The role of glycemia in acute heart failure patients

Abstract: Acute heart failure (AHF) is one of the most important cardiovascular syndromes associated with high cardiovascular morbidity, and is the major cause of admission in emergency departments worldwide. The clinical complexity of AHF has significantly increased, mostly due to the comorbidities: diabetes, arterial hypertension, dyslipidemia, obesity, peripheral vascular disease, renal insufficiency and anemia. Numerous clinical trials have demonstrated a frequent association of AHF and diabetes. Since AHF is a very heterogeneous condition, it is important to identify clinical and laboratory parameters useful for risk stratification of these populations. Hyperglycemia may be one of the most convenient, since it is widely measured, easily interpreted, and inexpensive. Acute coronary syndrome (ACS), arrhythmias and poor compliance to chronic medications are considered to be the most frequent precipitating factors of AHF in diabetics. Several studies identified diabetes as the most prominent independent predictor of morbidity and mortality in both acute and chronic heart failure (HF) patients. The following parameters were identified as the independent predictors of in-hospital mortality in patients with AHF and diabetes: older age, systolic blood pressure <100 mmHg, ACS, non-compliance, history of hypertension, left ventricular ejection fraction (LVEF) <50%, serum creatinine >1.5 mg/dL, marked elevation of natriuretic peptides, hyponatremia, treatment at admission without ACE inhibitors/ARBs/β-blockers, and no percutaneous coronary intervention (PCI) as a treatment modality. The most frequent cause of AHF is ACS, both with ST segment elevation (STEMI) or without (NSTEMI). Hyperglycemia is very common in these patients and although frequently unrecognized and untreated, has a large in-hospital and mortality significance.

Keywords: acute heart failure; diabetes; mortality; prevalence.

DOI 10.1515/cclm-2014-0239
Received March 4, 2014; accepted May 13, 2014; previously published online July 2, 2014

The scope of clinical problem

Acute heart failure (AHF) remains a major cause of cardiovascular (CV) morbidity and mortality, in part because of the lack of optimal patients risk stratification and management strategies. It is an increasing cause of admission in emergency departments worldwide, with most patients being hospitalized because of worsening chronic heart failure (HF). The patients presenting to the emergency departments are mostly 70–75 years old with both genders equally represented. In almost half of patients the LVEF is moderately or severely reduced (<40%), and the predominant clinical finding is pulmonary and systemic congestion due to increased left- and right-heart filling pressures [1]. Patients with a new, first-time-seen diagnosis of AHF are more likely to present with acute pulmonary edema or cardiogenic shock, while decompensation of HF usually occurs with weight gain, exertional dyspnea, or orthopnea that start days or weeks before admission [2]. The demographic and clinical characteristics of both diabetics and non-diabetics with AHF are presented in Table 1 [3]. The incidence of HF hospitalizations due to AHF has tripled in the last three decades, owing to the aging population, improved survival of patients after acute myocardial infarction (due to interventional and surgical treatment), and improved medical and device therapies causing longer life-span of these patients [4].
Table 1  Demographic and clinical characteristics of patients with acute heart failure (diabetics and non-diabetics). Selected variables, only p<0.0001.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Diabetics (n=2229)</th>
<th>Non-diabetics (n=2724)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>10.2%</td>
<td>20.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>56–80</td>
<td>76.8%</td>
<td>62.7%</td>
<td></td>
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<tr>
<td>&gt;80</td>
<td>12.7%</td>
<td>16.8%</td>
<td></td>
</tr>
<tr>
<td>Clinical classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acutely decompensated</td>
<td>69.1%</td>
<td>59.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic HF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute de novo HF</td>
<td>30.9%</td>
<td>40.4%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>39.3%</td>
<td>34.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Precipitating factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>44.1%</td>
<td>30.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>11.1%</td>
<td>15.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic HF</td>
<td>41.6%</td>
<td>32.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>35.5%</td>
<td>26.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>10.5%</td>
<td>14.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>81.6%</td>
<td>60.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-cardiovascular co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>29.5%</td>
<td>14.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anemia</td>
<td>16.8%</td>
<td>12.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD</td>
<td>29.3%</td>
<td>21.1%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HF, heart failure; COPD, chronic obstructive pulmonary disease.

The importance of the co-morbidities in acute heart failure

The clinical complexity of AHF patients has significantly increased, mostly due to the co-morbidities. The analyses of various registries/surveys demonstrated that in AHF population in the sixth- and seventh-decade, individuals without associated co-morbidities are rare. The major co-morbidities observed in this population are diabetes, arterial hypertension, dyslipidemia, obesity, peripheral vascular disease, renal insufficiency and anemia [5]. The same observation can be applied to ALARM-HF cohort with acute decompensation of HF, in whom various co-morbidities in AHF were revealed, in particular the high prevalence of atrial fibrillation/flutter, valvular disease, and dilated cardiomyopathy. In addition, the history of coronary artery disease was revealed in 60% of patients [6].

Diabetes as one of the major co-morbidity in acute heart failure

The importance of hyperglycemia as marker of risk should be distinguished from the role of detrimental effects of high glucose levels in clinically manifested diabetes.

In some instances, hyperglycemia may occur in AHF as the response to myocardial dysfunction, without previously known diabetes. However, most of the experts consider impaired glucose tolerance among patients with AHF as a sign of adverse outcome [7]. It is mostly stress-induced and represents a transient increase in blood glucose concentration during AHF episode. This may occur in patients with undiagnosed diabetes, or only with impaired glucose tolerance. It is common and the mechanism include increased substrate availability in the form of lactate [8], increased gluconeogenesis and decreased glycogenolysis due to increased secretion of counteregulatory hormones (catecholamines, cortisol, and glucagon) [9], and peripheral insulin resistance [10].

Postprandial hyperglycemia is also seen as one of the clinically relevant risk factors for the development of AHF. This phenomenon is associated with an overproduction of superoxide and interactions with nitro-oxide are causing endothelial damages, microvascular and macrovascular complications [11, 12]. Reducing postprandial variations can diminish the oxidative stress particularly marked in type-1 diabetes, but also in patients with type-2 diabetes treated with insulin and in non-insulin-dependent diabetics [13]. The studies investigating HbA1c in AHF are lacking. In chronic HF, the relationship between mortality and HbA1c in diabetic patients with HF seems to be U-shaped, with the lowest risk of death in patients with humble glucose control (7.1% < HbA1c ≤ 7.8%), making this area attractive for the further prospective studies [14].

Numerous clinical trials have demonstrated a frequent association of AHF and diabetes [5, 6, 15]. The prevalence of diabetes among AHF patients was 45%, the majority in the age group of 56–80 years, with both genders almost identically represented (51% males vs. 49% females) [5]. The same prevalence has been reported in multinational registry of Mebazaa et al. [15] and in three other registries: The Acute Decompensated Heart Failure National Registry (ADHERE, 44%), the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF, 42%), and the EuroHeart Failure Survey II (EHFS II, 33%) [6, 16, 17]. In OPTIMIZE-HF registry, the AHF patients were slightly younger, but no difference regarding gender and co-morbidities in comparison to ALARM-HF was observed. In ALARM-HF registry, acute decompensation of HF was also more frequent in comparison to new acute decompensation. In the group of diabetics this phenomenon was more pronounced (69.1% chronic vs. 30.9% new), compared to non-diabetic group (59.6% chronic vs. 40.4% new). In addition, acute
coronary syndrome (ACS), arrhythmias and poor compliance to chronic medications were observed more often as precipitating factors of AHF in diabetics [4].

Key pathophysiological mechanisms of developing acute heart failure in diabetics

The duration and magnitude of chronic sustained hyperglycemia and the acute fluctuations of glucose over a daily period [18–20] could be essential in explaining the pathophysiological aspects of myocardial dysfunction. Prolonged hyperglycemia is associated with hyperinsulinemia, hyperlipidemia, formation of reactive oxygen species (ROS) and advanced glycation end-products (AGEs). These metabolic changes are leading to structural and functional damage of myocardium and HF. Hyperglycemia is creating a toxic cellular milieu, causing intracellular and extracellular dehydration, inducing electrolyte abnormalities, and depressing immune function [21, 22].

There are several molecular and metabolic factors involved in development of myocardial dysfunction in patients with AHF and diabetes. Initially, long-lasting hyperglycemia causes glucose oxidation and mitochondrial generations of superoxide, damaging DNA and activating poly-polymerase, diverting glucose from glycolytic into alternative biochemical pathways. Also, hyperglycemia activates protein kinase C enzyme affecting Ca²⁺ handling in cardiomyocytes, [23] resulting in myocardial necrosis and fibrosis [24]. In addition, hyperglycemia stimulates the production of ROS in the myocardium, which impairs the endothelial function, reduces the nitric oxide concentration, and leads to an inflammatory reaction, accelerating the process of apoptosis, and increasing the activity of angiotensin I [25].

At the later stage, high glucose levels activates local myocardial renin-angiotensin and endothelin systems, contributing to myocyte necrosis, fibrosis (interstitial and perivascular) [26, 27], myocardial hypertrophy and capillary endothelial changes [28]. Interaction of collagen with glucose is leading to the formation of AGEs, which have detrimental effect on blood vessels, resulting in arterial and myocardial stiffness, endothelial dysfunction, and atherosclerotic plaque formation. AGEs also cause dysfunction in cellular nitric oxide signaling and exacerbate intracellular oxidative stress and cell damage [29].

Simultaneously, the dysfunction of glucose transporter proteins (glucose transporter 1 and 4) occurs, causing major shift in energy production from β-oxidation to free fatty acids [30], resulting in accumulation of glycolytic toxic intermediates and ceramide. These products are causing lipotoxicity, enhancing apoptosis and worsening myocardial contractility [31–36]. High sympathetic activity associated with hyperinsulinemia, insulin resistance and lipolysis (caused by insulin deficiency) results in additional increase in concentration of free fatty acids [37, 38]. Described molecular and metabolic disturbances result in myocyte necrosis, LV hypertrophy, and finally in myocardial dysfunction and HF [39].

The morbidity and mortality of diabetic patients with acute heart failure

Recent understanding stresses the major importance of overt diabetes in patients with AHF in comparison to acutely developed hyperglycemia. Diabetes is seen as the most prominent independent predictor of morbidity and mortality in AHF patients [40–48].

In ALARM-HF registry, all-cause in-hospital mortality of diabetics was higher compared to non-diabetics (11.7% vs. 9.8%, respectively). However, in OPTIMIZE-HF registry no difference in hospital, 60- and 90-days mortality between these two groups of AHF patients can be demonstrated [16]. These differences between registries can be explained with more precise and intensive AHF treatment of diabetics in OPTIMIZE-HF, and with longer follow-up period in other registries [40–58]. In addition, in both registries, the length of hospitalization and rehospitalization rate was higher in diabetic group.

The following parameters were independent predictors of in-hospital mortality in patients with AHF and diabetes: older age, systolic blood pressure <100 mmHg, ACS, non-compliance, history of hypertension, LVEF<50%, serum creatinine >1.5 mg/dL, marked elevation of natriuretic peptides, hyponatremia, treatment at admission without ACE inhibitors/ARBs/β-blockers, and no percutaneous coronary intervention (PCI) as a treatment modality [5, 59]. In addition, AHF hospitalization was a powerful predictor of readmissions and death after discharge, with 10% mortality in diabetics within 30 days [15, 60].

Acute heart failure, diabetes and acute coronary syndrome

The most frequent cause of AHF is ACS, both with ST segment elevation (STEMI) or without (NSTEMI). The
relationship between ACS and glycemia variations is close and clinically very important. Hyperglycemia is very common in these patients and although frequently unrecognized and untreated, has a large in-hospital and mortality significance [61–68]. Furthermore, hyperglycemia is shown to have a prognostic role in development of HF and cardiogenic shock complicating STEMI in patients with and without diabetes [69–73]. In ACS, insulin resistance is recognized as an important part of the glyco-metabolic response to stress [74–76]. In patients with STEMI hyperglycemia is associated with higher free fatty acid concentrations, impaired myocardial glucose use, and insulin resistance. These metabolic disturbances are increasing oxygen consumption and are potentially worsening ischemia, leading to AHF development [77–79]. Several trials showed that in patients with STEMI (diabetics or non-diabetics), insulin resistance (quantified by the HOMA index), seems to have a significant important prognostic role, both in primary and secondary prevention [80, 81]. Treatment with insulin could be beneficial in these patients by inhibiting lypolysis, reducing free fatty acid concentrations and improving myocardial glucose use. On the clinical ground, antithrombotic, anti-inflammatory, and vasodilatory properties of insulin are described [82, 83]. In contrast to the prognostic role of ACS in development of AHF these findings failed to be confirmed in AHF patients of other etiologies [84–87], suggesting differences in a interaction between specific etiology and injury from hyperglycemia. Several reports suggest that between 25% and 70% of hyperglycemic patients with STEMI have undiagnosed diabetes, and they are treated less frequently with antidiabetic treatment [88].

The data from several investigations using glucose-insulin-potassium (GIK) in the treatment of STEMI varied to a higher extent. However, there is a general agreement that GIK cannot be recommended as standard adjunctive treatment to PCI or streptokinase [89].

Clinical implications for diabetes in acute heart failure

Diabetes in AHF may have been largely under-diagnosed resulting in underestimation of its prevalence. This applies mainly to patients with reduced LVEF, while the interactions between diabetes and HF with preserved LVEF are less known.

Since AHF is a very heterogeneous condition, in whom it is important to identify clinical and laboratory parameters useful for risk stratification of this population. Hyperglycemia may be one of the most convenient, since it is widely measured, easily interpreted, and inexpensive. In addition, glucose levels correlates well with 30-day CV outcomes, which are a very relevant endpoint in AHF.

Hyperglycemia per se, and not previous diabetes, is considered to be a significant independent risk factor for HF hospitalization, development of AHF and cardiovascular death [90]. Elevated glucose, even borderline, is seen as risk factor for CV outcomes and is associated with higher mortality in healthy subjects and in patients with chronic HF, without known diabetes [53, 91–93]. In trial of Umpierrez et al. [94], patients with new hyperglycemia had higher mortality rate (16% vs. 3%), more severe form of HF and longer hospitalization than those with known diabetes.

The vulnerability of diabetics in AHF could be due not only to impaired myocardial performance and increased risk of ventricular remodeling but are also caused by autonomic dysfunction, higher possibility for sudden cardiac death, and lower effectiveness of therapy. Interestingly enough, the risk associated with an elevated blood glucose level was seen in both patients with and without previous diabetes. Hyperglycemia in a patient without previous history of diabetes is connected with insulin resistance and increased catecholamine levels that induce endothelial dysfunction, thrombosis and impair myocardial metabolism [95, 96]. It is important to recognize that in-hospital hyperglycemia strongly predict adverse clinical outcomes and, needed to be monitored and managed carefully.

Conclusions

AHF is an increasing cause of admission in emergency departments worldwide and in almost half of patients the LVEF is moderately or severely reduced (<40%). Numerous clinical trials have demonstrated a frequent association of AHF and diabetes [3]. Diabetes in AHF may have been largely under-diagnosed resulting in underestimation of its prevalence. This applies mainly to patients with reduced LVEF, while the interactions between diabetes and HF with preserved LVEF are less known. Since AHF is very heterogeneous condition, in whom it is important to identify clinical and laboratory parameters useful for risk stratification of these population. Hyperglycemia may be one of the most convenient, since it is widely measured, easily interpreted, and inexpensive. In addition, glucose levels correlates well with 30-day CV outcomes, which are a very relevant endpoint in AHF. Postprandial
Hyperglycemia is also seen as one of the clinically relevant risk factors for the development of HF. Stress-induced impaired glucose tolerance among patients with AHF represents a transient increase in blood glucose concentration during AHF episode. This may occur in patients with undiagnosed diabetes, or only with impaired glucose tolerance. Several studies identified diabetes as the most prominent independent predictor of morbidity and mortality in both acute and chronic HF patients. The most frequent cause of AHF is acute coronary syndrome, both with ST segment elevation (STEMI) and without (NSTEMI). Hyperglycemia is very common in these patients and although frequently unrecognized and untreated, has a large in-hospital and mortality significance.

Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

References


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