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The prognostic value of exercise-induced ventricular arrhythmias in patients with and without coronary artery disease: A meta-analysis

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ABSTRACT

Background: Significance of exercise-induced ventricular arrhythmias (EIVAs) is controversial. This meta-analysis aimed to determine the prognostic value of EIVAs in patients with and without coronary artery disease (CAD).
Methods: Relevant studies were searched on Pubmed though December, 2015. Pooled odds ratio (OR) of endpoints (all-cause death, cardiac death or cardiac events) for all included studies was calculated at first to explore the significance of EVIAs in unselected population. Then, sensitivity analysis based on CAD status of population was performed to determine ORs of endpoints in CAD population, non-CAD population and mixed population, respectively.
Results: A total of 14 studies examining 23,002 patients were included, with 5 studies involved CAD population, 4 involved non-CAD population, and 5 involved mixed population (%CAD ranged from 51.2% to 76.8%). EIVAs in unselected population were associated with a pooled OR of 1.626 (95%CI 1.334 to 1.983, $p < 0.001$) of endpoints when compared with those without EIVAs. Sensitivity analysis further indicated that pooled ORs of endpoints were 1.395 (95%CI 1.061 to 1.833, $p = 0.017$) in CAD population, 1.933 (95%CI 1.567 to 2.384, $p < 0.001$) in non-CAD population, and 1.402 (95%CI 1.198 to 1.640, $p < 0.001$) in mixed population. Heterogeneous among studies was identified. Meta-regression analysis found that study quality, mean follow-up period, percentage of lost, percentage of diabetes were associated with ORs of endpoints.
Conclusions: EIVAs were associated with increased risk of worse outcomes, no matter the patients had CAD or not. However, more studies are required to confirm this finding due to the variation of current evidences.
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1. Introduction

Exercise-induced ventricular arrhythmias (EIVAs) are common findings during clinical treadmill testing. It is thought that the significance of EIVAs is largely dependent on the clinical characteristics of the studied population [1]. However, long-term prognostic value of EIVAs is controversial among previous studies, no matter in subjects with coronary artery disease (CAD) or not [2–15]. In patients after myocardial infarction, for example, Henry et al. [6] found that EIVAs were good predictors of cardiac death, while Fiotetti et al. [5] got an opposite conclusion. For healthy asymptomatic subjects, EIVAs were considered to be associated with increased risk of death in the Framingham Heart Study [13]. However, this finding is challenged by the BLSA (Baltimore Longitudinal Study of Aging) study, which showed that EIVAs in asymptomatic volunteers did not independently increase the risk of total mortality [15]. Therefore, the prognostic significance of EIVAs remains uncertain. The present meta-analysis aimed to summarize the relevant literatures to provide insights into the controversy over the prognostic value of EIVAs in patients with and without CAD.

2. Methods

2.1. Search strategy

A computerized search was performed in the PubMed database (last search update December 13, 2015), using the following search terms without further restrictions: “exercise test”, “exercise testing”, “treadmill testing”, “ventricular arrhythmias”, “ventricular ectopic beat”, “extrasystole”, “ventricular premature complexes”, “premature ventricular contractions (PVCs)”, “ventricular tachycardia (VT)” and “ventricular fibrillation (VF)”. Furthermore, a hand-searching of reference lists of retrieved reports and pertinent reviews was also performed for searching additional relevant literatures.

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[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2.2. Study selection

English-language studies were included in the present meta-analysis if they met all the following criteria: 1) Prospective cohort, nested case–control, or retrospective cohort studies; 2) Study population that comprised CAD adults (age ≥ 18 years), healthy asymptomatic (non-CAD) adults, or mixed; 3) Studies that compared the prognosis of patients with EIVAs against those without.

Studies were excluded on the basis of the following criteria: 1) Case–control and cross-sectional studies; 2) Study population that comprised subjects with other organic heart diseases, such as hypertrophic cardiomyopathy and Chagas' heart disease; 3) EIVAs in children; 4) Studies that compared patients with frequent/complex EIVAs against those with infrequent EIVAs; 5) Studies that did not provide adequate data for calculating odds ratios (ORs) of endpoints; 6) There was possible overlapping of study samples or overt verification bias.

The titles and abstracts were examined to exclude obviously irrelevant records at first. Then, the potentially eligible studies were double-checked in the full text by two reviewers. If there was a discrepancy, a session was organized to reach a consensus.

2.3. Data extraction

Two investigators extracted independently the following data for eligible studies using a standardized abstraction form: 1) Characteristics of the studies: Author, publication date, journal, country, and study design; 2) Study quality: the quality of the included studies was assessed by the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies; [16] 3) Characteristics of patients: mean age, gender, number of patients, CAD status, CAD risk factors, and medications; 4) Exposure measurements: exercise test protocol, EIVAs definition, and prevalence of EIVAs; 5) Outcomes: mean follow-up period, the type of outcome events and their ORs with their 95% confidence intervals (CIs), and the covariates adjusted for in regression models. When one study gave multiple outcomes, the outcome with the highest OR was counted. When one study reported ORs with various degrees of adjustment for covariates, the OR from the model with the greatest degree of covariate adjustment was chosen. When the ORs and their 95% CIs were lacking, crude ORs and CIs were calculated on the basis of the reported number of subjects with or without the outcome according to EIVAs status. If no event occurred during follow-up, the authors would add 0.5 to each cell with 0 vale in the contingency table for calculating the crude ORs. In addition, some studies may give other measures of relative risk, such as risk ratios, hazard ratios and mortality ratios. Since the outcome was rare in study populations, the distinctions can be generally ignored among these measures of relative risk [17–18]. Therefore, they were considered to be equivalent and referred to as odds ratios.

2.4. Statistical analysis

Between-study heterogeneity was expected a priori in the present meta-analysis, since it combined ORs from studies with potentially considerable clinical and methodological diversity, such as differences in characteristics of patients, exposure definition, and study outcomes. Therefore, pooled ORs of endpoints and their 95% CIs were calculated using a random effects model. Meanwhile, heterogeneity between studies was quantified using Cochran's Q statistic and the I^2 statistic. Publication bias was assessed by funnel plot, Begg's adjusted rank correlation test and Egger's regression asymmetry test. Meta-regression analysis was performed to investigate if any continuous variable (e.g., mean age, number of patients, prevalence of EIVAs, study quality, mean follow-up period, % of lost, % of male, % of CAD, % of HTN, % of DM, and % of Smoker) was associated with study outcomes. Studies that did not provide data for a particular characteristic were excluded from the meta-regression analysis. Meanwhile, sensitivity analysis was performed to see if any categorical study characteristic (e.g., CAD status, study design, exercise test protocol, EIVAs definition, and endpoints) affected study outcomes.

Data synthesis and statistical analysis were performed by using COMPREHENSIVE META-ANALYSIS software version 2, Biostat, Englewood, USA. All p values are 2-tailed.

3. Results

3.1. Literature search

A total of 3052 records (3045 from Pubmed, 7 from form hand-searching) were yielded. After exclusion on basis of title, abstract and/or text, 14 studies were finally included in the present meta-analysis. Fig. 1 showed the flow chart of articles search and selection process.

3.2. Characteristics of the included studies

The present meta-analysis involved a total of 23,002 patients in 14 prospective cohort studies. Five studies involved patients with CAD, including 1 study involved patients with stable CAD, 3 involved patients after MI, and 1 involved patients after CAGB. Meanwhile, four studies involved patients without CAD, and five studies involved mixed population (the percentage of CAD patients ranged from 51.2% to 76.8%). More males than females were examined, with mean age ranging from 25 to 64 years. Patents in 7 studies underwent exercise test based on Bruce protocol, while those in the other 7 studies underwent exercise test based on other protocols, such as Naughton protocol, Astrand protocol and Balke protocol. Half of studies investigated subjects with any PVCs induced by exercise, while the other half of studies investigated subjects with frequent or complex PVCs/VT/VF. The prevalence of EIVAs in the studies ranged from 2.3% to 42.3%. Study outcomes included cardiac events (6 studies), total mortality (9 studies) and cardiac mortality (3 studies). If one study gave multiple outcomes, the outcome with the highest OR was selected. The incidence of outcomes ranged from 0.4% to 23.24% over a mean follow-up period of 1 to 23 years. Characteristics of the included studies were summarized in Tables 1 and 2. The Newcastle–Ottawa Quality Assessment Scale was

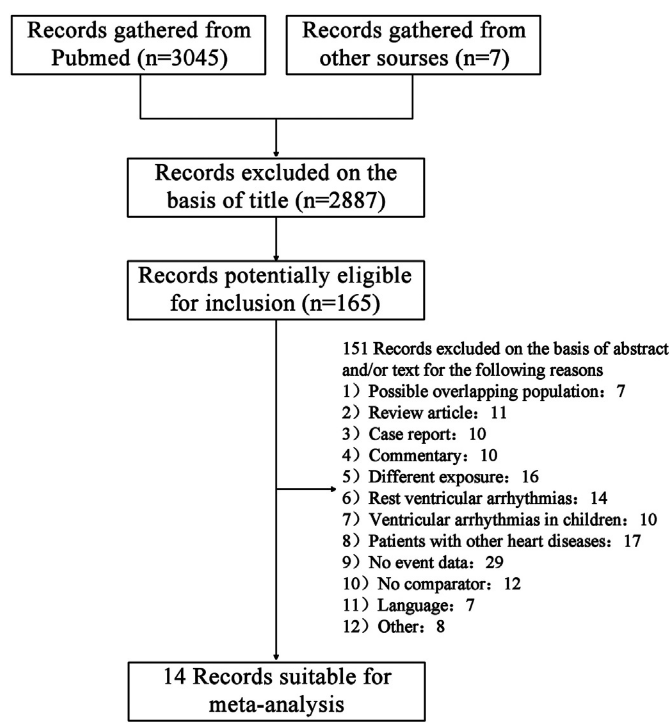

Fig. 1. Meta-analysis flow chart.

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