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Role of Serum Bio-Adrenomedullin (Bio-ADM) and Electrical Cardiometry in Evaluation of Heart Failure Decongestion Therapy

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ABSTRACT

Background: Bio-active adrenomedullin (bio-ADM) represents a promising biomarker of tissue congestion. Electrical cardiometry (EC) non-invasively measures electric bio-impedance across the thorax allowing the assessment of the fluid status in HF patients. **Objectives:** This study aimed to assess the role of serum bio-active adrenomedullin (bio-ADM) and electrical cardiometry (EC) in monitoring decongestion during heart failure (HF) therapy.

Patients and methods: This prospective observational study included 90 patients with decompensated HF admitted to Menoufia University Hospital and the National Heart Institute, Egypt. All patients underwent clinical evaluation with congestion scores, electrocardiography, chest X-ray, routine laboratory testing and echocardiography. Daily central venous pressure (CVP) and fluid balance were assessed. Serum bio-ADM and EC parameters using Osypka Medical EC ™ device were measured at admission and prior to clinically planned discharge.

Results: Prior to clinically planned discharge, there was a decrease in congestion scores and CVP owing to net negative fluid balance achieved by HF decongestion therapy. Serum bio-ADM levels significantly decreased. EC showed a significant reduction in thoracic fluid content (TFC). Bio-ADM showed positive correlations with TFC in addition to CVP. Residual congestion was detected in 37 patients, which was identified by elevated TFC above normal device range in addition to slightly elevated bio-ADM levels despite apparent clinical improvement. This prompted delaying hospital discharge till normal TFC values were achieved.

Conclusion: Serum bio-ADM and EC proved to be effective in more precise assessment of fluid status during HF decongestion therapy. EC provided valuable non-invasive guidance in managing fluid overload and detected residual congestion, which allowed better optimization of discharge timing.

Keywords: Bio-adrenomedullin, Congestion, Electrical cardiometry, Heart failure.

INTRODUCTION

Heart failure (HF) affects over 60 million individuals worldwide. It is considered the first reason for hospitalization in patients aged above 65 years. Approximately 24% of those patients were re-hospitalized within 30 days predominately due to residual congestion at discharge [1]. During admission, it may be challenging to accurately identify the degree of congestion. Existing clinical tools including grading of edema, rales, jugular venous pressure (JVP), and chest X-rays have their limitations and considerable inter-observer variations. Therefore, objectively assessing the state of congestion is becoming increasingly important for patients' follow up, dosage titration of diuretics and better timing of discharge [2].

Bioactive adrenomedullin (bio-ADM) is a 52-amino acid vasodilator peptide hormone released by the smooth muscle and endothelial cells of arteries. It is important for controlling blood pressure and maintaining vascular integrity [3]. The endothelium's barrier function is crucially maintained by bio-ADM and if this function is lost, vascular leakage and resultant systemic and pulmonary edema can occur [4]. Individuals with HF have raised amounts of physiologically active bio-ADM in their blood stream [5]. Recent data indicate a relationship between bio-ADM levels and the amount of congestion in acute HF (AHF) patients during hospitalization as well as after discharge [6, 7].

Electrical cardiometry (EC) non-invasively determines beat-to-beat variations in the electric impedance of the neck and chest throughout the cardiac cycle. Numerous hemodynamic indicators including cardiac performance, vascular resistance in addition to fluid status can be measured at the bedside. It is becoming more often used in the evaluation and therapy of individuals with dyspnea [8]. The thoracic fluid content (TFC) determined by EC is an estimate of the total amount of fluid present in the intravascular and extravascular compartments of the thorax. It is calculated based on the principle that greater amount of fluids offer less impedance to the electrical current emitted from the electrodes and vice versa. Normal range of TFC is considered between 25 and 35 $kOhm^{-1}$. In cases of pulmonary oedema, there is an increase of all the alveolar, interstitial as well as the intravascular fluids leading to greater TFC values [9]. EC also evaluates stroke volume variation (SVV) in response to respiration, which is normally between 5 and 10%. When compared to conventional volume status indicators as CVP, SVV demonstrated to possess a very high sensitivity and the capacity to assess cardiac preload and anticipated response to fluids. High intravascular volume status with increased cardiac pre-load led to low SVV values and vice versa [10].

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The aim of this study was to assess the role of serum bio-ADM and EC-derived fluid status parameters in monitoring congestion during heart failure (HF) therapy.

PATIENTS AND METHODS

This prospective observational study was performed on 90 individuals with decompensated HF admitted at Menoufia University Hospitals and National Heart Institute through the period from December 2021 to December 2022.

Exclusion criteria: Pericardial effusion, pleural effusion, atrial fibrillation, frequent extrasystoles, tachycardia above 150 beats per minute, morbid obesity and bad echogenic window.

Every patient underwent history taking, clinical heart failure scoring (Table 1), routine laboratory tests, electrocardiography, chest x ray and conventional echocardiography. Daily invasive CVP monitoring and fluid balance were assessed. Serum bio-ADM level and EC were obtained at admission and before planned discharge [11, 12].

Conventional Echocardiography was done for all patients on admission to evaluate Left ventricular (LV) dimensions and LV ejection fraction (EF) utilizing M-Mode and 2D Simpson method. Doppler echocardiography (continuous and pulsed wave) and colour doppler were also done for all valves to detect any flow abnormalities. TAPSE (Tricuspid annular plane systolic excursion) was measured to evaluate Right Ventricular (RV) function. The estimated pulmonary artery systolic pressure (EPASP) was assessed from the tricuspid valve regurge systolic flow using a modified Bernoulli equation.

The Electrical Cardiometry (EC) hemodynamic monitor (ICON® Cardiotronics, Osypka Medical, Berlin, Germany) was used to perform measurements after applying sensor electrodes on the patients for 5-minutes. Results were obtained from the device and printed. According to the diagram provided with the device, four electrodes were placed at the following positions: At the left side of the neck below the ear, the left side of the neck base, the left mid-axillary line at the level of the xiphoid and about 5 cm beneath the third electrode. With every heartbeat, RBC alignment changes with corresponding changes in impedance and electrical conductivity. A high-frequency low-amplitude current is derived from the outermost electrodes and seeks the route of the lowest resistance through the blood-filled aorta. Furthermore, increased amount of fluids in the thorax will offer less impedance to the electrical current and vice versa. Utilizing the previous concepts, EC allowed the assessment of fluid status parameters as TFC and SVV in addition to cardiac parameters as Stroke volume (SV), Cardiac Output (CO) and Cardiac Index (CI).

Serum bioactive adrenomedullin (bio-ADM) levels were assessed by obtaining blood samples from separate punctures on the day of admission and the day of planned patient discharge. After centrifugation for 20 minutes at 2000-3000 rpm the supernatant was stored at 2-8 degree Celsius and analyzed within 30 days using BT-Lab Human Adrenomedullin ELIZA kit with standard curve 0.1-40 ng/L.

Ethical approval: The Local Ethical Committee approved the study and the patients' written authorizations were obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Utilizing SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA), data collected were examined. The mean and standard deviation (SD) were used to convey quantitative parameters. Frequency and percentage were used to convey qualitative parameters. When assessing two means, the independent-samples t-test of significance was utilized. In non-parametric variables, two-group comparisons were performed using the Mann Whitney U test. The proportions between qualitative measures were compared using the Chi-square (X^2) test of significance. The allowable margin of error was set at 5%, while the confidence interval was set at 95%. As a result, the p-value was deemed significant if it was < 0.05.

RESULTS

Table (1): Clinical scoring system for heart failure signs

Sign or system	Points	Findings
Peripheral edema	0	Up to 2 mm of depression, immediate rebounding.
	1	3-4 mm of depression, rebounding in 15 seconds or less.
	2	5-6 mm of depression, rebounding in 60 seconds.
	3	8 mm of depression, rebounding in 2-3 minutes.
Orthopnea	0	None
	1	2 pillows
	2	3 pillows
	3	> 30º
Dyspnea	0	Grade I NYHA*
	1	Grade II NYHA
	2	Grade III NYHA
	3	Grade IV NYHA
Rales	0	None
	1	Basal
	2	To < 50%
	3	To >50%

*** NYHA:** New York Heart Association dyspnea grading: **Grade I NYHA:** dyspnea only with unusual exertion. **Grade II NYHA:** dyspnea on doming ordinary activity. **Grade III NYHA:** dyspnea on doming less than ordinary activity. **Grade IV NYHA:** dyspnea at rest.

Demographic characteristics, comorbidities and drugs used among patients under the study (Table 2).

Table (2): Demographic data, co-morbidities, intracardiac devices and drugs used in the studied patients at presentation

Variable		Patients (n=90)
Age (years)		56.2 ± 12.49
Sex	**Male**	49 (54.44%)
	Female	41 (45.56%)
Co-morbidities		
Smoking		48 (53.33%)
Hypertension		39 (43.33%)
Diabetes mellitus		41 (45.56%)
Dyslipidemia		53 (58.89%)
Stroke		11 (12.22%)
RHD		9 (10%)
COPD/Asthma		27 (30%)
IHD		65 (72.22%)
CRT		16 (17.78%)
ICD		6 (6.67%)
Drugs used before admission		
Betablocker		54 (60%)
ACEI /ARBS		66 (73.33%)
SGLT2 inhibitor		39 (43.33%)
MRA		87 (96.67%)
ARNI		27 (30%)
Ivabradine		24 (26.67%)

BSA: Body surface area, **BMI:** Body mass index, **RHD:** Rheumatic heart disease, **PCI:** Percutaneous coronary intervention, **IHD:** Ischemic heart disease, **CABG:** Coronary artery bypass graft surgery. **ICD:** Implantable cardioverter-defibrillator, **CRT:** Cardiac resynchronization therapy, **ACEI:** Angiotensin-converting enzyme inhibitors, **SGLT2:** Sodium-glucose Cotransporter-2, **MRA:** Mineralocorticoid receptor antagonists, **ARBS:** Angiotensin receptor blockers, **ARNI:** Angiotensin receptor neprilysin inhibitor.

Laboratory investigations and echocardiographic parameters of the patients under the study **(Table 3).**

Table (3): Laboratory investigations and echocardiographic parameters of the patients under the study on admission

	Patients (N=90)
Laboratory investigations	
Hemoglobin (g/dL)	12 ± 1.56
Serum creatinine (mg/dL)	1.2 ± 0.42
Serum urea (mg/dL)	44.7 ± 10.25
Serum sodium (mEq/L)	128.8 ± 5.29
Serum potassium (mEq/L)	4.6 ± 0.43
TLC (cells x 10^9 /L)	11.6 ± 3.19
PaO_2 (mmHg)	63.9 ± 6.37
$PaCO_2$ (mmHg)	31.3 ± 5.82
Echocardiographic parameters	
LVEF (%)	38 ± 6.55
LVIDd (mm)	59.8 ± 13.54
LVIDs (mm)	52.3 ± 9.2
TAPSE (mm)	14.8 ± 3.43
Basal RVd (mm)	40.7 ± 5.14
IVCd (mm)	27 ± 3.37
LAd (mm)	43.5 ± 8.82
MR grade	1.6 ± 1.15
TR grade	1.2 ± 1.34
AR grade	0.3 ± 0.53

TLC: Total leucocytic count, **$PaCO_2$:** Partial pressure of carbon dioxide, **PaO_2:** Partial pressure of oxygen, **LVIDd:** Left ventricular internal diameter at end-diastole, **LVEF:** Left ventricular ejection fraction, **LVIDs:** Left ventricular internal diameter at end-systole, **RVd:** Right ventricular diameter, **TAPSE:** Tricuspid annular plane systolic excursion, **IVCd:** Inferior vena cava diameter, **LAd:** Left atrial diameter. **TR:** Tricuspid regurgitation, **MR:** Mitral regurgitation, **AR:** Aortic regurgitation.

In response to HF decongestion therapy, our results showed a statistically significant reduction in dyspnea, orthopnea, rales and peripheral oedema scores at discharge ($p<0.001$). In addition, CVP as well as body weight were also significantly reduced in response to diuresis ($p<0.001$). Serum Bio-ADM and TFC were reduced significantly at discharge compared to at admission ($p<0.001$). However, SVV was higher at discharge compared to at admission ($p<0.001$) (Table 4).

Table (4): Dyspnea, orthopnea, rales, peripheral oedema scores, vital signs, CVP, bio-ADM, diuresis, weight, net balance and electrical cardiometry parameters.

Variable	Admission (n=90)	Discharge (n=90)	p
Dyspnea score	2.5 ± 0.5	1 ± 0.81	<0.001*
Orthopnea score	2.5 ± 0.5	0.8 ± 0.8	<0.001*
Rales score	2.5 ± 0.5	1.4 ± 1.03	<0.001*
Peripheral oedema score	1.9 ± 0.78	1.1 ± 0.81	<0.001*
HR (beat/min)	100.8 ± 13.97	82.8 ± 8.24	<0.001*
RR (cycle/min)	35.93± 3.64	23.93 ± 3.68	<0.001*
CVP (cmH2O)	20.76± 4.72	11.46± 2.63	<0.001*
Serum bio-ADM (ng/L) Mean ± SD	21.82± 15.84	15.45± 7.34	<0.001*
Weight (kg)	86.1 ± 9.79	83.2 ± 9.75	<0.001*
Weight reduction (kg)	---	2.82± 0.88	---
TFC ($kOhm^{-1}$)	55.98± 12.68	33.81± 11.83	<0.001 *
SVV (%)	9.23 ± 3.79	20.86± 4.43	<0.001 *

***:** Significant as P value ≤0.05. **bio-ADM:** bio-Adrenomedullin, **CVP:** Central venous pressure, **HR:** Heart rate, **RR:** Respiratory rate, **SVV:** Stroke volume variation. **TFC:** Thoracic fluid content.

There was a positive correlation between TFC and serum bio-ADM level at admission and at discharge. CVP also had a positive association with TFC and serum bio-ADM level at admission and at discharge. A negative association existed between SVV and CVP and bio-ADM at admission and at discharge (Table 5).

Table (5): Correlation between TFC, Bio-ADM, and SVV with other parameters

	Admission		Discharge	
	r	**P**	**r**	**P**
TFC				
Net balance (negative balance)	---	---	0.323	<0.001*
Weight reduction	---	---	0.484	<0.001*
CVP	0.482	<0.001*	0.405	<0.001*
Bio-ADM	0.454	<0.001*	0.477	<0.001*
SVV	-0.308	0.003*	-0.328	<0.001*
Bio-ADM				
Net balance (negative balance)	---	---	0.443	<0.001*
Weight reduction	---	---	0.682	<0.001*
CVP	0.417	<0.001*	0.224	0.033*
SVV				
CVP	-0.576	<0.001*	-0.402	<0.001*
Bio-ADM	-0.354	0.006*	-0.318	0.002*
Net balance (negative balance)	---	---	-0.354	0.006*
Weight reduction	---	---	-0.413	<0.001*

CVP: Central venous pressure, **bio-ADM:** bio-Adrenomedullin, **SVV:** Stroke volume variation ***:** Significant as P value ≤0.05

At routine planned discharge, we noticed that patients who were clinically improved and reached normal range of TFC determined by EC i.e., 25-35 $kOhm^{-1}$ had a mean value of 26.43 ± 5.44 $kOhm^{-1}$ and bio-ADM levels mean value was 13.7 ± 3.07 ng/L. However, some patients despite apparent clinical improvement, had elevated TFC above upper normal range with a mean value of 44.38 ± 10.41 $kOhm^{-1}$ also had slightly higher bio-ADM levels with a mean value of 17.95 ± 4.11 ng/L, which we considered a result of residual congestion. There was a significant positive relation between TFC and Bio ADM at discharge in both types of patients (P value <0.001) (Table 6).

Table (6): Comparison between TFC and Bio-ADM at discharge in normal and abnormal patients

TFC values at discharge normal range (25-35 $kOhm^{-1}$)	TFC at discharge ($kOhm^{-1}$)	ADM at discharge(ng/L)	P value
	Mean ± SD	**Mean ± SD**	
Below URL (n=53)	26.4 ± 5.44	13.7 ± 3.07	<0.001*
Above URL (n=37)	44.4 ± 10.41	18 ± 4.11	<0.001*

***:** Significant as P value ≤ 0.05

In those patients, Bio-ADM detected residual congestion (P <0.035 and AUC = 0.634) at cut-off >17.2 ng/L with 51.35% sensitivity, 84.91% specificity, 70.4% PPV and 71.4% NPV (Table 7).

Table (7): Role of ADM in diagnosis of residual congestion of the studied patients

Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	P value
>17.2 (ng/L)	51.35%	84.91%	70.4%	71.4%	0.634	0.035*

PPV: positive predictive value, **NPV:** negative predictive value, **AUC:** area under the curve, ***:** Significant as P value ≤0.05.

DISCUSSION

Precise assessment of congestion in HF patients represents a major challenge as residual congestion upon discharge increases the rate of hospital re-admission, morbidity and mortality. Emerging evidence suggests that biologically active adrenomedullin (bio-ADM) levels are correlated with the severity of congestion. High plasma concentrations of bio-ADM were linked to more severe peripheral edema in addition to an extended duration of hospital stay and an increased risk of death from all causes. Furthermore, recent data indicate a relationship between bio-ADM levels and the degree of congestion in AHF patients on admission, as well as during and after hospitalization [6]. Increased rates of hospital readmission, morbidity, and death, as well as residual congestion, were linked to high bio-ADM levels upon discharge [7].

Pandhi *et al.* [7] reported that the evaluation of a patient's discharge bio-ADM levels has the potential to serve as a conveniently applicable marker for the identification of patients with persisting congestion who are at a greater risk of early hospital readmission. **Self *et al.*** [13] showed that patients who had a cardiovascular incident had greater plasma bio-ADM concentrations than those who did not. Plasma bio-ADM remained a robust predictor of a cardiovascular incident after controlling for the other biomarkers.

In our study, higher levels of serum bio-ADM in addition to high TFC values by EC were related to increased congestion scores for dyspnea, orthopnea, rales and peripheral oedema during the admission of decompensated HF patients. After receiving adequate treatment and achieving weight reduction with negative fluid balance, there was a statistically significant reduction in all previously mentioned scores in addition to lower bio-ADM levels and lower TFC values prior to discharge. Bio-ADM and TFC also showed a positive correlation with CVP. SVV, which is inversely related to the intravascular volume status was lower at admission and significantly elevated at discharge. SVV had a negative correlation with bio-ADM and CVP. These findings can be explained by the reduction in the intravascular as well as the extravascular thoracic fluid content in response to sufficient diuretic therapy. Additionally, optimizing the remaining guidelines directed heart failure medications led to adequate decongestion evident in previously mentioned parameters. In the scope of our study, **Testani *et al.*** [14] found that clinically evident congestion at the time of discharge is a robust predictor of poor outcomes as well as readmission. Yet, even in patients who had improved dyspnea and minimal clinical signs and symptoms of congestion at the time of discharge, the result may still be poor, indicating that subclinical congestion may play a role in the condition. Patients who no longer have dyspnea often nevertheless have severe clinical or hemodynamic congestion, making the relief of dyspnea alone an unreliable indicator of congestion being relieved.

In our study, there was a statistically significant reduction in CVP and body weight of the patients at discharge. This finding is supported by **Mullens *et al.*** [2] who conducted a study to assess usage of net fluid output and body weight loss as an indicator of decongestion or diuretic response. It was noted that fluctuations in weight may not reflect alterations in volume redistribution. In addition, a weak correlation exists between weight loss and fluid excretion [14]. However, it has been shown that 54% of patients admitted for acute HF gain less than 1 kg in the month before admission, indicating that volume overload only partially describes the pathophysiology of AHF and that redistribution of volume may also be a factor in the emergence of congestion symptoms and signs [15].

Fathy *et al.* [16] found that the correlation between TFC and pulmonary ultrasound in estimating extravascular lung water was strong. Consequently, a high TFC value may be an indirect indicator of pulmonary hypervolemia in the scope of advanced heart failure.

EC is a recent tool in the arsenal of devices used for noninvasive hemodynamic assessment of critical patients utilizing the concept of electrical bioimpedance. EC estimates hemodynamic parameters by monitoring variations in thoracic electrical bioimpedance throughout the cardiac cycle. Using four electrocardiogram (ECG) electrodes, the ICON (electrical cardiometry device) calculates the maximum rate of change of impedance to peak aortic blood acceleration [17,18]. The governing principle is that red blood cells change from a random orientation over diastole (high impedance) to an aligned state during systole (Low impedance). Additionally, the greater the amount of fluid in the thorax, the less resistance it will offer to the electrical signal provided from the electrodes. As a result, EC allows the assessment of fluid status [Thoracic fluid content (TFC) and stroke volume variation (SVV)] in addition to cardiac performance [Stroke volume, cardiac output, cardiac index], systemic vascular resistance (SVR) in alongside other hemodynamic parameters [19].

Despite the clinical decongestion at discharge and the reduction in TFC levels, our results showed that not all patients reached the normal values of TFC which is between 25-35. Some patients despite apparent clinical improvement and decrease in CVP, the TFC and bio-ADM remained relatively elevated. Prior to discharge, the patients below URL of TFC (n=53), had a mean value of 26.43 ± 5.44 $kOhm^{-1}$ and bio-ADM levels had mean value of 13.7 ± 3.07 ng/L. In patients still above URL of TFC at planned discharge (n=37), TFC values had a mean of 44.38 ± 10.41 $kOhm^{-1}$and bio-ADM levels also were slightly higher with mean value of 17.95 ± 4.11 ng/L showing a strong positive correlation.

This was considered residual extravascular thoracic congestion that was not clinically detected. As a result, Bio-ADM, which is related to increased vascular permeability and tissue oedema and can diagnose residual congestion in patients despite improvement in routine clinical scores. (P value <0.035 and AUC = 0.634). At cut-off >17.2 ng/L with 51.35% sensitivity, 84.91% specificity.

Using different tools to assess the congestion status of heart failure patients can aid in proper tailoring of treatment and timing of patient discharge. EC and Bio-ADM can offer objective assessment of congestion status and can detect residual congestion despite apparent clinical improvement, which can lead to better patient outcome. EC has the advantage of being non-invasive, objective and provides data regarding fluid status in addition to other hemodynamic parameters in realtime at bedside.

Limitations: EC needs to receive a good stable signal to achieve a good result. Serum bio-ADM kits are very expensive.

RECOMMENDATIONS

Serum bio-ADM can be used as a congestion marker in HF. EC through the assessment of TFC can be used as an indicator of total thoracic volume status during HF therapy. SVV can be used as an indicator of intravascular volume status. EC should be more widely used for HF patients during hospital stay as this is a non-invasive method to assess volume status of the patients and can be used complimentary or supplementary with serum bio-ADM level.

CONCLUSION

Bio-ADM was found to be elevated in cases of increased vascular permeability and tissue congestion and can be used in follow up of HF patients. EC is an easy noninvasive tool that can provide detailed assessment of several hemodynamic parameters including parameters of volume status as TFC and SVV. Both can help detect residual congestion despite apparent improvement in routine clinical scores. Using different tools to assess the congestion status can aid in avoiding discharge of patients with residual congestion till full decongestion is achieved in order to improve patient quality of life and prognosis.

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