The Prognostic Value of Holter Monitoring in Congestive Heart Failure

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Congestive heart failure (CHF) is an increasingly widespread, costly and deadly disease, frequently named as epidemia of the XXI century. The clinical spectrum of patients with CHF is changing. Advances in modern treatment resulted in aging of population. The incidence of CHF increases with age raising up to 10 per 1000 population in patients older than 65 years (1). Widely spread use of revascularization procedures resulted in growing percentage of patients with respectively preserved left ventricular function. It is estimated that patients with diastolic heart failure may account for up to 50% of the entire CHF population (2).

Despite advancement in management of CHF patients the mortality rate remains high. Population studies showed that approximately 50-60% of CHF patients will die within 5 years of diagnosis (3). The prognosis worsens with advancement of heart failure and the mortality rate in patients in NYHA class IV is as high as 50% a year. The mode of death depends mainly on the functional class NYHA. Patients with less advanced CHF die mainly due to sudden death, while death in NYHA class IV is related more to progression in heart failure (4,5). Therapeutic progress is rapid, and both pharmacological and non-pharmacological therapies have been shown to improve the prognosis of CHF patients. Therefore, prediction and prevention of cardiac events have become the main challenge of contemporary cardiology.

Risk stratification in CHF is based on various parameters describing functional status of studied patients. Clinical examination , echocardiography , biochemistry and electrocardiology provide complex insight in the prognosis in CHF patients. Functional capacity expressed as NYHA class, severity of systolic dysfunction reflected by impaired left ventricle ejection fraction and the levels of natriuretic peptides a touted as the main risk markers (1). Even though continuous Holter ECG monitoring is not considered as a basic diagnostic method in the diagnosis of CHF, it may serve as a valuable tool in risk stratification. The number of ECG changes contributed to underlying structural disease, electrical instability or imbalance in ANS may be evaluated during Holter monitoring. Recent years brought an increased interest in an early activation of neurohumoral system and its role in the progression of heart failure (6). Such influence of autonomic nervous system on cardiovascular system may be assessed by means of Holter monitoring, that allows for analysis of dynamic changes in electrocardiographic parameters reflecting heart rate and ventricular repolarization changes. The possibility of dynamic parameters evaluation and the ability of prolonged ECG monitoring in the ambient setting when the patients are involved in their daily activities constitute the main advantages of Holter analysis as compared to standard surface ECG.

Standard ECG risk predictors: heart rhythm, heart rate, arrhythmia.

With no doubt surface 12-leads ECG remains one of the basic diagnostic tests in the diagnosis and prognosis of CHF patients, giving us data on the heart rhythm, heart rate frequency, and morphological changes of subsequent ECG curve's components. The presence of atrial fibrillation, sinus tachycardia or wide QRS is related with worse prognosis. Nevertheless, Holter monitoring provides broad spectrum of information inaccessible from surface ECG. Ambulatory ECG monitoring allows for detection of paroxysmal arrhythmias, evaluation of heart rate and frequency of arrhythmia thorough a whole day, giving insight to electrical activity of the heart during daily activities of a patients and covering the early-morning periods of increased risk of sudden death. Modern Holter monitoring assess also parameters reflecting the influence of the autonomic nervous system on heart rate and repolarization.

Atrial fibrillation is markedly more prevalent in CHF patients than in general population. The prevalence of atrial fibrillation in heart failure patients varies from 10% to 30% (7) . Heart failure predisposes to AF and AF may worsen the prognosis of CHF patients significantly aggravating heart failure symptoms. In some patients AF leads to the development of tachycardiomyopathy (8). There are conflicting data whether the presence of atrial fibrillation is an independent predictor for an increased mortality in heart failure (9-12). As both rate control and rhythm control strategies are nowadays accepted Holter monitoring is useful for monitoring appropriate ventricular response rate as well as to document the presence of AF crises. Paroxysmal AF that coincides with heart failure decompensation was shown to be a predictor of worse prognosis (13). Tachycardia-related unfavorable impact of AF on CHF has been recognized for years. The question whether tachycardia itself or heart rate irregularity related to AF are responsible for the worsening of heart failure also remains unclear (14), but Holter monitoring may provide information of both these AF characteristics. Recently data appeared showing that lower and not higher rates may be associated with worse prognosis (15)

Heart rate is probably the easiest ECG parameter to assess, however the results of different studies evaluating its prognostic value yield conflicting results. Unfavorable tachycardia is a common feature in CHF related to sympathetic overdrive. The adequate control of the heart rate is essential in all, not only AF patients with heart failure. Prolonged heart rate monitoring in nowadays included in home-monitoring systems in CHF patients, being one of the markers of the need for therapy modification (16). High resting heart rate is well accepted risk predictor for all-cause mortality, but its relation to cardiac and sudden death remains controversial . Similarly, the cut off value of high risk heart rate frequency in CHF patients remains unclear (17-19) . On the other hand, Holter monitoring showed that not only high resting heart rate but also heart rate ranges during 24 hours expressed by simple parameters as delta heart rate may identify patients at risk of progressive pump failure death (20,21)

Ventricular arrhythmias are frequently observed in patients with CHF and the frequency of their occurrence increases with the advancement of heart failure. Ventricular arrhythmias have been documented in up to 85% of patients with severe heart failure. Complex form of ventricular arrhythmia like pairs or episodes of ventricular tachycardia are also frequently observed (22-24). Death due to arrhythmic events occurs mainly in patients in NYHA class II-III . Relationship between ventricular arrhythmia and sudden death is not clear, however the majority of trials show a significant correlation between the presence of nsVT and death. In Captopril-Digoxin Multicenter Study (25) VPB, couplets and nsVT were univariate predictors of total mortality. Frequency of nsVT (>2 runs a day) was related with 3-fold increase in total mortality and was an independent predictor of sudden death. In V-HeFT II study (26) nsVT and pairs identified patients with increased mortality. In GESICA trial (27) the presence of nsVT was associated with increased risk for all-cause mortality and sudden death. In a study of Singh et al. nsVT was only univariate predictor of total mortality and sudden death, however lost its predictive value after adjustment for clinical covariates (28). There are also data demonstrating that length but not the rate of nsVT increases the risk of major arrhythmic events (29).Spontaneous sustained ventricular tachycardia is infrequent in Holter recordings, but if present, predicts sudden death (30) . The role of ventricular tachycardia VT in the long term prognosis may be supported by observation from MADIT II trial where appropriate therapy by an ICD for VT/VF was associated with an increased risk for heart failure and non sudden death (31)

Holter-derived risk predictors related with autonomic nervous system and repolarization

Heart rate variability

Heart rate variability (HRV) is a measure of the cyclic variation of normal-to-normal RR intervals that reflects cardiac autonomic function and may be considered as a marker of sympathetic and parasympathetic influence on the modulation of heart rate . Therefore, the assessment of HRV has become one of the integral component of autonomic nervous system assessment in different subsets of patients, especially in those with known cardiovascular disorders as postinfarction patients or patients with cardiomyopathies and/or heart failure. Decrease in HRV has been for years considered as an independent and strong marker of risk for all cause mortality or even sudden death (32) .

Congestive heart failure is characterized by signs of neurohumoral sympathetic activation. Therefore, heart rate variability has been explored in this subset of patients in two aspects: detection of abnormalities of autonomic nervous system balance and prognostic value of HRV in prediction of all cause mortality and sudden death.

Patients with CHF have decreased spontaneous heart rate variability (33). Recent report showed that even patients with diastolic heart failure present altered HRV parameters (34) . For years reduced HRV parameters in CHF patients have been explained by sympathetic overdrive. It has been also shown that the extent in reduction of HRV pameters correlates with the advancement of CHF (35)

Depressed HRV consistently predict all-cause mortality or death due to progression of heart failure. However data regarding its prognostic value in prediction of sudden death is conflicting. First observations on prognostic value of HRV parameters both in time and frequency domain were based on postmyocardial infarction cohorts (32). It is difficult to compare the predictive value of HRV parameters in prognosis of CHF patients as they are analyzed by different methods and in different time intervals. Early reports on predictive value of HRV showed that reduced HRV parameters were related with 20-fold increased risk of death in patients awaiting heart transplantation (36*).* Standard deviation of NN intervals *(*SDNN) is the best known, best validated and easiest HRV parameter, however different cut off were proposed as predictive. In UK-Heart Study a reduction in SDNN (<100ms) was associated with death due to progressive heart failure, but failed to predict sudden death (37). The same cut off was independently related to death in patients with heart failure due to ischemic and idiopathic etiology (38). SDNN below 67 ms was independently related to mortality in a study of Boveda et al. (39) while SDNN below 65.3 ms was an independent risk predictor in the CHF-STAT population (40) . Lower than 55ms SDNN identified increased risk of mortality in patients awaiting cardiac transplantation (36) Jiang et al (41) observed that in CHF patients SDNN<50 ms was a strong predictor of event free survival, stronger even than LVEF, cardiothoracic ratio and premature ventricular beats. Similarly, SDNN<50 ms identified patients at risk of progressive heart failure in patients with dilated cardiomyopathy (42).

Even more controversies exist in terms of frequency domain components. The findings of these studies are difficult to compare mainly due to different methodological approaches. Decreased LF and VLF component are the most frequently reported HRV spectral measures related with mortality in CHF patients (43,44*).* It was documented that different components of spectral analysis are related to different types of death. Decreased night-time VLF was related to progressive heart failure, while decreased night-time LF values were associated with sudden death (45). Non-linear measures of heart rate variability were also reported as markers of mortality in CHF patients (46-48)

Prognostic role of HRV in prediction of SCD remains controversial (37,40,48). Nevertheless, there are data some trials that demonstrated correlation between HRV indices and sudden death. In a study of Fauchier et al (49) reduced SDNN<100 ms was independent risk predictor of sudden death and arrhythmic events in patients with dilated cardiomyopathy.

Heart rate turbulence

Heart rate turbulence (HRT), defined as a biphasic reaction of sinus node in response to a premature ventricular beat, was introduced into electrocardiology in 1999, and since then has been proved as a powerful predictor of mortality in postinfarction patients (50-53). Blunted HRT reaction has been observed in various subgroups of patients with cardiomyopathies and heart failure independently on the underlying etiology (54-56). Significantly altered HRT parameters were also observed in Chagas disease, characterized by increased risk of sudden death and autonomic nervous system impairment as well as progressive impairment of left ventricular structure (57) Only patients with hypertrophic cardiomyopathy did not differ in terms of HRT values from control subjects (58). It has been suggested that HRT, considered as vaguely-dependent effective measure of baroreflex sensitivity (59, 60) and related to the advancement of heart failure, might be used as a marker of congestive heart failure staging. Such a relationship was suggested in a study of Lin et al. (61) who found that abnormal HRT may be restored by 3 months beta-blocker therapy in 10 patients with congestive heart failure.

The predictive value of HRT in patients with cardiomyopathies remains controversial. The majority of data related abnormal HRT with progression of disease (54-56). In patients with mild to moderate heart failure turbulence slope was found to be an independent risk predictor of death due to decompensated heart failure (56). In the Marburg Study (55) turbulence onset was found as a significant predictor of transplant free survivals in 242 patients with idiopathic cardiomyopathy. In a study of Koyama (54) including 50 patients with heart failure (both ischemic and idiopathic etiology) abnormal turbulence slope defined as >3 ms/RR was predictive for progression of heart failure including both deaths and hospitalizations due to CHF worsening. There are contradictory results regarding prognostic value of HRT in prediction of arrhythmic events in patients with cardiomyopathies. Neither Grimm nor Koyama showed predictive value of HRT for prediction of arrhytmias. Only one study in ICD patients with dilated cardiomyopathy showed significant association of abnormal TS (defined as below 4.1 mm/RR) with arrhythmic events (62). In patients with hypertrophic cardiomyopathy HRT failed to predict any cardiac events (58).

Repolarization dynamics

Static measures of QT duration and QT dispersion were considered as risk factors in patients with CHF, however their predictive value was usually overwhelmed by clinical covariates (63-67). Early neurohumoral activation with sympathetic overdrive constitutes one of the main mechanism in the pathogenesis and development of heart failure, therefore, it seems that parameters reflecting dynamics of ECG should improve risk stratification in CHF patients (68). Dynamicity of repolarization has been described in different forms (69-71). Our group reported increased increased number of peaks of prolonged QTc interval, e.g. the proportion of QTc intervals above the prespecified threshold (QTc>500ms) as a marker of life-threatening arrhythmias in postinfarction patients (70). Similarly to coronary patients increased percentage of QT peaks was found in patients with dilated cardiomyopathy as compared to healthy subjects (72). In recent years, QT/RR slope analyzed from long term Holter recordings has become a popular method to evaluate QT adaptation to changing heart rate. Increased QT/RR slopes were observed in patients at risk of cardiac death including postinfarction patients, long QT syndrome patients, and patients with dilated cardiomyopathy (73-76). Steeper QT/RR indicates decreased vagal tone and increased sympathetic activity reflecting the higher vulnerability of myocardium to arrhythmias. At the cellular level sympathetic stimulation prolongs ventricular refractoriness. Therefore, increased QT slope represents increased vulnerability of myocardial substrate to its modulation by autonomic nervous system (77). Increased values of QT/RR slope were found to predict cardiac events in various populations, mainly in postinfarction patients (73,75). Pathak et al (76) found that in a population of 175 patients with chronic heart failure due to ischemic (43%) or idiopathic (57%) cardiomyopathy increased QTc/RR slope assessed over 24 hours was a strong, independent predictor of sudden death.

There is an increasing interest in the analysis of QT variability in Holter recordings. Berger et al developed a time-stretching algorithm to quantify changes in repolarization duration and morphology. They found that patients with CHF have increased variability when compared to agematched healthy subjects (78). Increased beat-to-beat changes in repolarization duration and morphology predisposes to electrical instability of myocardium and may favor initiation and maintenance of reentry arrhythmias. Haigney et al reported the association between QT variability and arrhythmic events documented by ICD interrogation in MADIT II patients (79). Microvolt T wave alternans, reflecting beat-to-beat 2:1 changes in the amplitude and sometimes the polarity of repolarization is a well-known marker of arrhythmic events in patients with heart failure (80-81). There are data indicating that T wave alternans may be assessed in long term Holter monitoring instead of traditional exercise test. The new method of modified moving average (MMA) analysis was used to measure TWA magnitude in 24-hour Holter recordings from ATRAMI and was documented to predict arrhythmic events (82,83). So far, this method has not been applied in a population of CHF patients.

Conclusions

Holter monitoring has a well established position in prediction of total mortality and progression of heart failure. It seems, that modern Holter monitoring may be a valuable tool for investigating factors that may contribute to the mechanism of sudden death. As it is widely accepted that structural changes reflecting myocardial substrate are better identified by means of imaging techniques, Holter monitoring provides complementary information on myocardial vulnerability and autonomic nervous system. Nevertheless, data regarding its prognostic value in prediction of SCD remains controversial and the positive predictive value of majority of Holter-based risk stratified is low. Therefore, combining of electrocardiographic stratification with assessment of myocardial substrate may provide the complex insight into interplay between factors contributing to death. On the other hand, negative predictive value of Holter risk markers is usually high, therefore it may be used to identify low risk patients.

It is not likely that we will find one specific ECG risk predictor to predict total and sudden death in a heterogeneous population of patients with congestive heart failure. Therefore, it seems that the combination of various ECG risk markers covering different arms of SCD risk triangle may be considered as better approach. Furthermore, changing clinical spectrum of CHF patients with rising population of patients with preserved or relatively preserved left ventricular function, treated according to modern guidelines requires reanalysis of the prognostic value of Holter predictors. Summing up, in the light of conflicting results of previously published studies prediction of sudden death in CHF patients needs further investigation. We hope that on-going MUSIC trial (Muerte Subita e Insuficiencia Cardiaca- Sudden Death in Heart Failure), a multicenter prospective study on the risk predictor of sudden death in CHF patients NYHA class II-III including over 1000 patients, will answer some of above mentioned questions.

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