SPECIAL REPORT

The Year 2005 in Electrophysiology

Shlomo Stern, M.D.

From the Hebrew University of Jerusalem, Jerusalem, Israel

A.N.E. 2006;11(2):187–193

In spite of more than 100 years in use and a technology nearly unchanged for over 60 years, electrocardiography (ECG) provides us an ever-increasing amount of new information about the physiological and pathological processes involving the heart. This article tries to summarize the articles from the relevant scientific literature published during the year 2005. In the descriptions of their innovations and advancements in interpreting and understanding the classical electrocardiographic pattern, new clues were provided not only for diagnosis but also for therapy and even for prognosis.

P WAVE

It has been recommended that if an interatrial block is suspected, the P wave should be scrutinized in all 12 leads rather than heeding the usual advice in the literature to record lead II only, sometimes with one other lead.¹ The investigators stressed that by looking for a P duration of ≥ 120 ms in all 12 leads doubled the diagnosis of interatrial block and called attention to an impending atrial fibrillation and a large and dysfunctional left atrium. Surface 12-lead P-wave morphology leads Kistler and coworkers² to the diagnosis of focal atrial tachycardia from the ostium of the coronary sinus; a characteristic P-wave morphology, together with activation timing, enabled to diagnose this form of tachycardia. Hoppe and coworkers³ separated atrial flutter with atypical F waves from fibrillation with "apparent organization." In ambiguous ECGs with atypical F waves, spectral evidence for a solitary activation cycle separates atrial flutter from atrial fibrillation with "apparent

organization." This approach might improve bedside ECG diagnosis and shed light on intraatrial organization of both rhythms. Accurate ECG diagnosis of atrial flutter from atrial fibrillation might guide the approach to ablation, including the need for transseptal catheterization, choice to catheters, and/or mapping systems, could avoid misdiagnosis and help guide antiarrhythmic drug selection. The differentiation between upper loop reentry from reverse typical atrial flutter was the subject of a study by Yuniadi and coworkers.⁴ An algorithm based on flutter-wave polarity and amplitude in lead I had the best discriminative power among 12 leads. If the flutter wave in lead I is positive, a flutter-wave amplitude > 0.07 mV is indicative of reverse typical atrial flutter. A negative, isoelectric, or flat-flutter wave or an amplitude ≤ 0.07 mV is indicative of upper loop reentry. The accuracy of this algorithm was 90–97%, with a sensitivity of 82–100% and specificity of 95%.

QRS COMPLEX

An increased QRS duration of ≥ 120 ms was a marker of ventricular dyssynchrony in the Framingham Heart Study⁵ and was positively related to left ventricular mass, dimensions, and inversely associated with left ventricular fractional shortening in individuals without heart failure or prior myocardial infarction. A QRS duration of > 144 ms in patients with chronic heart failure was poorer in the presence of restrictive filling pattern on Doppler echo and added incremental value to determining prognosis.⁶ While an increased QRS duration predicted cardiac deaths in patients with

Address for reprints: Shlomo Stern, M.D., Emeritus Professor of Medicine, 1 Shmuel Hanagid Street, Medical Building, Jerusalem 94592, Israel. Fax: 972-2-6258862; E-mail: sh_stern@netvision.net.il

implanted cardioverter-defibrillators, the QRS width and conduction abnormalities were not useful to predict VT/VF events in the investigation by Buxton and coworkers.⁷ On the other hand, Sweeney and coworkers⁸ have shown that a baseline QRS width ≥ 120 ms was associated with increased risk of death during pacemaker therapy for sinus node dysfunction.

QRS complex parameters were quite unique in allowing for differentiation between patients with positive and negative dobutamine stress echocardiography, most significant being the mean QRS complex amplitude and the sum of all QRS complex amplitudes; this suggests their predictive value in assessing the presence of viable myocardium in patients with ischemic left ventricular dysfunction.⁹

Voltage-only criteria for detecting left ventricular hypertrophy was found to be inferior to composite ECG criteria, which were strongly predictive of cardiovascular mortality, a conclusion reached following analysis of nearly 50,000 consecutive ECGs of veterans and scrutinizing 17 commonly used ECG criteria for left ventricular hypertrophy.¹⁰ In the same cohort, Richardson and coworkers¹¹ demonstrated that during a mean follow-up of 6 years the Cardiac Infarction Injury Score outperformed all other ECG classifications in determining prognosis.

The standard method for identifying patients who will most likely benefit from cardiac resynchronization therapy (CRT) are those who have left bundle-branch block and a QRS duration > 120 ms. The success of CRT was recently evaluated by Lecoq and coworkers¹² and the only independent predictor of a positive versus negative response was the amount of QRS shortening induced by the therapy. Ammann and coworkers¹³ developed an ECG-based algorithm to evaluate CRT. An R-S ratio ≥ 1 in lead V_1 was indicative of left ventricular (LV) capture. The R-S ratio < 1 in V_1 , and an R-S ratio ≤ 1 in lead I was indicative of LV capture. Accuracy of the algorithm was tested by blinded analysis of 108 ECGs recorded during biventricular and right ventricular pacing in 54 patients with a CRT device.

QT INTERVAL

Vrtovec and coworkers¹⁴ demonstrated that atorvastatin increases heart rate variability (HRV), decreases QT variability, and shortens QTc interval, and may thereby reduce the risk of arrhythmias in patients with advanced heart failure. The same

authors found that short-term chromium supplementation shortens QTc interval in patients with type 2 diabetes mellitus.¹⁵

Beasley and coworkers¹⁶ discarded an effect of even high doses of tadalafil on the QT interval, while Zitron and coworkers¹⁷ showed that in the ensuing 6–8 hours after drinking grapefruit juice a transient QTc prolongation was observed, instead of an expected shortening in that parameter due to normal diurnal variation.

T WAVE

The prognostic value of T-wave abnormalities in patients with non-ST-elevation acute coronary syndromes was studied in the FRISC II population.¹⁸ They demonstrated that the new quantitative analysis of nine different categories of T-wave abnormalities on the admission ECG gives additional predictive information concerning clinical outcome and identifies patients who benefit from early coronary angiography. The predictive value of microvolt T-wave alternans for predicting arrhythmic events was studied by Gehi and coworkers¹⁹ and was found to be dependent on the characteristics of the study population; the positive predictive value was highest (51%) in patients with a history of arrhythmic events while the negative predictive value was highest in postinfarction patients.

MYOCARDIAL ISCHEMIA AND INFARCTION

The prevalence of unrecognized myocardial infarctions and the optimal ECG criteria for its identification were studied by Ammar and coworkers.²⁰ In a random population-based study of over 2000 adults, they estimated the proportion of infarctions which go unrecognized to vary between 32% and 61%, due to variations of the criteria used. They scrutinized the Reykjavik II and I studies, the MRFIT study, ECG criteria sensitive to weight and body mass index, the Cardiovascular Health Study, and the British Regional Heart Study, once using only major and once all Q-codes. The highest sensitivity (36.6%) was found in the last and best positive predictive value (30.99%) in the first study. The authors stressed that in view of the wide variations in the prevalence estimates there is a need for a better standardization of the diagnostic ECG criteria of unrecognized myocardial infarctions.

Postpacing precordial T-wave inversion, "cardiac memory," mimics an ischemic pattern and Shvilkin and coworkers²¹ used his phenomenon to describe a distinctive T-vector pattern induced by right ventricular pacing that allows discrimination from ischemic precordial T-wave inversions, regardless of the coronary artery involved. In women, several 12-lead ECG parameters such as the QRS-T angle and the QRS, and age- and gender-adjusted QT interval duration were found to be predictive of future cardiovascular events with suspected myocardial ischemia and the incorporation of these ECG parameters as part of a global risk factor score was suggested in the WISE study.²²

Vesterinen and coworkers²³ demonstrated that the ST-T integral and T-wave maximum amplitude recorded by body surface potential mapping outperformed QRS integral in detecting myocardial infarction and suggested to include this measurement when old infarction is suspected.

Silent myocardial ischemia, diagnosed by episodes of down-sloped or horizontal ST depressions of ≥ 1 mm at a duration of ≥ 1 minute on Holter monitoring was studied by Sajadieh and coworkers.²⁴ In men and women between 55 and 75 years of age and with no history of cardiovascular disease or stroke, silent ischemia was found in 11.4% of the patients. During a follow-up of 5 years, this was associated with more than three-fold increase in the cardiac event rate, after correction for risk factors.

HEART RATE, RHYTHM, AND CONDUCTION DISTURBANCES

The predictive value of exercise-induced ventricular arrhythmias was studied in over 5000 consecutive male veterans referred for exercise testing.²⁵ In a Cox hazards model adjusted for age, cardiovascular disease, exercise-induced ischemia, ECG abnormalities, exercise capacity, and risk factors, exercise-induced ventricular arrhythmias were significantly associated with time to cardiovascular death. Their combination with resting premature ventricular contractions was associated with the highest hazard ratio.

An S-wave upstroke > 55 ms in V_1 - V_3 in the absence of right bundle-branch block was found to be an indicator of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C).²⁶ An S-wave upstroke of ≥ 70 ms was predictive of inducible ventricular tachycardia. This prolongation of the

S-wave upstroke had the highest diagnostic utility for differentiating the localized form of ARVD/C from right ventricular outflow tract tachycardia, correlated well with a degree of right ventricular involvement and was an independent predictor of ventricular tachycardia induction. The authors suggested to consider a prolonged S-wave upstroke in V_1 - V_3 , a diagnostic ECG marker for ARVD/C.

In patients with unexplained cardiomyopathy repetitive monomorphic ventricular ectopy from the right ventricular outflow tract is an underappreciated cause. Yarlagadda and coworkers²⁷ stressed that in such patients if presenting with repetitive monomorphic ventricular ectopy with left bundle-branch, inferior-axis morphology, the left ventricular function should be carefully assessed; unexplained ventricular dysfunction should raise concern about an ectopy-induced cardiomyopathy, and these patients should be considered for ablation, even if they are otherwise asymptomatic.

The electrocardiographic (and electrophysiologic) pattern of ventricular tachycardia originating within the pulmonary artery was the subject of the study of Sekiguchi and coworkers.²⁸ Several characteristics were described for this type of tachycardia different from those which originate from the right ventricular outflow tract, and it was stressed that radiofrequency catheter ablation within the pulmonary artery should be considered when the ECG shows the characteristics of VT originating within the pulmonary artery.

Isolated left anterior hemiblock should not be considered a benign ECG abnormality. In patients with suspected coronary artery disease referred for stress testing, this pattern was associated with increased risk of cardiac death,²⁹ persistent even after adjustment for major clinical data and abnormalities on the stress echocardiogram.

BRUGADA SYNDROME

Evidence was recently provided by Ikeda and coworkers³⁰ that a noninvasive strategy can detect a high-risk group with this syndrome. In a 40-month follow-up of subjects with a Brugada-type ECG, and no history of cardiac arrest, of 12-risk indices spontaneous changes in the ST segment had the most significance. Combined assessment of this index and other significant indices obtained higher positive predictive values (43-71%).

Bradyarrhythmic complications were found in all four patients who had Brugada syndrome (BS)

caused by *SCN5A* gene mutations: three of these patients had sick sinus syndrome and the other had paroxysmal complete atrioventricular block.³¹ In children *SCN5A* mutation causing BS and type-3 long QT syndrome, Beaufort-Krol and coworkers³² studied the age at which the characteristic ECG abnormalities appear. It was demonstrated that in carriers the characteristic ST elevation of BS appeared at the age of 5 years and became increasingly prevalent with age, being present in 80% of carriers who were 12–16 years old. The QTc was longer in carriers than noncarriers at all age groups between 0 and 16 years. In the carriers with age, the QTc became progressively longer, with a mean QTc of 490 ms at ages of 12–16 years.

Patients with the ECG pattern of BS despite an apparently normal heart have at clinical and non-invasive investigation concealed structural abnormalities that are localized mainly in the right ventricle, as demonstrated by Frustaci and coworkers.³³ The investigators also confirmed previous reports that in a minority of patients with the typical ECG pattern of BS, fatty tissue replacement may be observed and proposed that the ECG pattern of ST-segment elevation in the right precordial leads is not a marker of a specific syndrome; rather, it is a common electrical manifestation of structural abnormalities in the right ventricle that may have genetic, infective, and inflammatory origins.

A possible overdiagnosis of the BS may be a consequence of modified upward positioning of right precordial leads, as was stressed by Priori and Napolitano³⁴ who advocated the use for diagnostic purposes only ECG recordings obtained via conventional positioning of the right precordial leads. On the other hand, an unmasking of this syndrome was reported in two patients after administration of lithium,³⁵ a commonly used drug not previously reported to block cardiac sodium channels.

SUDDEN DEATH

Tan and coworkers³⁶ assessed surviving relatives of sudden cardiac death victims with resting 12-lead and exercise ECG. These tests had a high diagnostic yield and unmasked presymptomatic disease carriers and identified the disease in 40% of families. Thus, resting and exercise ECG, with supportive molecular genetics information, constitute excellent diagnostic strategies. An increased QRS voltage increased the risk of out-of-hospital cardiac

arrest in women but not in men, as demonstrated in the Reykjavik Study.³⁷

A "heart-rate profile" consisting of a resting heart rate that was > 75/min, an increase in heart rate during exercise that was < 89/min and a decrease in heart rate of < 25/min after the termination of exercise, was suggested by Jouven and coworkers.³⁸ This heart-rate profile, after adjustment for potential confounding variables, remained strongly associated with an increased risk of sudden death.

Krahn and coworkers³⁹ studied survivors of unexplained cardiac arrest with 12-lead resting and continuous ECG telemetry for 72 hours, treadmill and signal-averaged ECG, and other noninvasive tests, followed by adrenaline and procainamide infusions. Family members were similarly examined, followed by invasive testing, if justified. The pharmacological challenge helped to diagnose primary electrical disease such as catecholaminergic ventricular tachycardia and BS and was helpful in identifying asymptomatic family members.

ECG AS A SCREENING TOOL

Hedberg and coworkers⁴⁰ found that in an elderly unselected population, both men and women, the sensitivity, specificity, and negative and positive predictive values for the 12-lead ECG to detect left ventricular systolic dysfunction were 96%, 79%, 100%, and 26%, respectively. B-type natriuretic peptide had a diagnostic value in addition to the ECG only in subjects with abnormal ECGs.

HEART RATE VARIABILITY AND TURBULENCE

One of the most important contributions and new concepts in 2005 concerned our understanding of the variability and the turbulence of the heart rate. A new measure of HRV, the "HRV fraction," combining magnitude, distribution, and heart rate influences obtained from Holter recordings was suggested by Sosnowski and coworkers⁴¹ as being a useful index for global HRV. Guzzetti and coworkers⁴² proposed a method of simple symbolic analysis based on three-beat periods to quantify HRV, which seems to overcome some limitations of power spectrum analysis of HRV. They also applied this method to the ECG recordings obtained from implantable cardioverter defibrillators in patients who had episodes of ventricular arrhythmias and detected signs of sympathetic overactivity

preceding these major arrhythmic events. The same group of investigators⁴³ evaluated indices derived from time domain, spectral domain, and fractal analyses of 24-hour automatic HRV; in patients with chronic heart failure in sinus rhythm, automatic spectral analysis provided independent risk indices related to mode of death.

In depressed postmyocardial infarction patients HRV was significantly lower, as demonstrated on 24-hour Holter monitoring⁴⁴ and this was shown to be partially responsible for the excess mortality of these patients. Twenty-four-hour Holter recordings were used to study heart rate turbulence after atrial premature beats preceding spontaneous onset atrial fibrillation.⁴⁵ Turbulence onset was significantly less negative during the 1-hour preceding atrial fibrillation than during the nonatrial fibrillation hours, both in patients with structural heart disease and those with lone fibrillation; a transient enhancement of vagal outflow occurring before atrial fibrillation was suggested.

SUBARACHNOIDAL HEMORRHAGE

Serial ECG changes were recorded in a patient during the progression of subarachnoidal hemorrhage by Inoko and coworkers.⁴⁶ The tracing, which was normal before, showed sinus tachycardia with frequent ventricular ectopics after 15 seconds, wide QRS tachycardia (ventricular or sinus with intraventricular conduction delay) after 5 minutes, and sinus tachycardia with marked ST elevation in almost all leads after 7 minutes. Thereafter, the ST elevation gradually improved, and the QT interval was prolonged and the following day an inverted T wave appeared. These alterations were explained first by release of humoral substances such as epinephrine and norepinephrine. Second, direct control occurs through efferent and afferent connections with the parasympathetic and the sympathetic nervous system. The authors suggested that the myocardial damage induced in both takotsubo cardiomyopathy and subarachnoidal hemorrhage are induced by the same mechanisms.

GENETIC ASSOCIATIONS

The genetic associations in cardiology were increasingly studied during the last several years and several important contributions were published during 2005. A cooperation between clinicians and basic scientists led to the discovery of

new clinical expressions of genetic abnormalities and studying the ECG recording provided during 2005 new and important data in this field.

Royer and coworkers used heterozygous SCN5A-knockout mice as a model for the human hereditary Lenegre's disease.⁴⁷ Surface ECG recordings showed age-related lengthening of the P wave and PR- and QRS-interval duration, coinciding with previous observations in patients with Lenegre's disease providing the first demonstration that a monogenic ion channel defect can progressively lead to myocardial structural anomalies. Crotti and coworkers⁴⁸ provided important clinical and genetic evidence that coinheritance of a novel, low penetrance mutation in the *KCNH2* gene and a common, nonsynonymous single nucleotide polymorphism in the same gene are associated with increased QTc duration and sudden death from cardiac arrhythmia, whereas heterozygous carriers of either gene variant alone were asymptomatic or exhibited only transient and mild QTc prolongation.

The ECG features of the Andersen-Tawil Syndrome, a heterogeneous autosomal dominant genetic disorder, part of which is also arrhythmias, was reassessed by Zhang and coworkers.⁴⁹ Gene-specific T- and U-wave patterns resulting from decreased I_{ki} owing to *KCNJ2* mutations aided diagnosis and directed genotyping. The normal QTc, distinct ECG, and other clinical features were shown to distinguish ATS1 from long-QT syndrome, and it is best designated as ATS1 rather than LQT7. In a large Jewish family, Shushi and coworkers⁵⁰ identified a new PAS-domain HERG mutation (M124R) as causing long QT syndrome, with high penetrance and frequent disease-related symptoms. This mutation significantly decreased the tail-current density and accelerated the deactivation kinetics of the HERG channel in transfected CHO cells.

SUMMARY

Dr. Weyman⁵¹ in his outstanding résumé of "The Year (2004) in Echocardiography" raised the question whether magnetic resonance imaging will eventually replace echocardiography. "The answer is in the wheels" he wrote, meaning that echocardiographers should be concerned only if this newer method will be seen "wheeled down the hall and into the patient's room." I personally believe that even if echocardiography, which is the next widely used noninvasive method today, will use machines as portable and compact as the ECG machines, and

as a matter of fact there are echo machines like that today, even then, there will be no reason for the clinicians and scientists using the electrocardiograph to be concerned. The 50 articles quoted here demonstrate that electrocardiography continues to provide new and important data, is being used more and more extensively, and its applications will continue to grow and expand in the future.

Acknowledgment: *I thank Dr. Wojciech Zareba for his most valuable suggestions in preparing this manuscript. The most important and excellent editorial assistance of Liane Herman is greatly acknowledged.*

REFERENCES

1. Frisella ME, Spodick DH. Confirmation of the prevalence and importance of a 12-lead investigation for diagnosis. *Am J Cardiol* 2005;96:696-697.
2. Kistler PM, Fynn SP, Haqqani H, et al. Focal atrial tachycardia from the ostium of the coronary sinus. *J Am Coll Cardiol* 2005;45:1488-1493.
3. Hoppe BL, Kahn AM, Feld GK, et al. Separating atrial flutter from atrial fibrillation with apparent electrocardiographic organization using dominant and narrow F-wave Spectra. *J Am Coll Cardiol* 2005;46:2079-2087.
4. Yuniadi Y, Tai CT, Lee KT, et al. A new electrocardiographic algorithm to differentiate upper loop re-entry from reverse typical atrial flutter. *J Am Coll Cardiol* 2005;46:524-528.
5. Dhingra R, Ho Nam B, Benjamin EJ, et al. Cross-sectional relations of electrocardiographic QRS duration to left ventricular dimensions. The Framingham Heart Study. *J Am Coll Cardiol* 2005;45:685-689.
6. Bruch C, Gotzmann M, Stypmann J, et al. Electrocardiography and Doppler echocardiography for risk stratification in patients with chronic heart failure. *J Am Coll Cardiol* 2005;45:1072-1075.
7. Buxton AE, Sweeney MO, Wathen MS, et al. QRS duration does not predict occurrence of ventricular tachyarrhythmias in patients with implanted cardioverter-defibrillators. *J Am Coll Cardiol* 2005;46:310-316.
8. Sweeney MO, Hellkamp AS, Lee KL, et al. Association of prolonged QRS duration with death in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2005;111:2418-2423.
9. Sosnowski M, Gabrylewicz B, Parma R, et al. Routine electrocardiogram parameters for myocardial viability assessment in patients with left ventricular dysfunction qualified for revascularization procedures. *Folia Cardiol* 2005;12:548-553.
10. Hsieh BP, Pham MX, Froelicher VF. Prognostic value of electrocardiographic criteria for left ventricular hypertrophy. *Am Heart J* 2005;150:161-167.
11. Richardson K, Engel G, Yamazaki T, et al. Electrocardiographic damage scores and cardiovascular mortality. *Am Heart J* 2005;149:458-463.
12. Lecoq G, Leclercq C, Alonso E, et al. Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure. *Eur Heart J* 2005;26:1094-1100.
13. Ammann P, Sticherling C, Kalusche D, et al. An electrocardiogram-based algorithm to detect loss of left ventricular capture during cardiac resynchronization therapy. *Ann Intern Med* 2005;142:968-973.
14. Vrtovec B, Okrajsek R, Golicnik A, et al. Atorvastatin therapy increases heart rate variability, decreases QT variability, and shortens QRc interval duration in patients with advanced chronic heart failure. *J Card Fail* 2005;11:684-690.
15. Vrtovec M, Vrtovec B, Briski A, et al. Chromium supplementation shortens QTc interval duration in patients with type 2 diabetes mellitus. *Am Heart J* 2005;149:632-636.
16. Beasley CM, Mitchell MI, Dmitrienko AA, et al. The combined use of ibutilide as an active control with intensive electrocardiographic sampling and signal averaging as a sensitive method to assess the effects of tadalafil on the human QT interval. *J Am Coll Cardiol* 2005;46:678-687.
17. Zitron E, Scholz E, Owen RW, et al. QTc prolongation by grapefruit juice and its potential pharmacological basis. HERG channel blockade by flavonoids. *Circulation* 2005;111:835-838.
18. Jacobsen MD, Wagner GS, Holmvang L, et al. Quantitative T-wave analysis predicts 1 year prognosis and benefit from early invasive treatment in the FRISC II study population. *Eur Heart J* 2005;26:112-118.
19. Gehi AK, Stein RH, Metz LD, et al. Microvolt T-wave alternans for the risk stratification of ventricular tachyarrhythmic events. A meta-analysis. *J Am Coll Cardiol* 2005;46:75-82.
20. Ammar KA, Yawn BP, Urban L, et al. Identification of optimal electrocardiographic criteria for the diagnosis of unrecognized myocardial infarction: A population-based study. *Ann Noninvasive Electrocardiol* 2005;10:197-205.
21. Shvilkin A, Ho KKL, Rosen MR, Josephson ME. T-vector direction differentiates postpacing from ischemic T-wave inversion in precordial leads. *Circulation* 2005;111:969-974.
22. Triola B, Olson MB, Reis S, et al. Electrocardiographic predictors of cardiovascular outcome in women. *J Am Coll Cardiol* 2005;46:51-56.
23. Vesterinen P, Hanninen H, Karvonen M, et al. Spatial repolarization abnormalities in old myocardial infarction. *J Electrocardiol* 2005;38:264-270.
24. Sajadieh A, Nielsen OW, Rasmussen V, et al. Prevalence and prognostic significance of daily-life silent myocardial ischaemia in middle-aged and elderly subjects with no apparent heart disease. *Eur Heart J* 2005;26:1402-1409.
25. Beckerman J, Mathur A, Stahr S, et al. Exercise-induced ventricular arrhythmias and cardiovascular death. *Ann Noninvasive Electrocardiol* 2005;10:47-52.
26. Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity. A need to broaden diagnostic criteria. *Circulation* 2004;110:1527-1534.
27. Yarlagadda RK, Iwai S, Stein KM, et al. Reversal of cardiomyopathy in patients with repetitive monomorphic ventricular ectopy originating from the right ventricular outflow tract. *Circulation* 2005;112:1092-1097.
28. Sekiguchi Y, Aonuma K, Takahashi A, et al. Electrocardiographic and electrophysiologic characteristics of ventricular tachycardia originating within the pulmonary artery. *J Am Coll Cardiol* 2005;45:887-895.
29. Biagini E, Elhendy A, Schinkel AFL, et al. Prognostic significance of left anterior hemiblock in patients with suspected coronary artery disease. *J Am Coll Cardiol* 2005;46:858-863.
30. Ikeda T, Takami M, Sugi K, et al. Noninvasive risk stratification of subjects with a Brugada-type electrocardiogram and no history of cardiac arrest. *Ann Noninvasive Electrocardiol* 2005;10:396-403.
31. Makiyama T, Akao M, Tsuji K, et al. High risk for bradyarrhythmic complications in patients with Brugada syndrome caused by SCN5A gene mutations. *J Am Coll Cardiol* 2005;46:2100-2106.

32. Beaufort-Krol GCM, van den Berg MP, Wilde AAM, et al. Developmental aspects of long QT syndrome and Brugada syndrome on the basis of a single *SCN5A* mutation in childhood. *J Am Coll Cardiol* 2005;46:331–337.
33. Frustaci A, Priori SG, Pieroni M, et al. Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. *Circulation* 2005;112:3680–3687.
34. Priori SG, Napolitano C. Management of patients with Brugada syndrome should not be based on programmed electrical stimulation. *Circulation* 2005;112:285–292.
35. Darbar D, Yang T, Churchwell K, et al. Unmasking of Brugada syndrome by lithium. *Circulation* 2005;112:1527–1531.
36. Tan HL, Hofman N, van Langen IM, et al. Sudden unexplained death. Heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. *Circulation* 2005;112:207–213.
37. Thorgeirsson G, Thorgeirsson G, Sigvaldason H, et al. Risk factors for out-of-hospital cardiac arrest: The Reykjavik Study. *Eur Heart J* 2005;26:1499–1505.
38. Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;352:1951–1958.
39. Krahm AD, Gollob M, Yee R, et al. Diagnosis of unexplained cardiac arrest. Role of adrenaline and procainamide infusion. *Circulation* 2005;112:2228–2234.
40. Hedberg P, Lonnberg I, Jonasan T, et al. Electrocardiogram and B-type natriuretic peptide as screening tools for left ventricular systolic dysfunction in a population-based sample of 75-year old men and women. *Am Heart J* 2004;148:524–529.
41. Sosnowski M, Clark E, Latif S, et al. Heart rate variability fraction—a new reportable measure of 24-hour R-R interval variation. *Ann Noninvasive Electrocardiol* 2005;10:7–15.
42. Guzzetti S, Borroni E, Garbelli PE, et al. Symbolic dynamics of heart rate variability. A probe to investigate cardiac autonomic modulation. *Circulation* 2005;112:465–470.
43. Guzzetti S, La Rovere MT, Pinna GD, et al. Different spectral components of 24 h heart rate variability are related to different modes of death in chronic heart failure. *Eur Heart J* 2005;26:357–362.
44. Vikman S, Lindgren K, Makikallio TH, et al. Heart rate turbulence after atrial premature beats before spontaneous onset of atrial fibrillation. *J Am Coll Cardiol* 2005;45:278–284.
45. Carney RM, Blumenthal JA, Freedland KE, et al. Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Arch Intern Med* 2005;165:1486–1491.
46. Inoko M, Nakashima J, Haruna T, et al. Serial changes of the electrocardiogram during the progression of subarachnoid hemorrhage. *Circulation* 2005;112:e331–e332.
47. Royer A, van Veev TAB, Le Bouter S, et al. Age-related conduction slowing and myocardial fibrosis. *Circulation* 2005;111:1738–1746.
48. Crotti L, Lundquist AL, Insolia R, et al. *KCNH2*-K897T is a genetic modifier of latent congenital long-QT syndrome. *Circulation* 2005;112:1251–1258.
49. Zhang L, Benson DW, Tristani-Firouzi M, et al. Electrocardiographic features in Andersen-Tawil syndrome patients with *KCNJ2* mutations. Characteristic T-U-wave patterns predict the *KCNJ2* genotype. *Circulation* 2005;111:2720–2726.
50. Shushi L, Kerem B, Goldmit M, et al. Clinical, genetic, and electrophysiologic characteristics of a new pas-domain HERG mutation (M124R) causing long QT syndrome. *Ann Noninvasive Electrocardiol* 2005;10:334–341.
51. Weyman AE. The year in echocardiography. *J Am Coll Cardiol* 2005;45:448–455.