The Prognostic Role of ECG in Arterial Hypertension

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1. Introduction

Hypertension is very common and affects around 50 million Americans of which about 30% are not yet diagnosed. Hypertension is an under-diagnosed syndrome causing damage to the various target organs with no symptoms or only mild symptoms, also called a "silent killer" for this reason. Early diagnosis of arterial hypertension remains an important element in evaluating cardiovascular risk factors in general population. It is well established that isolated arterial hypertension increases the risk of left ventricular hypertrophy (LVH) and sudden death and prognostic indexes are necessary for risk stratification of these patients. The electrocardiogram (ECG) is a simple, non-invasive, low-cost method that can detect LVH, ventricular arrhythmias and ventricular repolarization abnormalities and confers useful prognostic information for patients with arterial hypertension

2. Prognostic data

It is well known that left ventricular hypertrophy (LVH) is associated with an increased incidence of ventricular arrhythmia and sudden cardiac death. Systemic arterial hypertension is one of the most important causes of pathological LVH and there is evidence indicating that hypertensive patients with LVH are at increased risk of sudden cardiac death (Haider 1998, Korren 1991). These patients are characterized by a high incidence of ventricular arrhythmias (Gallinier 1997, Messerli 1999, Dimopoulos 2009) and this observation has led to the logical hypothesis that these arrhythmias may be the cause of sudden cardiac death in these patients. However, the exact mechanism by which LVH, ventricular arrhythmias and sudden cardiac death are linked to each other has not been fully clarified yet. Premature ventricular beats, multiform beats, couplets and non-sustained ventricular tachycardia are commonly found in ECGs of hypertensive patients, are associated with LVH, and have a negative prognostic value (Gallinier 1997, Messerli 1999). Furthermore, ventricular repolarization abnormalities in the 12-lead surface ECG such as QT-interval prolongation, increased QT dispersion (Dimopoulos 2008,2009), T wave axis

(Salles 2008) and T wave alternans (Hennersdorf 2001) have all been associated with ventricular arrhythmias and sudden cardiac death in arterial hypertension; however further research is required to establish their prognostic significance.

2.1 LVH

In arterial hypertension, LVH is a physiologic and expected response to pressure or volume overload and it is a well known marker of increased cardiovascular morbidity. Previous studies have extensively shown that antihypertensive agents can partially reverse LVH and their efficacy is well documented (Haider 1998, Kannel 1969,1970, Sokolow & Lyon 1949, Deverreux & Reichek 1982, Okin 2004,2009). Development of the typical strain pattern in response to LVH may reflect true subendocardial ischemia in the absence of coronary artery disease, since the increases in coronary artery blood flow (through coronary artery dilatation and capillary recruitment) are inadequate to compensate the demand posed by increased LV mass and wall thickness, in the setting of LVH. The increased mass of the left ventricle (representing both myocardial interstitial fibrosis and/or myocyte hypertrophy) can cause abnormalities of the QRS complex and QT-interval. Although the ECG has a low sensitivity (less than 50%) for detecting LVH, when LVH is identified by ECG, the specificity is higher than 90%. From these observations several criteria have been proposed so far, however none is considered to have optimal accuracy (Sokolow & Lyon 1949, Hancock 2009). A variety of ECG abnormalities have been described, as shown in Tables 1,2,3:

R or S in any limb lead ≥20mm
R waves in aVL > 11mm
R in lead I + S in III > 25mm
S waves in V1 or V2 ≥ 30mm
R waves in V5 or V6 ≥ 30mm
S waves in V1 + R waves in V5 or V6 > 35mm
R waves in aVL+ S waves in V3 > 28mm (men) and 20 mm (women)
Total QRS voltage from all 12 leads ≥175mm
Onset of intrinsicoid deflection >0.05 seconds in V5 or V6
Increased duration of the QRS complex ≥0.09 seconds
Left axis deviation ≥-30º

Table 1. Abnormalities in the QRS complex

Terminal negativity of the P wave in V1 1mm X 1mm

Table 2. Left atrial abnormality

ST depression and T inversion in leads with tall R waves (left ventricular strain)

Table 3. Abnormalities in the ST segment and T wave

The following are the most frequently used criteria for the diagnosis of LVH, including the Sokolow-Lyon Index, Romhilt and Estes score, Cornell voltage criteria, Cornell product, total QRS voltage (Table 4,5,6,7,8):

S waves in V1 + R waves in V5 or V6 > 35mm
R waves in aVL > 11mm

Table 4. Sokolow-Lyon Index

Score of ≥ 5 points predicts LVH, score of 4 points = probable LVH
3 points each
1) P wave from left atrial abnormality
2) any increase in voltage of the QRS complex (R or S in any limb lead ≥20mm or S waves in V1 or V2 ≥ 30mm or R waves in V5 or V6 ≥ 30mm)
3) ST-T abnormalities any shift in the ST segment but without digitalis
2 points (left axis deviation ≥-30º)
1 point each (duration of the QRS complex ≥0.09 seconds or intrinsicoid deflection ≥0.05 seconds in V5 or V6 or ST-T abnormalities with digitalis)

Table 5. Romhilt and Estes score

R waves in aVL+ S waves in V3 > 28mm (men) and 20 mm (women)

Table 6. Cornell voltage criteria

Cornell voltage criteria x QRS duration in ms ≥ 2440 (in women 6 mm is added to Cornell voltage)

Table 7. Cornell product

Total QRS voltage from all 12 leads ≥175mm

Table 8. Total QRS voltage

Various epidemiological studies have previously demonstrated the importance of LVH for predicting cardiovascular events and sudden cardiac death. In the Framingham Heart Study the 3.4% of 5581 participants with ECG LVH and ST depression and T-wave flattening or inversion had a 3-fold increased risk for developing coronary heart disease after adjusting for age, gender, and blood pressure, (Kannel 1969, 1970). Similar results were found in the Copenhagen City Heart Study with enrollment of 11,634 participants with no evidence of ischemic heart disease at initial evaluation. In this study it was shown that ST depression and/or T-wave inversion (as defined by the Minnesota code) remained strongly predictive for cardiac events in multivariate analyses (Larsen 2002). The left ventricular (LV) strain-pattern of ST segment depression and T-wave inversion on the left precordial leads of the standard resting ECG is now considered a valid marker of the presence of anatomic LV hypertrophy (LVH) (Salles 2006). The presence of typical ECG strain pattern is also independently associated with increased LV wall thickness and mass and independently associated with other adverse factors: increased 24-hour systolic blood pressure, prolonged maximum QTc-interval duration, higher serum creatinine and fasting glycemia, physical inactivity, as well as with the presence of two types of important target organ damage (CHD and peripheral arterial disease). In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, it was demonstrated that therapy with losartan was more

effective than atenolol in preventing CV morbidity and mortality with nearly identical reductions in systolic and diastolic pressure in both treatment arms. The presence of typical strain on the ECG in hypertensive patients with ECG LVH also identified patients at higher risk of CV morbidity and mortality in the setting of antihypertensive therapy associated with large decreases in systolic and diastolic pressure. The increased CV risk associated with ECG strain was independent of the improved prognosis with losartan therapy in the LIFE trial and persisted after adjusting for the greater baseline severity and prevalence of ECG LVH and the higher prevalence of other CV disorders in patients with strain pattern. The development of new ECG strain between baseline and year 1 during the LIFE study identified patients at increased risk of cardiovascular morbidity and mortality and all-cause mortality in the setting of antihypertensive therapy associated with substantial decreases in both systolic and diastolic pressure. The increased risk associated with new ECG strain was independent of the improved prognosis with losartan therapy and with regression of ECG LVH in LIFE (Okin 2004,2009). These findings suggest that more aggressive therapy may be warranted in hypertensive patients who develop new ECG strain to reduce the risk of cardiovascular morbidity, cardiovascular and all-cause mortality, and sudden death. The relationship of cardiovascular risk to ECG strain pattern on a single ECG has been demonstrated in population-based studies and in patients with hypertension.

2.2 Ventricular arrhythmias, Lown score

Previous studies have shown an increased incidence of number and severity of ventricular arrhythmias in patients with hypertensive LVH (Galinier 1997, Messerli 1999, Dimopoulos 2008, Hennersdorf 2001). The average number of premature ventricular beats (PVB), and their severity according to a modified Lown's score (a: absence of PVB; b: PVB < 30/h; c: PVB ≥ 30/h; d: multiform; e: couplets; f: nonsustained ventricular tachycardia; g: R on T = RR / QT ≤ 0.75) during a 24-hours ECG Holter are independent predictors of echocardiographically determined LVMI in normotensive and hypertensive elderly patients, as demonstrated in a previous study (Dimopoulos 2008). In that study, patients with arterial hypertension had a higher Lown's score compared with normotensive subjects, and this increase was found to be higher in those hypertensives with LVH. The elderly population group had a greater number of PVB in contrast to younger subjects. Elderly patients were also characterized by a higher Lown's score and a greater LVMI. Another study has previously shown that patients with LVH present frequent and complex ventricular premature beats and that the presence of non-sustained ventricular tachycardia has negative prognostic value in this population (Galinier 1997). However, the role of ventricular arrhythmias in arterial hypertension is still under investigation, with no clear evidence for high prognostic significance.

2.3 Silent ischemia

Transient changes of ST-segment (ST depression) is a phenomenon commonly observed in patients with arterial hypertension; although reported prevalence varied widely (from 15 to 80%-Stramba 1998, Asmar 1996), it seems that the true value is around 20% (Uen 2006). These findings on ECG are interpreted as silent ischemia, due to the absence of angina pectoris or other angina equivalent symptoms and are attributed to transient mismatch of myocardial blood flow to the myocardial demands. It seems that more than 90% of these episodes, identified in the Holter electrocardiogram (ECG) of hypertensive patients, are silent. When transient ST depressions are detected, the risk of cardiovascular events

increases (Uen 2006, Sigurdson 1996, Szlachcic 1992). It is also well known that there is a circadian rhythm of transient ST depressions with a distinct peak in the early hours of the morning, similar to the peak period of myocardial infarction or sudden cardiac death (Asmar 1996). The ST depression is significantly more frequent in patients with known coronary heart disease, positive Sokolow index, as well as in patients who complain of dyspnea, have a smoking history or are on diuretics. The ST-segment depression is also observed more frequently in men than in women. The prevalence of ST-segment depression in patients with coronary heart disease is influenced by the severity of coronary heart disease (Uen 2006, Sigurdson 1996, Szlachcic 1992). This phenomenon is characterized by a significant rise of blood pressure, heart rate and double product before the appearance of ST depression. These parameters reach their peak during the ST depression. After ST depression resolution, they return to lower values. Apart from the systolic blood pressure, however, the other two parameters will remain significantly elevated compared with the mean 24-hour values. Other clinical predictors for the occurrence of cardiac ischemia during daily life are risk factors for silent ST-depression, indicating the presence of ischemic heart disease. A study showed that 24-hours ambulatory blood pressure monitoring (ABPM) has high predictive value, in contrast to office-based blood pressure measurements, for silent ST-segment depression. Interestingly, the office-based measurements, apart from the pulse pressure, are not predictive of the occurrence of ST-segment depression either in treated or in untreated hypertensive and normotensive hypertensive individuals. To what extent the 24-hours mean values of the ST segment depression analysis reflect the severity of ischemic heart disease or have prognostic significance regarding the development of an ischemic event remains so far unknown, although a study has previously reported that silent ischemia may be predictive of adverse outcome in arterial hypertension (Schillaci 2004).

2.4 QT-interval and QT-dispersion

Increased left ventricular mass, as mentioned before has a high prevalence in patients with arterial hypertension, particularly in the elderly and has been associated with increased cardiovascular risk, including sudden death, (Haider 1998, Koren 1991, Dimopoulos 2009, Kannel 1969,1970, Bednar 2001, Okin 2000). The increased electrical instability due to non-uniform left ventricular mass distribution has been suggested as a possible mechanism linking LVH and cardiovascular death. QT interval prolongation has been implicated in the origin of ventricular arrhythmias, possibly because of less uniform recovery of ventricular excitability in the setting of regional differences in cardiac sympathetic nervous system activity. In addition, the increased inhomogeneity of ventricular repolarization, induced by LVH, can be indirectly detected by QT dispersion, a relatively simple measurement of 12-lead electrocardiogram (ECG) variability, and this index has been recently shown to be related to poor prognosis in large population studies (Okin 2000, Salles 2005, Elming 1998, Bruyne 1998, Sheehana 2004). Interestingly, heterogeneous ventricular repolarization was initially recognized in standard ECGs as early as 1934; however only recently QTc interval dispersion was identified as a marker of arrhythmia risk and sudden cardiac death in patients after myocardial infarction or with heart failure (Barr 1994, Glancy 1995, Anastasiou-Nana 2000). Furthermore, other studies subsequently demonstrated the presence of increased QT-dispersion in patients with systemic arterial hypertension, associated with ventricular arrhythmias and LVH (Dimopoulos 2008, Clarkson 1995, Mayet 1996). QTc dispersion (QT-dispersion corrected for HR) was found to be an independent predictor of echocardiographically determined LVMI in normotensive and hypertensive elderly patients (Dimopoulos 2008). Patients with arterial hypertension had an increased

QTc dispersion compared with normotensive subjects, and this increase was found to be higher in those hypertensive patients with LVH. In a prospective study, patients with QTcD ≥45 ms had a higher rate of major cardiovascular events, higher LVMI, increased values of systolic and diastolic blood pressure, higher number of PVB and higher Lown's score than patients with QTcD <45 ms (Dimopoulos 2009) . After adjustment for multiple known predictors of adverse outcome, QT interval corrected for heart rate remained associated with both all-cause and cardiovascular mortality. Increased QTc interval dispersion was also a significant predictor of cardiovascular mortality in LIFE trial (Saaden & Jones 2001). This additive risk prediction suggests that increased QTc and QTc interval dispersion on the surface ECG reflect different aspects of abnormal ventricular repolarization. However only few studies have investigated the prognostic role of QT-dispersion and QT-interval in arterial hypertension (Galinier 1997, Dimopoulos 2009, Oikarinen 2004, Saaden & Jones 2001). Antihypertensive therapy with angiotensin-converting enzyme inhibitors, calcium antagonists and beta-blockers has been shown beneficial in terms of QT-dispersion normalization and/or LVH decrease (Tomiyama 1998, Karpanou 1998, Galetta 2005,Lim 1999). Beta blockers are associated with a reduction in both QT and QTc interval dispersion, raising the possibility that a reduction in dispersion of ventricular repolarization may be an important antiarrhythmic mechanism of beta blockade.

The direct linking mechanism between QT-dispersion, ventricular arrhythmias, LVH and adverse outcome has not been fully clarified yet. Increased QTc dispersion has been associated with increased regional heterogeneity of ventricular repolarization and it has been considered as a possible noninvasive surrogate marker of susceptibility to malignant ventricular arrhythmias and cardiovascular mortality in large population studies and, in cardiac patients (Okin 2000, Elming 1998, Bruyne 1998, Sheehana 2004, Barr 1994, Glancy 1995, Anastasiou 2000). The degree of myocardial interstitial fibrosis induced by either systemic arterial hypertension and/or by ageing, as well as the inhomogeneous myocyte hypertrophy caused mainly by arterial hypertension, might play an important role in increasing action potential duration and amplitude in different myocardial regions (Dimopoulos 2008,2009). These myocardial electrical abnormalities may affect ventricular repolarization and might be the main cause of increased QTc dispersion in hypertensives. In order to maximize reproducibility of QT-dispersion measurements, it is important to follow certain methodological rules that are reported below.

All 12-leads ECGs are obtained at a speed of 25 mm/sec. The ECG registration should be a simultaneous 12-lead ECG. QT intervals are measured manually on all possible leads. QT interval is defined as the interval from the onset of the QRS complex to the end of the T wave, which is defined as its return to the T-P baseline. If U wave is present, the QT interval is measured to the nadir of the curve between the T and U waves. QT intervals are then corrected with the Bazett's formula to compensate for its known dependence on heart rate: QTc = QT / √RR. Measurements on QT and RR intervals should be carried out in 3 consecutive cardiac cycles in all leads, and average values are then obtained. QTc dispersion is determined as the difference between the maximal and minimal QTc interval in different leads. No subject should have fewer than 9 measurable ECG leads. Various studies have also demonstrated the predictive value of the QT interval and QTc interval dispersion measured automatically by computerized ECG for noninvasive risk stratification in a population-based sample.

It should be mentioned that there are some methodological difficulties related to QT dispersion measurements, including the circadian variation of the QT interval. The QTc

interval dispersion has obvious predictive value, but inter- and intraobserver varialbility limits the wider clinical use. In perspective, it is important to decrease measurement errors by improving measurement technique, define precisely normal values and demonstrate predictive value in studies with large number of patients with arterial hypertension.

2.5 T wave axis

Two electrocardiographic markers of ventricular repolarization abnormalities have been recently proposed: spatial T-wave axis deviation and T (peak)-T (end)-interval duration. In a cross-sectional study (Salles 2008), 810 treatment-resistant hypertensive patients were evaluated. Maximum T(peak)-T(end)-interval duration (Tpe(max)) was considered prolonged if it was beyond the upper quartile value (120 ms), and the spatial T-wave axis on the frontal plane was considered abnormally deviated if >105 degrees or < 15 degrees. Tpe(max)-interval prolongation, as well as QTc-interval prolongation, was found to be associated with body mass index, 24-h systolic blood pressure (SBP), indexed LVM, serum potassium, and heart rate. Abnormal T-axis deviation was associated with male gender, presence of coronary heart disease, serum creatinine, 24-h SBP, LVM, and serum potassium. All three repolarization parameters (T-wave axis deviation, T (peak)-T (end)-interval and QTc-interval) were shown to be associated with increased LVM, after adjustment for possible confounders. However, when included together into the same model, only abnormal T-axis and QTc-interval prolongation remained independently associated with LVM. All three parameters were also increased in patients with concentric hypertrophy. It seems that only abnormal T-wave axis deviation appears to have distinct and additive prognostic value compared with the more classic marker, the QTc interval. More investigational studies are needed to evaluate the prognostic value of T-wave axis abnormalities in arterial hypertension, prior to clinical application of this index.

2.6 T wave alternans (TWA)

An association between the occurrence of TWA and inducibility of tachyarrhythmias has been reported in a previous electrophysiological study (Rosenbaum 1994). Another significant study (Hennersdorf 2001) has evaluated the significance of TWA in 51 patients with arterial hypertension. The patient population was divided into a group of 11 consecutive patients who had survived arrhythmic events or cardiogenic syncope and a group of 40 consecutive patients without documented ventricular arrhythmias. Patients exercised with a gradual increase of workload to maintain a heart rate of at least 105/min. Workload was increased in a stepwise fashion to avoid a sudden increase of the heart rate, which could provoke a false positive test result. After recording 254 consecutive heartbeats, ECG signals were digitally processed by a spectral analysis method and analyzed. The beat domain power spectrum of the T wave (J point 160 ms through end of the T wave) was calculated every 16 beats from sequential overlapping 128-beat sequences. The magnitude of the TWA was measured at a frequency of 0.5 cycles per beat. The results of this study showed that the prevalence of TWA was higher in patients with LVH. There was also a significant correlation between patients with a positive TWA and a survived arrhythmic event. None of the patients without documented ventricular arrhythmias had a positive alternans tracing. The underlying mechanism of a positive TWA is not clear yet; it seems that there is an alteration in action potential morphology or dispersion of repolarization. The changes in morphology of the action potentials might lead to spatial inhomogeneity in refractoriness and may result in increased vulnerability to ventricular fibrillation. During

repeated episodes of ischemia, action potential alternans was detectable in 95% of the cases with ventricular fibrillation. The dispersion of repolarization is closely related to the temporo-spatial pattern of depolarization-repolarization, which can alternate on a beat-to-beat basis. The temporo-spatial dispersion of cellular refractoriness seems to predispose the myocardium to wave front fractionation and subsequent reentry. It is noteworthy that the TWA can be influenced by various conditions such as ischemia, hypothermia, heart rate, and sympathetic tone. Drugs such as procainamide and amiodarone reduce magnitude of alternans and sotalol can lead to the conversion of TWA from negative to positive. In the case of cardiomyopathies, the development of small areas of scars and ischemia is considered to be of pathological relevance for the development of alterations in action potentials or dispersion of repolarization. Whether T wave alternans can be used as a clinical marker of susceptibility for sudden cardiac death and cardiovascular events is under research.

3. Conclusions

The electrocardiographic findings in patients with arterial hypertension are valuable tools for risk stratification of these patients, by predicting cardiovascular events and sudden cardiac death. The ECG strain pattern, an old parameter of well established value, should always be searched as it provides additional prognostic information beyond the one derived from echocardiographic LVH and LVM. Also among hypertensive patients with left ventricular hypertrophy, the presence of non-sustained ventricular tachycardia on ECG Holter monitoring identifies patients with a high risk of mortality, who need more aggressive care. Silent ischemia on ECG Holter should be taken into account as ST depression episodes have a high prevalence (about 20%) in hypertensive patients. ST depression and T-wave inversion may reflect true subendocardial ischemia in the absence of coronary artery disease. The prolonged QT interval and increased QT interval dispersion have been associated with LVH and ventricular arrhythmias and seem to contain significant predictive value, but inter- and intraobserver varialbility limit their wider clinical applicability. The analysis of T wave axis and T wave alternans might also be helpful for risk stratification in patients with arterial hypertension. However, the clinical usefulness of these indices in arterial hypertension and their possible role in monitoring medical treatment is under investigation and further research is needed prior to its clinical application.

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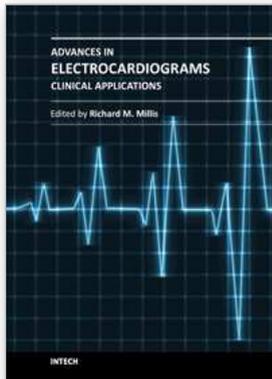
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Electrocardiograms have become one of the most important, and widely used medical tools for diagnosing diseases such as cardiac arrhythmias, conduction disorders, electrolyte imbalances, hypertension, coronary artery disease and myocardial infarction. This book reviews recent advancements in electrocardiography. The four sections of this volume, Cardiac Arrhythmias, Myocardial Infarction, Autonomic Dysregulation and Cardiotoxicology, provide comprehensive reviews of advancements in the clinical applications of electrocardiograms. This book is replete with diagrams, recordings, flow diagrams and algorithms which demonstrate the possible future direction for applying electrocardiography to evaluating the development and progression of cardiac diseases. The chapters in this book describe a number of unique features of electrocardiograms in adult and pediatric patient populations with predilections for cardiac arrhythmias and other electrical abnormalities associated with hypertension, coronary artery disease, myocardial infarction, sleep apnea syndromes, pericarditides, cardiomyopathies and cardiotoxicities, as well as innovative interpretations of electrocardiograms during exercise testing and electrical pacing.

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