Published in final edited form as:
Int J Clin Pract. 2014 January ; 68(1): . doi:10.1111/ijcp.12218.

Screening electrocardiograms in psychiatric research: Implications for physicians and healthy volunteers

Adriana J. Pavletic, MD, MS[a], **Maryland Pao, MD**[a], **Daniel S. Pine, MD**[b], **David A. Luckenbaugh, MA**[c], and **Douglas R. Rosing, MD**[d]

[a]Office of the Clinical Director, National Institute of Mental Health

[b]Section on Development and Affective Neuroscience, National Institute of Mental Health

[c]Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health

[d]Cardiovascular and Pulmonary Branch, National Heart, Lung, and Blood Institute

Abstract

Aims—While there is controversy regarding utility of screening electrocardiograms (ECGs) in competitive athletes and children exposed to psychostimulants, there is no data on the use of screening ECGs in psychiatric research. We aimed to examine the prevalence and clinical significance of ECG abnormalities and their impact on eligibility for studies.

Methods—We analyzed 500 consecutive ECG reports from physically healthy volunteers who had a negative cardiac history, normal cardiovascular examination and no other significant medical illnesses. For the purpose of this report, all ECGs were over-read by one cardiologist.

Results—The mean age of our cohort was 28.3+/−8.0 years. A total of 112 (22.4%) ECGs were reported as abnormal (14.2%) or borderline (8.2%). These abnormalities were considered clinically insignificant in all but eight subjects (1.6%) who underwent evaluation with an echocardiogram. All echocardiograms were normal. No subject was excluded from studies. After the over-reading, no abnormalities or isolated bradycardia were present in 37 of 112 (33%) ECGs that were initially reported as abnormal or borderline, while minor abnormalities were found in 7 of 204 (3.4%) ECGs that were reported as normal.

Conclusions—Although screening ECGs did not detect significant cardiac pathology or affect eligibility for our studies, over 20 % of subjects were labeled as having an abnormal or borderline ECG which was incorrect in one third of cases. Strategies to minimize unintended consequences of screening are discussed.

1. Introduction

The presence of cardiac disease is often an exclusion criterion for volunteers participating in mental health research. This occurrence is usually ascertained by history and physical examination, but some protocols also require a screening electrocardiogram (ECG).

Corresponding author: Adriana J. Pavletic, MD, MS, National Institute of Mental Health, 10 Center Drive, 6-5340, MSC 1276, Bethesda, MD 20982-1276, pavletia@mail.nih.gov, Phone: 301-594-7386, Fax: 301-402-2588.

Disclosures: Authors declare no conflict of interest

Disclaimer: The views expressed in this article do not necessarily represent the views of the National Institute of Mental Health, the National Heart, Lung, and Blood Institute, the National Institutes of Health, the United States Department of Health and Human Services, or the United States Government.

Author Contributions

AJP and DRR contributed to the research design and acquisition of data. DAL performed statistical analysis. All authors contributed to data interpretation, critical revision and approval of the submitted version.

Screening ECGs are not recommended in the general population at low risk for coronary heart disease (CHD) (1), and there is an ongoing controversy regarding the utility of screening ECGs to prevent sudden cardiac death (SCD) in competitive athletes (2–4) or in children and adolescents exposed to stimulant medications (5–7). While prior research considers the benefits and harms of screening ECGs in these settings (1–6), no data exist on the usefulness of screening ECGs among healthy subjects volunteering for psychiatric research.

In our experience, screening ECGs in healthy volunteers are often reported as abnormal or borderline. Therefore, we aimed to examine more closely the prevalence and clinical significance of ECG abnormalities and their impact on eligibility for studies. We then discuss the rationale for ECG screening in a setting of psychiatric research, challenges involved in ECG interpretation and handling of abnormal results, and strategies to reduce any unintended harmful results of screening.

2. Methods

2.1. Subjects

We analyzed 500 consecutive ECG reports from physically healthy volunteers aged 18–55 years who had a negative cardiac history, normal cardiovascular examination and no other significant medical illnesses. Our cohort was comprised of 405 subjects without psychopathology and 95 volunteers with generalized anxiety disorder (GAD)and/or social anxiety disorder (SAD) as ascertained by history and the Structured Clinical Interview (SCID) (8,9).

Subjects with cardiac symptoms (palpitations, chest pain) or an abnormal examination (elevated blood pressure, tachycardia, arrhythmia, heart murmur) were not included.

Volunteers were recruited through the National Institutes of Health (NIH) Clinical Research Volunteer Program or through advertisements posted in local newspapers and at universities. Subjects who were accepted after phone screening were evaluated in person.

These evaluations were done to determine eligibility for various National Institute of Mental Health (NIMH) protocols. All protocols were approved by the NIMH Institutional Review Board. All protocols required subjects to be free of heart disease as ascertained by a history and physical examination and a screening ECG. Protocols involved fear conditioning with electric shocks and/or brief administration of psychoactive medications including alprazolam, D-cycloserine, hydrocortisone, vasopressin, oxytocin, citalopram and amino acids with or without tryptophan.

All volunteers had a history and physical examination by the first author. Three hundred and three consecutive volunteers were seen between April 2008 and September 2010, while one hundred ninety-seven consecutive volunteers from an earlier study (10) had medical evaluations between May 2003 and April 2005.

2.2. Electrocardiograms

All ECGs were recorded at 25 mm/s with amplitude of 1 mV/10 mm and with 60 Hz filtering.

The following definitions were employed in this study:

Normal PR interval: 120–200 ms

Normal QT interval corrected for heart rate (QTc): </= 450ms for men and </= 460 ms for women

Normal QRS duration: <100 ms- report posted in electronic medical record, </= 110 ms- at time of over-reading due to recent standardization guideline (11)

Left ventricular hypertrophy (LVH): Sokolow-Lyon (12), Cornell (13), or Romhilt-Estes (14) criteria

Bradycardia: heart rate below 60 beats per minute

The detailed description of other definitions employed in this study was previously published (15).

2.3. Interpretation of electrocardiograms

Initially, 96% of ECGs with computer interpretations were read by two cardiologists. ECGs were reported in electronic medical record as “normal”, “otherwise normal”, “borderline” or “abnormal”.

For the purpose of this study, all ECGs were over-read by one of the cardiologists (D.R.R.) who had access to the initial reader interpretation, but was blinded to the reader. ECG findings at the time of over-reading were classified in three categories: “no abnormalities”, “isolated bradycardia” and “abnormalities”.

2.4. Eligibility Determination

A family physician (A.J.P.) determined volunteers’ eligibility for studies based on medical history including cardiac risk assessment, cardiovascular examination, study risks, initial ECG interpretation posted in the electronic medical record, and, when appropriate, consultation with a cardiologist.

2.5. Statistical analysis

Chi-square tests were used to examine the influence of gender on the prevalence of ECG abnormalities. Significance was evaluated at $p<.05$, two-tailed.

3. Results

The mean age of our cohort was 28.3+/−8.0 years. 81% of volunteers were younger than 35 years and 56% of participants were women.

71 (14.2%) of all ECGs were reported as abnormal, 41(8.2%) as borderline, 184 (36.8%) as otherwise normal and 204 (40.8%) as normal. Eight subjects or 1.6% (seven with no psychopathology, one with GAD) underwent further evaluation with an echocardiogram (Table 1). All echocardiograms were normal. No subject was excluded from studies due to an abnormal ECG.

One healthy volunteer (42 year old male without psychopathology) experienced an adverse cardiovascular event while participating in a study, vasovagal syncope after a fear conditioning experiment. His screening ECG was normal.

After the over- reading, abnormalities were found in 109 (21.8%) cases, isolated bradycardia was found in 135 (27%) cases while no abnormalities were present in 256 (51.2%) of all ECGs. No abnormalities or only isolated bradycardia were found in 37 of 112 (33%) ECGs that were originally reported as abnormal or borderline, including four cases of intraventricular conduction delay (IVCD) that were reclassified due to the standardization of the definition of IVCD from QRS duration>100 ms to >110 ms (11). On the other hand,

minor abnormalities were found in 7 of 204 (3.4%) ECGs that were initially reported as normal and in 27 of 184 (14.7%) ECGs that were initially reported as otherwise normal. The prevalence of ECG abnormalities after the over-reading is depicted in Table 2. While there was no difference in the prevalence of ECG abnormalities between men and women (21.6% vs. 21.9%), nonspecific T wave abnormalities (NSTWA) were more prevalent in women (9.3% vs. 2.7%, p=0.002) and left ventricular hypertrophy (LVH) by voltage criteria was more prevalent in men (4.5% vs. 1.1%, p= 0.017).

4. Discussion

The over 20% prevalence of ECG abnormalities in our cohort is similar to the prevalence of ECG abnormalities in other young healthy populations (16–18). However, comparison with other studies is difficult due to differences in study populations and design and lack of standardization for interpretation of ECG results.

There are many potential explanations for the high prevalence of ECG abnormalities (both true and false positives) in healthy subjects beginning with the fact that an ECG contains multiple measurements, thus increasing the probability of a single measurement falling outside the “normal range”. Other causes include erroneous lead placement, “abnormalities “caused by physical training such as LVH by voltage criteria, incomplete right bundle branch block (IRBBB), first degree AV block or marked bradycardia (19), body habitus (e.g. low voltage in subjects with thick chest wall and vice versa) and findings that are affected by gender, age, and race (20). For example, the high prevalence of NSTWA, particularly in the anterior precordial leads, observed in our healthy women is probably gender specific and not a true abnormality.

All abnormalities in our cohort were considered clinically insignificant except in eight volunteers who underwent further evaluation with echocardiography that was unremarkable in all eight. It is well known that screening ECGs have high rates of false positives in asymptomatic people (1, 18). For example, in one study of collegiate athletes, 17% of screening ECGs were determined to be false positives when echocardiography was used as a gold standard (18). Not surprisingly, none of our LVH or old myocardial infarction (MI) cases who underwent echocardiography was confirmed.

Screening ECGs did not affect eligibility for our studies, but 112 healthy volunteers were originally labeled as not having a normal ECG which was incorrect in 37 cases. It is well known that computer-generated reports can be erroneous and that cardiologists sometimes accept erroneous computer interpretation in generating final ECG reports (21–23). In most cases, this was the reason for the discrepancy between the initial ECG report and over-reading in our cohort. More conscientious reading by cardiologists, realizing that an abnormal reading has important implications that are discussed below, would eliminate the majority of these erroneous interpretations.

The purpose of a screening ECG in a setting of psychiatric research is to identify volunteers with subclinical cardiac pathology, not detectible by physical examination, who are at risk for cardiac adverse events that may be triggered by study procedures or medications (ischemia, QT prolongation, arrhythmia) or in whom cardiac pathology may confound interpretation of the results (e.g. palpitations due to arrhythmias confused with anxiety -like symptoms).

Unlike in a clinical setting or in competitive sports, there is no direct benefit for volunteers who participate in research studies. Exposing volunteers to greater than minimal risks (cardiac in this example) when the focus is on the improvement of generalizable knowledge, rather than the benefit of the individual, is a very different situation than exposing people to

the same risk when benefit to that individual is anticipated. A relatively unfavorable risk / benefit ratio justifies the use of screening ECGs in populations with low pretest probability of cardiac disease. In a young healthy cohort such as ours, where the prevalence of cardiac disease is low, the positive predictive value of an abnormal test is also low. Moreover, there are risks associated with the screening test such as false positives, labeling, unnecessary further testing and anxiety.

When an ECG abnormality is reported, several questions arise for the ordering clinician: What is the meaning and implication of the ECG diagnosis? Can the volunteer safely participate in the study? Is further work-up required? How, when, and who should follow - up an abnormal ECG? Protocols usually state that incidental findings will be conveyed to research subjects who are then advised to follow-up with their primary care physician. This raises the question whether it is ethical to refer healthy volunteers to a primary physician for a follow-up of a likely falsely abnormal ECG that would have not been ordered if the individual were not participating in a research protocol. In our setting, ECG abnormalities are discussed with a cardiologist who receives additional pertinent clinical information obtained during history and physical examination such as history of cardiac symptoms, physical activity, family history of heart disease, height, weight, blood pressure and other findings on physical examination. In rare occasions, further work-up is advised and offered at the National Institutes of Health.

Receiving a diagnosis of an abnormal ECG can cause anxiety and denial of participation in other studies as some mental health researchers are not familiar with the clinical significance of various ECG abnormalities. For example, a 20 year old healthy subject with the ECG diagnosis of a first degree block was excluded from another study “due to an abnormal ECG”. He was wondering if “this is something I should be concerned about” as “I am just a little nervous when it comes to my heart health”. He was reassured that this is a minor abnormality of no clinical significance that may be related to his physical fitness and may resolve with deconditioning (19).

In our experience, informing volunteers that an ECG is an imperfect test with a high rate of minor abnormalities and false positive results is very helpful in preventing anxiety associated with the finding of an abnormal result. This discussion occurs prior to testing as a part of informed consent for screening. Discussing abnormal results with the explanation that an ECG abnormality does not necessarily imply cardiac disease is also very important. While there are no studies specifically examining the harm of performing screening ECGs, effective communication was shown to decrease anxiety and other negative effects of false positive screening tests in other settings (24, 25).

One of the limitations of our study is due to the fact that the cardiologist who performed the over-reading of all ECGs initially interpreted 76% of the ECGs. However, he was blinded to the initial reader. Another limitation in both the study and the reading of ECGs is that the same ECG finding may be called “borderline” on one occasion and “otherwise normal” on another, and we did not determine how often this occurred. These diagnostic categories lacked clear definition, and, as a result, were sometimes inconsistently applied in the initial interpretation. Therefore, for the purpose of this study, we decided not only to over-read the ECGs, but also to simplify their classification into three categories: “no abnormalities”, “isolated bradycardia”, and “abnormalities”. As a result of these considerations, we suggest ECG readers make a concerted effort to reduce the use of “borderline” to those measurements which are truly at the margin between normal and abnormal and are imprecise due to waveform morphology, i.e. a QTc in males between 450–453 ms. Likewise, we suggest readers use the “otherwise normal” category for findings deviating

from normal that have no clinical significance, i.e. a T wave flattening or inversion in a single lead or early or late precordial transition.

Psychiatric research studies sometimes require screening ECGs in young healthy volunteers who are at low risk for cardiac disease. While screening ECGs are intended to protect research participants and increase their safety, a significant proportion of subjects experience unintended consequences of screening including being labeled abnormal with abnormalities of low or unknown clinical significance, receiving a false positive result, becoming anxious, and being denied participation in other protocols. Unintended consequences of screening may be reduced by education of research subjects and mental health researchers, careful reading of ECGs by cardiologists to minimize errors in interpretation, and not requiring the routine performance of ECGs for protocols where there is no or minimal cardiac risk involved with participation.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute of Mental Health.

References

1. Chou R, Arora B, Dana T, Fu R, Walker M, Humphrey L. Screening asymptomatic adults with resting or exercise electrocardiography: a review of the evidence for the U.S Preventive Task Force. Ann Intern Med. 2011; 155:375–85. [PubMed: 21930855]
2. Corrado D, Basso C, Pavei A, Michieli P, Sciavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA. 2006; 296:1593–601. [PubMed: 17018804]
3. Maron BJ. National Electrocardiography Screening for Competitive Athletes: Feasible in the United States? Ann Int Med. 2010; 152:324–26. [PubMed: 20194239]
4. Estes MNA. ECG screening for athletes: letting evidence and reason advance the debate. Heart Rhythm. 2011; 8:728–30. [PubMed: 21199685]
5. Veter V, Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young, Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. Circulation. 2008; 117:2407–23. [PubMed: 18427125]
6. Perrin JM, Friedman RA, Knilans TK. Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder. Pediatrics. 2008; 122:451–53. [PubMed: 18676566]
7. American Academy of Pediatrics and the American Heart Association. American Academy of Pediatrics/ American Heart Association Clarification of Statement on Cardiovascular Evaluation and Monitoring of Children and Adolescents with Heart Disease Receiving Medications for ADHD. May 16.2008 [Press release].
8. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders, Research Version, Non-Patient Edition. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
9. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders, Research Version, Patient Edition with Psychotic Screen. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
10. Pavletic AJ, Luckenbaugh DA, Pao M, Pine DS. The Importance of Medical Screening of Volunteers Participating in Research on Mental Illness. Primary Psychiatry. 2008; 15:71–76.
11. Surawicz B, Childers R, Deal BJ, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram. Part III. J Am Coll Cardiol. 2009; 53:976–81. [PubMed: 19281930]
12. Sokolow M, Lyon T. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J. 1949; 37:161–86. [PubMed: 18107386]

13. Casale P, Devereux R, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, Phillips MC. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. J Am Coll Cardiol. 1985; 6:572–80. [PubMed: 3161926]

14. Romhilt DW, Estes EH. A point-score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J. 1968; 75:752–59. [PubMed: 4231231]

15. Bondy CA, Van PL, Bakalov VK, et al. Prolongation of the cardiac QTc Interval in Turner Syndrome. Medicine. 2006; 85:75–81. [PubMed: 16609345]

16. Pelliccia A, Maron BJ, Culasso F, et al. Clinical Significance of Abnormal Electrocardiographic Patterns in Trained Athletes. Circulation. 2000; 102:278–84. [PubMed: 10899089]

17. Liesemer K, Flanagan R, Johnson E, Devenport M, Cartwright V, Puntel R. The Role of Screening Electrocardiograms in the Evaluation of ROTC Cadets Applying for Flight Status. Military Medicine. 2010; 7:525–28. [PubMed: 20684458]

18. Baggish AL, Hutter AM, Wang F, et al. Cardiovascular Screening in College Athletes With and Without Electrocardiography. Ann Intern Med. 2010; 152:269–75. [PubMed: 20194232]

19. Corrado D, Biffi A, Basso C, Pelliccia A, Thiene G. 12-lead ECG in the athlete: physiological versus pathological abnormalities. Br J Sports Med. 2009; 43:669–76. [PubMed: 19734501]

20. Macfarlane PW, McLaughlin SC, Devine B, Yang TF. Effects of Age, Sex, and Race on ECG Interval Measurements. J Electrocardiol. 1994; 27:14–19. [PubMed: 7884351]

21. Hongo RH, Goldschlager N. Overreliance of computerized algorithms to interpret electrocardiograms. Am J Med. 2004; 117:706–708. [PubMed: 15501211]

22. Surawicz B. How to increase the accuracy of electrocardiogram's interpretation and stimulate the interest of the interpreters? J Electrocardiol. 2010; 43:191–93. [PubMed: 20035950]

23. Alpert JS. Can You Trust a Computer to Read Your Electrocardiogram? Am J Med. 2012; 125:525–26. [PubMed: 22624683]

24. Young PC. The morbidity of cardiac nondisease revisited: Is there lingering concern associated with an innocent murmur? Am J Dis Child. 1993; 147:975–77. [PubMed: 8362816]

25. Gurian EA, Kinnamon DD, Henry JJ, Waisbren SE. Expanded newborn screening for biochemical disorders: The effect of a false -positive result. Pediatrics. 2006; 117:1915–21. [PubMed: 16740831]

What's known

Screening electrocardiograms (ECGs) are not recommended in the general population at low risk for heart disease and there is ongoing controversy regarding the utility of screening ECGs in competitive athletes and in children exposed to psychostimulants. There are no studies that address the use of screening ECGs in healthy volunteers participating in biomedical research.

What's new

Screening ECGs in healthy volunteers did not detect significant cardiac pathology or affect eligibility for mental health research studies. A significant proportion of healthy subjects experienced unintended consequences of screening including being labeled abnormal or borderline with abnormalities of low or unknown clinical significance (22.4%), receiving a false positive result, becoming anxious, and being denied participation in other protocols. Strategies to minimize unintended consequences of screening are discussed.

Table 1

Abnormalities that led to further workup with an echocardiogram

Age	Gender	Abnormality
19	Male	LVH[1]
24	Male	ST depression, inferior and lateral
33	Male	Right and left atrial abnormality, inferior ST depression
30	Female	NSTWA anterior leads[2]
44	Male	LVH[1]
34	Male	Old MI[3]
22	Male	LVH[2]
23	Female	Old MI[3]

[1] Left ventricular hypertrophy

[2] Nonspecific T wave abnormality

[3] Myocardial infarction

Table 2

The prevalence of ECG abnormalities after the over-reading

Abnormality	Isolated	Combined	Total	% of Total Abnormalities
NSTWA[2]	20	12	32	6.4
LVH[1]	9	4	13	2.6
Short PR	8	3	11	2.2
First degree heart block	8	3	11	2.2
Poor R progression	3	8	11	2.2
Early precordial transition	5	4	9	1.8
IRBBB[4]	4	3	7	1.4
LPFB[5]	3	1	4	0.8
Left atrial abnormality	3	1	4	0.8
IVCD[4] (QRS>110 ms)	1	2	3	0.6
ST segment abnormality	1	2	3	0.6
LAFB[6]	1	2	3	0.6
Long QTc	1	1	2	0.4
Low voltage	2	0	2	0.4
MI[3]	2	0	2	0.4
Junctional rhythm	2	0	2	0.4
Late precordial transition	1	0	1	0.2
Right atrial abnormality	0	1	1	0.2
SVE[7]	0	1	1	0.2

[1] Left ventricular hypertrophy

[2] Nonspecific T wave abnormality

[3] Myocardial infarction

[4] Incomplete right bundle brunch block

[5] Left posterior fascicular block

[6] Left anterior fascicular block

[7] Supraventricular ectopic