The Year of 2010 in Electrocardiology

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INTRODUCTION

In my first attempt on the pages of this Journal to summarize advancements in electrocardiography of a foregone year, the year was 2005¹, I wrote about the "ever increasing amount of new information," providing "new clues not only for the diagnosis but also for therapy and even for prognosis." Even today I can find no words better than these, to introduce the following article in which I try to present last year's abundantly produced top quality investigations in the field of electrocardiology.

APPRECIATION OF THE 12-LEAD RESTING ELECTROCARDIOGRAM (ECG)

The year of 2010 produced several important studies that demonstrated that certain parameters on the 12-lead ECG can provide important information on predisposition to ventricular arrhythmias and sudden cardiac death (SCD) and may have a role in improving future-risk stratification.

Lee and coworkers² conducted a 10-year follow-up study in 81 countries in the US on population recruited between 1988 and 1994 and showed that individuals with high-estimated 10-year risk for coronary heart disease (CHD) by the NCEP/ATP guideline had higher heart rate (HR), left ventricular mass index (LVMI) and cardiac infarction injury score (CHS), shorter PR and longer QTc intervals, than those with low risk. After multivariate anal-

ysis, including conventional coronary risk factors, dose-dependent associations between HR, LVMI, CHS, and QTc intervals were found in the 10-year risk group. Q- and ST-T wave abnormalities in the 12-lead ECG were evaluated by the Minnesota Code and the Novacode to predict coronary heart disease and total mortality;³ over 3000 participants were followed upon average of eight years. The authors concluded that major ST-T abnormalities by both of these coding systems were stronger predictors than the presence of Q waves alone.

The standard 32-point Selvester QRS score on the discharge ECG was found to be an independent and prognostically relevant metric in patients with ST elevation MI undergoing primary percutaneous intervention.⁴

The 12-lead ECG features showed a significant correlation with risk of sudden death in hypertrophic cardiomyopathy (CM).⁵ Qualitative analysis of the ECG amplitude sums, as well as pathological T-wave inversion, ST depression, and dominant S wave in V₄ were risk factors for sudden death. The authors propose that ECG features should be included in routine risk-stratification of hypertrophic CM patients.

Sweeney and coworkers⁶ demonstrated that analysis of the standard 12-lead surface ECG before and after cardiac resynchronization therapy can shed a light on ventricular activation and allows to predict left ventricular (LV) reverse remodeling. In this study patients with asynchronous heart failure and left bundle branch block (BBB), longer LV

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activation time and smaller LV scar volume on the baseline ECG predicted higher probability of reverse remodeling. This study prompted an editorial comment by Drs. Kalahasty and Ellenbogen* entitled "Simpler is Better: New Lessons Learned from the 12-lead Electrocardiogram."

The importance of serial 12-lead ECG recordings in pregnant women was stressed by the Glasgow group of investigators.⁷ As evidence from previous studies suggests that some ECG parameters are, indeed, altered by the pregnant state, the investigators studied the characteristics of the maternal ECG during pregnancy and in a subgroup looked for the impact of delivery on the ECG. The mean QRS and T axes in pregnancy were 14° and 17° superior to the normal values, respectively. After delivery the mean QRS shifted inferiorly by 5° and 12°, respectively.

The combination of right BBB was associated with less LV mechanical dyssynchrony than left BBB and ischemic CM was associated with doubling of the adjusted hazard for death after CRT-D, relative to left BBB with nonischemic CM. A wider QRS duration was predictive of better outcomes in left BBB but not in right BBB.⁸

In patients with acute inferior MI from the Hirulog and Early Reperfusion or Occlusion-2 trial, ST elevation in V₁ at baseline had incremental adverse prognostic significance, that was independent of the adverse effect of any precordial V₃ ST depression. Resolution of V₁ ST elevation after fibrinolytic therapy was associated with lower 30-day mortality.⁹

The earlier described pattern of right BBB, S₁ S₂ S₃ or S₁ Q₃ T₃ as characteristics for acute pulmonary embolism (APE) were not helpful in the differentiation between APE and NSTEMI-ACS in studied group, but coexistence of negative T waves in precordial leads V₁₋₃ and inferior wall leads at the bedside was suggestive of the diagnosis of APE.¹⁰

An Increasing Prognostic Role of Premature Ventricular Contractions (PVCs)

For several decades it has been accepted that the presence of PVCs, even if they occur frequently, in the absence of structural heart disease have no influence on cardiovascular prognosis. Several recent investigations seem to contradict this assumption.

The presence ≥ 1 PVCs on the resting ECG was found to be a powerful predictor of cardiovascular

mortality during a median follow-up period of 6.2 years, even after adjusting for confounding factors.¹¹ Stein and coworkers¹² studied a healthy population >65 years for risk factors for CHD and stroke and found that a high-PVC count and increased T-wave alternans (see below), were independently associated with sudden cardiac death (SCD).

In a prospective study by Aquaro and coworkers¹³ on patients with ≥ 1000 PVCs of left bundle branch block (LBBB) morphology and inferior axis, i.e., originating from the right ventricle but otherwise normal ECG and echo and exercise tests and without family history of arrhythmogenic right ventricular cardiomyopathy (ARVC) and no suspicion for any cardiac disease, cardiac magnetic resonance (CMR) testing in one-third of the individuals demonstrated right ventricular abnormalities.

THE IMPORTANCE OF THE HEART RATE (HR) VELOCITY

The importance of changes in HR, i.e., faster or slower than the norm, have been entertained quite extensively over the last years. In a retrospective study by Piccini and coworkers¹⁴ in over 11,000 post-MI patients a high-resting HR predicted SCD during hospitalization, from discharge to 30 days, 30 days to 6 months, and 6 months to 3 years; higher HR with lower creatinine clearance was a strong predictor of SCD prior to discharge and in the first-30 days of follow-up, but not later. As the time passed, the association between baseline clinical characteristics, like high-baseline HR and SCD decreased and only post-MI atrial fibrillation was associated with an increased risk of SCD over the entire follow-up period. Soliman and coworkers¹⁵ found that a high-resting HR was associated with ventricular arrhythmogenesis, independently from LV ejection fraction, history of coronary heart disease, and the presence of ST-depression on Holter. However, because of the inability of this study to adjust for unrecognized confounders, it is possible that high-resting HR is a surrogate for one or more unmeasured variables that may be casually linked to SCD.

Phan and coworkers¹⁶ studied the HR recovery following a maximal exercise test and found chronotropic incompetence in patients with heart failure, even if they had preserved LV ejection fraction and normal valvular function. Although the precise mechanism of this impaired autonomic

dysfunction is still unclear, an impaired cardiac vagal tone has been implicated. These findings raise a question of whether rate-limiting therapy, such as beta-blockers, nondihydropyridines calcium blockers are appropriate in this group of patients. The possibility, however, raised by the authors of applying HR responsive pacing in this group of patients to improve exercise tolerance and quality of life, seems to be somewhat far-fetched. It should be mentioned that these patients were generally women (70%), overweight, and aged 69 ± 8 years, while the control group was comprised of similar percentage of similar gender and similar age, but were not overweight.

In contrast with the above quoted studies, Anselmino and coworkers¹⁷ working on behalf of the Euro Heart Survey on Diabetes and the Heart, demonstrated that a 10-beat per minute increase in the resting HR was independently associated with survival only in patients with diabetes mellitus (DM) but not in those without DM. However, the follow-up of their patients was only one year and difference in the method acquiring the resting HR may explain the results somewhat differing from results of others.

Gender Differences in the Electrical Activity of the Heart

Several previous studies have suggested that not only anatomical but also hormonal and genetic factors may explain differences in various ECG parameters between men and women. Mayuga and coworkers¹⁸ studied the circadian variations in the dispersion of myocardial repolarization as measured by both QT-dispersion and T-wave peak to T-wave end (Tp-Te) in healthy women and men: they demonstrated a greater QT dispersion in men with more circadian variations, than in women. QT dispersion in men was greatest in the early morning hours (the time when the risk of arrhythmic sudden death is high). Tp-Te in the lateral chest leads was longer in men than in women, but no difference was found between the sexes concerning their circadian pattern. Although no day-to-day or beat-to-beat variability were evaluated in this study, the results gave an important contribution to our understanding of the complex interaction between gender and repolarization.

The HR response to exercise stress testing in asymptomatic women was investigated in the St.

James Women Take Heart Project.¹⁹ HR reserve, chronotropic index, and age-predicted peak HR were calculated. This study demonstrated that the traditional estimate of the maximum HR for age with exercise, based on male standard, appears to be an over estimate in women. The mean age at baseline was much lower (52 ± 11 years) in this study as compared to the previously quoted one and only 88 of the 5437 women tested were older than 75 years. The authors found that the equation for females used by them [$\text{peak HR} = 206 - 0.88(\text{age})$] improved risk prediction in women, even so the exercise capacity was estimated and not measured directly, which could have affected the calculation of the metabolic reserve and chronotropic index. As mentioned above,⁴ QRS score was used as a prognostic marker in post-MI patients; male gender was associated with higher QRS scores than the female ones.

Based on samples from nondiseased human hearts, Gaborit and coworkers²⁰ demonstrated that male and female human hearts have significant differences in ion-channel subunit composition, findings which are important for understanding sex-related differences in the susceptibility to ventricular arrhythmias, particularly for conditions associated with repolarization abnormalities.

The T-Wave Alternans (TWA)—Is It Here to Stay?

As mentioned above, Stein and coworkers⁹ demonstrated that TWA, independently of the high-PVC count, was significantly associated with SCD. In primary prevention patients with left ventricular dysfunction, Chan and coworkers²¹ concluded that the predictive power of microvolt TWA is inconsistent, as it depends on whether beta-blocker therapy was or wasn't withheld prior to its assessment. A superior ability to detect TWA, as compared to previously reported methods was demonstrated by Monasterio and coworkers²² by a multi-lead periodic component analysis, with a potential to improve TWA's prognostic value.

Yet, in spite of the large number of investigations in the past and also during 2010, Verrier, and coworkers* in their review article entitled "Microvolt T-Wave Alternans" concluded that although TWA appears to be a useful marker of risk for arrhythmic and cardiovascular death, there is still no definitive evidence that it can guide therapy.

Has the Position of Early Repolarization (ER) been Finalized?

After decades of considering ER a benign condition, during the last several years in general populations an association between it and an increased risk of SCD has been suggested. This year again, increasing attention has been paid to this syndrome.

A high prevalence of ER was found in patients with short-QT syndrome (SQTS) by Watanabe and coworkers,²³ who suggested that this pattern may be useful in identifying risk of cardiac events in SQTS patients; other ECG parameters including QT and QTc intervals were not associated with arrhythmic events in the cohort. Abe and coworkers²⁴ demonstrated that in patients with J waves there are ventricular late potentials (VLP) in patients with idiopathic ventricular fibrillation. The incidence of VLP in those idiopathic VF patients with a J wave was higher than in those without. Based on experimental evidence, Antzelevitch and Yan²⁵ found that in patients with J-wave syndrome and also with Brugada syndrome, the arrhythmias are linked to abnormalities in the manifestation of the transient outward current I_{to-} mediated J wave. The authors suggested that ER and Brugada syndrome, although the former is differing from the latter with respect to the magnitude and lead location of the abnormal J-wave manifestation, the two can be considered to represent a continuous spectrum of the same phenotypic expression and proposed the term "J-wave syndromes." This terminology however, has met objection on behalf of Dr. Borys Surawicz who discouraged the use of this "illegitimate nomenclature" as one "that cannot be defined."^{*}

In spite of all the recent informations about this intriguing syndrome, our present knowledge still seems to be inadequate to classify it or not as a true predictor of SCD.

Long-QT Syndrome (LQTS): The Show Goes On

The findings of Goldenberg et al.,²⁶ based on investigating over 500 LQT1 and over 400 LQT2 patients from the International LQTS registry suggested that beta-blocker therapy should be rou-

tinely administered as a first-line measure to all high-risk LQT1 and LQT2 patients without contraindications, whereas primary defibrillator therapy should be recommended for those who experience syncope during medical therapy. Although high-risk patients who experienced syncope during beta-blocker therapy had a relatively high rate of subsequent aborted cardiac arrest or SCD, the authors pointed out that such events rarely occur as a presenting symptom among patients who are treated with beta-blockers and that there was a significant reduction in the risk of cardiac events in each high-risk patient subset on beta-blocker therapy. These results are in some contrast with the results of Jons et al.²⁷ who, after following a thousand patients came to the conclusion that these patients with syncope during beta-blocker therapy are at high risk of life-threatening events.

The connection between LQTS and life-threatening ventricular arrhythmias was further evaluated by Viskin and coworkers²⁸ who found that the QT-interval response to the brisk tachycardia induced by standing is different between LQTS patients and control subjects. While the heart rate acceleration of $28 \pm$ bpm was similar in both groups, the QT interval shortened in controls but lengthened in LQTS patients; this simple bedside test may be an aid in diagnosing LQTS. A phenotypic manifestation of latent congenital LQTS was suggested by Subbiah et al.²⁹ to be an underlying predisposition to reduced repolarization reserve in patients with torsades de pointes; these individuals had also longer Tp-Te intervals. The prognostic importance of the late phase of repolarization was demonstrated by Szydlowski and coworkers³⁰ who found that patients who had on the fifth day after an anterior myocardial infarction a prolonged Tp-Te, had at six-months follow-up left ventricle remodeling.

Healthy newborns at days 1, 2, and 4 after birth were studied³¹ with 24-hour ambulatory monitoring and demonstrated isolated premature beats, mostly supraventricular, pauses of sinus rhythm less 1000 ms, steep slope of QT/RR by analysis of QT dynamicity. The low HRV, and symmetrical AC/DC capacity was typical for autonomic regulation of HR, probably due to high-sympathetic activity at this age. In spite of earlier data from Italy showing that ECG screening of infants for LQTS is cost-effective, 90% of most pediatric cardiologists in North America remain skeptical about ECG screening of infants for this syndrome.³²

* In Stern S. Clinical Aspects of the Early Repolarization Syndrome: A 2011 update. *Ann Noninvasive Electrocardiol* 2011; 16:192-195.

A QT interval of >316 ms during recovery at HR of 120-beat per minute was an independent predictor of death at a mean follow-up of 7.6 years, even after adjusting for multiple other risk factors, including LV ejection fraction.³³ An increased short-term variability of the QT interval in patients with dilated CM and moderate heart failure was found to increase susceptibility to sudden death.³⁴

New Information on the ECG of Athletes

Retrospectively, studying the ECGs of healthy competitive athletes who suddenly died or were resuscitated, Cappato and coworkers³⁵ found more frequently J waves and/or QRS slurring than in control athletes. Nonetheless, in the authors' opinion the presence of this ECG pattern appears not to confer a higher risk for recurrent malignant ventricular arrhythmias. Juntilla and coworkers demonstrated that the frequently found ER pattern in athletes was significantly associated with LV hypertrophy voltage, but not among females and the African-American athletes.³⁶

The performance of 12-lead ECG in all competitive athletes was recommended by the experts of the European Society of Cardiology,³⁷ an opinion not shared by their American counterparts

Contributions Using the Holter Method

Several investigations quoted in this review, as Aquaro and coworkers,¹³ Stein and coworkers,¹² Soliman and coworkers,¹⁵ Szydlo and coworkers,³⁰ Makarov and coworkers,³¹ reached their results by continuous 24-hour Holter monitoring. Using automated QT interval measurements in Holter ECGs, which were recorded at 180 and 1000 samples per second, Panicker and coworkers³⁸ demonstrated a longer QT interval with lower sampling rates. While lower sampler rate may be satisfactory for detection of arrhythmias and ischemia, i.e., 1000 sample per second study shows a shorter QT interval. Marcus and coworkers³⁹ identified ventricular late potentials on Holter ECG as a minor criterion for arrhythmogenic right ventricular dysplasia; they stated that a signal-averaged ECG is positive if two of the following three of the parameters are abnormal: filtered-QRS duration, root-mean square voltage of the terminal 40 ms of the QRS, or duration of the terminal QRS signal <40 μ V. Heart rate turbulence, measured automatically using an algorithm based on Holter ECG was found

to be a powerful risk-stratification index for cardiac events, defined as cardiac mortality and sustained VTs in patients with nonischemic dilated CM.⁴⁰

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