www.jmscr.igmpublication.org

Impact Factor 3.79
Index Copernicus Value: 5.88
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: http://dx.doi.org/10.18535/jmscr/v3i12.14

IGM Publication Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

# Intensive Insulin Therapy versus Conventional Insulin Therapy in Post Myocardial Infarction Left Ventricular Remodelling

Authors
**Lobna Farag El Tony[+], Salah Abdel-Azeem Argoon[+], Ahmad B. Elden[×], Walaa A. Khalifa[+]**
[+]Endocrinology Unit, ×Critical Care Unit
Department of Internal Medicine, College of Medicine, Assiut University, Egypt
Corresponding Author
**Ahmad B. Elden**
Assiut University, P.O. Box 71111 Assiut, Egypt
Email: *ahmadbahie@yahoo.com Telephone: +20-1009820300 Fax: +20-2333327*

**ABSTRACT**

**Objectives***: This study aimed to assess left ventricular (LV) remodelling in acute myocardial infarction (AMI) patients presented with admission hyperglycaemia (AH) with or without history of diabetes treated with either intensive insulin therapy (IIT) or conventional insulin therapy (CIT) and to compare the effect of both therapies on LV remodelling.*

**Patients and Methods:** *We conducted a prospective cohort study and analysed LV remodelling in 77 AMI patients. AH was defined as a glycaemia on admission > 140 mg/dl. We randomly assigned patients either IIT or CIT. Systematic echocardiographic study was performed at baseline and at 12 months later.*

**Results:** *The changes in LV end-diastolic volume (LVEDV) from baseline to 12 months follow up was 37.31±41.4 $cm^3$in the CIT group and 39.49±41.18 $cm^3$ in the IIT group (p value NS).When LV remodelling was defined as a >20% increase in LVEDV, it was observed in 94.4% of CIT group and in 91.3% in IIT group (p value NS).*

**Conclusions:** *We concluded that IIT hadn't any significant difference than CIT on post AMI remodelling.*

**Keywords:** *admission hyperglycaemia, post myocardial infarction remodelling, intensive insulin therapy*

## INTRODUCTION

Patients with or without a prior history of diabetes mellitus may present with hyperglycemia during AMI [(1)]. Several studies have reported an association between elevated blood glucose upon admission and subsequent increased adverse events [(2)]. Among the pathophysiological mechanisms that may lead to an adverse prognosis after AMI is LV remodelling. LV remodelling is a dynamic and complex process that occurs in response to damage to the myocardium after AMI [(3)].

*Raffaele et al* have shown that hyperglycemia during AMI is associated with increased levels of inflammatory markers, including C-reactive protein and interleukin-18 [(4)]. Animal studies showed increased

levels of oxidative stress indexes in the ischemic heart tissue of hyperglycemic mice. Both inflammation and oxidative stress correlated strictly with the glucose levels. These studies suggested that hyperglycemia by amplifying oxidative stress and inflammatory responses to myocardial ischemia might affect the prognosis of AMI [5].

It is evidenced that the use of insulin to lower glucose concentrations decreases mortality in diabetic patients who have AMI [6]. Insulin suppresses reactive oxygen species generation, tissue factor, and plasminogen activator inhibitor type 1 concentrations, also induces nitric oxide generation and inhibits platelet agreeability [7]. It is demonstrated that an insulin infusion associated with glucose concentrations below 140 mg/dl was potentially cardioprotective as insulin infusion leads to a marked reduction in plasma C-reactive protein and serum amyloid A concentrations by > 40% at 24 and 48 h [8]. Also a Serbian study randomized patients with AMI within the first 3 h of chest pain to an insulin infusion demonstrated 88% reduction in major adverse clinical events and an improvement in left ventricular ejection fraction [9].

The question of whether hyperglycemia is a mediator or marker of adverse outcomes remains unclear. Recommendations are being developed for strict glucose management in all hospitalized patients; however, current guidelines do not suggest specific insulin regimen for glucose control in AMI.Moreoverthereis a lack of knowledge about the effect of specific insulin regimens for glucose control on post AMI remodelling.We conducted this study to test the hypothesis that intensive insulin therapy (IIT) has better post MI remodelling than conventional therapy (CIT).

## PATIENTS AND METHODS

We conducted a prospective cohort study, carried out on 77 patients with AMI admitted in internal medicine department CCU at Assiut University Hospital, between January 2010 and March 2014.We included patients with blood glucose level > 140 mg/dl [10], with or without history of DM, presented by the first AMI within 12 h from symptom onset, treated by thrombolytic agents, with at least 50% resolution of ST segment elevation and infarct zone comprised at least three hypokinetic LV segments by echocardiography. The diagnosis of AMI was based on prolonged chest pain lasting ≥ 30 min, ST segment elevation ≥ 2 mm in at least two contiguous electrocardiographic (ECG) leads of $v_1$ to $v_3$ or ≥ 1 mm in at least two contiguous other leads, and a more than threefold increase in serum creatine kinase (CK) level [11]. We then classified reperfused patients into two groups; completely reperfused with resolution of ST elevation by > 70% [12] and partially reperfused with ST resolution by > 50-70%.We excluded patients with inadequate echocardiographic image quality, age ≥ 85 years, life-limiting non-cardiac disease, significant valvular disease, prior Q-wave MI, presence of LBBB. Written consents were obtained from most of the participants; illiterate participants gave their consent by finger prints. The study was approved by the ethical committee of college of medicine in Assiut University. All patients received treatment of AMI according to 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction [13]. All patients were randomized (by computer based randomization) to be treated with either IIT or CIT.IIT included continuous insulin infusion using short acting insulin (Humulin R), (50 units in a 50 ml using 0.9 % sodium chloride in a 50 ml syringe), adjusted to maintain BG: 110 to < 140mg/dl. The infusion lasted until the stable glycemic goal was maintained for at least 4 hs. Total daily dose (TDD) was calculated as follow: units of insulin per hour infused in the last 2h x 24. 50% the TDD was taken as basal insulin (Glargine) while the remaining 50% was divided as premeal doses (Humulin R). CIT included the use of 2/3 of weight based dose of premixed insulin SC before breakfast & 1/3 SC before dinner.BG level was measured hourly during insulin infusion and at average 4 hours intervals after then and in the CIT regimen. According to ADA report 2009, hypoglycemia was defined as BG level < 50 mg/dl.Serum potassium was monitored at 6 hours intervals in each group.

All echocardiograms were performed with an HDI 5000 instrument (Philips Medical Systems, Bothell, Washington, USA) equipped with a broad band harmonic transducer. A standard echocardiography was used within the 3±2 days of admission based on apical four and two-chamber views; 2D echocardiograms of the LV short axis were recorded at three levels: mitral valve, mid-papillary muscle level, and apex. All echocardiograms were analyzed at Assiut University Internal Medicine Echo Laboratory. LV volumes and ejection fraction (EF) was calculated using a modified Simpson's rule. The mean value of three measurements of the technically best cardiac cycles was taken from each examination. To evaluate regional systolic function, the left ventricle was divided according to a 16-segment model as recommended by the American Society of Echocardiography 2002. For each segment, wall motion was scored from 1 (normal) to 4 (dyskinetic) and a global segmental wall motion score (SWMS) was calculated as the average over 16 segments[14]**.** Conventional echocardiography was performed at a mean of twelve months follow up. Significant global LV remodelling was defined as a Delta LVEDV > 20% from the acute stage ***(15).***The primary endpoint was the percentage change in LV end diastolic volume (% LVEDV) by > 20% after a mean of twelve months' follow up.

**STATISTICAL ANALYSIS**

All calculations were performed with the computer program SPSS version 16.Continuous variables were described as mean ± standard deviation and frequencies were expressed as percentages. Continuous variables were compared among the groups of patients with T test. A p value < 0.05 was considered statistically significant.

**RESULTS**

The study included 83 patients with BG level > 140 mg/dl with or without history of DM and were randomly assigned to either CIT or IIT. 41 patients were assigned in the CIT group and 42 patients were assigned in the IIT group. During follow up one patient in each group died while one patient lost in the CIT group and 3 patients in IIT. Patients' characteristics of each group are shown in table (1).The study showed insignificant differences between groups as regard age, gender, risk factors, history of previous angina and onset of angina. There were insignificant differences between groups as regard BMI, admission hemodynamic parameters. ECG data showed insignificant difference between groups in ECG infarction size estimated by number of involved leads and summation of ST elevations. Also, there was insignificant difference in the degree of reperfusion between groups. Laboratory data showed insignificant differences in LDL, serum creatinine, peak CK and admission BG level. Figure (1) shows that there was a statistically significant lower BG level in the IIT group than CIT in the first day but with insignificant differences in the following admission days. The IIT group had a significantly higher attacks of hypoglycemia and hypokalemia than CIT group (Table 2). Echocardiographic data showed insignificant differences between groups in the baseline and follow up diastolic and systolic volumes, EF and SWMS also, there was insignificant difference in the incidence of LV remodelling (Table 2 and figure 2).

**DISCUSSION**

Both groups showed a good matching with insignificant differences in all patients' characteristics, admission laboratory and ECG data, which minimized any confounders.

Both the conventional insulin therapy and intensive one had a statistically insignificant Delta LVEDV differences. Studies that have infused insulin in hyperglycemic patients with AMI with the intent to reduce glucose, including the original DIGAMI, DIGAMI-2 and HI-5 trials.While the original DIGAMI study was able to demonestrate a decrease in both mortality and BG levels, the DIGAMI-2 and HI-5 studies show no

such a significant decrease [16]. Despite these shortcomings, insulin infusion was shown to lower the risk of heart failure (absolute risk reduction of 10%), reinfarction (absolute risk reduction of 3.4%) [17], and showed improvement in left ventricular ejection fraction [9].

**Table (1):** Baseline characteristics, ECG and laboratory data of each studied group

| Variables | CIT | IIT | P-value |
|---|---|---|---|
| **Age ≥ 60 years (n)** | 19 | 20 | 0.731 |
| **Male (n)** | 28 | 31 | 0.310 |
| **Previous angina (n)** | 3 | 3 | 0.974 |
| **Onset of angina (h)** | 4.69 ± 1.75 | 4.74 ± 1.67 | 0.909 |
| **Hx of HTN (n)** | 9 | 7 | 0.615 |
| **Hx of DM (n)** | 22 | 15 | 0.137 |
| **Dyslipidemia (%)** | 1 | 0 | 0.320 |
| **Smoking (n)** | 22 | 23 | 0.714 |
| **BMI(kg/m2)** | 29.70 ± 4.56 | 31.45 ± 4.77 | 0.105 |
| **HR(b/min)** | 89.72 ± 12.42 | 86.34 ± 11.80 | 0.519 |
| **Systolic BP(mmhg)** | 113.85 ± 18.86 | 123.68 ± 26.35 | 0.063 |
| **Diastolic BP(mmhg)** | 72.56 ± 11.63 | 77.90 ± 16.13 | 0.100 |
| **Killip Class III (%)** | 10.3 | 18.4 | 0.591 |
| **Sum ST (mm)** | 29.74 ± 6.95 | 31.21 ± 7.33 | 0.436 |
| **>70% resolution** | 30 (76.9%) | 24 (63.2%) | 0.187 |
| **Number of leads** | 5.89 ± 1.76 | 6.01 ± 1.35 | 0.113 |
| **LDL (mg/dl)** | 129.01 ± 17.94 | 131.90 ± 16.67 | 0.204 |
| **SCR(µmol/l)** | 104.92 ± 33.28 | 112.32 ± 37.26 | 0.361 |
| **Peak CK(U/l)** | 4467.26 ± 1555.87 | 4945.58 ± 1365.40 | 0.156 |

CIT: conventional insulin therapy, IIT: intensive insulin therapy, n: number, h: hour, HTN: hypertension, DM: diabetes mellitus, BMI: body mass index, HR: heart rate, BP: blood pressure, sum ST, summation of ST segment elevation, SCR: serum creatinine.

*Raffaeleet al*speculated that tight glycemic control during the ischemic insult might be associated with reduction of post-infarction remodelling astight glycemic control (128 ± 15 mg/dl) in the immediate post-infarcted period, for almost 3 days, was associated with significant reduction of inflammatory cytokines, nuclear factor κB (NF κB) activation, oxidative stress, and apoptotic cell death[18].

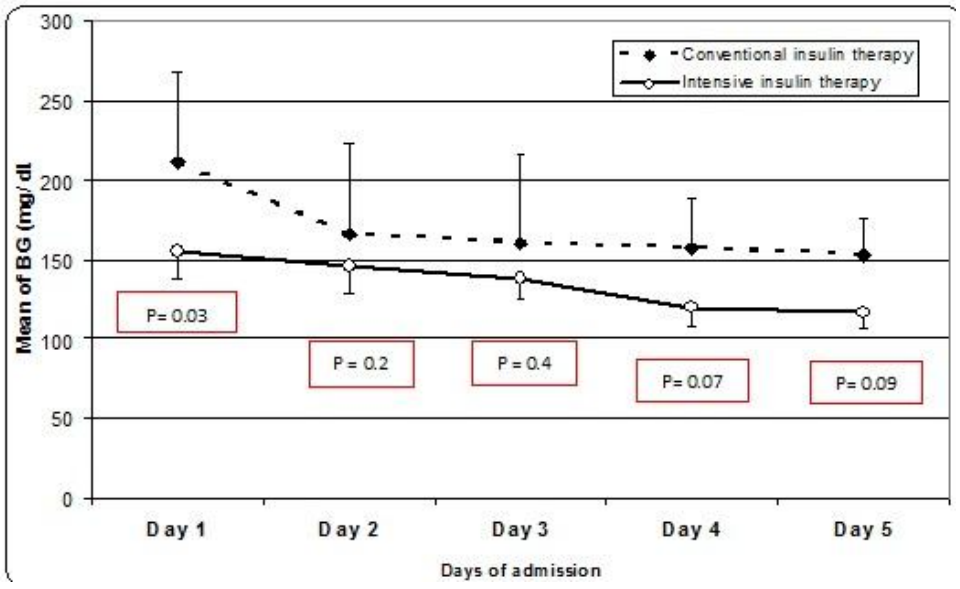


**Figure (1):** Mean, stander deviation of BG level in each day of admission in each studied group and p values

**Table (2):** Admission BG, hypoglycemic attacks and serum potassium in each studied group

| Variables | CIT | IIT | P-value |
|---|---|---|---|
| **Admission BG (mg/dl)** | 255.40 ± 64.39 | 263.63 ± 51.16 | 0.300 |
| **Hypoglycemic attacks (n)** | 12 | 9 | 0.02 |
| **Serum Potassium** | 4.5 ± 66 | 3.4 ± 32 | 0.049 |

CIT: conventional insulin therapy, IIT: intensive insulin therapy, n: number, BG: blood glucose

Because oxidative stress has been shown to induce inflammation through NF κB activation, *Raffaele et al* speculated that tight glycemic control by reducing oxidative stress might inhibit the cytokine expression and apoptosis in peri-infarcted area through NF κB inhibition and that might reduce apoptosis in peri-infarcted areas and therefore remodelling in AMI patients***(18).***

**Table (3):** Echo parameters in each studied group

| Variables | CIT | IIT | P-value |
|---|---|---|---|
| **LVEDV ($cm^3$)** | | | |
| **Baseline LVEDV** | 96.11 ± 26.67 | 93.31 ± 28.25 | 0.554 |
| **Follow up LVEDV** | 133.42 ± 68.07 | 132.80 ± 69.43 | 0.443 |
| **Delta LVEDV** | 37.31±41.4 | 39.49±41.18 | 0.143 |
| **> 20% change** | 17(94.4%) | 21(91.3%) | 0.066 |
| **LVESV ($cm^3$)** | | | |
| **Baseline LVESV** | 48.09 ± 19.86 | 56.68 ± 22.12 | 0.077 |
| **Follow up LVESV** | 92.31 ± 65.43 | 118.13 ± 62.59 | 0.092 |
| **EF (%)** | | | |
| **Baseline EF** | 43.26 ± 9.45 | 39.63 ± 7.88 | 0.071 |
| **Follow up EF** | 17.30 ± 10.13 | 16.36 ± 8.76 | 0.662 |
| **SWMS** | | | |
| **Baseline SWMS** | 1.79 ± 0.18 | 1.77 ± 0.18 | 0.339 |
| **Follow up SWMS** | 0.38 ± 0.24 | 0.35 ± 0.21 | 0.120 |

CIT: conventional insulin therapy, IIT: intensive insulin therapy, LVDEV: left ventricular end diastolic volume, Delta: present of changes between baseline and follow up, LVESV: left ventricular end systolic volume, EF: ejection fraction, SWMS: segmental wall motion score.

*Raffaele et al* study only suggested that, reduced inflammatory, oxidative stress and apoptotic markers might be associated with reduction in the LV remodelling by intensive insulin therapy. That study was not a follow up study comparing the incidence rate of remodelling between the two types of treatment, and their suggestion should be tested by a follow up study with a control group on conventional insulin therapy

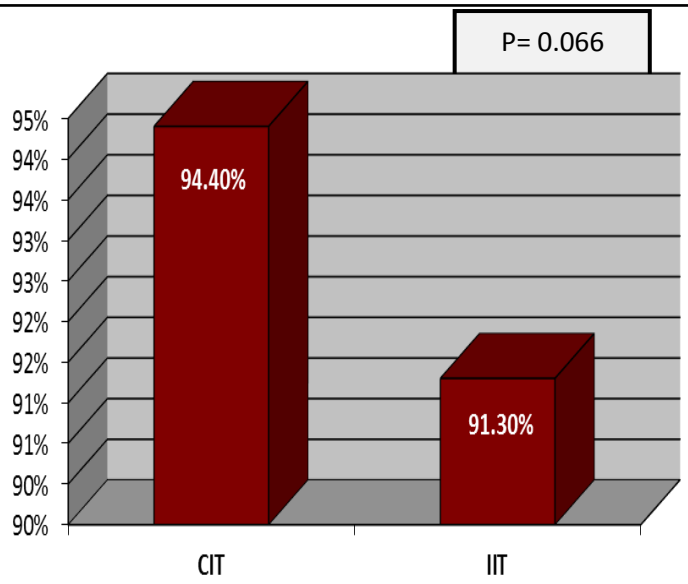


**Figure (2):** Percentage of patients developed LV remodeling after 12 months in each studied group.

Unfortunately, our follow up study failed to show a statistically significant difference between both types of therapy on post infarction remodelling. We can explain that by failure of both therapies to maintain a continuously tight control target between 110 to <140mg/dl in some hourly scheduled interval measurements (although both group daily means masked that fact). The failure to maintain target BG can be explained partly by the short duration of usage insulin infusion (only 4 hs after reaching the target) that, could followed by rebound hyperglycemia by the severe insulin resistant state in AMI, while DIGAMI study used it for at least 24 hs after achieving the target. Another factor is that, cardiac therapies took the priority over insulin therapy so, the delay in starting insulin therapy by the using of pain killers medications, hemodynamic stabilizing drugs and thrombolytic therapy, all can attenuate any benefits of rapid starting of insulin therapy. Also, the high numbers of hypoglycemic episodes and hypokalemia in the intensive insulin therapy might increase the injury to the ischemic myocardium and attenuate the benefits. Furthermore, hypoglycemic attacks, unfortunately, usually associated with over correction with dextrose and delay in restarting insulin therapy, all of that may cause fluctuation of BG level and attenuate the benefits of IIT. we only use the tight control in the admission days and most patient either continue on their oral antidiabetic treatment (if previously diabetic), or had been prescribed an oral antidiabetic (if predischarge OGTT of diabetic values), so it was only a short duration to test the intensive insulin therapy as the insulin resistant state may persist for months after AMI and abolish any short term benefits of intensive insulin therapy. Lastly the small sample size of the groups decreased the study power and increase vulnerability of type II error that may interfere with detection of significant difference between them.

## STUDY LIMITATIONS

Financial factors interfering with performing a diagnostic coronary angiography in the admission days, so we depended on ST segment resolution only, which was documented to reflect myocardial perfusion rather than epicardial perfusion [(19)].We did not perform systematic angiographic follow-up to document the long-term patency of the infarct-related artery (IRA). A larger sample size is recommended to increase study power and lower type II error.

## ACKNOWLEDGEMENTS

The authors wish to acknowledge the staff and workers in the CCU and echocardiography unit of internal medicine department at Assiut University Hospitals for their support to this study.

## CONFLICT OF INTERESTS

The authors declare that there was no conflict of interests as regard the publication of this paper.

## REFERENCES


1. **Capes SE, Hunt D and Malmberg K et al.** Stress hyperglycemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet 2000*; 356: 773–8.
2. **Norhammer AM, Ryden L and Malmberg K.** Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. *Diabetes Care1999*; 22:1827– 31.
3. **Pfeffer MA and Braunwald E.**Ventricular remodelling after myocardial infarction. Experimental observations and clinical implications. Circulation1990; 81:1161–1172.
4. **Raffaele Marfella, Siniscalchi M and Esposito K et al.** Effects of stress hyperglycemia on acute myocardial infarction: role of inflammatory immune process in functional cardiac outcome. *Diabetes Care2003*; 26:3129 –35.
5. **Raffaele Marfella, Di Filippo C and Esposito K at al.** Absence of inducible nitric oxide synthase reduces myocardial damage during ischemia reperfusion in streptozotocin-induced hyperglycemic mice. *Diabetes2004*; 53:454–62.
6. **Malmberg K, Ryden L and Efendic S et al.** Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *Journal of American college of Cardiology1995*; 26:57– 65
7. **Dandona P and Chaudhuri A et al.** Effect of hyperglycemia and insulin in acute coronary syndromes. *American journal Cardiology2007*; 99:12H–8H.
8. **Chaudhuri A, Janicke D and Wilson M. F et al.** Anti-inflammatory and profibrinolytic effect of insulin in acute ST-segment elevation myocardial infarction. *Circulation2004*; 109(7):849–54.
9. **Krljanac G and Vasiljevic Z et al.** Effects of glucose insulin- potassium infusion on ST-elevation myocardial infarction in patients treated with thrombolytic therapy. *American Journal of Cardiology2005*; 96: 1053–8
10. **Moghissi ES, Korytkowski MT and DiNardo M et al.** American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocrine Practice2009*; 15(4): 353–69.
11. **Elliott M. A, Daniel T. Anbe and Frederick G. Kushner et al.** ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction) Developed in Collaboration With the Canadian Cardiovascular Society. *American College of Cardiology 2004,Web Site*(www.cardiosource.org/acc).
12. **Schröder K, Wegscheider K and Zeymer U et al.** Extent of ST-segment deviation in the single ECG lead of maximum deviation present 90 or 180 minutes after start of thrombolytic therapy best predicts outcome in acute myocardial infarction. *Zeitschrift für Kardiologie2001*; 90:557–67.
13. **Elliott M. A, Mary Hand and Paul W. Armstrong et al.** 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: *Circulation2008*; 117: 296-329.

14. **Manuel D. Cerqueira, Neil J. Weissman and Vasken Dilsizian et al.** Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart. American Heart Association. Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging.*Circulation2002*; 105:539-42
15. **Temporelli PL, Giannuzzi P and Nicolosi GL et al.** Doppler-derived mitral deceleration time as a strong prognostic marker of left ventricular remodelling and survival after acute myocardial infarction: results of the GISSI-3 echo substudy. *Journal of American College of Cardiology2004*; 43:1646–53.
16. **Anjan K. Chakrabarti, Priyamvada Singh and Lakshmi Gopalakrishnan et al.** Review Article; Admission Hyperglycemia and Acute Myocardial Infarction: Outcomes and Potential Therapies for Diabetics and Non diabetics. *Research and Practice2012*; Volume 2012, Article ID 704314, 6 pages. doi:10.1155/2012/704314.
17. **Cheung N. W, Wong V. W and Mclean M.**The hyperglycemia. Intensive insulin infusion in infarction (HI-5) study. A randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care2006*; 29(4):765– 70.
18. **Raffaele Marfella, Clara Di Filippo and Michele Portoghese et al.** Tight Glycemic Control Reduces Heart Inflammation and Remodelling During Acute Myocardial Infarction in Hyperglycemic Patients. *Journal of American College of Cardiology2009*; 53:1425–36.
19. **Birnbaum Y and Drew B. J.**The electrocardiogram in ST elevation acute myocardial infarction: correlation with coronary anatomy and prognosis. *Postgrad Medical Journal2003*; 79:490–504.