Review Article

Admission blood glucose and echocardiography to predict major adverse cardiac events in acute coronary syndrome: a review

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ABSTRACT

A life-threatening presentation of coronary artery disease is acute coronary syndrome (ACS). The major adverse cardiac events (MACE) after acute coronary syndrome include life threatening arrhythmias, cardiac failure, cardiogenic shock, recurrent ischemia and sudden death. Patients with severe and moderate LV dysfunction are more likely to have triple vessel disease. Regional wall motion abnormality assessed by regional wall motion index using 2D-echocardiography correlates with infarct size which in turn predicts the occurrence of major adverse cardiac events (MACE) in patients with acute coronary syndrome. The cause for cardiogenic shock is left ventricular pump failure due to extensive damage to the myocardium and infarct related mechanical complications. In patients admitted with acute coronary syndrome, 5% develop ventricular tachycardia or ventricular fibrillation especially after 48 hours after hospital admission. Hyperglycemia causes stronger sympathetic activation in patients with severe illness and hence increased glucose levels. Insulin resistance not only causes hyperglycemia but can also lead to reduced energy production in the heart and lower tolerance to hypoperfusion and acts as an indicator of systemic and organ specific metabolic dysregulation and also stress hyperglycemia is implicated in the activation of pathological processes that cause cellular and tissue injury like increasing free radical formation and oxidative stress, inducing prothrombotic stress and worsening endothelial function. Hence higher levels of admission time blood glucose, hypoglycaemia during hospital stay, persistent hyperglycemia are considered as poor prognostic markers in patients with acute coronary syndrome.

Keywords: Coronary artery disease, Heart failure, Insulin resistance, Ventricular fibrillation

INTRODUCTION

Coronary artery disease (CAD) is one of the leading cause of morbidity and mortality in India. Coronary heart disease has caused 26% of adult deaths in 2001-2003, which has increased to 32% of adult deaths in 2010-2013.¹ A life threatening presentation of coronary artery disease is acute coronary syndrome (ACS). Acute coronary syndrome includes ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA).

The major adverse cardiac events (MACE) after acute coronary syndrome include life threatening arrhythmias, cardiac failure, cardiogenic shock, recurrent ischemia and sudden death.

Reduced left ventricular ejection fraction (LVEF) is associated with poor short and long-term outcomes in patients with ACS. Patients with severe and moderate left ventricular (LV) dysfunction are more likely to have triple vessel disease.² Regional wall motion abnormality (RWMA) assessed by regional wall motion index using
2D-echocardiography correlates with infarct size which in turn predicts the occurrence of major adverse cardiac events (MACE) in patients with acute coronary syndrome.3

The prevalence of increased blood glucose in patients with ACS ranges from 51-58%.4 Admission time hyperglycemia is associated with larger infarct size and increased inflammatory process. Higher blood glucose may not be the cause for MACE but an indicator of extent of myocardial damage which influences the occurrence of MACE.4,5

Early prediction of MACE is essential in patients with acute coronary syndrome.5 Admission blood glucose along with conventional echocardiography is a cost effective and easily feasible method compared to N-terminal proB-type natriuretic peptide (NT-proBNP) in predicting MACE in ACS patients.5 The narrative review insights into association of admission blood glucose levels and echocardiographic findings with major adverse cardiac events in patients with acute coronary syndrome. The literature search was retrieved from databases like Pubmed and Google scholar. The following keywords were used for the search: acute coronary syndrome, major adverse cardiac events, admission blood glucose, echocardiography.

**REVIEW OF LITERATURE**

**Classification of ACS**

Acute coronary syndrome (ACS) includes ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction and unstable angina(UA).7 Acute myocardial infarction can be classified into six types as follows:

- Type 1 - infarction caused by coronary atherothrombosis.
- Type 2 - infarction caused by supply-demand mismatch which is not due to atherothrombosis.
- Type 3 - infarction leading to sudden death even before confirmation with cardiac biomarkers and ECG
- Type 4a - infarction which is related to Percutaneous coronary intervention (PCI).
- Type 4b - is infarction which is related to thrombosis of coronary stent.
- Type 5 - is due to infarction which is related to coronary artery bypass grafting(CABG).8

**Pathophysiology of ACS**

STEMI is caused by complete occlusion of the coronary artery by the thrombus whereas partial occlusion or occlusion in the presence of collateral circulation results in NSTEMI or unstable angina.9,9 The anatomic characteristics of the atherosclerotic plaque which makes it more likely to rupture and leads to acute coronary syndrome include the presence of a thin fibrous cap, a large lipid core with numerous inflammatory cells, increased production of matrix metalloproteinases and relative deficiency of smooth muscle cells, systemic inflammatory changes, local shear stress, platelet hyperreactivity, prothrombotic states like transient hypercoagulability due to smoking, dehydration, infection, cocaine and malignancy. Myocardial ischemia or necrosis can also occur from coronary artery spasm, emboli or dissection in the absence of atherosclerotic coronary artery disease.9

**Echocardiography in ACS**

Echocardiography is used to assess the cardiac structure and function especially myocardial thickness, thickening/thinning and motion. RWMA because of ischemia can be identified immediately after onset when >20% transmural myocardial thickness is affected. Intravenous echocardiographic contrast agents improve the visualization of endocardial border and assess myocardial perfusion and microvascular obstruction. Global and regional function can be quantified by tissue doppler and strain imaging.10

Echocardiography is used to assess the LV function and RWMA in ACS patients. Multiple image views like parasternal long axis, short axis, apical four chamber, two chamber, three chamber and subcostal views are used to assess RWMA. Currently a 17-segment model is recommended by American Heart Association. The location of the segments corresponds to the territory of the coronary arteries and hence for evaluation of ischemia. The severity of contractile dysfunction is scored as 1 for normal contraction, 2 for hypokinesia, 3 for akinesis, 4 for dyskinesia and 5 for aneurysmal segments. The average is used for calculating the global wall motion score.

The normal regional wall motion index is 1 and it increases as the severity increases. Regional wall motion index (RWMI) correlates well with functional impairment. A RWMI of 1.1-1.9 predicts a small infarct size and an index equal to or more than 2 can predict the occurrence of complications.

Echocardiography is more accurate for localization of infarction except multivessel disease, previous infarction and overlap between perfusion territories. Absence of wall motion abnormality rules out a clinically significant infarction.3

The RWMA reflects the extent of an infarction. For right ventricular infarction, echocardiography is the investigation of choice for diagnosis. Echocardiography also plays a role in identifying the complications of RV infarction like ventricular septal rupture and severe tricuspid regurgitation which occurs as a result of papillary muscle ischemic dysfunction and annular dilatation.3
**ACS and LV dysfunction**

The hemodynamic disturbances as a result of circulatory failure due to severe LV dysfunction or other complications observed in patients with ACS include cardiogenic shock, hypovolemia due to haemorrhage and arrhythmias which contribute to the mortality of patients with ACS.9

ACS along with the presence of reduced LVEF is associated with poor outcomes and with high one-year mortality risk. According to a study conducted in Spain LVEF in patients with heart failure is not related to long term prognosis in patients with ACS whereas LVEF is a strong predictor of prognosis in patients without heart failure during admission.11

LVEF is a strong prognostic predictor in patients with acute coronary syndrome. ACS causes irreversible myocardial damage and remodelling which causes progressive dilatation and deterioration in contractile function and hence impaired left ventricular ejection fraction causing heart failure, increased mortality and life-threatening arrhythmias.11

**Cardiogenic shock and its association with ACS**

Up to one tenth of patients with acute coronary syndrome are complicated by cardiogenic shock and the mortality rate is high in such patients. Cardiogenic shock is characterised by systemic hypotension and vital organ hypoperfusion due to low cardiac output. The cause for cardiogenic shock is left ventricular pump failure due to extensive damage to the myocardium and infarct related mechanical complications. Early primary revascularization in recent years have reduced the mortality rate of patients with cardiogenic shock in ACS.12

**ACS and the occurrence of atrial fibrillation**

The patients who develop atrial fibrillation post infarction are more likely to have left main coronary artery disease compared to patients with previous history of atrial fibrillation. The risk factors for the development of new onset atrial fibrillation are previous history of hypertension, hypotension and tachycardia during admission, higher Killip class, NSTEMI and inferior wall myocardial infarction. The presence of atrial fibrillation in patients with ACS increases the long term mortality, risk of heart failure increases from 62% to 70% and also the increases the risk of ventricular arrhythmias.13

**ACS and associated ventricular arrhythmias**

Patients who develop cardiac arrest with the first rhythm as ventricular fibrillation (VF) or ventricular tachycardia (VT) even before hospital admission were identified to have ACS. The extent of infarction determines the development of accelerated idioventricular rhythm than reperfusion. Polymorphic VT or VF is more common in case of sustained ventricular arrhythmia in ACS. The development of VT or VF post primary PCI is associated with hypotension, tachycardia, incomplete resolution of ST elevation and poor coronary flow at the end of PCI. Late VT or VF which occurs 48 hours after hospital admission has high mortality than early VT or VF which occurs with 48 hours of hospital admission.14

**ACS and heart block**

Complete atrioventricular (AV) block is a very severe manifestation of AV conduction disturbance and it occurs in 3-14% of the patients with ACS and is associated with very poor prognosis irrespective of the location of myocardial infarction. AV block is more commonly observed in inferior wall STEMI because of hypoperfusion of the AV nodal artery which normally arises from the right coronary artery and increased parasympathetic activity. The incidence of AV block has reduced after thrombolysis and primary PCI which reduces the incidence if severe conduction disturbance which develops secondary to prolonged ischemia and irreversible necrosis. The presence of AV block in patients with ACS is also associated with higher risk of heart failure, cardiogenic shock, ventricular arrhythmias and during hospital stay.15

**Admission time blood glucose and mace**

Higher levels of admission time blood glucose, hypoglycemia during hospital stay, persistent hyperglycemia are considered as poor prognostic markers in ACS.16 In a study conducted by Stranders et al the mortality rate was 43.1% in diabetic patients compared to 28.2% in non-diabetic patients and they found that admission time blood glucose is an independent predictor of mortality in patients with ACS irrespective of whether they have diabetes or not.17

High levels of blood glucose after ACS are attributed to high levels of circulating stress hormones and incipient beta cell failure which becomes unmasked under stressful conditions. In many patients hyperglycemia itself is a cause for ischemic myocardium and it indicates insulin resistance and higher risk of cardiovascular disease.17

Hyperglycemia causes dehydration which results in hypovolemia, reduced stroke volume and hence output failure of the compromised LV. Admission time hyperglycemia is considered as an indicator of stress can be related to more extensive cardiac damage after acute myocardial infarction but in a study conducted by Stranders et al they found that there is no correlation between admission blood glucose and myocardial infarction size.17

Admission hyperglycemia also known as stress hyperglycemia which is associated with increased risk of congestive cardiac failure especially in non-diabetic
patients, however the mechanism underlying this association is not clear. Stress hyperglycemia may lead to more extensive myocardial damage and impaired LVF. Bauters et al. found that admission time hyperglycemia is a major and independent predictor of left ventricular remodelling in non-diabetic patients after anterior myocardial infarction.18

There are three main hypotheses which explains hyperglycemia and increased mortality in acute illness. The first being stronger sympathetic activation in patients with severe illness and hence increased glucose levels. The second hypothesis is insulin resistance not only causes hyperglycemia can also lead to reduced energy production in the heart and other organs and lower tolerance to hyperperfusion and acts as an indicator of systemic and organ specific metabolic dysregulation and the third hypothesis states that stress hyperglycemia is implicated in the activation of pathological processes that causes cellular and tissue injury like increasing free radical formation and oxidative stress, inducing prothrombotic stress and worsening endothelial function.19 Few studies demonstrated that in hyperglycemic patients there is higher incidence of no reflow phenomenon, endothelial dysfunction and prothrombotic state.20

A 10-year retrospective cohort study focusing on ventricular arrhythmias requiring defibrillation in young patients with first attack of acute myocardial infarction demonstrated that admission time hyperglycemia and WBC count were associated with higher risk for occurrence of life threatening arrhythmias. Ventricular arrhythmias after acute myocardial infarction increase inhospital mortality. Increased stress levels will cause increased catecholamine secretion which in turn rises the blood glucose levels thus involving in occurrence of ventricular arrhythmias after acute myocardial infarction. Thus identifying patients with high risk for complications after ACS and preventing them will markedly improve the outcome.21

In 2017, a study conducted by Mi et al, concluded that in-hospital glycemic variability seems to be of greater importance than admission blood glucose in predicting the short term cardiovascular outcomes in non-diabetic patients with STEMI after PCI.22 Takahashi et al concluded that glycemic variability is predictor of poor prognosis ACS patients without severe diabetes. Glycemic variability plays an important role in predicting left ventricular remodelling in patients with STEMI.16 The predictive value of admission time blood glucose for long term prognosis has to be further evaluated. The cause and significance of admission time hyperglycemia after acute myocardial infarction is not fully understood but insulin therapy reduces the mortality rate in both diabetics and non-diabetics.17

Even though hyperglycemia is regarded as an indicator of stress and correlated with more extensive cardiac damage after myocardial infarction, in a study they found there is no association between admission time blood glucose and infarct size.17

DISCUSSION

Based on the above discussion, stress hyperglycemia can be a result of acute coronary syndrome or it can result in ACS.23 One of the most common and severe complication of acute coronary syndrome is heart failure. Congestive cardiac failure and LV dysfunction predicts the mortality in patients with acute coronary syndrome. Extensive coronary artery disease can result in severe LV dysfunction and carries a poor prognosis. Hence early intervention and revascularisation is needed in such groups.24 In transmural myocardial infarction, there is alteration in the structure and function of the left ventricle which results in dilatation of LV ventricle and impaired systolic function which is referred as LV remodelling. As the LV dilates, the LVEF reduces and the papillary muscles are displaced, rising the degree of mitral regurgitation resulting in exacerbation of heart failure and increase in mortality rate.3

However in a study conducted by Al Jumaily et al, angiograms were done to assess the severity of ischemic heart disease and it was found that there was no correlation with admission time hyperglycemia.23 RWMA can occur with significant CAD and it can also be normal in CAD with significant ischemia. Angiographic studies may not correlate well with RWMA because of the tendency of coronary arteriogram, as it may underestimate the degree of stenosis when compared with pathological examination, mainly if it is associated with coronary artery spasm occurring during angiography. Hence the usage of 2D echocardiogram has provided a non-invasive method of detecting wall motion abnormality which is a good index of CAD.25

CONCLUSION

Echocardiographic findings such as left ventricular function along with regional wall motion index were reliable predictors for the occurrence of MACE in patients with ACS. In addition to echocardiography, raised blood glucose levels at the time of admission have a positive predictive outcome with higher incidence of MACE in them. A few studies have also shown a positive co-relation between hypoglycaemia and cardiovascular mortality.

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