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Clinical and prognostic association of total atrial conduction time in patients with heart failure. A report from SICA-HF.

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Abstract

Background: The total atrial conduction time can be measured as the time from the onset of the P wave on the ECG to the peak of the A wave recorded at the mitral annulus using tissue Doppler imaging (A´; P-A´TDI); when prolonged, it might predict incident atrial fibrillation (AF).

Methods: We measured P-A´TDI in outpatients with heart failure (HF) and sinus rhythm enrolled in the SICA-HF programme.

Results: P-A´TDI measured at the lateral mitral annulus was longer in patients with HF with reduced (LVEF<50%, N=141; 126 (112-146 ms); P=0.005) or preserved left ventricular ejection fraction (LVEF≥50% and NT-proBNP>125 ng/l, N=71; 128 (108-145) ms compared to controls (N = 117; 120 ms (106-135); P=0.026). Increasing age, left atrial volume and PR interval were independently associated with prolonged P-A´TDI.

During a median follow up of 1251 (956 - 1602) days, 73 patients with HF died (N=42) or developed AF (N=31). In univariable analysis, P-A´TDI was associated with an increased risk of the composite outcome of death or AF, but only increasing log [NT-proBNP], age and more severe symptoms (NYHA III vs I/II) were independently related to this outcome. Patients in whom both P-A´TDI and left atrial (LA) volume were above the median (127 ms and 64 ml, respectively) had the highest incidence of AF (HR: 6.61 95% CI: 2.27-19.31; P<0.001 compared to those with both P-A´TDI and LA volume below the median).

Conclusions: Measuring P-A´TDI interval identifies patients with chronic HF at higher risk of dying or developing AF during follow-up.

Keywords: atrial fibrillation, PA-TDI, heart failure, echocardiography, SICA-HF.

Introduction

Atrial fibrillation (AF) and heart failure (HF) often coexist: in registries and clinical trials the prevalence of AF in patients with HF ranges between 15% to 50%, depending on HF severity and phenotype (1). Incident AF might precipitate symptoms and negatively impact on costs, morbidity and mortality of patients with HF (2); however, in many cases, AF coincides with, or precedes, the development of HF itself, perhaps making clinically evident an asymptomatic, or undiagnosed cardiac condition. The identification of patients at high risk of developing AF might lead to strategies to prevent and target interventions (3). Many risk scores have been studied and validated to predict incident AF in the community, but similar models are lacking for patients with heart failure (4). Evaluating atrial structure and function by imaging might be a useful tool to identify patients with HF at higher risk of developing AF (5, 6).

The total atrial conduction time is a measure of the length of time between the initiation of atrial depolarisation and the peak of atrial mechanical activity. It can be measured as the interval between the onset of the P wave on the ECG to the peak of the A wave recorded at the mitral annulus using tissue Doppler imaging (A´; P-A´TDI). Increasing P-A´TDI predicts incident atrial fibrillation in the general population (7), in patients suffering a myocardial infarction or a cryptogenic stroke (8, 9), and in those who have had radiofrequency catheter ablation for atrial fibrillation (10). It might also be a simple and useful method for identifying

patients with severe HF at risk of developing AF (11). We studied the clinical associations and the predictive role of P-A´TDI measured in ambulatory patients with a broad range of HF severity.

Methods

Study Population

Between October 2010 and March 2014, 711 control subjects and patients with heart failure were enrolled in Kingston-Upon-Hull, UK, for the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF, ClinicalTrials.gov Identifier: NCT01872299)(12). SICA-HF is an international observational study of the prevalence, incidence and impact of key co-morbidities in ambulatory patients with a clinical diagnosis of HF. For the purpose of this analysis, we considered patients to have heart failure if they had signs or symptoms and confirmed evidence of cardiac dysfunction, either reduced left ventricular ejection fraction on echocardiography (LVEF <50%, HFrEF) **or** abnormal NT-proBNP (>125 ng/L; heart failure with preserved LVEF, HFpEF)(13). Patients with end-stage renal failure or on renal dialysis, an alternative cause for raised NT-proBNP, were not enrolled in the study. Subjects who were paced or in atrial fibrillation at baseline were excluded from the current analysis.

Patients were managed according to contemporary guidelines and were assessed after their medical therapy was optimised. Patients provided a detailed clinical history and had blood tests (including haematology, biochemistry profile and NT-proBNP), ECGs and echocardiograms done on the same day.

Controls were subjects aged >60 years who had no history of heart failure, who were recruited to the SICA-HF study by invitation from primary care practice lists. Because of the design and focus of the trial, a substantial proportion of the control population had to be at a

high risk of developing HF and had a clinical diagnosis of type 2 diabetes or hypertension, or both; however, they were included only if they were asymptomatic, had normal left ventricular function on echocardiography, and an NT-proBNP< 400 ng/L.

The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent.

Outcome

This is a retrospective study, but the primary outcome of interest was decided *a priori* to be the time to the composite of all-cause mortality and incidence of atrial fibrillation. We also considered all-cause mortality and incident atrial fibrillation separately as secondary outcomes.

Our hospital is the only one in the region offering acute medical services. We have access to both primary and secondary care records. Outcome is censored at the point of last medical contact in primary or secondary care. Data regarding deaths and incident AF were collected from the hospital's electronic systems, supplemented by information from patients, discharge letters and their family doctors. Only episodes of AF documented by treating clinicians or other health care providers in discharge letters, follow-up ECGs, hospital electronic records, and correspondence, which might include results of 24h tape, were included. We did not specifically investigate for incident atrial fibrillation, unless clinically indicated, and did not distinguish between permanent or paroxysmal episodes of AF. All data regarding admissions and deaths were entered into a dedicated online database, and were adjudicated at regular intervals by different researchers blind to any other measurement collected at the time of the clinical visit.

Echocardiographic measurements

Echocardiography was performed by an experienced operator using a Vivid Seven (GE Health care, UK) system operating at 1.7-3.4MHz. Doppler tracings and two-dimensional images were obtained from parasternal long- and short- axis, apical and subcostal views. Echocardiograms were stored and reviewed by an experienced operator (AB) blinded to other patient details using an EchoPAC station (GE Health care, UK). LVEF was measured using Simpson's biplane method. Maximal (LA max) and minimal (LA min) left atrial volumes were measured in the four chamber view, and left atrial emptying fraction was calculated accordingly ((LA max-LA min/LA max)*100). Tricuspid annular plane systolic excursion (TAPSE) was used to assess right ventricular (RV) systolic function. The maximum trans-tricuspid systolic velocity was also measured by echocardiography.

P-A´TDI *interval*

Of the 711 patients and controls, 499 (70%) were in sinus rhythm. P-A´TDI interval was retrospectively measured from stored echocardiograms (by VN) in only 329 (70%) of them, with the exclusions chiefly due to a poor ECG trace with low voltage P wave (n=100, figure 1 supplementary).

P-A´TDI was measured from the beginning of the P wave at the ECG trace to the peak of the A wave (A') obtained by placing the TDI sampling volume at both the lateral and septal mitral annulus (lateral and septal P-A´TDI interval). P-A´TDI interval was measured in three consecutive heart cycles, and their average value was used for the analysis.

Statistical methods

Categorical data are presented as number and percentages; normally distributed continuous data as mean ± SD and non-normally distributed continuous variables as median and interquartile range.

25 patients were randomly selected and medial and lateral P-A´TDI were measured separately by two operators blind to each other's results (VN and SD). The inter- and intra-operator reproducibility of the P-A´TDI measurements were tested using Bland-Altman plots.

Because lateral P-A´TDI interval was more closely related to the primary endpoint in univariable analysis than medial P-A´TDI interval, we decided to group patients with HF by terciles of lateral P-A´TDI interval to illustrate the relation between P-A´TDI and outcome. Patients in tercile 1 were those with the shortest lateral P-A´TDI interval.

One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test was used for categorical variables.

Simple and multiple linear regression models were used to identify variables associated with lateral and septal P-A´TDI interval. Only variables that were significantly associated with P-A´TDI in univariable analysis ($p<0.1$) were entered into the multivariable analysis.

Univariable and multivariable Cox proportional hazard regression models were used to investigate the relationship of clinical, biochemical and echocardiographic variables with outcome. Given the low number of events, different multivariable models were tested by

choosing, prospectively, clinical, biochemical or echocardiographic variables of interest in addition to lateral P-A´TDI interval to prevent overfitting.

Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome.

All analyses were performed using SPSS (v.22) software. A 2-sided p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

Of the 329 patients, 212 had HF (of whom 141 had HFrEF and 71 HFpEF) and there were 117 controls. The mean (± standard deviation) age of patients with HF (n=212) was 70±11 years, 24% were women, 72% had IHD; mean LVEF was 44±13% and median plasma NT-proBNP was 482 (IQR: 254 –1204) ng/l. Their demographic, clinical and echocardiographic characteristics are reported in table 1 and table 1 supplementary. Nearly 90% of those with HFrEF were receiving a beta-blocker and an ACE-I (or ARB), and >50% an MRA. Amongst control subjects, 85% had diabetes (DM), 78% had a clinical history of hypertension (HTN) and 12% had history of IHD. Their mean age was 70±10, 52% were men; their mean LVEF was 61±6% and median NT-proBNP was 90 (44 -157) ng/l.

P-A´TDI measurements

Reproducibility of measurements of P-A´TDI was good (intra-operator reproducibility: septal P-A´TDI mean difference = 1.9 (95% limits of agreement: -23.5 - 27.4) ms with 3 values outside limits of agreement (12%); lateral P-A´TDI mean difference = 4.8 (95% limits of

agreement: -23.7 – 33.3) ms with 2 values outside limits of agreement (8%); inter-operator reproducibility: septal P-A´TDI mean difference = 0.7 (95% limits of agreement: -32.7 – 34.1) ms with 2 values outside limits of agreement (8%); lateral P-A´TDI mean difference = 2.1 (95% limits of agreement: -30.0 – 34.1) ms with 1 value outside limits of agreement (4%)) (figure 2 supplementary).

Patients with heart failure, either HFpEF or HFrEF, had a longer lateral P-A´TDI interval than controls; patients with HFrEF had the longest septal P-A´TDI interval, which was, however, similar between patients with HFpEF and controls.

Compared to those with HF in the lowest tercile of lateral P-A´TDI interval (shorter interval), those in the highest tercile were older, had more severe symptoms, higher NT-proBNP and creatinine plasma levels, and longer PR interval at ECG. Other than a more dilated left atrium in the highest P-A´TDI interval tercile, there were no echocardiographic differences between the three terciles (Table 1).

Increasing septal and lateral P-A´TDI correlated with increasing log [creatinine] and log plasma [NT-proBNP]. Increasing lateral P-A´TDI also correlated with increasing QRS interval and decreasing heart rate (table 2 supplementary). P-A´TDI interval, either measured at lateral or septal mitral annulus, was longer in patients with IHD, but there was no association between other clinical variables (sex, presence of diabetes, mitral or tricuspid regurgitation, or clinical signs of congestion) and P-A´TDI (table 3 supplementary). There was no relation between P-A´TDI and measures of LV dimension or systolic function and measurements of diastolic function expressed as E/E’ ratio.

In patients with HF, increasing age, PR interval and LA volume were independently associated with increasing lateral P-A´TDI interval (Table 2 supplementary) (overall R^2=0.12); only decreasing body mass index and increasing left atrial volume were independently associated with increasing septal P-A´TDI interval (R^2=0.18).

Outcome

There were 82 primary outcome events during the median follow up of 1251 (IQ range: 956 - 1602) days. The first qualifying event was incident AF in 4 controls and 31 patients and death in 5 controls and 42 patients.

Patients in the highest tercile of lateral P-A´TDI had a much higher risk of death or incident AF than those in the lowest (lateral P-A´TDI: HR 2.52, 95% CI: 1.42 – 4.46; p=0.002) (Figure 1). Patients in the highest tercile of lateral P-A´TDI had a much higher risk of incident AF than those in the lowest (HR 5.86, 95% CI: 1.98 – 17.15; p=0.001) but the risk of death was similar (HR: 1.68, 95% CI: 0.86-3.31; p=0.13).

For those patients in whom *either* lateral P-A´TDI or LA volume were above the median (127 ms for lateral P-A´TDI, 64 ml for LA volume), the risk of incident AF was similar to those who had *both* lateral P-A´TDI interval and LA volume below the median; patients in whom both lateral P-A´TDI interval and LA volume were *above* the median had the highest incidence of AF (HR: 6.61 95% CI:2.27-19.31; P<0.001 compared to those with lateral P-

A´TDI interval and LA volume below the median, figure 2). There were too few events amongst the control population to be able to establish any relation between P-A´TDI and risk.

In univariable Cox regression analysis (Table 4 supplementary), both lateral and septal P-A´TDI were associated with an increased risk of events. Increasing lateral P-A´TDI was significantly related to an increase in the risk of the primary outcome either in patients with LVEF <50% (HR: 1.01 (95% CI: 1.00-1.02), X^2 : 5.1, p=0.024) or in those with LVEF≥50% (HR: 1.03 (95% CI: 1.01-1.04), X^2 : 9.5, p=0.002). However, it did not predict outcome when analysis was restricted to those with an LVEF <40% (HR:1.01 (95% CI: 1.00-1.02), X^2 : 3.6, p=0.056). In multivariable analysis, increasing log [NT-proBNP], age and more severe symptoms (NYHA IIIvsI/II) were the only variables independently related to an adverse outcome in the different models we tested. Lateral P-A´TDI interval entered these models only when the strongest variables associated with outcome were removed (table 2).

Discussion

We have found that an increased total atrial conduction time measured by tissue Doppler imaging amongst patients with heart failure in sinus rhythm is associated with higher NT-proBNP plasma levels and a higher risk of developing atrial fibrillation, particularly when a prolonged lateral P-A´TDI interval is associated with a dilated left atrium.

AF is the most common arrhythmia in patients with HF. Although the consequences of AF are to reduce quality of life, and to increase mortality, its pathophysiology is not completely understood. Indeed, left atrial enlargement and impaired function, reflecting the long term consequences of a stiff and dysfunctional LV leading to increased LA pressure, are only part of the factors contributing to AF development. Atrial stretch might enhance production of

natriuretic peptides, but also trigger arrhythmias (14) and increase fibrosis. Aging, oxidative stress and neurohormonal activation might further contribute to the development of atrial fibrosis, which further predisposes to, or maintains, AF (15). Atrial wall fibrosis might also increase inter-atrial conduction time and enhance the risk of developing AF (16-18). A prolonged P-A´TDI interval might thus be a marker of electrical and structural atrial remodelling and reflect the combined effects on atrial conduction of a dilated left atrium (which increases conduction time from the sinoatrial node to the atrioventricular node) and fibrosis (which slows conduction velocity) (19, 20).

We found that lateral P-A´TDI was longer than the septal, and differentiated between different populations with or without HF, regardless of LVEF. The difference between lateral and septal P-A´TDI may be due to the difference in conduction distances. The distance between the sinoatrial node (SAN) and the lateral side of left atrium is greater than the distance between the SAN and the medial side of left atrium. Thus electrical and structural atrial remodelling is likely to have a greater effect on lateral, rather than septal, P-A´TDI.

Our findings are in agreement with previous studies conducted amongst patients with cardiac dysfunction in different settings. Antoni and colleagues (8) studied P-A´TDI interval measured within 48 hours following an acute myocardial infarction in 613 patients in sinus rhythm, many of whom had systolic dysfunction (mean LVEF 46%). They found that left atrial volume and P-A´TDI were independent predictors of incident AF during 12 months follow-up; P-A´TDI interval also improved model prediction if added to clinical (age, troponin levels, PR interval) and echocardiographic (mitral regurgitation and left atrial volume) variables. In another study, Bertini and colleagues (11) studied 495 patients with severe heart failure, in sinus rhythm, who had an ICD implanted for primary or secondary prevention, many of whom (97%) also received a CRT device. They found that P-A´TDI (as well as female sex and history of AF) was an independent predictor of incident AF during

follow-up. Our study confirms and extends these findings to patients with HF and a broad range of left ventricular ejection fraction and HF severity.

Our findings also confirm the role of well-known risk factors for incident AF, such as advanced age or severe symptoms. Our findings also support the emerging notion that raised circulating levels of natriuretic peptides plasma levels are powerful predictors of incident AF, at least amongst those patients with a reduced LVEF (3, 21).

Study limitations

Our study has several limitations. It was a retrospective study and it was not possible to analyse 30% of the stored echocardiograms, mainly because the ECG trace was not optimized for timing measurements. Prospective studies are needed to validate these data and their possible clinical implications. Although the patient population enrolled in the present study was relatively large, the number of events was small. The incidence of AF in our patients was in agreement with previous studies (incidence of AF at 12 months: 5%), and higher to that which we have previously reported (3); however, is still possible that short runs of AF, or prolonged asymptomatic episodes, were undetected.

More than 25% of our control group had natriuretic peptides plasma levels between 125-400 ng/l, probably reflecting subtle cardiac dysfunction and high cardiovascular risk (22). Although they were asymptomatic and the vast majority was free of clinical congestion, some were treated with loop diuretic and, had they been breathless, would have fulfilled our criteria for a diagnosis of HFpEF, a difficult diagnosis to make (22-24). Moreover, many of the controls suffered from hypertension and/or type II diabetes, two common comorbidities that might increase the risk of heart failure (22), atrial fibrillation and prolong the P-A´TDI

interval (25): is possible that P-A´TDI interval might be shorter in individuals who are entirely free of cardiovascular risk factors. In those without HF, those with DM had a longer lateral, but not septal, P-A´TDI interval than those without DM (septal P-A´TDI: DM – 99 (21) ms, no DM: 90 (18) ms, p=0.078; lateral P-A´TDI: DM – 121 (22) ms, no DM: 109 (22) ms, p=0.026). We did not find any differences between those with or without hypertension. Only 5 controls were free of cardiovascular risk factors.

Conclusion

P-A´TDI is a simple novel echocardiographic variable which identifies patients with HF at higher risk of developing atrial fibrillation.

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Legend to figures

Figure 1. Kaplan Meier curves for the primary outcome of death from all causes and incident AF. Comparing the highest (HF-T3, yellow line) and lowest (HF-T1, purple line) terciles of P-A´TDI interval for patients with HF, those in the highest tercile had a much higher risk of death or incident AF. Those in the highest tercile of P-A´TDI interval had a >7 fold risk of this outcome than those considered without HF (No-HF).

Figure 2. Risk of incident AF according to left atrial size and lateral P-A´TDI**.** For those patients with either lateral P-A´TDI interval or LA volume above the median (127 ms for lateral P-A´TDI, 64 ml for LA volume) the risk of incident AF was similar to those who had both lateral P-A´TDI interval and LA volume below the median; patients in whom both lateral P-A´TDI interval and LA volume were above the median had the highest incidence of AF (HR: 6.61 95% CI:2.27-19.31; P<0.001 compared to those with lateral P-A´TDI interval and LA volume below the median).

Figure 1 supplementary. Consort diagram showing the disposition of patients enrolled. Of 499 patients in sinus rhythm, 100 had a poor ECG trace and for another 38 the quality, or absence, of the images limited the analysis. 32 patients with paced rhythm were not enrolled in the study. Of the remaining 329, 212 patients had HF and 117 were controls.

Figure 2 supplementary. The inter- (right panel) and intra-operator (left panel) reproducibility of the P-A´TDI measurements tested using Bland-Altman plots is shown.