The impact of echocardiographic substrate on short and medium term prognosis in non-acute coronary syndrome pulmonary edema

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Abstract. Background: Acute pulmonary edema (APE) is a severe clinical form of acute heart failure (AHF) with a high in-hospital (IH) and early post-discharging mortality. Aim: To identify the morphofunctional substrate in non ACS APE, based on the clinical, anamnestic and echocardiographic evidence and to analyze how it correlates with the short and medium term prognosis. Material and methods: The study included 228 patients divided into two samples of 136 patients suffering from chronic decompensated acute heart failure, and 92 patients admitted for APE. Echocardiography was performed in every patient and three etiologies were taken into analysis: ischemic, valvular and hypertensive. The survivors were followed up for one. We recorded the IH, 30 days and 12 month mortality. Results: There were 47.83% (44) patients with ischemic etiology, 23.91% (22) valvular, and 28.26% (26) hypertensive. In entire group the IH, 30 days and 12 months mortality was: 9.64%, 4.48% and 28.25%. We did not find a significant correlation between the IH mortality and the etiology (p=0.63), but we found a high IH mortality for each underlying etiology: 57.27% for ischemic, 18.18% for valvular and 23.08% for hypertensive. Thirty days mortality was influenced by ischemic etiology, the only cause for 30 days death, at the limit of significant statistical data (p=0.053, RR 1.0750, 95% CI 1.0145-1.1391). The 12 months mortality was significantly influenced by ischemic etiology (RR 1.4321, 95% CI 1.0288-2.0022, p=0.01); 12 month death was 68.42% for ischemic and 31.58% for valvular etiology. A low BP (blood pressure) at presentation was significantly correlated with 12 months mortality in ischemic APE patients (p=0.04). A high heart rate (HR) at presentation was correlated with IH mortality for hypertensive patients (p=0.07) and a low HR with 12 month mortality in valvular APE patients (p=0.02). The only biological parameter with independent prognostic value for the mortality at any given moment was sodium seric levels at presentation (p<0.01). Conclusions: Ischemic etiology was significantly correlated with medium and long term prognosis in APE patients. In-hospital mortality was high and significantly correlated with APE clinical form. BP and HR were linked with mortality according to etiology. Only seric sodium had independent prognostic value. The high mortality for hypertensive etiology suggests that in some cases there may be an ischemic etiology associated.

Key Words: heart failure, echocardiography, acute pulmonary edema, prognosis.

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Introduction

Acute pulmonary edema (APE) is a severe clinical form of acute heart failure (AHF) with a high in hospital and early post-discharging mortality. Under a common clinical presentation there can hide different morphofunctional etiologies, each etiology/substrate having particular therapeutic and prognostic evolution (Nieminen et al 2006). Early identification of morphofunctional substrate becomes priority for correct risk stratification and therapeutic management.

Over one million per year hospitalizations for AHF occur in the US and about the same number was recorded in Western European countries; as a discharge diagnostic rate it tripled over the last three decades, and this trend is likely to continue with the same tendency. This can be due to the increased life expectancy and the aging of the population, to the better management of hypertension, dyslipidemia and coronary heart disease, in the same way with the increased survival after myocardial infarction and a better prevention for sudden cardiac death (Gheorghiade et al 2005). The significance of the issue is evidenced by the increasing number of national and international registers realized in the last decade. But the registers that characterize the clinical form APE in AHF are few: from 16% in EHFSII (Nieminen et al 2006), to 29% in ROAHFS (Chioncel et al 2011) and up to 36.7% in ALARM HF (Parissis et al 2010). In-hospital mortality is high in all registers (6.7% in EHFS, respectively 7.4% in ROAHFS and ALARM HF), as it was outlined in previous studies (Chioncel et al. 2011, Nieminen et al. 2006, Parissis et al. 2010).

From etiopathological point of view we can talk about APE in the context of an acute coronary syndrome (ACS) or the APE outside of ACS. APE in the context of ACS is often an event of "de novo" AHF (first event AHF), and the prognosis and treatment depend on the type of infarction (with or without ST-segment elevation), on its location (according to Topol classification) and the extent of coronary heart disease. Non ACS APE is hiding behind a common clinical picture an important pathologically polymorphism. Depending on the pathological substrate we can speak of several clinical/paraclinical profile in non ACS APE: 1. Ischemic Profile, when there was a history of myocardial infarction or angina, and/or are documented significant coronary lesions (by angiography or other imaging methods), and/or there are changes in segmental kinetics – by echocardiography. 2. Valvular profile when echocardiography highlights valve lesions (aortic, mitral, tricuspid – isolates or in combination) quantified as at least moderate and it does not fulfill the criteria for ischemic substrate. 3. Hypertensive profile associated with hypertensive crisis and preserved left ventricular ejection fraction (LVEF), without associated valvular and ischemic substrate. 4. Non-ischemic dilated myocardial profile characterized by the presence of a dilated cardiomyopathy, documented as non-ischemic 5. Dysrhythmic profile, for which there is a persistent supraventricular arrhythmia associated with high frequency, difficult to control, in the absence of significant valvular or ischemic substrate. 6. Non dilative myocardial profile characterized by the presence of hypertrophic or restrictive infiltrative type. 7. Primary non cardiac profile in which the primary pain is not cardiac: thyrotoxicosis, neurogenic heart – Takotzubo syndrome, brain injury. 8. Mixed profile combining at least two types of profile, most often ischemic with valvular or valvular with dysrhythmic/ischemic. Regardless of the substrate, an APE episode can be precipitated by several factors like anemia, worsening renal function, acute respiratory infection, myocardial ischemia, arrhythmias, use of NSAID or beta blockers.

The aim of the study was to identify, based on the clinical, anamnestic and echocardiographic evidence, the morphofunctional substrate in non ACS APE and to analyze how it correlates with the short and medium term prognosis. We wanted to establish correlation between clinical or biological parameters proved to be risk factors from the national and international registers and morphofunctional substrate.

Material and methods

The study included 228 patients admitted to the Cardiology and Internal Medicine Wards of St. Pantelimon Emergency Hospital between 01.01 – 31.12.2013. The group was divided into two samples of 136 patients suffering from chronic decompensated acute heart failure (CDAHF), and 92 patients admitted for APE. The patients were evaluated by echocardiography within the first 48 hours of hospitalization. Non ACS APE and CDAHF NYHA IV diagnosis was established in the first 48 hours after admission, based on clinical and laboratory data. The ESC classification was used in order to establish the clinical type and NYHA classification, for functional class in CDAHF. The differential diagnosis between the two clinical forms was based mostly on the clinical and anamnestic data: sudden onset of the symptoms, dyspnea at rest with orthopnea, low O2 saturation, therapeutic

response, and less on the paraclinical findings (pulmonary radioscopy or biomarkers like Nt-proBNP, which were measured in only 28.6% of the cases).

Only four substrates/profile types were analyzed: ischemic, valvular, hypertensive and mixed (ischemic + valvular). The four etiologies were established based on historical, ECG, echocardiography and biological data. The other types of etiologies have been excluded due to the small number of cases. The patients were followed during hospitalization and after discharge for a period of 12 months, and were contacted by phone at 1 and 12 months. The clinical and paraclinical data recorded were: systolic blood pressure (SBP) and heart rate (HR) at presentation before treatment, blood urea nitrogen (BUN), serum creatinine, hemoglobin and seric sodium at the admission time, morphofunctional substrate, and the vital status (cardiovascular mortality) at hospital discharge, at 1 and 12 months post-hospitalization. The study was approved by the Ethics Committee of the "Sf. Pantelimon" Emergency Hospital and all patients signed an informed consent form for the use of their data

For the statistical analysis we used SPSS 20.0 and EPIINFO 7.0. The impact of clinical and laboratory variable on short term outcome was determined by using multiple regression equations, while the differences between variables were calculated by using the analysis of variance for continuous variables and chi – square test for categorical variables.

Results

Ninety two of non ACS APE patients, distributed by substrate as follows: 47.83% (44) ischemic, 23.91% (22) valvular, 28.26% (26) hypertensive. Prevailing valvulopathies for valvular substrate were: mitral insufficiency (36.11% - 8) or aortic stenosis (13.88% - 3), and concomitant mitral insufficiency and aortic stenosis in 31.94% (7) cases. In the half of the cases of valvular APE, at least one new valvulopathy was diagnosed. Eighteen 19.56% patients presented the mixed profile: ischemic and valvular. The mean age, distribution by gender, risk factors and depending on the type of substrate AHF are found in Table 1 and 2. In non ACS APE the ischemic etiology is dominant, the mean age is relatively equal, males predominate in the substrate ischemic 61.4% (27) vs 38.6% (17), with a higher share of women for the hypertensive 77.77 (20) vs 22.23% (6), statistically significant differences (p=0.003).

SBP at admission showed in our analysis statistically significant differences (p<0.001) between the two clinical forms, non ACS APE vs. CDAHF IV NYHA, with higher values for APE (174.06±37.9 vs 145.33±33.37 mmHg). In patients with non ACS APE we found a statistically significant difference between substrates regarding the SBP, with the highest values for hypertension substrate (200.92±34.17) and the lowest for the ischemic one (158.86±31.92 mmHg) (p<0.001). No statistically significant correlations were found between SBP and in hospital mortality (IHM) or in 30 days after discharge, both in the whole lot and in the substrate. The 12 months mortality was statistically correlated with the value of SBP at presentation (p=0.033), association that was maintained for ischemic substrate (p=0.043), with lower values associated with death (152.41±37.46 vs. 164.77±22.68 mmHg).

Our analysis showed no statistically significant correlations between HR and the clinical form (p=0.9) or between HR and

Table 1. Distribution by sex and age in the substrate

Variables	Ischemic	Valvular	Hypertensive	Ischemic+ valvular
% substrate	47.83	23.91	28.26	19.56
Average age	73.61±11.4	75.30±10.9	72.11±11.7	74.11±8.6
Gender male (%)	61.4	50	22.23	68.42

Table 2. Risk factors distribution depending on the substrate

Risk factor	Ischemic	Valvular	Hypertension	p
Hypertension, % (N)	71.93 (32)	80.56 (18)	100 (26)	0.058
Dyslipidemia, % (N)	61.4 (27)	38.89 (9)	66.67 (17)	0.49
Type II Diabetes, % (N)	49.12 (22)	27.77 (6)	22.22 (6)	0.002
Active smoking, % (N)	12.28 (6)	5.56 (2)	19.44 (5)	0.06
More than 4FR cumulated, % (N)	38.60 (17)	22.22 (5)	33.33 (9)	0.24

Table 3: Mortality in relation to the clinical form

Variable	CDAHF IV NHYA	Non ACS APE	p
In-hospital mortality rate	7.89% (19)	9.64% (21)	0.057
Mortality at 30 days	3.16% (6)	4.48% (8)	0.2
Mortality at 12 months	22.58% (3)	28.36% (18)	0.5

Table 4: Mortality vs. substrate in non ACS APE subgroup

Substrate	Ischemic	Valvular	Hypertensive	Valvular + ischemic	p
IHM	58.74% (12)	18.18% (4)	23.08% (5)	8.69% (2)	0.6
Mortality at 30 days	100% (8)	0	0	0	0.053
Mortality at 12 months	68.42% (12)	31.58% (6)	-	50% (9)	0.013

morphofunctional substrate (p=0.1), for non ACS APE. The analysis by substrate identified some correlations between HR and prognosis: HR correlated with IHM with a borderline significance (p=0.07) for hypertensive substrate, with higher values associated with death (122±38.66 bpm vs 25.12±97.6 bpm), and with mortality at 12 months for the valvular substrate (p=0.026), but with lower values associated with death (80±11.5 bpm vs. 94±20.3 bpm), lower values which can be explained by degenerative valve disease more frequent association with impaired conductive system. For ischemic substrate we didn't find a statistically significant association between HR and short and medium-term prognosis.

Biological parameters like BUN and serum creatinine at presentation, were described by Pena-Gil et al. (2005), Shamagian et al. (2007), Margulescu et al. (2012) and Abraham et al. (2005) as prognostic factors for AHF. We did not find them to be prognostic factors for IHM, 30 days or 12 months mortality, for the entire group or for any substrate. The only biological parameters correlated significantly with prognosis in non ACS APE patients, regardless the substrate, were serum Na at admission, with prognostic value for all 3 events, IHM (p<0.001), 30-day mortality (p=0.001) and 12 months mortality (p<0.001) and hemoglobin at admission, compared with mortality at 12 months (p=0.042); only the serum sodium proved to be an independent predictor, data that is similar with the literature, respectively with results of OPTIME CHF and ACTIV CHF studies (Klein et al 2005, Gheorghiade et al 2004).

IHM for the whole lot of AHF was 17.54% (40), distributed as follows: 7.89% (18) patients as CDAHF NYHA IV and 9.64% (22) as non ACS APE. A Chi-square analysis shows a higher risk for IHM for APE, as the clinical form at presentation, statistically significant with a RR of 1.1403, 95% CI 0.9993 -1.3013, OR 2.0603 95% CI 1.0339 -4.1058, p = 0.05714.

In the APE subgroup, the analysis according to substrate showed a mortality of 58.74% (12) for ischemic substrate, 18.18% (4) for the valvular substrate, 23.08% (5) in the hypertensive substrate, 8.69% (2) mixed substrate, valvular and ischemic. Chi-square analysis did not identify statistically significant differences between the ischemic/non ischemic substrate and IHM (p=0.6)

Mortality at 30 days was not significantly statistically influenced by the clinical form at presentation in general group (p=0.2). The mortality rate was relatively equal between the two clinical forms 3.16% (6) for CDAHF IV NYHA vs. 4.48% (8) for APE. However, after the substrate analysis, we observed that all deaths at 30 days belonged to the ischemic substrate. In both the general group and APE subgroup, we found a statistically significant association between ischemic substrate and mortality at 30 days (p=0.05), with a RR 1.0750, 95% CI 1.0145 -1.1391. Mortality at 12 months was not influenced by the clinical form at presentation (p=0.5), with a higher percentage of the APE subgroup. In the APE subset, the mortality rate was 28.36% (18). The mortality rate was 68.42% (12) for the ischemic substrate, 31.58% (6) for the valvular substrate, and 50% (9) for concomitant valvular and ischemic substrate. We found a RR

of 1.4352, (p=0.01, 95% CI1.0288 -2.0022) for IHM and ischemic substrate in APE.

Discussion

Most national and international registries (ADHERE, EFICA, ATTEND, ALARM HF, RO AHFS, EHFS II, OPTIMIZE HF), support ischemic etiology as dominant substrate in AHF, varying from 33% in ATTEND up to 61 % in RO-AHFS and EFICA, with intermediate value of 46% OPTIMEZE-HF and 54% in EHFS II; as it was outlined by Chioncel et al. (2011). In our work, ischemic etiology was dominant (47.83% for the APE form), being a common denominator for the two severe forms APE and CDAHF IV NYHA, with higher percentage of the ischemic substrate in CDAHF IV (51.47%). This was similar to the literature data (Abraham et al 2008, Adams et al 2005, Chioncel et al 2011, Follath et al 2008 Nieminen et al 2006, Sato et al 2010, Zannad et al 2006). In our analysis, the ischemic etiology was associated with a high mortality, both IH (58.74%), 30 days (100%) and 12 months (68.42%), and it was in accordance with data from the literature (Cotter et al 2008). A long and medium term high mortality in non ACS APE with ischemic substrate is also suggested by the work of Shamagian et al. (2007). The survival of the patients with HF, managed according to guidelines, is significantly shorten by an APE episode, when there is an etiopathogenic ischemic substrate, but not by the presence of any of these factors, one without the other.

There are no precise data about acute ischemia in AHF; elevations in cardiac Troponin I or T over the cut off for an acute coronary syndrome, according to available data in the literature, in AHF being ~ 20% (Cotter et al 2008, Gheorghiade et al 2005, and Khot et al 2003); AHF association with elevated cardiac Troponin I or T, with or without ischemic substrate, was associated with IHM in ADHERE registry, 8% compared to 2% in those with normal Troponin I (Cotter et al 2008).

We found a high IHM for hypertensive substrate. This substrate is associated in literature with good prognosis, and it is surprising that we found otherwise. Other possible etiology for some of the patients from this subgroup could influence the prognosis. In our analysis, the accumulation of cardiovascular risk factors associated to the hypertensive substrate, similar to that of the ischemic substrate, makes probable the ischemic etiology. A study regarding this problem was published by Pena-Gil et al. (2005). It showed that APE behind a non ACS is in 85% of cases associated with at least bi-coronary heart disease. Moreover there are concerns in the medical world on this issue, concerns that support the need to evaluate coronary artery disease and the extension of its in AHF patients, with or without ischemic substrate, as shown by Flaherty et al. (2009), having an impact on the therapeutic strategy and short and long prognosis as was shown by the work of Beohar et al. (2008) and Abraham et al. (2008).

Quantification of the ischemic substrate in large registries was performed on clinical and, anamnesis data, ECG and noninvasive imaging. Assessment by coronary angiography, the gold standard for ischemic substrate is underused in AHF, approximately 9-16%, according to the same data. OPTIMIZE-HF Registry demonstrated that angiographic assessment during index hospitalization for an episode of AHF was followed by larger use of aspirin and statin and by the revascularization procedures with

risk reducing of mortality at 60 and 90 days after discharge, as it results from the papers of Beohar et al. (2008) and Flaherty et al. (2009). Thus it has born the hypothesis that assessing the presence and severity of the coronary ischemic disease in AHF has therapeutic implications with impact on short and long-term evolution (Beohar et al. 2008, Abraham et al. 2008).

Thus for patients with non ACS EPA or with or without ischemic substrate, clinical and laboratory data with prognostic values must be established to identify earlier the patients with high risk and make further assessment with diagnostic and / or therapeutic role.

Conclusions

Ischemic etiology was dominant in non ACS APE and had a statistically significant influence on short and medium term prognosis. IHM rate was high and statistically significantly correlated with the clinical form, patients presented with APE having a 1.14 times higher risk of death than those presented as CDAHF NYHA IV. Hypertensive substrate, seemingly benign, is associated with a high IHM, suggesting other possible etiology for these patients. Several procedures should be performed in non ACS APE patients, both ischemic and non-ischemic, as those with hypertensive substrate at high risk, both for diagnosis and treatment of coronary artery disease.

Acknowledgement

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