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Peak Early Diastolic Transmitral Velocity As A Surrogate Marker Of Short-Term Atrial Fibrillation Recurrence After Electrical Cardioversion

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Abstract

Objectives: The aim of this study was to assess if peak early diastolic transmitral velocity (E-wave) can be used as a surrogate marker of short-term atrial fibrillation (AF) recurrence.

Methods: We prospectively studied 57 consecutive patients who underwent electrical cardioversion (ECV) for AF and successfully converted to sinus rhythm. N-terminal brain natriuretic peptide levels (BNP) before and after ECV was measured in all patients. The follow-up included physical examination and a 12-lead electrocardiogram 14 days and one month after the ECV.

Results: In 42.1% patients AF recurred during one-month follow-up period. Gender, presence of mitral regurgitation, treatment with angiotensin II receptor blocker and left atrium diameter independently influenced E-wave velocity before ECV. E-wave velocity fell immediately after successful ECV (94.0±27 cm/s vs 79.7±23 cm/s, P<0.0001). E-wave velocity before ECV>94 cm/s and E-wave velocity after ECV >80 cm/s were predictors of one-month AF recurrence [(Hazard Ratio) HR=3.62 with 95% CI=1.49-8.78 and HR=3.76 with 95% CI=1.40-10.10, respectively]. E-wave velocity before and E-wave velocity after ECV remained predictors of AF recurrence but only in non-hypertensive patients (HR=1.01 with 95% C.I=1.01-1.03 and HR=1.03 with 95% C.I=1.01-1.06, respectively). Similarly, BNP levels before and after ECV were associated with an increased the risk of AF recurrence (HR=1.14 with 95% C.I 1.01-1.28 and HR= 1.16 with 95% C.I 1.03- 1.31, respectively). The addition of BNP levels to E-wave velocity before ECV appeared to have incremental value on short-term AF recurrence but at a marginally statistical significance (LR chi2=3.28, p=0.07).

Conclusions: E-wave velocity before and after ECV appears to be a marker of short-term recurrence of AF.

Introduction

Atrial fibrillation (AF) has a high risk of recurrence mainly in the first month after electrical cardioversion (ECV).[1] Several clinical and echocardiographic entities have been proposed as predisposing factors to AF recurrence such as: gender, age, AF duration before cardioversion, number of previous recurrences, left atrial size, left ventricular (LV) function, left atrial appendage velocities and the presence of coronary heart disease.[2-6] Furthermore, Doppler transmitral flow indices have been investigated as risk factors of AF[7] and several studies have investigated the changes in transmitral velocity pattern and N-terminal brain natriuretic peptide levels (BNP) after ECV.[8,9] The rational of this study was to find a simple echocardiographic index like peak early diastolic transmitral velocity as a surrogate marker of predicting short-term atrial fibrillation recurrence and to explore if the addition of BNP had an incremental value over this marker.

Key Words:

Transmitral Pattern, Atrial Fibrillation, BNP.

Disclosures:
None.

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Methods

Patients

We prospectively studied 57 consecutive patients who underwent ECV at the Onassis Cardiac Surgery Center for AF and who were successfully converted to sinus rhythm. The recruitment period was from January 2006 to December 2006.

The objective of the study was to assess if a simple echocardiographic diastolic index (E-wave) can be used as a surrogate marker of short-term AF recurrence in patients who successfully converted to sinus rhythm.

All patients continued the same antiarrhythmic medication and other drugs before, during and after the ECV. All patients received anticoagulation (per os acenocoumarol or warfarin) with a target INR 2-3 for 3 weeks before and 4 weeks after ECV in order to avoid embolic complications.

All patients underwent echocardiographic study before ECV including M-Mode, and 2D-examination as well as pulsed wave, continuous wave and color Doppler evaluation. We examined left

Table 1: Baseline clinical and echocardiographic characteristics of patients

	All patients N =57	SR Maintenance N =33	AF recurrence N =24	P
Mean age±SD (years)	65.2±12	65.9 ±11	64.2±13	0.607
Gender (male: female)	44:13	28:5	16:8	0.106
Fractional shortening±SD	30±13	31±15	30±9	0.671
LA size AP dimension±SD (cm)	4.7±0.8	4.7±0.7	4.7±0.9	0.879
LA Area±SD (A4C) (cm2)	35±12	35±11	35±12	0.998
Underlying disease n (%)				
CAD	15 (26.3%)	10 (30.3%)	5 (20.8%)	0.423
Mitral regurgitation	8 (14%)	5 (15.2%)	3 (12.5%)	0.776
Hypertension	34 (59.6%)	24 (72.7%)	10 (41.7%)	0.018
Diabetes Mellitus	7 (12.3%)	4 (12.1%)	3 (12.5%)	0.996
Lone AF	6 (10.5%)	2 (6.1%)	4 (16.7%)	0.198
Medication n (%)				
AT II Inhibitors	26 (45.6%)	13 (39.3%)	13 (54.2%)	0.206
Amiodarone	39 (68.4%)	22 (66.7%)	17 (70.8%)	0.716
Propafenone	5 (8.8%)	3 (9.1%)	2 (8.3%)	0.816
Sotalol	2 (3.5%)	2 (6.1%)	0 (0%)	0.214
Beta-Blockers	20 (35.1%)	12 (36.4%)	8 (33.3%)	0.567

LA=Left atrium, SD=Standard Deviation, A4C=Apical 4-chamber view, CAD=Coronary Artery Disease, AF=Atrial Fibrillation, AT II Inhibitors=Angiotensin Receptor II Inhibitors

ventricular function (measurement of fractional shortening) and left atrial size (measurement of left atrial diameter and area). Transmitral flow velocity was measured at the tip of mitral valve leaflets on long-axis view of the left ventricle. The peak atrial systolic (A) and peak early diastolic velocities (E) were measured from transmitral flow velocity. The function and anatomy of cardiac valves were also studied.

All blood samples were drawn by venipuncture and collected in EDTA-containing tubes. The samples were then centrifuged and plasma was stored in aliquots at -20oC within 30 minutes. Levels of plasma NT-proBNP were determined using an Elecsys 1010 Roche Diagnostics Pro-BNP (Roche Diagnostics, Germany) Electrochemiluminescence sandwich immunoassay. The analytical range extends

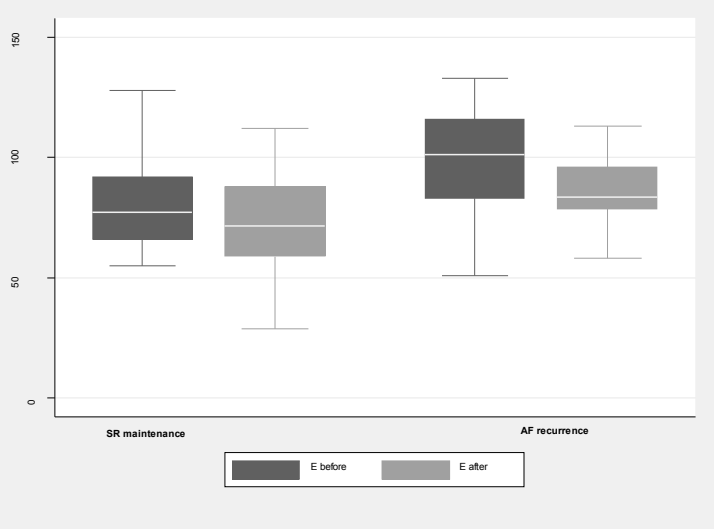

Figure 1: Boxplots of E-wave velocity before and after ECV between the two groups

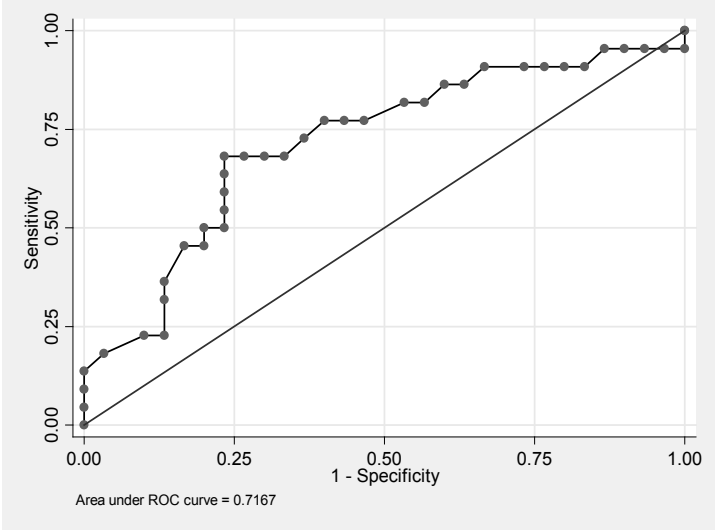

Figure 2: ROC analysis for E-wave velocity before ECV. Area Under Curve (AUC)=0.717, P=0.008

from 20 to 35,000 pg/mL.

The prospective follow-up of the patients included physical examination and an ECG 14 days and one month after the ECV. In addition to this, we advised every patient of our study that whenever he had symptoms, such as palpitations, or whatever would have suggested an AF recurrence to come for an urgent visit in order to perform an ECG and detect any possible recurrence of the arrhythmia.

The study complies with the Declaration of Helsinki and an informed consent of the subjects has been obtained.

Statistical Analysis

Categorical data were summarized as frequencies or percentages. Continuous data were summarized as mean ± Standard Deviation (S.D). We used t-test for independent samples to compare means of continuous variables and chi-square test for qualitative variables. We used the Kolmogorov-Smirnov test for normality in order to evaluate assumption of t-test. The natural logarithm of the variables BNP before and BNP after (as independent variables) was used to evaluate assumption of linear regression analysis. Cut-off analysis using Receiver-Operating-Characteristic (ROC) analysis revealed the level of early diastolic transmitral peak velocity with best combination of sensitivity and specificity that discriminate patients according to whether they had an AF recurrence or not. Discriminant analysis after calculating λ-Wilk's showed which of the continuous variables had the best discriminating ability for the outcome. We used linear regression analysis in order to identify linear correlations between continuous variables using R-square. Multiple linear regression analysis was conducted using the "backward stepwise" estimation with p-value (Wald test) for entry equal to 0.05 and p-value (Wald test) for removal equal to 0.10 beginning with full model. A Cox proportional hazard model was used to assess the association of baseline variables with the end point of AF recurrence during the first month of follow-up after the successful electrical ECV. The Cox analysis used to evaluate Hazard Ratios (HR) (and their 95 % C.I) of early diastolic transmitral peak velocity and BNP as predictors of one-month AF recurrence. We used likelihood ratio test to evaluate incremental value of BNP levels added on E-wave before ECV value on short-term AF recurrence using the Cox models.

We considered the results significant when the p value was <0.05.

Data was analyzed using STATA 9.1 College Station, Texas, USA.

Results

Follow-Up

During the one month follow-up period 24 patients (42.1%) had AF recurrence. Patient baseline demographic, clinical characteristics and echocardiographic variables are shown in Table 1.

Clinical Characteristics And Medication

There were no differences in age, gender and underlying diseases (All Ps>0.05) except for hypertension between patients with or without AF recurrence. Specifically, 34 patients (59.6%) had a history of arterial hypertension. The group of AF recurrence had significantly lower prevalence of history of hypertension compared to other group (27.3% vs 72.7% respectively, P=0.018). There were no differences concerning the antiarrhythmic medication and beta-blocking agents (Table 1).

Echocardiographic Parameters And AF Recurrence.

There were no differences in left atrial diameters, LV fractional shortening, before and after ECV, and in the prevalence of mitral regurgitation (All p-values>0.05). The early diastolic transmitral peak velocity before the ECV (E-wave before) was higher in patients with one-month AF recurrence compared to group with SR maintenance (104±28 cm/s vs 84.5±22 cm/s, P=0.006). Similarly, the early diastolic transmitral peak velocity after ECV (E-wave after) was higher in patients with AF recurrence compared to group with SR maintenance (88.3±19 cm/s vs 73.6±21 cm/s, P=0.012) (Fig. 1). Receiver-Operating-Characteristic (ROC) analysis identified appropriate cutoff values of E-wave before and E-wave after with best combination of sensitivity and specificity for predicting one-month AF recurrence (Figure 2 & 3) (Area Under Curve (AUC)=0.717, P=0.008 and AUC=0.693, P=0.018, respectively). The cutoff values of E-wave before was more than 94 cm/s (sensitivity=68%, specificity=77%) and of E-wave after ECV greater than 80 cm/s (sensitivity=76%, specificity=64%) provided the best discrimination between patients without and with AF recurrence. According to the above cutoff points, 27 patients (47.4%) had E-wave before > 94 cm/s and 31 patients (54.4%) E-wave after >80 cm/s.

Table 2: Results from univariate linear regression analysis using as independent variable E-wave before ECV. We present β regression coefficient with corresponding C.I and Wald test P-values

Dependent variable	β	95% C.I	P
Gender (male vs Female)	-28.81	-39.70 to -5.91	0.009*
Age (years)	0.60	0.03 to 1.18	0.039*
Underlying Disease			
CHD	10.70	-6.52 to 27.93	0.218
Mitral regurgitation	13.00	-7.13 to 33.13	0.201
History of hypertension	-0.58	-15.37 to 14.20	0.937
Treatment			
ATII Blockers (0: No vs 1: Yes)	12.90	-0.91 to 26.72	0.067
Beta-blockers (0: No vs 1: Yes)	-5.82	-21.42 to 9.76	0.455
Echocardiographic parameters			
LA diameter (mm)	0.67	-0.29 to 1.65	0.169
Fractional shortening	0.50	-0.32 to 1.34	0.224
*P<0.05			

ECV=Electrical cardioversion, LA= Left Atrium, CHD=Coronary Heart disease, AT II Blockers=Angiotension Receptor II blockers

Table 3: Results from multivariate linear regression analysis using as independent variable E-wave before Cardioversion. We present β regression coefficient with corresponding Confidence Intervals and P-values of Wald tests. Age, beta blockers treatment, History of hypertension, presence of CAD and ejection fraction were excluded from the final model

Dependent variable	β	95% C.I	P
Gender (male vs Female)	-28.56	-48.05 to -9.07	0.005*
Underlying Disease			
Mitral regurgitation (0:No vs 1:Yes)	26.66	4.84 to 48.47	0.018*
Treatment			
ATII Blockers (0:No vs 1:Yes)	19.44	5.43 to 33.45	0.008*
Echocardiographic parameters			
LA diameter (mm)	0.87	-0.06 to 1.81	0.068
*p<0.05			

LA= Left Atrium, CHD=Coronary Artery disease, AT II Blockers=Angiotensin Receptor II blockers.

Early diastolic transmitral peak velocity became lower after successful ECV than before ECV (94.0±27 cm/s vs 79.7±23 cm/s, P<0.0001).

Correlation Of E-Wave Before ECV With Clinical And Echocardiographic Predictors Of AF Recurrence.

We tried to correlate linearly E-wave before ECV with clinical and echocardiographic predictors. Firstly, we performed univariate linear regression analysis using several dependent variables. Results are shown in Table 2. Finally, multivariate linear regression analysis revealed that gender, presence of mitral regurgitation, antihypertensive treatment with angiotensin receptor II inhibitors (AT II inhibitors) and LA diameter (mm) influenced independently E-wave levels before ECV (Table 3). Specifically, female patients had greater E-wave levels than males (P=0.005) and patients with mitral regurgitation had higher E-wave levels (P=0.018)

Prediction Of Short-Term AF Recurrence Based On Clinical And Echocardiographic Parameters.

Univariate Cox regression analysis revealed that E-wave before >94 cm/s and E-wave after >80 cm/s were predictors of one-month AF recurrence, followed by E-wave before ECV and E-wave after

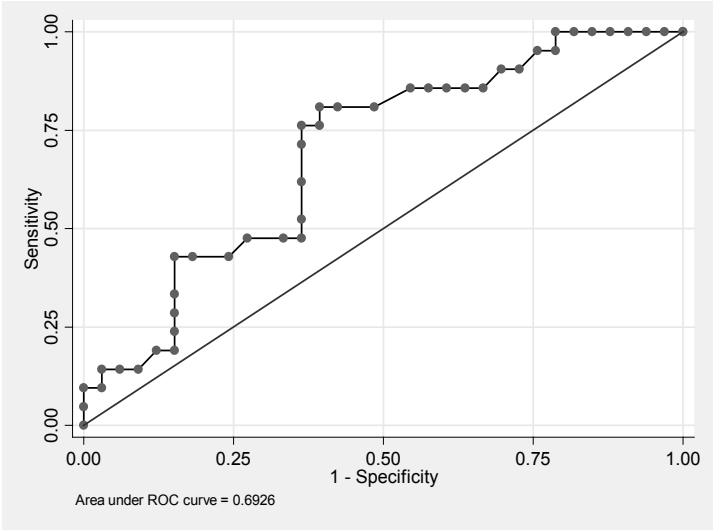

Figure 3: ROC analysis for E-wave velocity after ECV. Area Under Curve (AUC)=0.693, P=0.018

Table 4: Predictors of one-month AF recurrence. Results from univariate Cox regression analysis

Predictors	HR	95% C.I	P
Gender (male vs Female)	0.49	0.21 to 1.15	0.105
Underlying disease			
CAD	0.68	0.25 to 1.82	0.446
Mitral regurgitation	0.83	0.24 to 2.79	0.766
Echocardiographic parameters			
LA diameter (mm)	0.99	0.93 to 1.05	0.814
Fractional shortening	0.99	0.96 to 1.03	0.845
A-wave after ECV (cm/s)	1.01	0.97 to 1.03	0.954
E-wave before ECV (cm/s)	1.03	1.01 to 1.06	0.013*
E-wave after ECV	1.02	1.01 to 1.05	0.020*
E-wave >94 cm/s before ECV	3.62	1.49 to 8.78	0.004*
E-wave >80 cm/s after ECV	3.76	1.40 to 10.10	0.008*

*P<0.05

HR=Hazard Ratio, C.I=C.I, ECV=Electrical cardioversion, LA= Left Atrium, CAD=Coronary Artery disease

ECV as continuous variables (Table 4)

As far as the medication is concerned beta-blockers, Angiotensin Receptors II inhibitors did not seem to have influence on AF recurrence (All p values>0.05) (Data not shown).

Discriminant analysis showed that E-wave before ECV (λ-Wilk's=0.827) was the best discriminator for AF recurrence among all the aforementioned predictors followed by E-wave after ECV (λ-Wilk's=0.866) (Data not shown in texts or tables).

Log rank test showed that there was a difference between AF recurrence experience of patients with E-wave before >94 cm/s and those with <94 cm/s (P=0.002) (Fig. 4). As well, log rank test revealed a difference between the AF recurrence experience of patients with E-wave after >80 cm/s and those with <80 cm/s (P= 0.004) (Fig. 5).

Prediction Of Short-Term AF Recurrence Based On Clinical And Echocardiographic Parameters In Hypertensive And Non-Hypertensive Patients (Sub-Group Analyses)

In order to investigate whether the history of hypertension acts as a confounding factor to the relationship between the early diastolic transmitral peak velocity and the short-term AF recurrence we performed separate Cox regression analyses.

E-wave before and E-wave after (as continuous variables) remained predictors of AF recurrence during the follow-up only in non-hypertensive patients (HR=1.01 with 95% C.I=1.01-1.035, P=0.035 and HR=1.03 with 95% C.I=1.01-1.06, P=0.023, respectively). The corresponding HRs of Cox regression model in hypertensive patients were the following: HR=1.01 with 95% C.I=0.99-1.045, P=0.15 and HR=1.01 with 95% C.I=0.98-1.05, P=0.278.

BNP And Short-Term AF Recurrence

E-wave before and after ECV correlated linearly with natural logarithm of BNP levels before and after ECV (p=0.027 and p= 0.001).

It is interesting that logarithm of BNP levels dropped rapidly after successful ECV (6.9±0.9 vs 6.3±1.1, P<0.0001).

NT-pro BNP levels before and after ECV had a significant effect on short-term AF recurrence (HR=1.14 with 95% C.I 1.01-1.28 and HR= 1.16 with 95% C.I 1.03- 1.31, respectively).

NT-proBNP levels added on E-wave before ECV had incremental value on short-term AF recurrence at a marginally statistical significance (LR chi2=3.28, p=0.07).

Discussion

In our study we investigated the prognostic role of peak early diastolic transmitral peak velocity and we found a positive association between this marker and short-term atrial fibrillation recurrence.

The Framingham Heart study revealed that a one Standard Deviation increment in ratio of the velocity-time integrals of the early and late diastolic filling waves was associated with a 28% higher risk of AF.[7] This may be due to the fact that these markers reflect increased left atrial afterload probably because of left ventricular diastolic dysfunction.[10] However, other investigators did not find any association of E-wave and AF recurrence, even if the follow-up was longer i.e. for 1 year.[11] On the other hand, in patients following first anterior myocardial infarction AF recurrence was associated with significant reduction of E-wave.[12] But this study referred to a specific sub-group of AF patients and these patients were not followed-up after a successful cardioversion.

In our study we performed sub-group analysis and we found that E-wave before and E-wave after ECV remained predictors of AF recurrence only in non-hypertensive patients. This may be due to the fact that paroxysmal atrial fibrillation in hypertension is associated with depression of left atrial contractile function and "normalization" of the pattern of left ventricular filling.[13] In our study we found that gender, presence of mitral regurgitation, ATII inhibitors treatment and LA diameter (mm) influenced independently E-wave levels before ECV. So, further studies need to investigate the association of E-wave, hypertension, ATII inhibitors treatment and LA diameter with AF short-term recurrence. Thus, we would be ready to depict the common pathophysiologic entity of the above factors and its "causal pathway".

BNP is a ventricular hormone which is secreted from myocytes with the major determinant of secretion being the degree of ventricular stretch and work.[14] Several investigators reported that plasma BNP levels fell immediately following successful cardioversion.[15] In a recent study, pre- and post-cardioversion BNP concentrations were shown to be predictive of reversion to AF, independent of age, LV function or the prophylactic prescription of β-blockers.[14,16] Furthermore, even in patients with mild congestive heart failure, BNP before cardioversion was an independent predictor of AF recurrence.[17] Also,

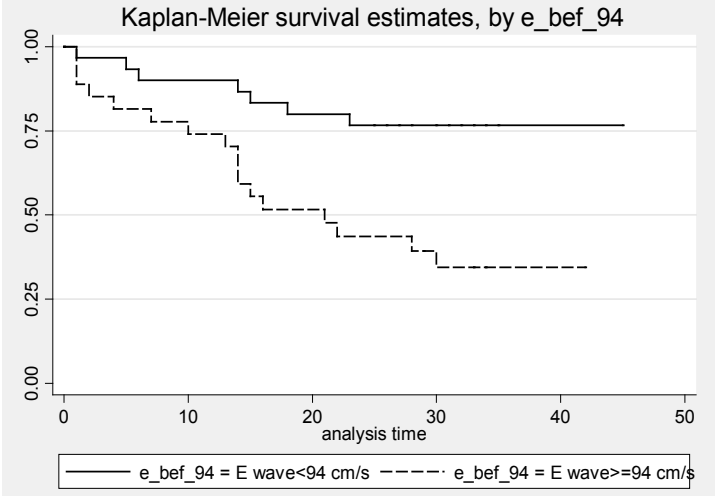

Figure 4: Kaplan-Meier Survival Estimates for patients with E wave velocity before ECV more and less than 94 cm/s

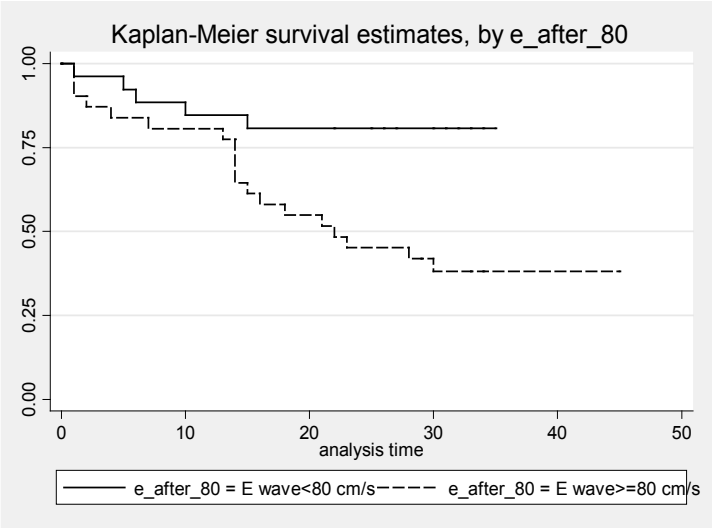

Figure 5: **Kaplan-Meier Survival Estimates for patients with E wave velocity after ECV more and less than 80 cm/s**

in a recent meta-analysis, researchers found that low preprocedural BNP levels were associated with SR maintenance.[18]

Limitations Of The Study

E-wave had prognostic significance on short-term recurrence of AF after ECV, but this was more prominent in non-hypertensive subjects. It would be of great interest to perform separate analyses of the predictive value of E-wave according to different underlying disease or to different antihypertensive medication (i.e. AT II inhibitors). But this was impossible to do because we enrolled small number of patients and, thus there was no enough statistical power to establish a difference that really exists. We cannot conclude from this study whether E-wave is a marker or an etiologic factor of AF recurrence, or whether acts as an indirect marker of left ventricular diastolic dysfunction in accordance with NT-pro BNP. We need large cohort studies after successful ECV in order to illuminate the relationship between E-wave itself, NT-pro BNP, antihypertensive therapy and AF recurrence. This study provides only an indication that these entities may play a role to a specific subgroup of patient (i.e non-hypertensive subjects), which remains to be further and better clarified with other studies. In addition to this, mitral E-wave velocity by itself does not accurately reflect left atrial function or left ventricular filling pressure as an it can be elevated due to many other conditions such as high output flow states (e.g. Anemia, tachycardia, sepsis, thyrotoxicosis and liver disease), which were not accounted for in the present study. Besides that, it seems that the use of more contemporary modalities such as tissue Doppler, Strain and speckle imaging techniques have better correlation with invasive measurements of LA pressure and LV filling pressure.

Conclusions

Peak early diastolic transmitral peak velocity had prognostic significance on short-term recurrence of AF after ECV, which was prominent in non-hypertensive subjects. The identification of predisposing factors for AF recurrence may affect the potential changes of antiarrhythmic medications or may also have consequences for choosing non-pharmacological treatment, for instance catheter-ablation.

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