International Journal of Cardiology 220 (2016) 87–101

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

The impact of renal sympathetic denervation on cardiac electrophysiology and arrhythmias: A systematic review of the literature

George Bazoukis [a], Panagiotis Korantzopoulos [b,*], Costas Tsioufis [c]

[a] Department of Internal Medicine, General Hospital of Athens "Elpis", Athens, Greece
[b] First Department of Cardiology, University of Ioannina, Medical School, Ioannina, Greece
[c] First Department of Cardiology, National and Kapodistrian University of Athens, Hippokration General Hospital, Athens, Greece

ARTICLE INFO

Article history:
Received 4 May 2016
Accepted 12 June 2016
Available online 14 June 2016

Keywords:
Renal denervation
Cardiac arrhythmias
Resistant hypertension
Atrial arrhythmias
Ventricular arrhythmias

ABSTRACT

Introduction: Increased central sympathetic activity has a central role in the pathophysiology of cardiac arrhythmias. Despite the recently published negative results regarding the impact of renal sympathetic denervation (RDN) on resistant hypertension treatment, the beneficial effects of this intervention on cardiac arrhythmias seems to be promising. The aim of this systematic review is to analyze the existing data regarding the impact of RDN on atrial and ventricular arrhythmias.
Methods: We systematically searched MEDLINE/PubMed database until January 2016 by using the algorithm "renal denervation AND (arrhythmias OR atrial OR ventricular)" without limitations. Additionally, the reference lists of the included studies and the relevant review studies were also manually searched.
Results: Of the 467 studies yielded from the initial search, 34 were finally included in the systematic review (15 human studies, 18 animal studies and 1 study with both experimental and clinical data). The critical analysis of data from both human and animal studies indicates that RDN can modulate atrial and ventricular electrophysiological properties and exerts favorable effects in the development and recurrence of atrial and ventricular arrhythmias.
Conclusion: In this systematic review we showed that RDN reduces the burden of atrial and ventricular arrhythmias in various experimental and clinical settings. Appropriately designed randomized sham controlled trials are needed in order to elucidate the exact impact of RDN on arrhythmia management.

1. Introduction

The kidneys are rich innervated by efferent and afferent sympathetic nerve fibers. Activation of the efferent sympathetic signals to the kidney, increases the blood pressure by reducing the renal blood flow and by acting in the juxtaglomerular apparatus, regulating the renin–angiotensin–aldosterone system (RAAS) and the sodium absorption [1]. The afferent signals contribute to the communication between the right and left kidneys and with the central nervous system [1]. In this context, it is known that the renal sympathetic tone plays a crucial role as a mediator of systemic sympathetic tone [2]. Indeed, sympathetic nervous system has a crucial role in both ventricular (reentry, triggered activity and enhanced automaticity) and atrial (prolongation of intracellular calcium current) arrhythmogenesis [3].

Catheter-based renal denervation (RDN) for the treatment of drug-resistant hypertension has been shown to be safe in many studies, but the issue of effective blood pressure (BP) reduction has not yet been settled. Also, a number of single center, non-randomized trials suggested favorable effects of RDN on a series of subclinical states (like left ventricular hypertrophy regression, improvement of arterial stiffness and reduction of arrhythmic burden, etc.) beyond BP reduction [4–6]. From a pathophysiological point of view, although the data are conflicting, it seems most possible that RDN significantly reduces the central sympathetic outflow leading to decreased cardiac sympathetic activity, an effect that may favorably affect atrial and ventricular arrhythmias [7]. The aim of this review was to systematically analyze studies that investigate the impact of RDN on cardiac conduction system as well as its effect on atrial and ventricular arrhythmias.

2. Methods

We identified case reports/case series, original research studies, randomized control trials or meta-analyses related to the impact of RDN on cardiac conduction system and cardiac arrhythmias.

* Corresponding author at: 1st Department of Cardiology, University of Ioannina, Medical School, 45110 Ioannina, Greece.
E-mail addresses: p.korantzopoulos@yahoo.gr, pkorantz@cc.uoi.gr (P. Korantzopoulos).

http://dx.doi.org/10.1016/j.ijcard.2016.06.043
0167-5273/

2.1. Inclusion criteria

Case reports, original research studies, randomized control trials or meta-analyses in humans or animals having data regarding the impact of RDN on cardiac conduction system or arrhythmias were eligible for our study.

2.2. Exclusion criteria

The exclusion criteria were as follows: Non-English language articles, review articles, papers describing study designs as well as editorials or letters to the editor without original data.

2.3. Search methodology

We searched MEDLINE/PubMed database until January 2016 by using the algorithm "renal denervation AND (arrhythmias OR atrial OR ventricular)" without limitations. Furthermore, the references lists of all included studies and relevant review studies were also manually searched.

2.4. Data extraction

The information that extracted for each study were: i) publication details (first author's last name, journal, year of publication, PMID), ii) general study characteristics (country of origin, inclusion and exclusion criteria, length of follow-up), iii) characteristics of the study population (age, gender, type of cardiomyopathy, NYHA, left ventricular ejection fraction (LVEF)) and iv) outcomes reported in each study.

3. Results

3.1. Search results

The initial search yielded 467 results. Subsequently, we excluded 365 studies at the title/abstract level while 68 studies were excluded at the full text level. Consequently, 34 studies were finally included in our systematic review (Fig. 1).

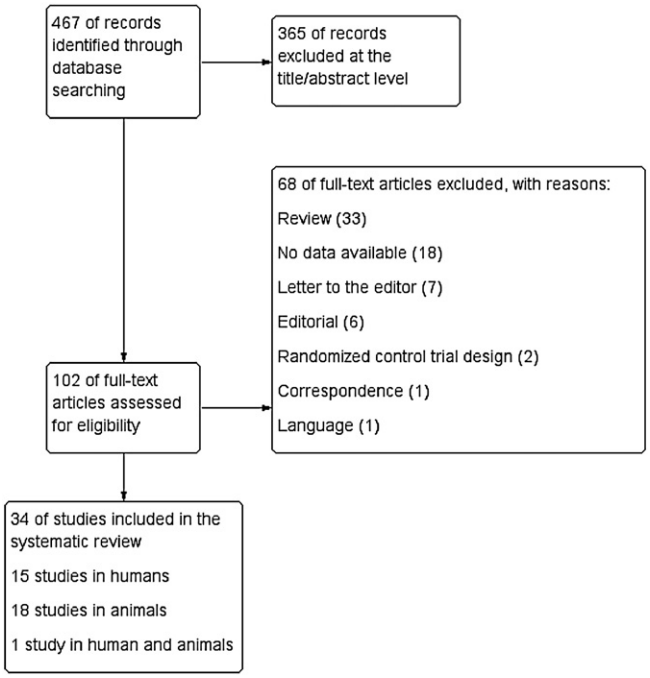

Fig. 1. Flowchart of the systematic review.

3.2. Impact of RDN on cardiac arrhythmias in animal models

3.2.1. Impact of RDN on ventricular electrophysiology and ventricular arrhythmias

Our search retrieved 5 studies which investigated the impact of RDN on ventricular arrhythmogenesis (Table 1). Specifically, in a heart failure (HF) dog model, RDN attenuated ventricular fibrillation (VF) but not ventricular tachycardia (VT) episodes which induced by programmed ventricular stimulation [8]. The authors also studied the Cx43 expression in the ventricles among all groups and they showed that RDN attenuated the heterogeneity in the Cx43 distribution which was associated with arrhythmogenesis in this model [8].

The impact of RDN on ventricular arrhythmias has also been studied in the setting of experimental cardiac ischemia in animal models. In an experimental study, RDN was performed in 10 dogs while sham intervention was performed in another 10 dogs [9]. Acute myocardial infarction was induced 30 min after RDN or sham interventions. After 1 h of continuous ECG monitoring after myocardial infarction, episodes of isolated premature ventricular contractions (PVCs), VT and VF were significantly lower in the RDN group compared to sham group with shorter VT duration in the RDN group. On the other hand, the impact of surgical RDN on ventricular arrhythmias during ventricular ischemia has also been studied in a swine experimental model [10]. VF occurred in 83% of all sham treated animals during left anterior descending (LAD) artery occlusion compared to only 14% of all RDN treated animals. During the first 10 min of LAD occlusion, RDN significantly reduced the occurrence of spontaneous PVCs. However, VF during reperfusion occurred in all sham treated and RDN treated animals.

The impact of RDN on ventricular electrophysiology has also been studied in an obstructive sleep apnea (OSA) swine model [11]. Specifically, after tracheal obstruction and negative tracheal pressure (NTP) a prolongation of the duration and dispersion of ventricular repolarization was noticed. These changes were inhibited by atenolol and RDN but not by atropine. Furthermore, the authors showed that in both human and pigs, hypoxia alone compared with hypoxia and NTP did not influence ventricular repolarization [11].

Electrophysiological studies after RDN in animal models have also been reported. Specifically, electrophysiological studies in 6 biomodels after 40 days of RDN were compared to those of 6 healthy animals (control group) [12]. In the RDN group basal heart rate (HR) was lower, PQ interval was longer, QTc intervals were comparable while effective refractory period (ERP) was prolonged significantly compared to control group. There was no difference in VF inducibility between the two groups.

3.2.2. Impact of RDN on atrial electrophysiology and atrial arrhythmias

Our search retrieved 14 studies investigating the impact of RDN on atrial electrophysiology and atrial arrhythmias in animal models (Table 1). Hou Y et al. [13], investigated the impact of catheter based RDN on atrial fibrillation (AF) induction in a canine model. All animals underwent rapid atrial pacing (RAP) and left stellate ganglion (LSG) stimulation. LSG stimulation increased the AF induction rate. After ablation, RDN significantly decreased AF induction rates compared to the control group [13]. Additionally, LSG stimulation induced ERP shortening and ERP dispersion changes that were attenuated in the RDN group compared to the control group [13]. In another study, the effect of RDN on AF inducibility after RAP was examined in a dog model [14]. The results showed that 7 h after cessation of pacing, the induced number and the duration of AF episodes were higher in the control group compared to the RDN group. These differences could be attributed to the effect of RDN on the RAAS activity [14]. There were no differences in the atrial ERP neither pre- nor post-RDN nor between the two groups. Furthermore, the impact of RDN on AF has been studied in dogs undergoing long-term intermittent atrial pacing [15]. In that study, the RDN group had fewer and lower duration AF episodes compared to the control group. Additionally, the increasing trends of atrial