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REVIEW ARTICLE

The Stanford Legacy and the Future of Electrocardiographic Screening of Athletes

Victor Froelicher *[1 2], Jason V Tso [1], Samuel Montalvo [1], Jeffrey Christle[1], Marco V Perez [1], David Hadley [2], Matthew Wheeler [1], Calvin E Hwang [3], Abhimanyu Uberoi [4], Geoffrey Abrams [3], Euan Ashley [1]

[1] Division of Cardiovascular Medicine, Stanford University School of Medicine, Palo Alto, CA
Department of Medicine, Division of Cardiovascular Medicine, 453 Quarry Rd MC 5687 Stanford, CA 94304
[2] Cardiac Insight Inc, Bellevue, Seattle
[3] Department of Orthopaedic Surgery, Stanford University School of Medicine, Stanford, CA
[4] Cardiology, Kaiser Permanente Physicians and Surgeons, Portland Oregon

***Corresponding author:** victorf@stanford.edu

ABSTRACT
Though some controversy remains regarding the place of the 12 lead Electrocardiogram (ECG) in the routine screening of young athletes and how and where the pre-participation examination should be performed, studies continue to support the ECG and properly organized mass screening. The purpose of this paper is to provide brief historical perspective, the experiences at our institution and our view of the future application of computerized Electrocardiography in screening for cardiovascular risk. The focus is on the process and improvement of Electrocardiographic criteria for estimating the cardiovascular risk of young athletes.

Introduction

The first meaningful application of ECG screening of athletes began with the Italian national mandate in 1982. [1] Subsequent meta-analysis has demonstrated the ECGs superiority to other elements of the pre-participation exam (PPE). [2] However, efforts have been made to improve the other elements of the PPE,[3] most notable being the screening video's developed by Levine.[4] Our position is that the elements of the PPE should not be competitive but integrated. The athlete, his or her health care system and electrocardiographer are better served by knowing the athlete's sport, training pattern, key CV risk factors (chest pain, syncope, exercise tolerance, palpitations) and family medical history. This paper will describe the Stanford Sports Medicine experience with ECG screening, possible changes in the criteria recommendations and our ideas for its future.

Historical Perspective and Methodology

Since the Italian experiment started, there has been a logical progression to applying the ECG for screening athletes. This culminated in International Guidelines for the interpretation of the ECGs of young athletes, introduced in 2011 and evolved to subsequent versions with the latest released in 2017.[5] Our Stanford Sports medicine group published the first definition of quantitative ECG criteria (**Figure 1**, as featured on the cover of Circulation) which markedly lowered the false positive rate for screening young athletes. [6 7]

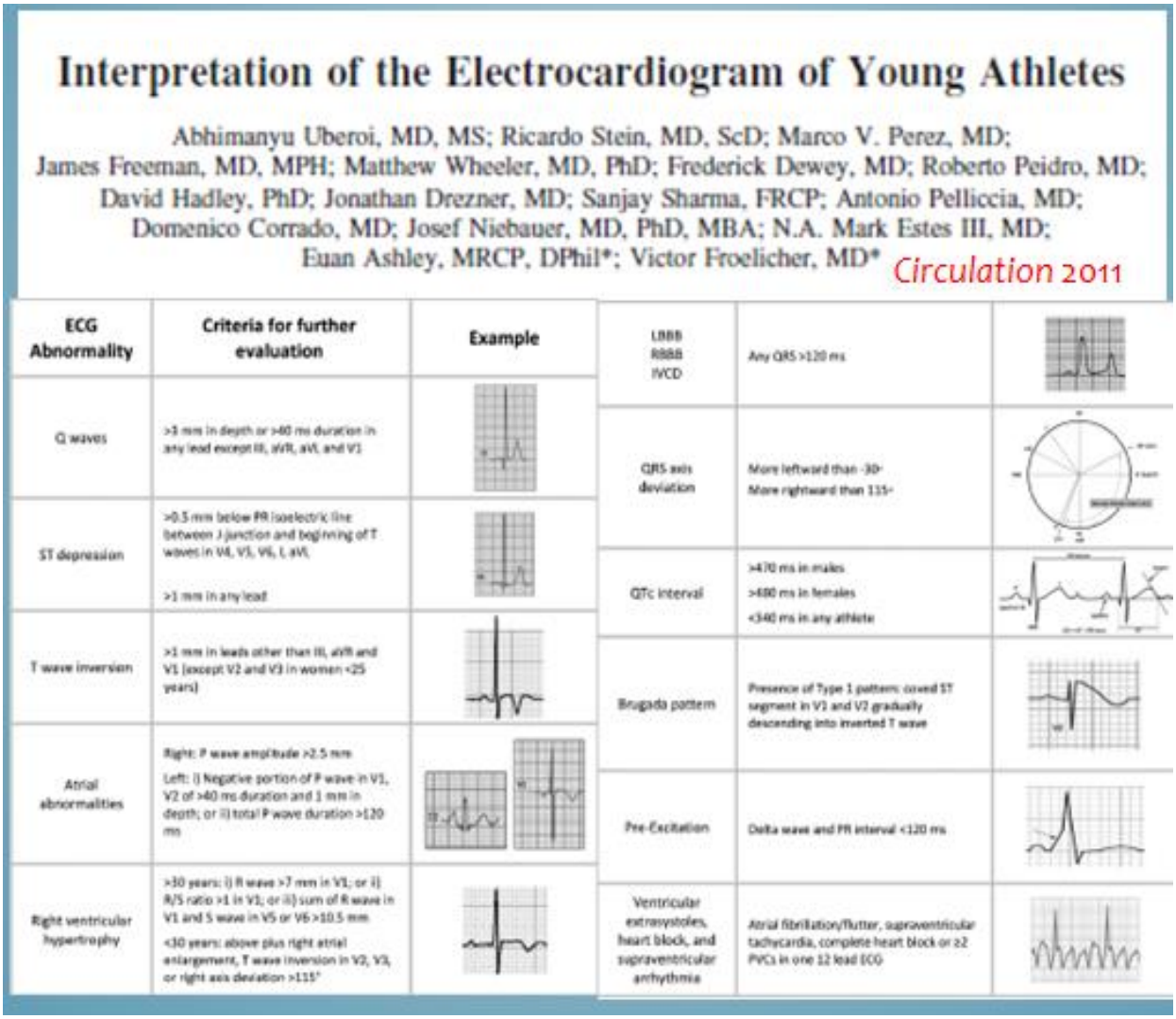

Figure 1. Cover of the first International Criteria for the Interpretation of the ECG of the Athlete

Our Initial work focused on gathering ECGs of athletes and identifying common findings that would otherwise be considered abnormal in the general population, thus attributing certain patterns to exercise training rather than cardiac pathology. Next was to apply established clinical ECG criteria for heart disease to athletes and determine if the criteria were meaningful in determining the use of echocardiographic, MRI, and electrophysiological testing. As such, criteria thus far are aimed at

detecting later stages of cardiac pathology and decreasing the rate of false positives. In this regard, the false positive rate has improved from over 10% in early studies to 1-4% with contemporary guidelines.[8] **Table 1** lists the origins of the currently recommended ECG criteria for screening young athletes for cardiovascular risk. The methodology we have applied is to focus on the header topics used which discuss concepts and areas where we have presented unique scientific studies. We close with recommendations for inclusions in future International consensus statements.

Table 1. Basis for Criteria for Interpretation of the ECGs of Athletes

1. Epidemiological studies of apparently healthy populations there are known ECG markers (Q waves, ST depression, T wave inversion, LVH patterns, BBB, long QT, etc) associated with adverse outcomes. Pro: established by hard endpoints, con: usually only available in older subjects, athletic status not determined
2. ECG findings that are physiological rather than pathological can be found in athletes performing aerobic, dynamic exercise training. Pro: they can be demonstrated to be "normal" or not by imaging studies, Con: uncertain whether they can be precursors of pathological conditions.
3. ECG observations in athletes (or family members) who are identified with conditions known to be associated with sudden cardiac death (SCD) and in non-athletes with conditions such as HCM, ARCVD, or LQTS. Pro: instant "epidemiology", no follow up needed, Con: usually older subjects and with later stages of disease.

Usually the next step would be to apply test characteristic methods to a large prospectively studied population with athletic status quantified with clinical and follow up endpoints. Unfortunately, traditional test evaluation (receiver operator characteristic curves [ROC] and area under the ROC [AUC]) cannot be applied with presently available data as AUC's are not valid if one compares the sickest to the most well. Under these circumstances, AUCs are greatly exaggerated and the cut-points inaccurate. We learned this from exercise testing.[9] Many studies have compared ECG data from older patients with younger athletes. However, ECG manifestations of cardiomyopathies generally have a time course where only the mildest abnormalities are present in the young where screening is performed.[10] Age and sex defined ECG values that include diverse athlete and non-athlete populations, inclusive of exercise training status, test results, and clinical outcomes continue to be needed. Until these data are available (and these studies are in progress [11]), one of the only possible ways to increase the sensitivity of ECG variables for CV risk is to consider the outliers in the apparently healthy young individuals we screen.

Percentile Outliers: We have proposed this approach to improve ECG sensitivity by identifying subtle ECG findings likely to be associated with cardiac disease. Studies can be used to identify statistical measurement outliers where early cardiac disease is likely to be found. Care must be taken in analysis since the extremes can also be due to noise or measurement errors. Percentile cutoffs must be carefully chosen to assure that the false positive rate is not increased. False positive results can lead to erroneous disqualification and significant financial burden on young athletes and their families.[12] Furthermore not all health care systems can afford to support a cadre of specialized sports medicine professionals as is the case in Italy.

Consider the experience with other demographic variables such as weight (obesity vs cachexia) or hemoglobin (anemia vs polycythemia). For example, Saarel et al use the 99th percentile of R and S wave measurements to define left ventricular hypertrophy rather than traditional criteria similar to what we have proposed. [13] Until age and sex defined digital ECG variables are available in a population screened for sports participation and longitudinally followed for clinical and diagnostic results, traditional ROC statistical methods cannot be applied. While we must be cautious whenever making additions to screening criteria, the use of the extreme values (1st and 99th percentiles for instance) warrant investigation as a possible means of improving sensitivity when using the ECG to screen young athletes.

Bayesian statistics show that, in low-risk populations, testing generates more false positives than true positives, raising the question of the necessity of screening a population with a low risk of disease. To this, we have several responses, the first being the senior author's experience screening pilots in the US Air Force which led to a great deal of empathy for individuals who were excluded from activities important to them. On the other hand, those who have been involved with athletics are aware of the palpable fear of sudden cardiac death generated by the public presentation of such an event during

athletic competition. Add to this the strong emotions of family members of young athletes who have actually died playing sports and we can understand how these forces motivate efforts to engage medical tools to diagnose underlying pathology to prevent sudden cardiac death.

The Stanford Approach: Attempting to use biostatistics to moderate the forces urging screening of athletes is nearly impossible, so at Stanford, we took another approach. Attempting to use biostatistics to moderate the forces urging screening of athletes is nearly impossible, so at Stanford, we took another approach. When the electrocardiograms (ECGs) were mandated as part of the annual preparticipation exam for all athletes in 2010, we did not insist that more research was necessary first but made sure they were applied in a reasonable manner. We collected thousands of digital ECGs to confirm that there are "abnormalities" in the ECGs of athletes due to physiological adaptationsWe collected thousands of digital ECGs to confirm that there are "abnormalities" in the ECGs of athletes due to physiological adaptations.[14] We applied our results to reduce the false positive rate from over 20% to <5% by adapting criteria based on clinical ECG studies and considering physiological ECG adaptations normal. [15]

The 20/20 Digital 12 lead ECG System: As a parallel effort, Hadley and Froelicher developed an inexpensive computer-based ECG system that allows capture of athletic status, symptoms, and cardiac risk factors to be recorded on the ECG tracing. This system was so efficient that ECGs were available quickly and properly read using the Stanford Criteria. It was "too successful" and became the standard of care at Stanford, lauded by parents and appreciated by our sports medicine colleagues. Although our approach became successful clinically, our main goal has been to improve the ECG as a screening tool by enhancing the criteria used to diagnose abnormalities through evidence-based research. The currently applied national and international criteria are largely qualitative and empirical.

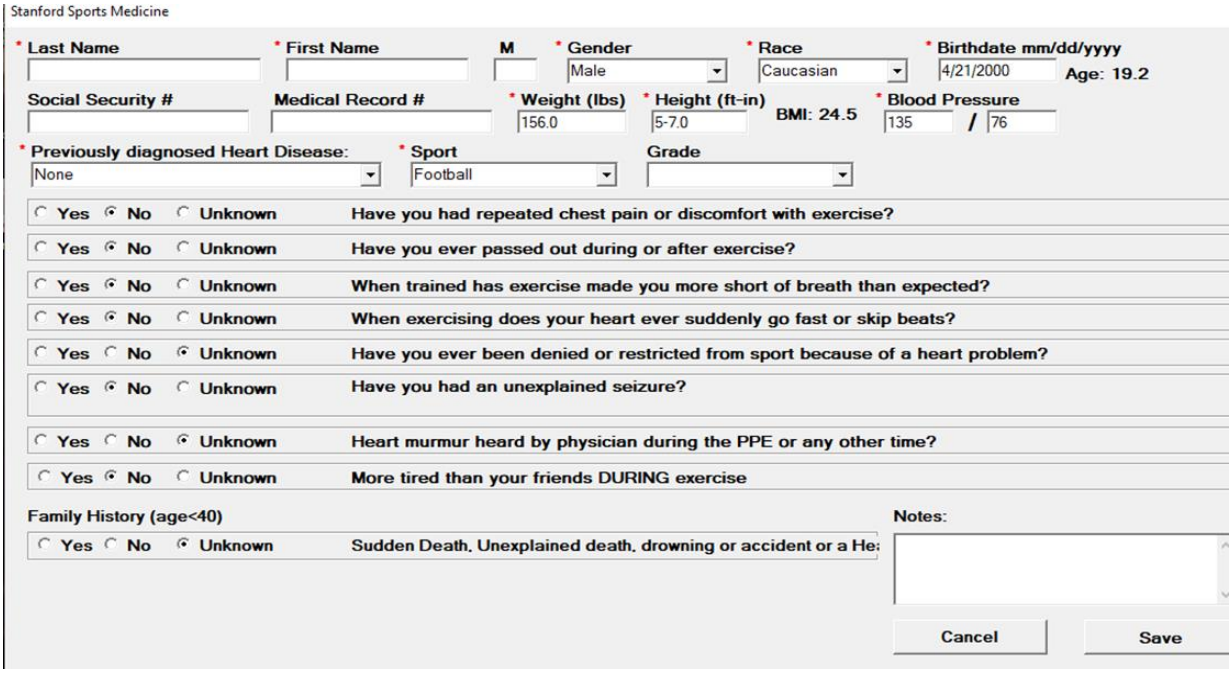

Figure 2. Demographic screen included in the 20/20 program completed as part of performing an ECG. This can be adapted by users by altering the preferences option in "set up".

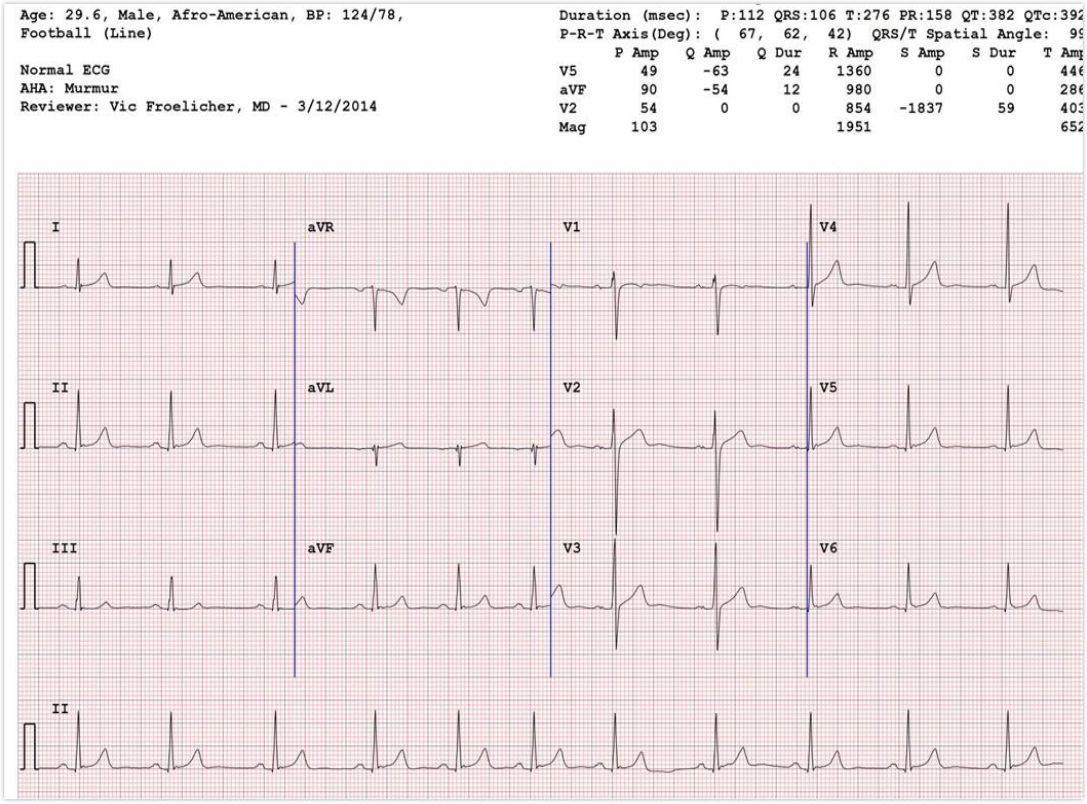

Figure 3. ECG printed from 20/20 with demographics, sport information and screening questionnaire results.

Table 2. Areas where the Stanford Approach was applied to problematic ECG Findings:

1. Early Repolarization
2. Left Atrial abnormality
3. ST shifts
4. Low Voltage QRS

Stanford Early Repolarization Studies

Our first impression when the first population studies of early repolarization appeared was that a new channelopathy had been discovered that explained more of the sudden cardiac death (SCD) in athletes with morphologically normal hearts. Unfortunately, all the excitement was due to semantic confusion[16] and differences in the definition of early repolarization in the US vs in Europe. Then we began to worry that the computerized ECG statements of early repolarization could cause ICD placements in healthy athletes.

Distinctive Characteristics

Criteria	Brugada	Haissaguerre
ECG Leads	V1-V2	Other leads
ECG Pattern	ST elevation with inverted T wave	R wave downslope phenomena (J waves, slurs in inferior leads) dynamic ST elevation
Na channel -	Increase V1-V2	No effect
ST pattern	Coved type	No elevation/Concave
Effect of temperature	Fever increases the pattern/arrhythmia	Hypothermia ? (Osborn Wave)
Conduction	± abnormal	normal
VF origin	RV	LV ± RV
Mutation	SCN5A, GP1DL, CACNA1C, CACNB2B, SCN1B, KCNE3,SCN3B	KCNJ8, CACNA1C, CACNB2B

Figure 4. Comparison of the Brugada and Haissaguerre (or Early Repolarization) syndrome.

Introduced in the New England Journal of Medicine in 2008 as "Early Repolarization",[17] this new ECG pattern and syndrome is more appropriately named after Michel Haïssaguerre who first reported it (as suggested by Viskin JACC, 2009).[18] The ECG pattern consists of J waves, slurs or notches particularly in the inferior leads and the syndrome requires sudden cardiac death (SCD) without cardiac abnormalities, family history and genetic markers. It has been compared to the Brugada syndrome (Figure 4).

However, Early Repolarization (ER) was already defined for two areas:

1. In cellular physiology, ER is defined as Phase 1 of the action potential
2. In clinical medicine, ER is defined as a resting ECG pattern of ST elevation in the lateral>Inferior leads sometimes accompanied by J waves or slurs on the R wave downslope, occurring particularly in athletic, young male African Americans.

Naming of this new syndrome with a name previously assigned to other entities created considerable confusion particularly in the US where physicians were taught since the 70's to consider "Early Repolarization" a normal variant of ST elevation. (Figure 5) In fact, though this new, rare syndrome may be found to be more prevalent now that it has been discovered, nomenclature and ECG measurement disagreements could cause more harm than good. This is particularly the case since many of the widely used automated ECG machines generated a diagnostic statement of "Early Repolarization" based on ST elevation in an otherwise normal ECG.

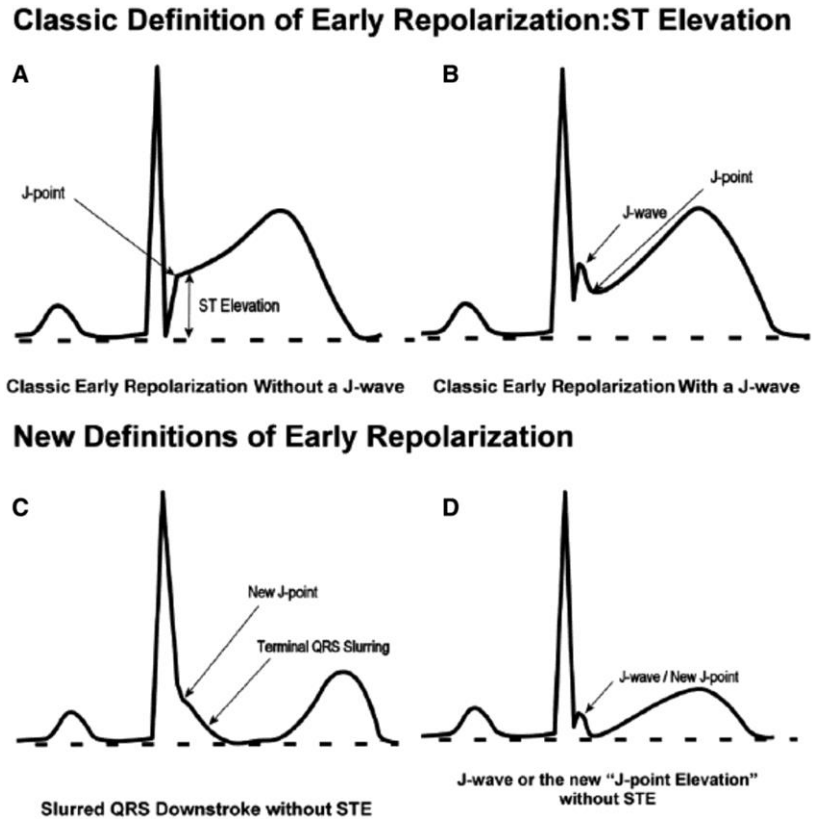

Figure 5. Comparison of the classic and the new definitions of early repolarization (STE=ST segment elevation);with the new definition, ST elevation could or could not be present

Problems with Defining QRS end. Before the prognostic significance of the Haïssaguerre Pattern can be demonstrated, there must be agreement on what measurements should be made. It appears that for stable ECG patterns with a QRS duration (including an end QRS slur J wave/slur) less than 120 msec, we should follow the CSE Measurement statement (1985) and consider the J point (also known as QRS end, J-junction, ST0 [zero msec] or ST beginning) to occur after the R wave downslope notch/slur/or J wave as determined across all 12 leads.[19] The CSE Project, or "Common Standards for Quantitative Electrocardiography", is a project in the European Communities (EC) that aims to establish standards for computer-derived ECG measurements. The project includes reference libraries of well-documented ECGs and reviewing schemes for visually and computer-analyzing ECGs.

The measurement baseline be set in an interval immediately preceding QRS onset as per the CSE Measurement statement. Some of the bizarre and dynamic ECGs may require other rules for measurements but for now the CSE statement should be followed. The figure below shows where the CSE experts indicated that these measurements be made.

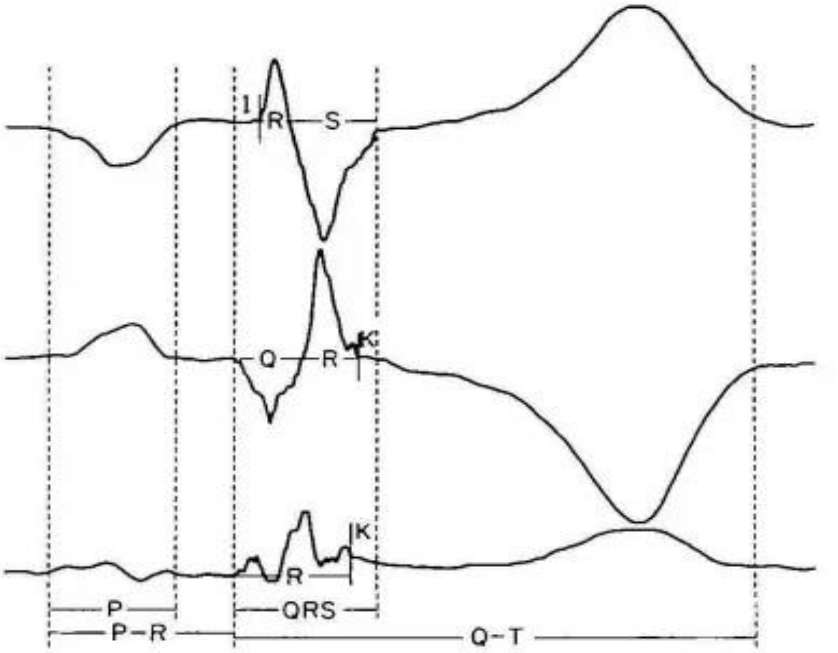

Figure 6. CSE Measurement figure of QRS end

We evaluated 29,281 resting ambulatory ECGs from the VA Palo Alto Health Care System.[20] With PR interval as the isoelectric line and amplitude criteria ≥0.1 mV, ST-segment elevation is defined at the end of the QRS, J wave as an upward deflection, and slur as a conduction delay on the QRS downstroke. Associations of ST-segment elevation patterns, J waves, and slurs with cardiovascular mortality were analyzed with Cox analysis. With a median follow-up of 7.6 years, there were 1,995 cardiac deaths. Of 29,281 subjects, 87% were male (55±14 years) and 13% were female (56±17 years); 13% were Afro-American, 6% were Hispanic, and 81% were white or other. Unfortunately, exercise status was not available. Six hundred sixty-four (2.3%) had inferior or lateral ST-segment elevation: 185 (0.6%) in inferior leads and 479 (1.6%) in lateral leads, 163 (0.6%) in both, and 0.4% had global elevation. A total of 4,041 ECGs were analyzed with enhanced display, and 583 (14%) had J waves or slurring, which were more prevalent in those with than in those without ST-segment elevation (61% versus 13%; P<0.001). ST-segment elevation occurred more in those with than in those without J waves or slurs (12% versus 1.3%; P<0.001). Except when involving only inferior leads, all components of early repolarization were more common in young individuals, male subjects, Afro-americans, and those with bradycardia. All patterns and components of early repolarization were associated with ***decreased*** cardiovascular mortality, but this was not significant after adjustment for age.

Galen Wagner and the senior author (VFF) were co-editors of a symposium issue (Figure 7) with the leading experts in this field presenting the best available data.[21] We concluded that the Haissaguerre Syndrome is rare and unlikely to be responsible for sudden cardiac death in athletes.

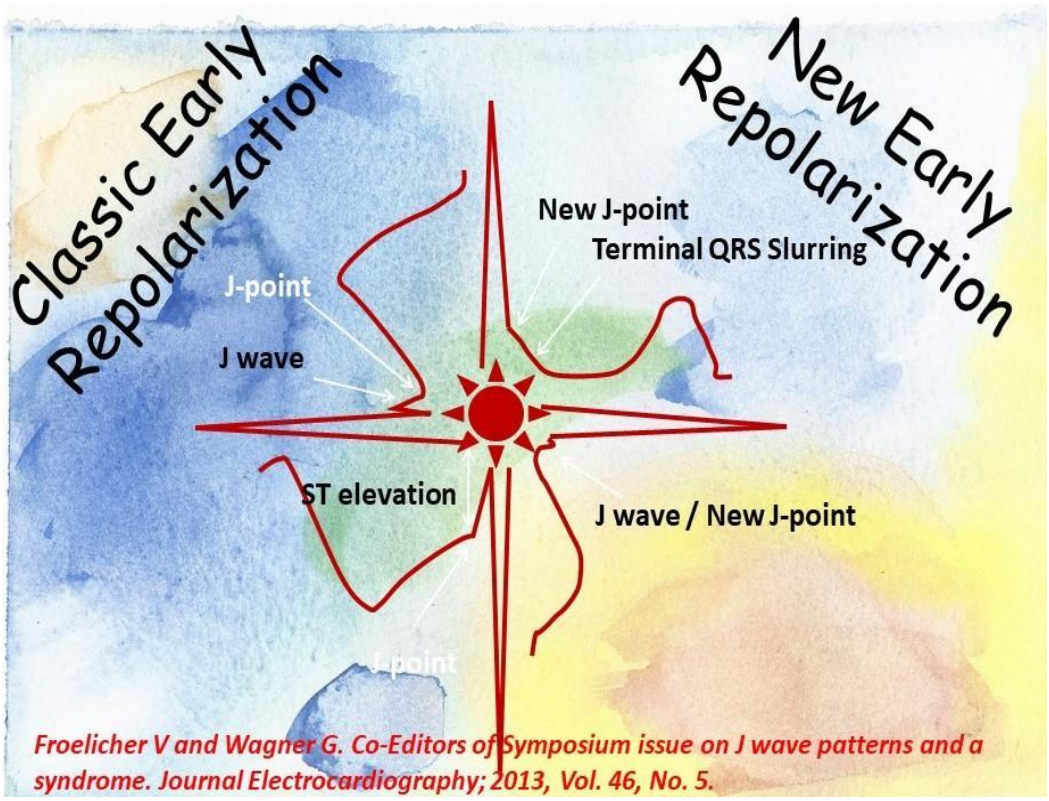

Figure 7. Cover from the Early Repolarization Symposium Issue of the Journal of Electrocardiography.

Stanford Left Atrial Abnormality Studies

Clinical utilization of electrocardiography for diagnosis of left atrial abnormalities is hampered by variable P-wave morphologies, multiple empiric criteria, and lack of an imaging "gold standard". We studied the prevalence of P-wave patterns and demonstrate which components have associations with cardiovascular death (CVD). It is a retrospective analysis of 20,827 veterans less than 56 years of age who underwent ECGs at a Veterans Affairs Medical Center from 1987 to 1999, followed for a median duration of 18 years for cardiovascular death (CVD).[22] Unfortunately, exercise training history was not available. Receiver Operating Characteristic, Kaplan-Meier and Cox Hazard analyses were applied, the latter with adjustment for age, sex and electrocardiography abnormalities. The mean age was 43.3 ± 8 years, and 888 CVDs (4.3%) occurred. A single positive deflection of the P-wave (Pattern 1) was present in 29% for V1 and 81% for V2. A singular negative P-wave (Pattern 2) was present in 4.6% for V1 and 1.6% in V2. A P-wave with an upward component followed by a downward component (Pattern 3) was present in 64.5% for V1 and 17.5% for V2. When the downward component in Patterns 2 and/or 3 is at least −100 μV, a significant association is observed with CVD (adjusted hazard ratios [HRs] 2.9–4.1, $P<0.001$). Total P-wave duration ≥140 ms was also associated with CVD (adjusted HR 2.2, $P<0.001$). Our conclusions were a negative P-wave in V1 or V2 ≤−100 μV, and P-waves with a duration of ≥140 ms, all have independent and significant associations with CVD, with Hazard Ratios comparable to other ECG abnormalities.

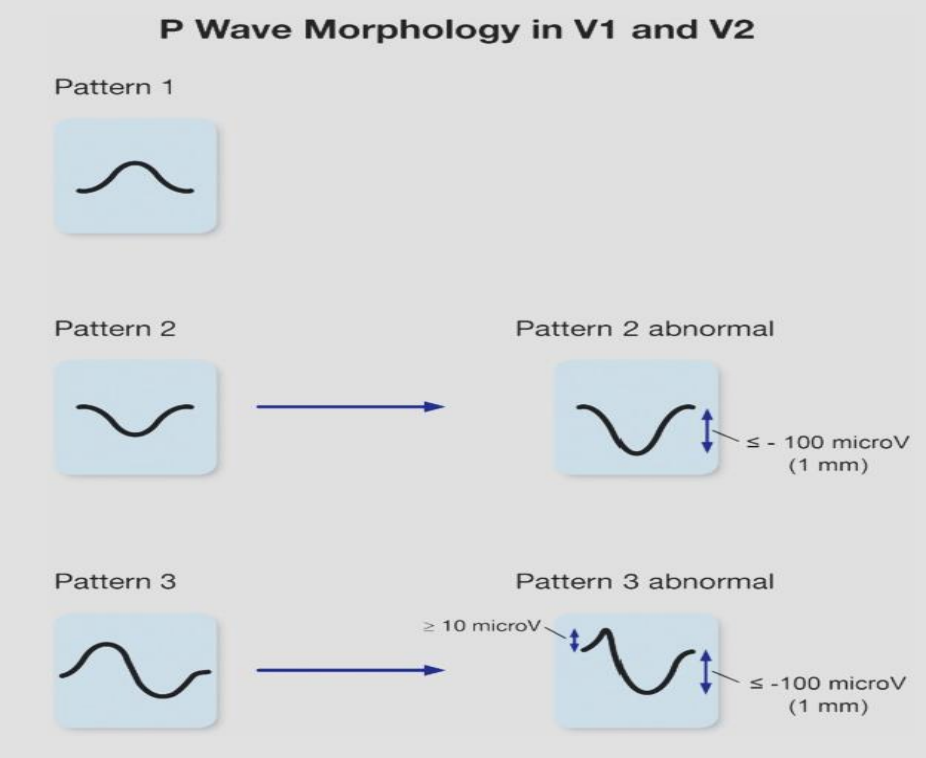

Figure 8, P wave morphology in V1 and V2

Because the International left atrial enlargement electrocardiographic (ECG) screening criteria (ECG-LAE) for athletes are rarely fulfilled in young athletes, we compared it with evidence-based criteria from our clinical outcome study of ECG left atrial abnormality (ECG-LAA).[23] Next we used ECGs from digitally recorded routine preparticipation ECG screening in California of 4,438 young individuals (mean 18.5 years old, 40% women). The International criteria for ECG-LAE were applied: prolonged P wave duration of >120 ms in leads I or II AND negative portion of >1 mm in depth in lead V1. This was compared with Stanford criteria for ECG-LAA: prolonged P wave duration of 140 ms OR negative portion in V1 and V2 greater than 1 mm. Differences in the classification of abnormal ECGs between the 2 criteria applied to the same population of young athletes: Only 33 (0.7%) of our subjects fulfilled the International criteria for ECG-LAE while 110 (2.5%) fulfilled the Stanford criteria. Adding our new ECG/LAA criterion and considering it a major criterion raised the abnormal ECG prevalence and athletes referred for further evaluation from 2.9% to 4.4%. The Stanford evidence-based criterion for ECG-LAA incorporating V2 and replacing "or" for "and" regarding P wave duration increased the yield of abnormal classification for P waves. Future follow-up studies are needed to confirm that this new criterion should be included in future ECG screening recommendations.

The Stanford ST Segment Studies

ST segment deviations around the isoelectric line are common findings in manifest cardiovascular disease.[24] [25] In athletes, ST elevation is common,[26] while ST depression is considered rare. However, clinical studies in athletes have associated ST depression with myocardial fibrosis and fatty infiltration [27] and ST elevation with pericarditis and myocarditis[28]. To better understand the significance of ST shifts in athletes we studied the association between resting ST segment deviations and resting heart rate, an indicator of training and autonomic tone and electrocardiography (ECG) markers of exercise training effect and cardiovascular health R and T wave amplitude. Retrospective analysis of digitized ECG data was performed on 7,836 young healthy people undergoing preparticipation exams (males 4,592 (59%), females 3,244) healthy asymptomatic athletes (14-35 years of age).[29] A series of correlations and regressions were conducted between ST depression (less than 0.0 microV) and ST elevation (greater than 0.0 microV), on R and T wave amplitudes, and heart rate in leads V2, V5, and aVF. Positive correlations between ST elevation and R and T wave (S wave in V2) amplitudes and leads V5, V2, and aVF in male and female athletes (range of r= 0.1-0.54). Moreover, there was a negative correlation between ST elevation and HR for male and female athletes. Finally, there was a negative correlation between ST depression and R wave and HR for male and

female athletes in V5 ($P < 0.01$). In athletes, ST segment elevation is correlated with R and T wave amplitudes and negatively correlated with heart rate. In addition, ST segment elevation is correlated with low heart rate, consistent with its higher prevalence in athletes. ST segment depression is not influenced by heart rate but is negatively associated with R and T wave amplitudes.

In this study of ECGs from a large cohort of athletes, R and T wave resting amplitudes are increased with ST elevation while R and T wave amplitudes exhibit minimal variation with ST depression. The presence of ST depression clusters at lower R and T wave amplitudes is consistent with the hypothesis that this is a marker for poor training effect and poor cardiac health. ST segment elevation increases with decreased heart rate, while ST depression exhibits minimal variation (ie, ST elevation is associated with high vagal tone, training effect, and cardiac health). Moreover, these findings support the hypotheses that ST elevation is more likely to be pathological if occurring at high heart rates, while ST depression is more likely to be pathological when associated with R and T wave abnormalities. If additional imaging studies continue to be supportive of the proposed pathology, these quantified findings identifying outliers should be used to improve the diagnostic value of ECG screening in young athletes.

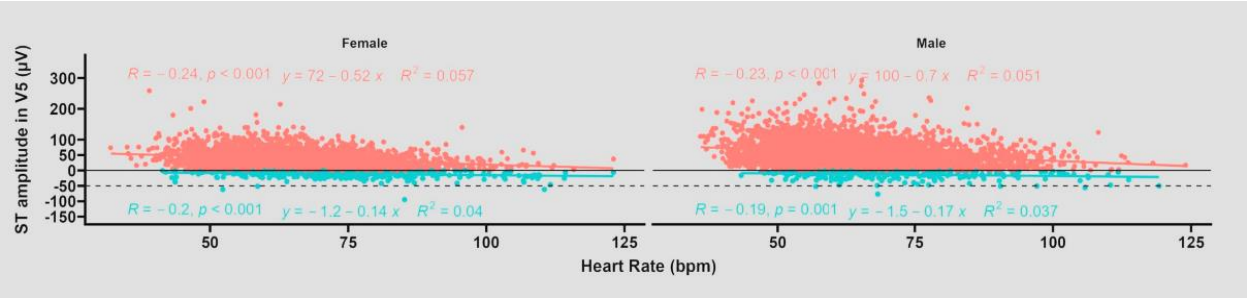

Figure 9. Scatterplots between T wave amplitude, R wave amplitude, and Heart Rate (bpm) vs ST segment amplitude with ST elevation (blue line) and ST depression (red line) in precordial lead V5. This lead presents the major ST vector for registering ischemia or fibrosis. *Solid line represents the "isoelectric line", while the "dashed line" represents the threshold for ST depression in athletes according to the International ECG Athlete criteria (ST <-50 mV)

Low QRS peak-to-nadir voltage (LQRSV) is associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) and other cardiomyopathies. Recent studies have proposed criteria for LQRSV when screening athletes for cardiovascular disease.[30] These criteria have not yet been evaluated in a large population of healthy young athletes. The target population was 10,728 (42.5% female, 57.5% male, mean age 18.1 ± 4.3 years) athletes who participated in mass ECG screenings between 2014 and 2021 at multiple sites across the United States including grade schools (11%), high schools (32%), colleges (50%), and professional athletic teams (6%) with digitally recorded ECGs and a standardized protocol.[31] Since by design, complete follow up for outcomes and the results of testing were not available. Including only ECGs from initial evaluation among athletes 14-35 years of age and excluding those with right or left bundle branch block, Wolf-Parkinson-White pattern, reversed leads and 3 clinically diagnosed cardiomyopathies at Stanford, 8,679 (58% males, 42% females) remained eligible for analysis. QRS voltage was analyzed for each ECG lead and LQRSV criteria were applied and stratified by sex. QRS voltage was lower in all leads in female athletes compared to male athletes. Using traditional limb lead criteria or precordial lead criteria, the prevalence of LQRSV was significantly lower in males than females ($P < .001$). Strikingly, LQRSV using the Sokolow-Lyon Index was present in 1.9% of males and 9.8% of females ($P < .001$). Applying the first percentile for LQRS amplitude criteria provided possible values for screening young athletes for LQRSV. LQRSV is more common among female athletes than male athletes using established criteria. Using first percentile sex-specific cut points should be considered in future analyses. Proposed novel LQRSV criteria in young athletes should be specific for males and females.

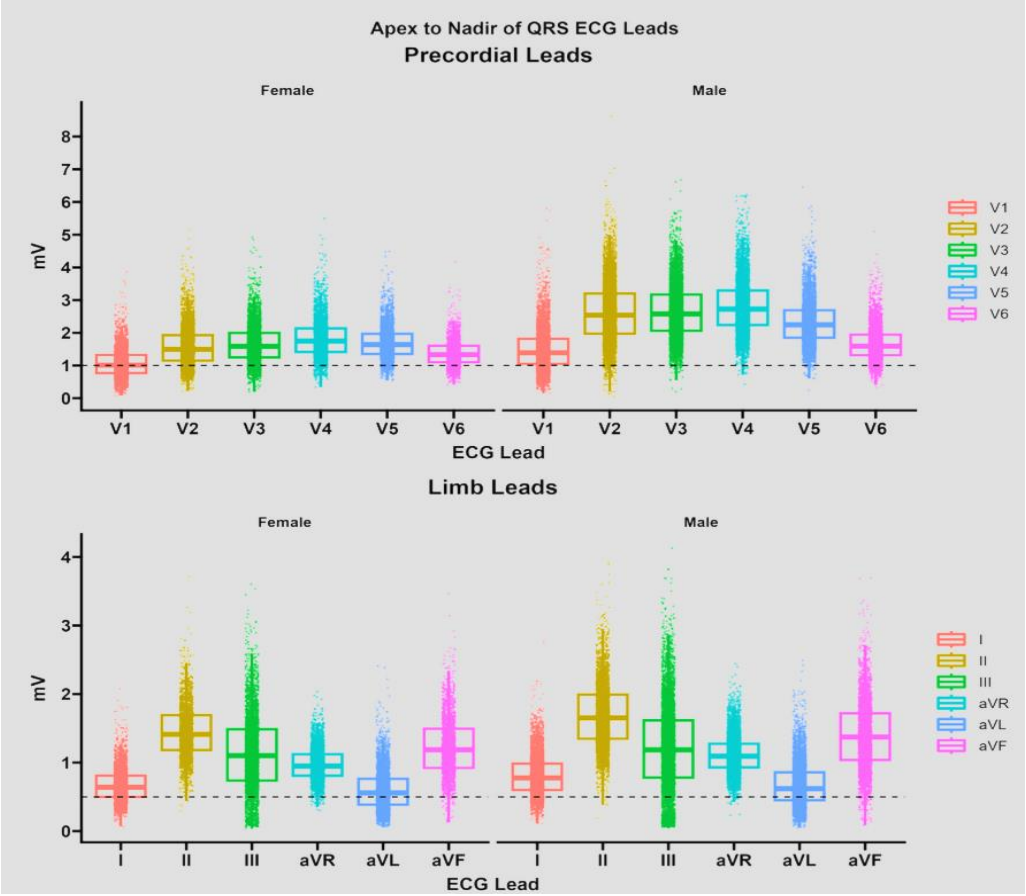

Figure 10. Plots of nadir to peak of QRS voltages in all leads from our athletes who presented for a Pre Participation Exam. Note the significantly greater values in males. The dashed lines are the cut points for LQRSV respectively for the precordial (1.0 mV) and limb leads (0.5 mV). Units are in milliVolts which can be converted to millimeters on an ECG recorded at 10 mm/milliVolt scale by multiplying by 10.

Conclusion

The future of ECG screening should include consideration of using outliers in "normal" population ECG measurements as potential consideration for identifying those with early forms of disease. Example candidates from our studies include left atrial abnormality, ST shifts and low voltage QRS. We propose that right bundle branch block [32] and low voltage QRS voltage are ready to be added to current recommendations requiring further evaluation in young athletes prior to participation in sports. We do not suggest that our findings with digital ECG measurement outliers are ready for "prime time," but require validation.

We anticipate a future where a simple smartphone attachment with minimal ECG leads, and a digital app that can be applied by trainers that flashes green, yellow, or red for the need of a 12-lead ECG or longer ECG monitoring. This democratization of the ECG would make it available to all, not just the "worried wealthy-well". Eventually, digital ECG data will be available on all, not just athletes, along with vital signs, height and weight. Serial ECG changes are very likely to be helpful in everyone's health care management. Also long term ECG monitoring for dynamic changes are likely to identify those at risk of long QT syndrome and other conditions with dynamic changes such as ST shifts and QRS duration. The International recommendations for the Interpretation of young athlete's ECGs has been an incredible vehicle for change in ECG screening for cardiovascular risk and should continue to evolve. Advances being made in ECG interpretation for screening can benefit everyone and not athletes alone.

Declaration of Competing Interest - There is no interest to declare

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