complication of coronary artery disease (CAD)[34]. Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from ST-segment elevation myocardial infarction (STEMI) to non-ST- segment elevation myocardial infarction (NSTEMI) and unstable angina. Most cases of ACS are caused by rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery[7]. Approximately 23% of patients with STEMI in the United States have diabetes mellitus[35], and three quarters of all deaths among patients with diabetes mellitus are related to coronary artery disease [26]. Diabetes mellitus is associated with higher (short and long term) mortality after STEMI [32]. Hyperglycemia at presentation in patients who do not have diabetes mellitus by history has been associated with worse hospital outcomes[31]. Diabetes Mellitus is a potent risk factor for all forms of atherosclerosis and is often associated with diffuse disease that is difficult to treat. Insulin resistance and glucose intolerance accounts for a major part of the high incidence of ischaemic heart disease in certain ethnic groups, *e.g.* South Asians [6, 34]. The complications of diabetes mellitus include retinopathy, nephropathy, and neuropathy (both peripheral and autonomic). The risk for microvascular and neuropathic complications is related to both duration of diabetes and the severity of hyperglycemia[15]. One of the earliest manifestations of diabetic autonomic neuropathy is denervation of cardiovascular system. Presence of symptoms along with abnormal cardiovascular function tests suggest poor prognosis and increased incidence of silent myocardial infarction, cardiac arrest and sudden death[27]. Of these, cardiac autonomic neuropathy (CAN) encompasses damage to the autonomic nerve fibers that

innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics. It is a significant cause of morbidity and mortality associated with a high risk of cardiac arrhythmias and sudden death[40]. The prevalence of confirmed CAN in unselected people with type 1 and type 2 diabetes is approximately 20%, but it can be as high as 65% with increasing age and diabetes duration [39]. Thus, a review of this topic is both timely and important for physicians to better understand how to assess the complexity of conditions present in patients with diabetes in order to establish safe treatment targets[29]. This study aims to identify some possible risk factors ( gender, smoking, duration of diabetes mellitus, type of diabetes…*etc*.) of myocardial infarction in Babylon and Karbala province and studying the effect of the presence of type 2 diabetes mellitus and it's duration on the treatment of ST-elevation myocardial infarction by actilyse. To measurements the prevalence of diabetic neuropathy in type 2 diabetic patients. Evaluating the effect of cardiovascular autonomic neuropathy on the response of ST-elevation myocardial infarction to actilyse and measurements of important haematological and biochemical abnormality in ST-elevation myocardial infarction patients with type 2 diabetes mellitus compare to control groups.

## MATERIALS & METHODS

The study was conducted in Merjan Teaching Hospital in Babylon Province and Al- Zahraa center of internal medicine in Al- Husain teaching hospital in Karbala Province from November/ 2012 to May/ 2013. All samples were collected from coronary care unit (CCU). This study included 111 patients, 69 males and 42 females with STEMI (ST- segment elevation myocardial infarction) clinically assessed by specialist. The age of most patients was above forty with percentage about (96.4%) of patients; mean age was (57.37 ± 10.988) year, as 41 patients considered a control group as they were not diabetics to compare with type 2 diabetic patients by the echocardiographic study and the remaining 70 considered a patient group. The control group was selected regarding the presence of type 2 diabetes mellitus or not, while all the patients included in the study were diagnosed as STEMI (ST- segment elevation myocardial infarction). The patients were diagnosed as STEMI (ST-segment elevation myocardial infarction) depending on positive troponin I tests plus ECG finding in addition to clinical features of acute Myocardial Infarction. All patients underwent medical history and physical examinations including : age, gender, history of ischemic heart disease, hypertension and its duration, diabetes mellitus, and its duration, history of smoking and family history of ischemic heart disease. All the patients were fasting when blood samples were taken. Patients were considered as diabetic when they had history of diabetes, on treatment including diet regime or when fasting blood glucose ≥ 7.0 mmol/ L (126 mg/ dl) or random blood glucose ≥ 11.1 (200 mg/ dl), or glycated hemoglobin ≥ (Hb A1C) ≥ 6.5% [1]. Electrocardiography Manifestations of Acute Myocardial Ischemia (in Absence of Left ventricular hypertrophy (LVH)). New ST elevation at the J point in two contiguous leads with the cut- points: ≥ 0.1 mV in all leads other than leads V2– V3 where the following cutpoints apply: ≥ 0.2 mV in men ≥ 40 years; ≥ 0.25 mV in men < 40 years, or ≥ 0.15 mV in women [36].

Echocardiographic examination was done for all patients to characterize:

1. Left Ventricular Wall motion abnormality was seen in Parasternal long axis (PLAX) view and other views.
2. Ejection Fraction (EF%) through the left ventricular internal dimensions during systole and diastole via the M- Mode .
3. The thicknesses of left ventricular muscles; interventricular septum (IVS) and left ventricular posterior wall (PW) by 2- D or M- mode at diastole.

In order to assess regional systolic function, the left ventricle is artificially divided into different segments. The left ventricle is divided into 6 walls: anterior, anteroseptal, inferoseptal, posterolateral, anterolateral and inferior. Each wall is divided into a basal, mid and apical segment and the apical cap represents the 17th segment. Wall motion score index is a semi-quantitative analysis of regional systolic function. Each segment is analyzed individually and scored on the basis of its motion and systolic thickening. Ideally, the function of each segment should be confirmed in multiple views. This score is a 5-level score defines as follows[25]: score 1= normokinesis or hyperkinesis, score 2= hypokinesis, score 3= akinesis, score 4= dyskinesis and score 5= aneurysm.

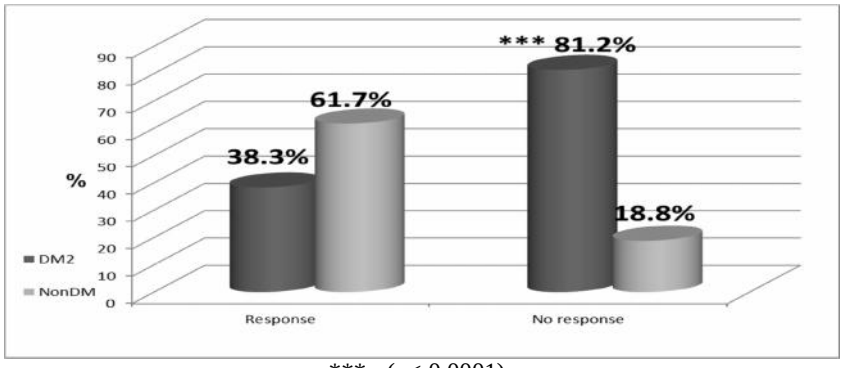
Wall motion score index is derived as a sum of all scores divided by the number of segments visualized. While the Ejection Fraction (EF %) was estimated in values at difference of 5% (20%, 25%, 30% and so on), LV systolic function was assessed by M- mode and 2D techniques [18].

It should be stressed that no single test can provide a global assessment of autonomic function. The normative values of these tests depend upon a large number of factors, including: the specific laboratory conditions (*e.g.* room temperature, instrumentation); the protocol followed (*e.g.* duration of the stimulus, body position during and prior to testing); and patient-related factors (*e.g.* age, medication, consumption of caffeine *etc*.), so that care must therefore be taken when interpreting individual results[19]. Five standardized tests are widely used in clinical practice three for assessment of cardiac parasympathetic function (heart rate (HR) response to Valsalva maneuver, to deep breathing and to standing upright from supine position) while the other two (blood pressure (BP) response to standing from supine and to sustained isometric exercise) are used for assessment of peripheral sympathetic function.

## RESULTS

Out of 111 patients in the studied groups, 70 patients were complaining from T2DM and 41 were not diabetic, there are 81 (73%) smokers whether they were previously, currently, heavy or light smokers, and 30 (27%) are not smokers, smokers were extremely significant ($p< 0.0001$) more than not smokers, In this study 65.8% of patients had positive family history of Myocardial Infarction and it was negative in 34.2% patients, those patients with positive family history were extremely significant ($p< 0.0001$)

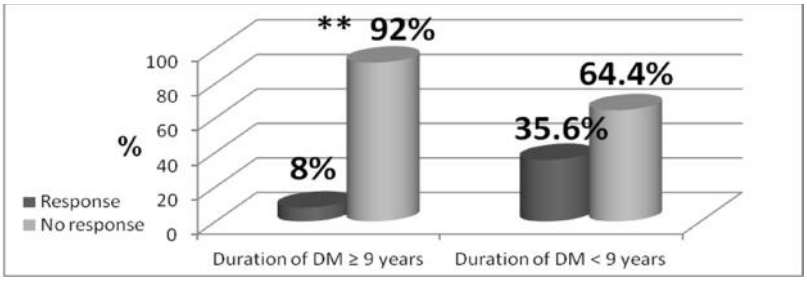
higher than patients with negative family history, The hypertension (as a risk factor of Myocardial Infarction in patients of this study) was present in 67 (60.4%) patients and not in 44 (39.6%) patients, hypertensive patients were significant (p< 0.05) higher than those not hypertensive. There was a statistically extremely significant relationship (p< 0.0001) between Type 2 diabetes mellitus (T2DM) and decrease in the response of the regional wall motion abnormality (RWMA) shown by echocardiography to the treatment of myocardial infarction by Actilyse, as 81.2% of patients with no response had T2DM (Figure 1).




***= (p< 0.0001).

**FIGURE 1:** Response of Regional Wall Motion Abnormality to Actilyse by echocardiography according to the presence of Type 2 Diabetic in patients with Myocardial Infarction.

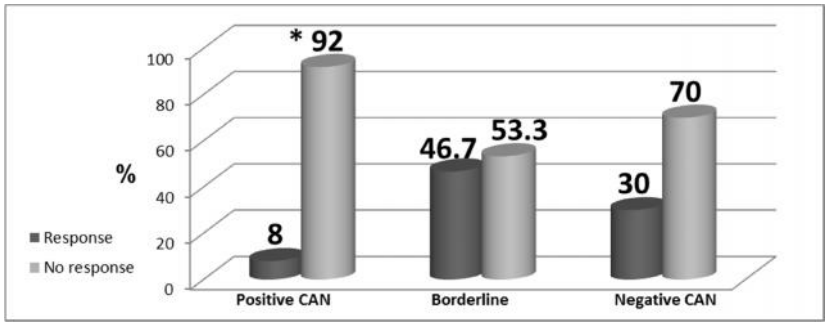
There was a statistically highly significant relationship (p< 0.01) between the increase in the duration of Type 2 Diabetes Mellitus (T2DM) ≥ 9 years and the decrease response of the regional wall motion abnormality (RWMA) shown by echocardiography to treatment of myocardial infarction by Actilyse (Figure 2).




**= (p< 0.01).

**FIGURE 2:** Response of Regional Wall Motion Abnormality to Actilyse by echocardiography according to the duration of Type 2 Diabetic in years in patients with Myocardial Infarction.

There was a statistically significant relationship (p< 0.0001) between the high admission glycemia in mg/dl (RBS: ≥ 200 mg/dl) and the decrease in the response of the regional wall motion abnormality (RWMA) shown by echocardiography to treatment of myocardial infarction by Actilyse. While the resulted data illustrated in figure (3) revealed that there was a statistically significant relationship (p< 0.05) between the presence of Cardiovascular Autonomic Neuropathy and the decrease in the response of the Regional Wall Motion Abnormality (RWMA) by echocardiography to treatment of myocardial infarction by Actilyse.




*= (p< 0.05)

**FIGURE 3:** Response of RWMA (by echocardiography) to treatment of myocardial infarction (Actilyse) according to the presence of CAN in Type 2 Diabetic patients with Myocardial Infarction.

Resulted data illustrated in table (1) revealed that there was a statistically significant difference ($p< 0.05$) and ($p< 0.01$) between the mean of the EF% and the presence of Type 2 Diabetes Mellitus in patients with Myocardial Infarction.

**TABLE 1:** Mean of The Ejection Fraction (EF %) and The Presence of Type 2 Diabetes Mellitus in patients with Myocardial Infarction.

| Variable | DM | No. | Mean± SD | P- value |
|---|---|---|---|---|
| EF1 | T2DM | 70 | 46.37 ± 10.898 | |
| | Non DM | 41 | 51.15 ± 10.790 | P<0.05 |
| EF2 | T2DM | 70 | 47.43 ± 11.291 | |
| | Non DM | 41 | 54.22 ± 12.007 | P<0.01 |

EF1: Ejection Fraction by echocardiography before treatment.
EF2: Ejection Fraction by echocardiography after treatment.
T2DM: Type 2 Diabetes Mellitus.
Non DM: Not Diabetic.
No.: patients' number.
SD: standard deviation.

There was a statistically extremely significant relationship ($p< 0.0001$) between the mean of the EF% and the response of the regional wall motion abnormality (RWMA) by Echocardiography to treatment of myocardial infarction. (Table 2).

**TABLE 2:** Mean of The Ejection Fraction (EF %) and The Response of The Regional Wall Motion Abnormality (RWMA) by Echocardiography to Treatment of myocardial infarction**.**

| Variable | RWMA | No. of patients | Mean ± SD | P- value |
|---|---|---|---|---|
| EF2 | Response | 47 | 57.38 ± 7.933 | |
| | No Response | 64 | 44.47 ± 11.507 | P<0.001 |

RWMA: Regional Wall Motion Abnormality
EF2: Ejection Fraction by echocardiography after treatment

Our resulted data illustrated in table (3) shows that there was a significant difference ($p< 0.0001$) between the presence or absence of Type 2 Diabetes Mellitus and the mean of Troponin titer after treatment and there was no significant difference ($p>0.05$) between the presence or absence of Type 2 Diabetes Mellitus and the mean of Troponin titer before treatment.

**TABLE 3:** The relationship between the presence of Type 2 Diabetes Mellitus and the mean of Troponin titer before and after Actilyse

| Variable | DM | No. of patients | Mean ng/I± SD | P- value |
|---|---|---|---|---|
| Troponin Pre-treatment | T2DM | 70 | 1.4041 ± 0.47758 | |
| | Non DM | 41 | 1.4602 ± 0.55288 | NS |
| Troponin Post- treatment | T2DM | 70 | 3.4964 ± 1.05894 | |
| | Non DM | 41 | 4.5968 ± 1.37046 | 0.0001 |

T2DM: Type 2 Diabetes Mellitus. Non DM: Not Diabetic**.**

## DISCUSSION

There was a statistically significant relationship ($p< 0.0001$) between Type 2 diabetes mellitus (T2DM) and decrease in the response of the regional wall motion abnormality (RWMA) shown by echocardiography to the treatment of myocardial infarction by actilyse, as 81.3% of T2DM had no response (Figure 1) this consistent with [3, 5, 21] and the possible mechanisms that influence the increased risk in diabetes for cardiovascular events include, insulin resistance, changes in endothelial function, dyslipidemia, chronic inflammation and release of mediators of inflammation, procoagulability and impaired fibrinolysis. Diabetic patients usually have poor coronary collateral circulation compared with not diabetic patients a fact that would augment the amount of jeopardized myocardium on occlusion of the supplying artery. The high level of oxidative stress in diabetes may also play an important role in the development and progression of myocardial remodeling and depression seen in diabetic patients[42]. Also the increase blood sugar in Type 2 Diabetic patients with STEMI is associated with an adverse prognosis and may induce a pro-thrombotic state and therefore be of influence on thrombolysis in Myocardial Infarction flow before percutaneous coronary intervention [37]. There was a statistically highly significant relationship ($p< 0.01$) between the increase in the duration of Type 2 Diabetes Mellitus (T2DM) ≥ 9 years and the decrease in the response of the regional wall motion abnormality (RWMA) shown by echocardiography to treatment of myocardial infarction by Actilyse (Figure 2) and that is because we found that when the duration of

Type 2 Diabetes Mellitus ≥ 9 years the patient develop cardiovascular autonomic neuropathy which Subsequently has adverse effect on the response of myocardial infarction to Actilyse[41]. Resulted data illustrated in Figure (3) revealed that there was a statistically significant association ($p<0.05$) between the presence of Cardiovascular Autonomic Neuropathy and the decrease in the response of the Regional Wall Motion Abnormality (RWMA) by echocardiography to treatment of myocardial infarction by Actilyse and this consistent with [17, 28, 29, 30] and this is because CAN itself leads to a reduced cardiac ejection fraction and systolic dysfunction and decreased diastolic filling, and increased contributions from insulin resistance, obesity, and hypertension in T2DM, also hyperglycemia is associated with reduced thrombolysis in Myocardial Infarction. The initial augmentation in cardiac sympathetic activity (as a result of CAN) with subsequent abnormal norepinephrine signaling and metabolism, increased mitochondrial oxidative stress [13], and calcium-dependent apoptosis[16] may contribute to increase myocardial injury and decrease the response to Actilyse.

Resulted data illustrated in Table (1) revealed that there was a statistically significant relationship ($p< 0.05$) and ($p< 0.01$) between the mean of the EF% and the presence of Type 2 Diabetes Mellitus in patients with Myocardial Infarction and this consistent with [10, 24, 33] and disagree with [20] and this was due to that the diabetic patients have reduced left ventricular systolic and diastolic function and these abnormalities are correlated with the duration of diabetes and with diabetic microangiopathies, like neuropathy and it is the strongest independent correlate of left ventricular diastolic dysfunction[24]. Resulted data illustrated in Table (2) revealed that there was a statistically extremely significant association ($p< 0.0001$) between the mean of the EF% and the response of the regional wall motion abnormality (RWMA) by Echocardiography to treatment of myocardial infarction (by Actilyse) and this agree with[4,8,14] and disagree with [12] and the explanation of this correlation is that after myocardial infarction there is a reduction in myocardial function in all segments, including the noninfarct-related lateral segments, and this may be considered an adaptive mechanism. Reduced function in the noninfarct-related myocardium will lead to redistribution of regional wall stress. Reduction of wall stress in the infarct-related ventricle is important, because wall stress determines oxygen consumption and is a stimulus for ventricular remodeling[22] and so that both ejection fraction and regional wall motion affected in a Harmonious way.

Our resulted data illustrated in Table (3) shows that there was an extremely significant association ($p< 0.0001$) between the presence of Type 2 Diabetes Mellitus or not and the mean of Troponin titer after treatment and there was no significant relationship ($p>0.05$) between the presence of Type 2 Diabetes Mellitus or not and the mean of Troponin titer before treatment and this consistent with [2,23,38] The explanation is that T2DM remains a major risk factor for poor short and long-term outcome even after thrombolytic therapy and the presence of diabetes mellitus is associated with larger infarct size, measured by nuclear imaging techniques, which is attributed to more extensive coronary artery disease, impairment of collateral recruitment and poorer restoration of tissue perfusion as compared with non-diabetic patients .This is reflected on the Troponin level (as a response to Actilyse) after the treatment of MI. For unknown reasons, thrombolytic therapy and direct PCI were less effective in Troponin - positive patients. It was speculated that the hazard associated with Troponin was due to more severe ischemic damage, less myocardial salvage, impaired microvascular perfusion, refractory thrombi, or a more thrombophilic milieu [11]. It is intriguing to speculate that Troponin may represent a more reliable marker of duration of ischemia than the subjective report of duration of pain. The accuracy of the latter is limited by different thresholds of pain perception, episodes of spontaneous reflow and occlusion, the alleviation of ischemia by collateral blood flow, and ischemic preconditioning[3]. Because pain perception and pain thresholds are altered in diabetes mellitus, it is not surprising that in our study, diabetic patients presented later and have less benefit of Actilyse represented by decrease mean of Troponin after treatment compared with non-diabetic patient.

## REFERENCES


[1]. ADA (American Diabetes Association) (2013) Standards of medical care in diabetes - 2013. Diabetes Care. 2013:36 (supp l 1):S11-S66.

[2]. Alegria, J.R., Miller, T.D., Gibbons, R.J., Yi, Q.L., Yusuf, S. (2007) Infarct size, ejection fraction, and mortality in diabetic patients with acute myocardial infarction treated with thrombolytic therapy. Am Heart J. 2007:154(4):743–750.

[3]. Angeja, B.G., de Lemos, J., Murphy, S.A., Marble, S.J., Antman, E.M., Cannon, C.P., Braunwald, E., Gibson, C.M.(2002) Impact of diabetes mellitus on epicardial and microvascular flow after fibrinolytic therapy. Am Heart J. 144(4):649–656.

[4]. Brian, D. Hoit.(2011) Advances in Cardiovascular Imaging, Strain and Strain Rate Echocardiography and Coronary Artery Disease. 4: 179-190, doi: 10.1161/CIRCIMAGING.110.959817.

[5]. Buyken, A.E., von Eckardstein, A., Schulte, H., Cullen, P., Assmann, G. (2007)Type 2 diabetes mellitus and risk of coronary heart disease: results of the 10-year follow-up of the PROCAM Study. Eur J Cardiovasc Prev Rehabil. 14:230–236.

[6]. Colledge Nicki, R., Brian, R., Walker Stuart, H. Ralston (2010) Davidson's Principles and Practice of Medicine 21st Edition:577-579.

[7]. David L Coven (2013) Acute Coronary Syndrome. http://emedicine.medscape.com.

[8]. Delgado, V., Mollema, S.A., Ypenburg, C., Tops, L.F., van der Wall, E.E., Schalij, M.J., Bax, J.J.(2008) Relation between global left ventricular longitudinal strain assessed with novel automated function imaging and biplane left ventricular ejection fraction in patients with coronary artery disease. J Am Soc Echocardiogr.2008:21:1244–1250.

[9]. Evangelos Giannitsis, Margit Müller-Bardorff, Stephanie Lehrke, Uwe Wiegand, Ralph Tölg, R., Weidtmann, B.; Hartmann, F.; Richardt, G., Katus, H.K. (2001) Admission Troponin T Level

Predicts Clinical Outcomes, TIMI Flow, and Myocardial Tissue Perfusion After Primary Percutaneous Intervention for Acute ST-Segment Elevation Myocardial Infarction . Circulation.; 104: 630-635.

[10]. From, A.M., Leibson, C.L., Bursi, F., Redfield, M.M., Weston, S.A., Jacobsen, S.J., Rodeheffer, R.J., Roger, V.L. (2006) Diabetes in heart failure: prevalence and impact on outcome in the population. Am J Med 2006; 119: 591–599. Cross Ref Medline Order article via Infotrieve Web of Science.

[11]. Frostfeldt, G., Lindahl, B., Nygren, A. Venge P, Wallentin L. (1999) Possible reasons for the prognostic value of troponin T on admission in patients with ST-segment elevation myocardial infarction. Eur Heart J. 1999; 20 (suppl P): P-2110.

[12]. Germain, P., Roul, G., Constantinesco A. (1996) Comparison between abnormalities in segmental endocardial motion and abnormalities in segmental wall thickening after anterior myocardial infarction. a cine magnetic resonance study. Eur Heart J. 17 1996:1350-1361.

[13]. Givertz, M.M., Sawyer, D.B., Colucci, W.S. (2001) Antioxidants and myocardial contractility: illuminating the "Dark Side" of beta-adrenergic receptor activation? Circulation 2001; 103: 782–783.

[14]. Gjesdal, O., Hopp, E., Vartdal, T., Lunde, K., Helle-Valle, T., Aakhus, S., Smith, H. J. (2007) Global longitudinal strain measured by two-dimensional speckle tracking echocardiography is closely related to myocardial infarct size in chronic ischaemic heart disease. Clin Sci. (Lond).113:287–296.

[15]. Hoogwerf Byron, J.(2010) Review complications of diabetes mellitus and Diabetes Mellitus: Disease Management. Dept of Endocrinology, Diabetes and Metabolism, Desk-53, 9500 Euclid Ave, Cleveland, OH, USA 44195; Email: hoogweb@ccf.org.

[16]. Iwai-Kanai, E., Hasegawa, K., Araki, M., Kakita, T., Morimoto, T., Sasayama, S. (1999) alpha- and beta-adrenergic pathways differentially regulate cell type-specific apoptosis in rat cardiac myocytes. Circulation, 100: 305– 311.

[17]. Julian W. Sacre, Bennett Franjic, Christine L. Jellis, Carly Jenkins, Jeff S. Coombes, Thomas H. Marwick (2010) Association of Cardiac Autonomic Neuropathy With Subclinical Myocardial Dysfunction in Type 2 Diabetes, jacc: cardiovascular imaging , vol. 3, no. 12, 2010 dece mber: 1207 – 15.

[18]. Kaddoura, S. (2009) Echo Made Easy. Second edition. Churchill Livingston, Chapters 2, 3.

[19]. Lahrmann, H., Rocha, I., Struhal, W., Thijs, R.D., Hilz, M. (2011) Diagnosing Autonomic Nervous System Disorders – Existing Guidelines and Future Perspectives, European Neurological Review, 2011;6(1):52-56.

[20]. MacDonald, M.R., Petrie, M.C., Varyani, F., Ostergren, J., Michelson, E.L., Young, J.B., Solomon, S.D., Granger, C.B., Swedberg, K., Yusuf, S., Pfeffer, M.A., McMurray, J.J. (2008) Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure. Eur Heart J. 29: 1377–1385.

[21]. Marco A. López Hernández (2013) Hyperglycemia and Diabetes in Myocardial Infarction.

[22]. Marco J.W Götte, Albert C van Rossum, Jos W.R Twisk, Joost P.A. Kuijer, J. Tim Marcus, Cees A Visser (2001) Quantification of regional contractile function after infarction: strain analysis superior to wall thickening analysis in discriminating infarct from remote myocardium.

[23]. Matetzky, S., Sharir, T., Domingo, M., Noc, M., Chyu, K.Y., Kaul, S., Eigler, N., Shah, P.K., Cercek, B. (2006) Elevated troponin I level on admission is associated with adverse outcome of primary angioplasty in acute myocardial infarction. Circulation. 2000; 102: 1611–1616.

[24]. Mishra, T.K., Rath, P.K., Mohanty, N.K., Mishra, S.K.(2008) Left ventricular systolic and diastolic dysfunction and their relationship with microvascular complications in normotensive, asymptomatic patients with type 2 diabetes mellitus, Indian Heart J. 2008 Nov-Dec;60(6):548-53.

[25]. Patrick Kleina, Eduard, R. Holmanb, Michel, I.M. Versteegha, Eric Boersmac, Harriette F. Verweyb, Jeroen J. Baxb, Robert, A. E., Dion Robert, Klautz J. M. (2008) Wall motion score index predicts mortality and functional result after surgical ventricular restoration for advanced ischemic heart failure. Presented at the 22nd Annual Meeting of the European Association for Cardio-thoracic Surgery, Lisbon, Portugal, September 14–17, 2008.

[26]. Patrick, T. O'Gara, Frederick ,G. Kushner, Deborah, D. Ascheim, Donald, E. Casey, Mina, K. Chung, James, A. de Lemos, Steven M. Ettinger, James, C. Fang, Francis M., Fesmire, Barry A. Franklin (2013) ACCF/AHA Guideline for the Management of ST Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines.

[27]. Phulpoto, J. A. & Siyal, J. K. (2012) Frequency of cardiac autonomic neuropathy in type 2 diabetic patients. Rawal Medical Journal: Vol. 37. No. 4, October-December 2012.

[28]. Poirier, P., Bogaty, P., Philippon, F., Garneau, C., Fortin, C., Dumesnil, J.G. (2003) Preclinical diabetic cardiomyopathy: relation of left ventricular diastolic dysfunction to cardiac autonomic neuropathy in men with uncomplicated well-controlled type 2 diabetes. Metabolism 2003;52: 1056–61.

[29]. Pop-Busui, R.., Gregory, W., Evans, M.A., Hertze,l C. Gersten, Vivian, F., Jerome, L.F., Byron, J.H., Saul, G., Richard, H.G., Marshall, A.C., Ronald, P. and the ACCORD study group (2010) Effects of cardiac autonomic dysfunction on mortality risk in the action to control cardiovascular risk in diabetes (ACCORD) trial. Diabetes Care 2010; 33: 1578–1584.

[30]. Pop-Busui, R., Kirkwood, I., Schmid, H., Marinescu, V., Schroeder, J., Larkin, D., Yamada, E., Raffel, D.M., Stevens, M.J. (2004) Sympathetic dysfunction in type 1 diabetes: association with impaired myocardial blood flow reserve and diastolic dysfunction. J Am Coll Cardiol 2004; 44: 2368– 2374.

[31]. Porter A., Assali A. R., Zahalka A. Iakobishvili, Z., Brosh, D., Lev, E.I., Mager, A., Battler, A., Kornowski, R., Hasdai, D. (2008) Impaired fasting glucose and outcomes of ST-elevation acute coronary syndrome treated with primary percutaneous intervention among patients without previously known diabetes mellitus, Am Heart J 2008 155 (284-289).

[32]. Rasoul, S., Ottervanger, J.P., de Boer, M.J., Dambrink, J.H., Hoorntje, J.C., Marcel Gosselink A.T., Zijlstra, F., Suryapranata, H., van 't Hof AW; Zwolle Myocardial Infarction Study Group. (2009) Predictors of 30-day and 1-year mortality after primary percutaneous coronary intervention for ST-elevation myocardial infarction, Coron Artery Dis 2009 20 (415-421).

[33]. Richard, M Cubbon, Brook Adams, Adil Rajwani, Ben, N., Mercer, Peysh A Patel, Guy Gherardi, Christopher P Gale, Phillip D Batin, Ramzi Ajjan, Lorraine Kearney, Stephen B Wheatcroft, Robert J Sapsford, Klaus K Witte and Mark T Kearney. (2013) Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology, Diabetes and Vascular Disease Research January 24, 14791641 12471064.

[34]. Rimmerman Curtis, M. (2013) www.clevelandclinicmeded.com/.../diseasemanagement/.../coronary-arter.

[35]. Roe, M.T., Messenger, J. C., Weintraub, W. S., Cannon, P.C., MD, Fonarow, G.C ., Dai, D., Chen, A.Y., Klein, L.W., Masoudi, F.A., McKay, C., Hewitt, K., Brindis, R.G., M.D, Peterson, E.D., Rumsfeld, J.S. (2010) Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention, J Am Coll Cardiol. 56: 254-263.

[36]. Thygesen, K., Alpert, J. S., Jaffe, A.S., Simoons, ML., Chaitman, B.R., and White, H. D. ( 2012) Third universal definition of myocardial infarction, Circulation 126: 2020-2035.

[37]. Timmer, J.R., Ottervanger, J.P., de Boer, M.J., Dambrink, J.H., Hoorntje, J.C., Gosselink, A.T., Suryapranata, H., Zijlstra, F., van 't Hof, A.W., Zwolle Myocardial Infarction Study Group (2005) Hyperglycemia is an important predictor of impaired coronary flow before reperfusion therapy in ST-segment elevation myocardial infarction, J Am Coll Cardiol. 2005 Apr 5:45(7):999-1002.

[38]. Vassilios, N. Nicolaou, John, E., Papadakis, Christina Chrysohoou, Demosthenes B. Panagiotakos, Xenofon Krinos, Panagiotis D. Skoufas and Christodoulos Stefanadis(2008) The Prognostic Significance of Serum Glucose Levels After the Onset of Ventricular Arrhythmia on In-Hospital Mortality of Patients with Acute Coronary Syndrome, Rev Diabet Stud. 2008 Spring; 5(1): 47–51.

[39]. Vinik, A., Maser, R., Ziegler, D.(2011) Autonomic Imbalance: Prophet of Doom or Scope for Hope? Diabet Med 2011; 28: 643–651.

[40]. Vinik, A.I., Ziegler, D. (2007) Diabetic cardiovascular autonomic neuropathy. Circulation, 115: 387–397.

[41]. W Todd Cade (2008) Diabetes Related Microvascular and Macrovascular Diseases in the Physical Therapy Setting, Phys Ther. 2008 November; 88(11): 1322–1335.

[42]. Walaa Adel and Wail Nammas (2010) Predictors of contractile recovery after revascularization in patients with anterior myocardial infarction who received thrombolysis, Int J Angiol. 2010 Summer; 19(2): e78–e82.

[43]. WHO Fact sheet N8310, updated June 2011, http://www.who.int/mediacentre/factsheets/fs310/en/index.html.