Impaired cardiac autonomic nervous activity predicts sudden cardiac death in patients with operated and unoperated congenital cardiac disease

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Objectives: Sudden cardiac death is a leading cause of mortality in patients with congenital cardiac disease after surgical correction and is potentially preventable. The identification of patients at risk is therefore of major interest. We sought to assess the prognostic value of impaired cardiac autonomic nervous activity in patients with congenital cardiac disease.

Methods: Forty-three consecutive patients with congenital cardiac disease were included in this prospective study. Parameters of heart rate turbulence and heart rate variability were calculated from Holter electrocardiograms. In addition, serum brain natriuretic peptide levels were measured. A combined end point of sudden cardiac death or nearly missed sudden cardiac death was used.

Results: During a mean follow up of 27 $\pm$ 12.7 months, 5 patients died, and another 2 were successfully resuscitated. On univariate analysis, both brain natriuretic peptide levels and parameters of heart rate variability and heart rate turbulence were associated with impaired prognosis. On multivariate analysis, pathologic heart rate turbulence was found to be the strongest independent risk stratifier (hazard ratio, 61.5; $P < .001$).

Conclusions: Impaired cardiac autonomic nervous activity is associated with an increased risk of sudden cardiac death in congenital cardiac disease. Our results suggest that heart rate turbulence might be superior to established markers of cardiac autonomic dysfunction, such as heart rate variability. The combined use of heart rate turbulence, heart rate variability, and markers of neurohormonal activation, such as brain natriuretic peptide, might further improve the prognostic value.

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Sudden cardiac death is a leading cause of mortality in patients with congenital cardiac disease (CCD) and is potentially preventable. The identification of patients at risk is therefore of major interest.

Cardiac autonomic nervous dysfunction is associated with an increased risk of death in noncongenital cardiovascular cohorts. Because cardiac autonomic nervous dysfunction is common in patients with CCD,[1,2] we hypothesized that it might have similar prognostic implications in adolescents or adults with CCD and could be a means of assessing risk in this evolving population.

Heart rate variability (HRV) is an established measure of cardiac autonomic nervous function. Pathologic HRV has been shown to be a powerful and independent predictor of adverse prognosis in patients with heart disease and in the general population.[3] Recently, a novel parameter of cardiac autonomic

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CCD = congenital cardiac disease
CI = confidence interval
ECG = electrocardiography
HRT = heart rate turbulence
HRV = heart rate variability
HRVTI = heart rate variability triangular index
RMSSD = square root of the mean square differences of successive RR intervals
SDANN = standard deviation of mean values for all normal-to-normal intervals over 5 minutes
SDNN = standard deviation of all normal-to-normal intervals
TO = turbulence onset
TS = turbulence slope
VPB = ventricular premature beat

nervous dysfunction, heart rate turbulence (HRT), has been introduced into clinical practice. Parameters of HRT have been shown to be powerful electrocardiography (ECG)–related risk predictors for mortality after myocardial infarction[4-8] and in patients with chronic heart failure.[9,10]

To the best of our knowledge, there are no data regarding the prognostic significance of HRT and HRV in patients with CCD. The objective of the current study was to assess the prognostic value of these parameters for risk stratification in patients with CCD.

Patients and Methods

Forty-three consecutive patients with CCD (27 male and 16 female patients; mean age, 27.0 ± 12.7 years) who underwent 24-hour ECG recording for clinical reasons (previous arrhythmias, palpitations, or syncope) at our institution were enrolled in this prospective study. Patients with a preexisting cardiac pacemaker were excluded. All patients were continuously followed up at a specialized center for adults with CCD. Functional status of the patients was determined by a specialist in adult CCD using the Perloff classification.[11]

Baseline demographic data are shown in Tables 1 and 2. We included 21 patients with a systemic right (morphologic) ventricle (20 atrial switch operations for transposition of the great arteries and 1 congenitally corrected transposition of the great arteries), 3 patients after late closure of an atrial septal defect (1 surgical and 2 interventional), 1 patient after repair of a complete atrioventricular septal defect, 5 patients with pulmonary atresia after allograft repair, 7 patients with single-ventricle physiology (2 with double-outlet right ventricle, 1 with double-inlet left ventricle, and 4 after Fontan-type repair), and 3 patients after repair of tetralogy of Fallot. In addition, there were 3 patients with miscellaneous lesions (1 patient with Ebstein's anomaly, 1 patient with repaired aortic coarctation, and 1 patient with aortic and mitral valve disease), as shown in Table 2. Twenty-one patients were in functional class I, 13 in class II, 3 in class III, and 6 in class IV. The vast majority of patients underwent corrective or palliative operations in infancy or childhood. Median time difference between surgical intervention and Holter monitoring was 18.3 years (interquartile range, 15.4-24.7 years).

A combined end point of sudden cardiac death or nearly missed sudden cardiac death was used. Sudden cardiac death was defined as death with documented ventricular fibrillation and unsuccessful resuscitation or unexpected death occurring in a short time period (generally at home).

Holter monitoring was performed for a mean of 23.1 ± 4.2 hours (Reynolds Pathfinder Software). The HRT parameters of turbulence onset (TO) and turbulence slope (TS) were calculated, as described previously.[4] Briefly, HRT reflects the physiologic biphasic response of the sinus node to premature ventricular contractions, most likely because of an autonomous baroreflex.[4,12-15] It consists of a short initial acceleration, followed by a deceleration of the heart rate. A premature ventricular ectopic beat causes a brief disturbance of the arterial blood pressure (low amplitude of the premature beat and high amplitude of the ensuing normal beat). When the autonomic control system is intact, this fleeting change is registered immediately, with an instantaneous response in the form of the HRT. If the autonomic control system is impaired, this reaction is either weakened or entirely missing. TO represents the percentage difference between the heart rate immediately after a ventricular premature beat (VPB) and the heart rate immediately preceding a VPB. It is calculated by using the following equation: $TO = ([RR1 + RR2] - [RR\text{-}2 + RR\text{-}1])/(RR\text{-}2 + RR\text{-}1) * 100$, with RR-2 and RR-1 being the first 2 normal intervals preceding the VPB and RR1 and RR2 being the first 2 normal intervals after the VPB. Initially, TO is determined for each individual VPB, followed by the determination of the average value of all individual measurements. Positive values for TO indicate deceleration, and negative values indicate acceleration of the sinus rhythm. Values 0 or greater were classified as pathologic.[4]

TS corresponds to the steepest slope of the linear regression line for each sequence of 5 consecutive normal intervals in the local tachogram. The TS calculations are based on the averaged tachogram and expressed in milliseconds per RR interval. Values of less than 2.5 ms were classified as pathologic.

From the same Holter recording, the following parameters of HRV were determined: standard deviation of all normal-to-normal intervals (SDNN), standard deviation of mean values for all normal-to-normal intervals over 5 minutes (SDANN), HRV triangular index (HRVTI; ie, the integral of the density distribution divided by the maximum density distribution), and square root of the mean square differences of successive RR intervals (RMSSD).

Patients' blood samples were collected in ethylenediamine tetraacetic acid tubes. B-type natriuretic peptide (BNP) was immediately determined by using a commercial fluorescence immunoassay (Triage BNP test; Biosite, San Diego, Calif). The measurable range of the Triage BNP test is from 5 to 1300 pg/mL.

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