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ORIGINAL ARTICLE

Relation between Inferior Vena Cava and Coronary Sinus Diameters as Predictors of Long-Term Outcomes in Patients with Heart Failure

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ABSTRACT

Background: Whenever heart failure (HF) become diagnosed either by hospital admission or even in patients without symptoms, should be treated as life-threatening condition with an adverse prognosis ,this study aims to evaluate diameters of coronary sinus and inferior vena cava with brain natriuretic peptide (BNP) level as predictors of outcomes, re-hospitalization, and cardiovascular deaths in heart failure. **Methods:** BNP level measurement and echocardiographic assessment of ejection fraction of left ventricle, diameter of coronary sinus and inferior vena cava. **Results:** In patients with heart failure with reduced ejection fraction (HFREF) ,by simple linear regression, high New York Heart Association (NHYA) class, BNP level, Inferior vena cava(IVC) ex , IVC in mean coronary sinus (CS) diameter, right ventricular diameter (RVD),
fractional area change (FAC), and pulmonary artery pressure (PAP) was significant predictors of poor , with multiple logistic regression BNP level(p value <0.5 , HR: 1.007 95%CI) , IVC ex (p value <0.5 , HR: 1.185 95%CI), mean CS (p value <0.5 , HR: 1.685 95%CI) were the independent prognostics of adverse outcomes in heart failure patients, In patients with heart failure with preserved ejection fraction (HFPEF) by simple linear regression NHYA class, BNP level , mean CS diameter , IVC ex, PAP,FAC, diastolic dysfunction grade were significant predictors of poor outcomes ,with multiple logistic regression only BNP level (p value <0.5 , HR: 1.50495%CI and IVC ex (p value <0.5 , HR: 1.006 95%CI) and mean CS diameter(p value <0.5 , HR: 1.07895%CI) were the independent predictors of poor outcomes .**Conclusions:** Diameters of CS and IVC and BNP level are a good and simple tools for prediction of adverse outcome in HF subjects.

Keywords: Heart failure; Ejection fraction; Inferior vena cava; coronary sinus; brain natriuretic peptide.

INTRODUCTION

Whenever heart failure (HF) become diagnosed either by hospital admission or even in patients without symptoms, should be treated as life-threatening condition with an adverse prognosis such as mortality and hospital readmissions [1]. HF could be categorized according to ejection fraction to reduced, mid-range and preserved. Description of heart failure is historically on base of assessment of the ejection fraction of left ventricle (LV), HF comprises a widespread array of patients. Reduced ejection fraction known when ejection fraction is below 40% and when ejection fraction ≥50% called "preserved "ejection fraction, and the area between 40-50% called" mid-range" HF [2].
The cardiac muscle discharges natriuretic peptides in response to cardiac muscle strain and expanded volume of intravascular compartment and provide accurate diagnosis for HF, in comparison with echocardiography or skilled clinical examination [3].
An elevated level of natriuretic peptides type B upon hospital admission could predict in-hospital death in HF with acute decompensation regardless the ejection fraction, independent of other clinically examined and laboratory parameters [4]**.**
When right atrial pressure increase IVC expands, evaluation of size of IVC by echocardiography is easy and assess pressure in right atrium quantitatively, in patients with HF irrespective to the ejection fraction, enlarged IVC diameter predicts patients with adverse outcomes [5].
Coronary sinus (CS) defined anatomically as tubular structure and by echocardiography is a sonolucency in the posterior atrioventricular

groove. The anatomic alteration with coronary sinus dilation could be assessed with echocardiography and considered part of cardiac remodeling process and gives additional information for prognosis and functional grade in HF population [6].

Methods

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Study design:

This cohort study was conducted in the period between March 2018 to September 2019 at emergency room (ER), cardiac care units (CCU), ward and echocardiography units of cardiology department, Zagazig University Hospitals.

Study Population

170 patients with acute HF enrolled to the study and divided into two equal groups regarding LV ejection fraction.

Inclusion criteria: According to HF guidelines, the included population was classified into:

(A) With reduced ejection fraction HF, diagnosed by the following criteria:

1-Clinical data suggesting HF as past history for hypertension and ischemic heart disease, symptoms at presentations as orthopnea, examination as lower limb edema, expanded pressure in jugular vein, and heart apex displacement)

2-LV ejection fraction is below 40%

(B) With preserved ejection fraction HF, diagnosed by the following criteria:

1- Clinical data suggesting HF.

2- Ejection fraction considered preserved if it more than 40 percent

3-BNP level more than 35 pg/ml

4-One more criteria as related heart disease as hypertrophy of LV of enlarged index of left atrium more than 34 mL/m2) [2].

Exclusion criteria: kidney disease (serum creatinine level more than 1.5 mg/dl regardless to hemodialysis therapy), liver cirrhosis, hypoalbuminemia, malignancy, rheumatic heart involvement, constrictive pericarditis, hypothyroidism, and chronic obstructive pulmonary disease

All patients expressed to:

widespread history taking for current state of dyspnea and NHYA score and for previous conditions as diabetes mellitus, hypertension and ischemic coronary arterial disease, physical tests as blood pressure (at systole and diastole), heart rate.

Electrocardiogram: for detection of atrial fibrillation and left bundle branch block.

Laboratory tests: BNP level by ELISA Kit assays which uses sandwich double-antibody enzyme-linked immunosorbent assay to detect the level of BNP in samples level above 100 pg/ml for exclusion of other causes of dyspnea and make diagnosis of HF.

Echocardiographic examination:

Echocardiography was performed on *SIEMENS ACUSON X300* echocardiography machine using two dimensional probe-M5S-with frequency between two and four megahertz with tissue doppler imaging (TDI) interrogation for cardiac velocities with simultaneous electrocardiogram recording .Subjects will be examined in the decubitus left lateral position while quite breathing. Recorded data calculated by different parameters was performed according to the quantification of chambers guidelines [7].

Measurements of IVC diameters: Through the subcostal window, away by one to two cm from opening to the right atrium with perpendicular alignment to IVC long axis, in consequence to inspiration the intrathoracic pressure becomes negative and cause pooling of blood from systemic veins to the right ventricle causing collapse of the IVC [7].

Measurements of coronary sinus diameters: Coronary sinus could be assessed by echocardiography in posterior groove between atria and ventricles as a sonolucency, during ventricular systole the size of coronary sinus reached its maximal level and coronary sinus diameter is measured at that time, three measurements were measured first at opening the coronary sinus to right atrium , one cm end , and mid-way between the previous points ,coronary sinus mean diameter could be calculated by summation of proximal diameter to mid diameter to distal diameter divided by 3 [6].

Left ventricular ejection fraction : M-mode measurements on parasternal long-axis window of left ventricle and at right angles of LV long axis , and assessed at tips of leaflet the mitral valve, calipers should be situated on the border between septum and cavity and the border between posterior wall and pericardium and ejection fraction calculated with Teichholz formula (EF=VD-VS/VD)[7].

Myocardial performance index or Tie index: Doppler on tricuspid flow in apical 4 chamber view to assess tricuspid rapid filling velocity and peak atrial velocity along with ejection time. MPI

was calculated using the following formula; RV MPI = (IVRT+IVCT) / ET [7].

Excursion of tricuspid annular plane systolic: Measuring tricuspid annular excursion from diastolic last period to systolic last period by motion mode on lateral tricuspid valve annulus in window of apical four chambers [7].

Change in RV fractional area: Calculated by subtraction of area of right ventricle at end systolic from area of right ventricle at end diastolic divided by area of right ventricle end diastolic multiplied with 100 in window of apical four chambers [7].

Pulmonary artery pressure: Mean pressure could be calculated by adding one third of systolic pressure to two thirds of diastolic pressure [7].

STATISTICAL ANALYSIS

Analysis of the study data was managed by version 23 of (SPSS). Data was presented and appropriate analysis was performed regarding the type of data gained for every parameter. Descriptive statistics includes mean and standard deviation (± SD) for data presented numerically. Frequency, percentage and chi square tests of data presented categorically. P>0.05 was non-significant, p <0.05 considered significant. Correlation by Pearson's test had been performed to estimate and test the relationship between coronary sinus diameter, IVC diameter and BNP level. Simple linear regression and then multiple regression to detect the independent variables linked to adverse HF outcomes.

RESULTS

Patients with acute decompensated HF classified into 2 groups regarding ejection fraction;

Group (1): 85 patients with ejection fraction below 40%.

Group (2): 85 patients with ejection fraction equal or more than 40%

Regarding to demographic data there was a significant difference between the two groups regarding history of hypertension, P value <0.05 while there was no considered difference among the study groups regarding sex, age, body mass index , history of diabetes mellitus, smoking p >0.05 , as represented in table no 1.

Regarding clinical and laboratory data there was a statistically significant difference among study groups regarding coronary artery disease history, systolic ,diastolic blood pressure and , LBBB in ECG P<0.05 while there was no difference noticed among the study groups regarding NHYA class, and heart rate and BNP level p>0.05 as represented in table no 2.

Regarding to echocardiographic data there was highly noticed difference among the study groups regarding IVC diameter in expiration , pulmonary artery pressure, TAPSE, FAC and P value <0.05 while there was no recorded difference between both groups regarding mean coronary sinus diameter , Tei index p>0.05 as represented in table no 3.

There was a significant positive correlation between BNP level and IVCex r=0.426, P<0.001 and coronary sinus mean diameter r=0.457, P<0.001 and there was significant positive correlation between coronary sinus mean diameter and IVC ex r=0.519, P<0.001.

In group (A) using regression (simple linear) test we found that high NHYA class, BNP level, IVC ex , IVC in mean CS diameter, RVD, FAC, and PAP was significant predictors of adverse outcomes in heart failure patients as represented in table no 4.

But multiple regression analysis we found that BNP level, IVC ex, CS mean diameter were the independent predictors of poor outcomes in patients with HF as represented in table no 5.

In group (B) by simple linear regression NHYA class, BNP level, mean CS diameter, IVC ex, PAP, FAC and diastolic dysfunction grade were significant predictors of undesired outcomes rehospitalization and CV death upon follow up as represented in table no 6.

By multiple logistic regression only BNP level, mean CS diameter and IVC ex were the significant predictors of poor outcomes rehospitalization and CV death as represented in table no 7.

Table1: Demographic data of study groups:

	Group A n=85		Group B n =85		t	P
Age (mean ±SD)	57.68±11.9		57.8±10.8		0.067	0.946
BMI (kg/m$^{2)}$	24.15±4.87		25.66±5.21		-1.96	0.493
	No	%	No	%	χ 2	P
Sex (no%)						
Female	38	44.7	40	47.1	0.095	0.758
Male	47	55.3	45	52.9		

	Group A n=85		Group B n =85		t	P
HTN	45	52.9	62	72.9	7.28	0.007
DM	51	60.0	41	48.2	2.36	0.124
Smoking	23	27.1	24	28.2	0.864	0.5

BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, SD: standard deviation, t:t test, χ 2: chi square test, p< 0.05 is significant.

Table 2: clinical and laboratory data of study groups:

		Study groups group A(HFREF)		group B (HFPEF)			
		No	%	No	%	χ^2	p-value
Past history	CAD	49	57.6	29	34.1	9.47	0.002
NHYA class							
II		35	41.2	33	38.8	0.506	.7760
III		31	36.5	29	34.1		
IV		19	22.4	23	27.1		
ECG	AF	44	51.8	36	42.8	1.511	0.141
	LBBB	43	50.6	24	28.2	8.89	0.002
		Mean ±SD		Mean ±SD		t	P
SBP (mmHg)		107.53±11.51		158.41±22.26		-18.721	.0000
DBP (mmHg)		68.76±8.45		98.12±12.56		-17.879	.0000
Heart rate (beat/minute)		96.46±15.15		90.18±13.99		2.804	0.525
BNP (pg/ml)		360.36±84.7		362.46±74.96		0.17	0.86

CAD: coronary artery disease, NYHA: New York heart association, AF: atrial fibrillation, LBBB: left bundle branch block, SBP: systolic blood pressure, DBP: diastolic blood pressure, BNP: brain natriuretic peptide. SD: standard deviation: t: t test ,χ^2:chisquare test, p< 0.05 is significant

Table 3: Echocardiographic data of both groups:

	Study groups Group A		Group B		t	p-value
MEANCSD (mm)	12.82±1.82		12.91±1.58		-0.356-	.7220
IVCEX (mm)	23.05±5.03		20.94±5.18		2.689	.0080
IVCIN (mm)	17.67±5.32		15.40±4.89		2.900	.0040
PAP (mm hg)	41.98±10.66		32.95±8.23		6.180	0.000
RVD (mm)	34.15±5.31		30.66±3.60		5.022	0.000
TAPSEE (mm)	19.04±5.97		23.94±5.18		-5.724-	.0000
FAC (%)	31.42±8.43		37.52±4.67		-5.831-	0.000
Left atrium volume index(ml/$m^{2)}$	34.18±6.98		31.75±4.68		2.660	0.009
Diastolic dysfunction I	68	80.0	28	32.9	39.64	0.0001
II	11	12.9	26	30.6		
III	6	7.1	31	36.5		
Tie index	0.82±0.1030		0.79±0.070		2.344	0.200

CS: coronary sinus, IVC ex :inferior vena cava in expiration , IVC in :inferior vena cava in inspiration , PAP: pulmonary artery pressure ,RVD: right ventricular diameter, TAPSE: tricuspid annual plane systolic excursion, FAC: fractional area change ,t: t test p< 0.05 is significant

Table 4: simple linear regression for predictors of poor outcome in Group (A):

Variables	Poor out comes in group A					*95% C.I.HR*	
	B	S.E.	Wald	Sig.	HR	Lower	Upper
NHYA class	3.069	0.468	42.947	0.000	21.516	8.593	53.872
BNP level	0.045	0.010	22.406	0.000	1.047	1.032	1.136
IVC ex	0.378	0.105	12.822	0.000	1.459	1.046	1.738
IVC in	0.230	0.043	28.965	0.000	1.259	1.158	1.369
Mean Cs	0.707	0.102	47.717	0.000	2.028	1.660	2.48
RVD	0.089	0.032	7.905	0.005	1.093	1.027	1.164
FAC	-0.065-	0.023	7.968	0.005	0.937	0.896	0.980
PAP	0.046	0.015	9.654	0.002	1.047	1.017	1.079

NYHA: New York heart association ,BNP: brain natriuretic peptide , IVC ex :inferior vena cava in expiration , IVC in :inferior vena cava in inspiration ,, CS: coronary sinus , RVD: right ventricular diameter, FAC: fractional area change ,PAP: pulmonary artery pressure ,SE: standard of error, HR: hazard ratio, CI: confidence interval p< 0.05 is significant, Sig: significance.

Table 5: Multiple logistic regression of predictors of poor outcome in Group (A):

Variables	Poor out comes in group A					95% C.I.HR	
	B	S.E.	Wald	Sig.	HR	Lower	Upper
BNB	.008	.004	6.834	.012	1.008	1.003	1.017
IVCEX	.168	.051	8.457	.004	1.185	1.060	1.344
Mean CSD	.482	.152	10.540	.001	1.685	1.204	2.089

BNP: brain natriuretic peptide, IVC ex: inferior vena cava in expiration CS: coronary sinus, SE: standard of error, HR: hazard ratio, CI: confidence interval, p< 0.05 is significant, Sig: significance

Table 6: simple linear regression for predictors of poor outcome in group (B):

Variables	Poor out comes in group B					95% C.I.HR	
	B	S.E.	Wald	Sig.	HR	Lower	Upper
NHYA class	3.276	0.636	26.556	0.000	26.459	7.612	91.969
BNP level	0.014	0.002	41.559	0.0001	1.014	1.010	1.018
IVC ex	0.339	0.053	40.653	0.000	1.403	1.264	1.557
Mean Cs	0.707	0.102	47.717	0.000	2.028	1.660	2.48
FAC	-0.065-	0.023	7.968	0.005	0.937	0.896	0.980
PAP	0.230	0.043	28.965	0.000	1.259	1.158	1.369
Diastolic dysfunction grade	0.072	0.028	6.752	0.009	1.074	1.018	1.13

NYHA :New York heart association ,BNP: brain natriuretic peptide , IVC ex :inferior vena cava in expiration,, CS: coronary sinus ,FAC: fractional area change ,PAP: pulmonary artery pressure ,SE: standard of error, HR: hazard ratio, CI: confidence interval p< 0.05 is significant, Sig: significance .

Table 7: Multiple logistic regression of predictors of poor outcome in Group (A):

Variables	Poor out comes in group B				95% C.I.HR		
	B	S.E.	Wald	Sig.	HR	Lower	Upper
BNB	0.462	0.185	5.770	0.010	1.504	1.086	2.248
IVCEX	0.009	0.005	12.782	0.000	1.006	1.003	1.022
Mean CSD	0.092	0.051	5.217	0.021	1.078	1.011	1.173

BNP: brain natriuretic peptide, IVC ex: inferior vena cava in expiration CS: coronary sinus, SE: standard of error, HR: hazard ratio, CI: confidence interval, p< 0.05 is significant, Sig: significance.

DISCUSSION

The present study was performed on one hundred and seventy cases of acute HF to assess the CS diameter, IVC diameters by echocardiography in addition to BNP as prognostics of poor outcomes on six months of HF follow up.

Population of the present study were allocated into two groups regarding ejection fraction 85 patients presented by HFREF, 85 patients with HFPEF.

Both groups were near similar regarding demographic criteria apart from history of hypertension that was statistically significant in patients with HFPEF that was concordant to **Bhatia et al.,** that found that HFPEF patients tend to be elder, with hypertension but less with coronary ischemic heart [8].

Coronary artery disease history was remarkable in HFREF population and patients with HFPEF had higher resting blood pressure that was concordant to **Tsuchihashi-Makaya et al.,** who found HFPEF patients were likely to be elder, women , currently hypertensive with atrial fibrillation and coronary arterial disease not the major cause of HF when compared to reduced EF patient [9].

Left bundle branch block was significantly more in patients with HFREF that was concordant to **Hawkins et al.,** in CHARM trial, found that patients with reduced ejection fraction HF have more bundle branch block incidence than patients with preserved ejection fraction HF [10].

There was no difference recorded between both groups in consideration of level of BNP and that was different to the results of van Veldhuisen et al., who found that patients has HFREF have larger levels of BNP when compared with HFPEF patients , patient incriminated to that study had mild HF with different group sampling for explanation to that difference [11].

BNP level was significant predictor of poor consequence as rehospitalization and CV death by simple linear regression and was independent prognostic of outcomes as rehospitalization and CV death by multiple logistic regression, **Imamura et al.,** found that the plasma level of BNP was a predictor of undesired consequence of HF as deaths of cardiac origin and hospitalization[12].

There was positive correlation between all CS measurements and NHYA functional grade, right ventricle diameter and function (TAPSE and FAC , LA volume index in both types of heart failure (HFREF, HFPEF) that results was parallel to **Yuce et al.,** who found that in patients with HF there was remarkable correlation in positive manner between coronary sinus diameters and volumes of left and right ventricles[6].

There was positive correlation between both IVC diameters and NHYA functional and that results could be explained as in left sided HF that right ventricular function may be diminished, diastolic dysfunction of right ventricle diminish RV filling and increases diastolic pressures of right atrium, there is close association between failure of right ventricle and NYHA grade [13].

Pulmonary artery pressure was markedly higher in patients with HFREF, **Bosch et al.,** found systolic and diastolic functions of right ventricle was higher in patients with HFREF. That results may be partly endorsed to primary diseases of right ventricle and or interdependence between ventricles. In our study, coronary arterial diseases and ischemia induced myopathy were more prevalent in patients with HFREF, these observations also propose that coronary arterial diseases and ischemia induced myopathy may have added to the RV impairment mechanism [14].

Pulmonary artery pressure was a significant predictor by simple linear regression of ominous outcomes such as rehospitalization and CV death that results were concordant with **Meluzin et al.,** who found that for hospitalization for HF decompensation is predicted by the summation of peak velocity at level of TV during systolic contraction of 10.8 cm/s or fewer added to peak

velocity of TV at early diastole of 8.9 cm/s or fewer added to RV Doppler index Tei index of 1.20 or extra 15].

Significantly ,IVC diameters in the current research was larger in patients with HFREF in difference with **Van Aelst et al.,** who found that there was no difference between IVC diameters in HPREF and HFPEF in patients with HF in acute decompensation thought it was also larger in HFREF patients [16].

Cardiac function and venous congestion could be instantly summarized with IVC diameter, systolic or diastolic LV impairment is responsible for left atrial hypertension, pulmonary arterial hypertension occurs in response to pressure back transmission into the pulmonary circulation **[**17].

IVC diameter in expiration was a significant predictor by simple linear regression of ominous consequences as rehospitalization and CV death and was independent predictor of outcomes by multiple regression analysis , and that results was concordant with **Pellicori et al.,** who found that for prediction of adverse prognosis as worsening HF that required admission or death due to CV causes , IVC diameter was the most prominent indicator for such prognosis[5].

Curbelo et al.,2018 found that in chronic HF patients in one year follow up, HF worsen in 70.9 percent of patients when index of IVC collapsibility below 30 percent and in 39.1 percent of patients when index of collapsibility above 50 percent , in regards to hospitalization, 45.3 percent of patients with index of IVC collapsibility below 30 percent hospital admission was required , in comparison with 5.9 percent of patients with index of IVC collapsibility above 50 percent. In the group of IVC collapsibility index below 30 percent the mortality was greater with 25.7 percent of deaths from all causes and 18.6 percent deaths due to HF , whereas in the index IVC collapsibility above 50 percent group deaths from all causes is 13 percent and deaths due to HF is 4.7 percent ,so IVC measurement is recommended as a valuable tool for follow up and detection of prognosis in patients with HF [18].

All coronary sinus diameters (proximal, mid, distal, and mean) by regression (simple linear) were significant predictors of hospital readmission and CV deaths upon follow up, by multiple logistic regression only mean coronary sinus diameter was independent predictor of hospital readmission upon follow up, as far as we know , this study is the first to examine the relation between the coronary sinus diameters and outcomes in patients presented with HF.

Pratt et al., documented that increased CS pressure depress contractility, prolong active process of relaxation and increases stiffness of the ventricles, these settlements of cardiac function determination do not seem to have a direct influence on the coronary sinus hypertension or reflex activation of autonomic nervous system but may be made by accumulation of fluids inside the interstitial compartment [19].

In routine practice, it is well known that the more ejection fraction is impaired or the more heart chambers are dilated, the CS becomes more dilated so expanded coronary sinus is a part cardiac muscle process of remodeling and indicates poor prognostic value [6].

Form all we know this research is the first to assess CS diameter, IVC diameter in addition to BNP level as predictors of adverse consequences of acute HF patients.

CONCLUSIONS

Both CS diameter and IVC measurement in addition to BNP are good and simple tools for detection of prognosis either rehospitalization or cardiovascular deaths in acute HF represented patients

Conflict of interest

The authors declare no conflict of interests.

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