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Intra-thoracic Impedance and the Onset of Atrial and Ventricular Tachyarrhythmias: A Meta-analysis

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ABSTRACT

Background and purpose: Advances of implantable cardioverter–defibrillator (ICD) devices allow correlating changes in the intra-thoracic impedance (TI), an indicator of fluid overload, with the onset of arrhythmic events. In an attempt to attain a better understanding of this relationship, we conducted a meta-analysis of studies that investigated the association between TI changes and the onset of AT/AF and/or VT/VF in patients with ICD devices.

Methods: We performed a meta-analysis of studies published through January 2017 that reported an association between a decrease in the TI measured by the OptiVol fluid index (OI) and occurrence of AT/AF and VT/VF. We searched four databases: PubMed, Embase, CINAHL and Cochrane. Effect estimates were extracted from each study in the form of odds ratio (OR) and 95% confidence intervals.

Results: We identified 8 articles with results of the original research, allowing us to extract data for the OR calculation. Our pooled sample included 94,666 patients from 4 studies for AT/AF and 23,601 patients from 6 studies for VT/VF. Two studies were included in both analyses. The pooled OR for fluid index threshold crossing of 60 Ω-days was 1.56 (95% CI 1.35, 1.81) for VT/VF and 1.8 (95% CI 1.43, 2.27) for AT/AF.

Conclusion: The findings of our meta-analysis based on the large pooled population of >110,000 patients, reveal that decreased TI (measured by OI threshold crossing of 60 Ω-days) is a significant risk factor for the onset of AT/AF and VT/VF.

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1. Introduction/background

In the United States, over 300,000 people with congestive heart failure (CHF) die each year and CHF is the underlying cause in >68,000 of these deaths [1]. A significant proportion of these deaths are due to cardiac arrhythmias and sudden cardiac death. CHF and consequent volume overload are well-known risk factors for atrial tachyarrhythmias/atrial fibrillation (AT/AF) and ventricular tachyarrhythmias/ventricular fibrillation (VT/VF) [2]. Chronic volume overload is associated with increased catecholamine levels and electrolyte disturbances, both of which contribute to the occurrence of tachyarrhythmias [2]. Mechano-electrical feedback is thought to be one of the main causes of rhythm disturbances in the setting of acute volume overload. This is a phenomenon in which myocardial stretch induced by pressure or volume loading causes alteration in cardiac electrophysiological properties [3]. This mechanism has been widely studied in experimental models in animals [4,5] and humans [6,7]. Mechanical stretch may contribute to arrhythmogenesis through triggered activity, inducing early and delayed after-depolarizations that may translate into premature ventricular beats and ventricular tachyarrhythmias if they reach a certain magnitude [8–10]. Furthermore, mechanical loading shortens action potential duration and alters effective refractory periods in different parts of the myocardium, creating electrophysiological heterogeneity, which facilitates arrhythmogenesis via the re-entry mechanism [8–10]. Similar studies were conducted in the atrial myocardium and conclusions were similar [11,12].

The wide availability of implantable cardioverter–defibrillator (ICD) and cardiac resynchronization therapy defibrillator (CRT-D) devices now offers an opportunity to clinically correlate the two disease processes described above by the devices' ability to detect and record episodes of both AT/AF and VT/VF [13], in addition to the detection of changes in fluid balance. Detection of fluid overload in these devices is measured indirectly through quantification of intra-thoracic impedance

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(TI) [13,14]. Yu et al. [15], reported that TI is inversely related to pulmonary wedge pressure and fluid balance and that its decrease is detected before the clinical manifestation of fluid overload. The authors also developed a novel method of TI quantification, the OptiVol fluid index (OI). Briefly, it is the calculated cumulative difference between daily measured impedance and the reference or baseline [15]. Multiple studies have attempted to investigate the association between decreased thoracic impedance quantified by the OI and both AT/AF and VT/VF. In an attempt to summarize the published evidence and attain a more thorough comprehension of the association between decreased TI and the development of tachyarrhythmias in patients with ICD or CRT-D devices, we conducted a systematic review and meta-analysis of relevant studies published to date.

2. Methodology

2.1. Search strategy

We conducted an extensive literature search of the PubMed, Embase, CINAHL, and Cochrane databases to identify studies relevant to our topic of interest and published by January 2017. Our search strategy is presented in Appendix 1. Search terms used for each database are presented in Appendix 2. Furthermore, we utilized the "related articles" function in PubMed to find relevant articles not identified by the search terms. In addition, reference lists of included studies were hand searched to further locate relevant articles that were missed by keyword searches and the "related articles" function. Lastly, Google search was conducted for additional relevant literature not identified by above search methods.

2.2. Study selection

All titles and abstracts of citations retrieved by the initial search were screened for relevance to the research objective. Details of the study selection process are provided in Appendix 1 in the supplementary material. Consequently, the full texts of the potentially relevant articles were reviewed, comprehensively applying the inclusion and exclusion criteria as defined below.

Inclusion criteria:

1. Studies assessing the association of decreased thoracic impedance (measured by the OI in ICD or CRT-D devices) and the onset of atrial or ventricular tachyarrhythmias.
2. Studies reporting the association using odds ratio (OR) or provided sufficient data to calculate the OR and 95% confidence interval (CI).

Exclusion criteria:

1. Editorial articles and case reports.
2. Non-English references.

2.3. Data extraction

In order to ensure accuracy, two investigators conducted data extraction from the included studies independently. Disagreements were settled by consensus between the two investigators. Information extracted from the included studies consisted of the following: the first author's name, year of publication, the country of participants, study design, sample size, mean age, % of male patients, follow-up duration, device type (ICD or CRT-D), OptiVol index threshold crossing (OITC) used in exposed group in Ω-days, number of cases exposed, number of controls, number of patients with new onset arrhythmias and frequency of new onset arrhythmias in exposed and non-exposed groups. We also extracted effect estimates [16], method of reporting effect estimate, CIs of effect estimates and, lastly, adjusted estimates when applicable.

2.4. Statistical analysis

Effect estimates were extracted from each study in the form of odds ratios. These were directly extracted from the article (when available) or calculated indirectly based on the available data presented in the text of the article. These effect measures were then pooled together using the random effect model of DerSimonian and Laird to account for between-study variation [17]. Two separate analyses were conducted:

1. Association of OITC of 60 Ω-days with onset of VT/VF.
2. Association of OITC of 60 Ω-days with onset of AT/AF.

Heterogeneity between studies was explored by the Cochran Q statistic ($p < 0.05$) and I-squared (I^2) statistic. We assessed potential sources of heterogeneity, such as year of publication, country, sample size, average age, sex distribution, and follow-up duration, by using meta-regression. We did not perform an assessment for publication bias given the small number of studies included in the analysis. For each endpoint, all statistical tests were two-sided and p values <0.05 were considered to be statistically significant. Analyses were conducted with STATA version 14 (StataCorp, College Station, Texas).

A sensitivity analysis was then conducted for the first defined analysis (OITC-VT/VF). It involved performing the meta-analysis for a second time, excluding studies that were conference abstracts and not full text articles. We also performed a sensitivity analysis for the second defined analysis (OITC-AT/AF); in this analysis, we excluded the article by Jhanjee et al. [18] that used a control group of patients that was in contrast to all other included articles.

3. Results

3.1. Study identification and selection

After the initial database search, 720 references were retrieved. An additional reference was identified through Google search using related keywords. After the exclusion of duplicates, 602 record titles and abstracts were screened for relevance to the research questions. The 18 articles retrieved after screening were subjected to detailed, full text review and application of the inclusion and exclusion criteria. Consequently, 3 articles were excluded as they were of a particular type of publication (case report or editorial article). Furthermore, seven articles were excluded, as they did not meet our inclusion criteria. Eight studies provided sufficient data to conduct a meta-analysis to obtain a pooled estimate assessing the desired association [18–25]. Five references were full text articles [18–22] and three were conference abstracts [23–25]. Six studies were used for VT/VF [20–25] and four studies were used for AT/AF [18–21]. Two studies reported both outcomes (AT/AF and VT/VF) and were included in both analyses [20,21]. All eight studies were in the English language. The study period ranged from 2007 to 2014. Sample sizes ranged from 32 to 73,108 patients. Characteristics of the eight selected references are included in (Appendix 3).

3.2. Quality assessment

Two investigators subjected seven of the eight studies included in the meta-analysis to quality assessment using the Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies (Appendix 4). One study did not provide enough information to be assessed for quality [23]. Disagreements were resolved by discussion and consensus amongst the investigators. Scores for all the studies ranged from 6 to 8 points. All articles scored a minimum of 3 points in the selection section of the tool. Selection of the non-exposed cohort was from the same community as the exposed cohort in all studies (patients with ICD or CRT devices). Ascertainment of exposure in all studies was from secure