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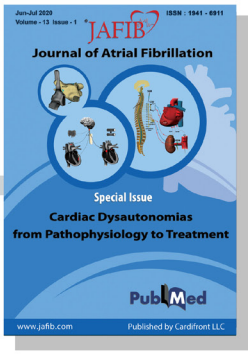

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Cardioneuroablation in the Management of Vasovagal Syncope, Sinus Node Dysfunction, and Functional Atrioventricular Block - Techniques

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Abstract

Cardioneuroablation is an emerging therapy to treat vasovagal syncope, functional atrioventricular block and sinus dysfunction. Currently, there are several effective approaches due to the complex modulation of autonomic nervous system. In this review, we describe techniques of this innovative therapy based on published literature and our experiences.

Introduction

The autonomic nervous system affects the physiological function of cardiovascular system.[1, 2] Tonic activation of the vagus may result in hypotension, bradycardia, and potentially vasovagal syncope (VVS).[2-5] Ganglionated plexi (GPs), intrinsic structures located in the epicardial atrial fat pads, connect preganglionic and postganglionic nerve fibers to affect heart rate, atrial and ventricular refractoriness and cardiac function. The GPs are selected as the primary targets for cardioneuroablation because of their physiological function and their anatomical location that can be targeted easily by ablation catheter.[6-8]

Although cardioneuroablation has been applied to treat VVS, functional atrioventricular block and sinus dysfunction for more than fifteen years, significant progress has been made in the last few years. There are different ablation strategies and approaches to localize and ablate GPs.[9-22] This review is dedicated to summarize available techniques of this therapy.

Targets of Cardioneuroablation

Previous studies have found that, there are seven major GPs located in protuberances and/or grooves of the heart wall, such as interatrial tissues, connective folding tissues between atrium and pulmonary veins, tissues adjacent to coronary arteries, and interventricular tissues. Since the atria are much thinner than the ventricles, radiofrequency energy can be transmitted more easily to the GPs via the atria,[23, 24] and thus effective autonomic denervation can be achieved via the endocardial approach in the atria.

Although there are different targeting approaches and ablation strategies, the GPs in left atrium (LA) and/or right atrium (RA) are mostly targeted. Pachon et al [9-11] performed comprehensive GPs ablation from both RA and LA via spectral mapping-guided ablation and additional anatomical-guided ablation to treat VVS, functional AV block and sinus dysfunction. Aksu et al [15, 22, 25, 26] simplified the strategy choosing major GPs via RA and LA as primary targets; and they achieved successful results. Zhao and Qin just performed anatomic GPs ablation in both LA and RA to treat symptomatic sinus bradycardia.[13, 18] Contrary to these bi-atrial ablation methods, different groups investigated the potential role of LA or RA only approaches. Our team defined a new technique via catheter ablation of GPs only in the LA on the basis of linear ablation of atrial fibrillation in which the vagal reflex was frequently observed.[12, 14, 21] Debruyne et al 20 performed unifocal right-sided ablation targeted in the posteroseptal side of the junction between the RA and the superior vena cava (SVC) to treat VVS and functional sinus node dysfunction.

Due to the complex intermodulation between GPs, it is necessary to select the essential GPs as primary ablation targets while avoiding the potential adverse effects caused by excessive ablation. Chiou et al 27 demonstrated that, most of the vagal fibers to the atria sinus and atrioventricular nodes travel through a fat pad located on the

Key Words

Cardioneuroablation; Ganglionated Plexus; Catheter Ablation; Vasovagal Syncope; Sinus Dysfunction; Atrioventricular Block

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right pulmonary artery between SVC and aortic root (SVC-aorta fat pad), which was proposed to be the "head station" between the extrinsic and the intrinsic cardiac autonomic nervous system. Debruyne et al [20] directly targeted this special GP site via RA during cardioneuroablation. In previous research, our team retrospectively analyzed the processes of cardioneuroablation in 115 VVS patients. Four targeted GPs located in the connective tissues between atrium and pulmonary veins (Figure 1), were ablated as order of the left superior GP (LSGP) –the left inferior GP (LIGP) –the right inferior GP (RIGP) –the right anterior GP (RAGP). Among the above ablated GPs, we observed a unique phenomenon that ablation of RAGP would immediately increase heart rate within few seconds and maintain this effect long-term, while there were just vagal responses observed during ablation of other GPs.[21] Supporting this observation, Aksu et al [28] demonstrated that cardioneuroablation, starting from the RAGP, results in significant decrease of positive vagal response ratio during radiofrequency application on the left superior GP in a retrospective study. These experiences may indicate that, RAGP would be the most important target for cardioneuroablation. However, there has been no comparison study between RSGP ablation only and ablation of all LAGPs. So, we still cannot argue whether an approach targeting RSGP only will be enough in all cases. Further study is needed to clarify the exquisite regulatory mechanism of GPs.

Approaches to Identify Ganglionated Plexi

The most difficult step for the cardioneuroablation procedure is to identify GPs. An anatomically guided approach is the basic method; few electrophysiologists use this simple way to perform GPs ablation.[13, 18, 20] The location of GPs can be marked according to the routine anatomical sites in the 3-dimensional electroanatomic mapping of the RA and LA (Figure 1). Debruyne et al [20] further applied both computed tomographic scan and electroanatomic mapping to localize the GPs sites.

Because of the individual variability of GP sites, it is not enough to use anatomical guidance alone. Currently, the commonly used identification approaches include high-frequency stimulation (HFS) and spectral guided method.[9, 11, 12, 14, 15, 21, 22] The HFS was initially designed to identify GPs location during circumferential pulmonary vein isolation for atrial fibrillation.[29] In this technique, HFS with frequency of 20 Hz, voltage of 10–20 V, and pulse duration of 5 ms is delivered to each GP site. During HFS, existence of positive vagal response defining as transient ventricular asystole, atrioventricular block, or R-R interval increased by 50% demonstrates vagal innervation sites (Figure 2). The main limitation of this method is inadvertent induction of atrial fibrillation. To avoid induction of atrial fibrillation, programmed HFS during atrial refractory period (10-20 ms followed initial designed atrial stimulation) and with duration of 3-5 seconds might be used.[14, 21] Even in case of induced atrial fibrillation, mean R-R interval increase of >50% could also be used to evaluate positive vagal response.[30]

Spectral guided method was first introduced by Pachon et al [9] to identify GPs location. The atrial myocardium was divided into a compact schema with normal working atrial myocardium and a fibrillar schema with neural fiber interposition. The anatomic locations

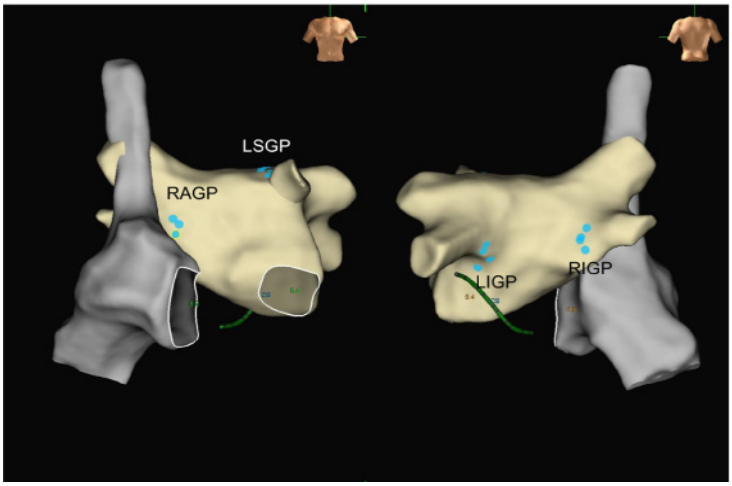

Figure 1: **The 3-dimensional endocardial surface of the left atrium, right atrium, and locations of ganglionated plexi.**

The blue points represent the locations of ganglionated plexi (GPs). LSGP: left superior ganglionated plexus; LIGP: left inferior ganglionated plexus; RAGP: right anterior ganglionated plexus; RIGP: right inferior ganglionated plexus.

of GPs with penetration of the nervous fibers changed myocardial conduction and the frequency spectrum of the endocardial potential which shifts from the compact conduction pattern to the fibrillar. Thus, while the compact atrial myocardium presents a homogeneous spectrum with one main frequency around 40 Hz and uniform conduction resulting from a mass of well-connected cells, fibrillar myocardium containing neural fiber interposition demonstrates a heterogeneous and fractionated spectrum with frequencies higher than 100 Hz. The limitation of spectral guided method is that,pecial pre-amplifier and spectral analysis software cannot be obtained by all electrophysiological labors.

Aksu et al[15, 22] further simplified this method by targeting the fractionated electrograms in the routine anatomical GPs locations. In their study, bipolar endocardial atrial electrograms were evaluated for amplitude and number of deflections at filter settings of 200–500 Hz and a sweep speed of 200 mm/s. Amplitude was defined as the voltage difference between highest and lowest deflections of each electrogram. Number of deflections was determined by counting the number of turning points (positive to negative direction or vice versa) in each electrogram. Electrograms were divided into: (1) normal atrial electrogram, which demonstrates deflection number of less than 4; (2) low-amplitude fractionated electrogram, which demonstrates greater or equal to four deflections and amplitude of less than 0.7 mV; and (3) high-amplitude fractionated electrogram, which demonstrates greater or equal to four deflections and an amplitude greater or equal to 0.7mV. The sites demonstrating low-amplitude and high-amplitude fractionated electrogram pattern in a region that is consistent with probable localization of GPs on LA were targeted (Figure 3).[15, 22] The main advantage of this technique is that, it can be performed with conventional electrophysiological equipment by changing filter settings of device.

Ablation of Ganglionated Plexi

It is worthy of note that, all of these approaches were performed with 3D navigation systems (Ensite™ system by Abbott or CARTO™

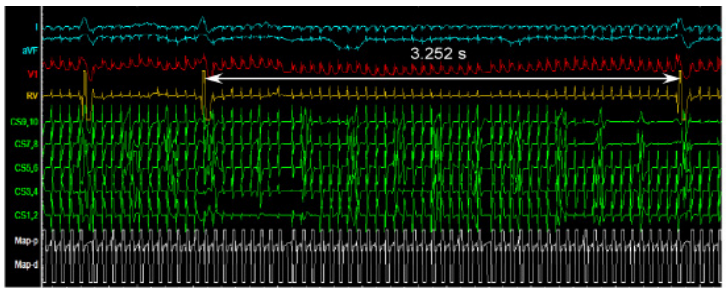

Figure 2: Vagal response to high frequency stimulation

During high frequency stimulation on the left superior ganglionated plexus site, a significant prolongation on RR interval is seen in surface ECG and intracardiac electrograms

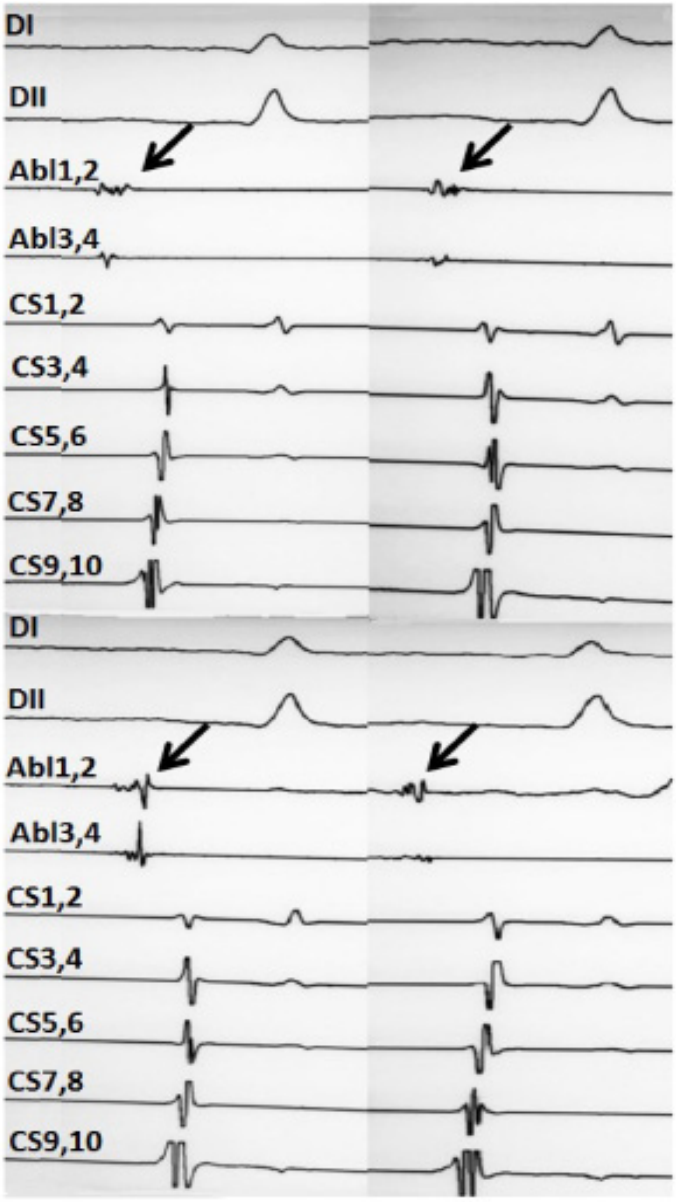

Figure 3: Low-amplitude and high-amplitude fractionated electrograms are seen during electroanatomic mapping guided cardioneuroablation

The arrows in above indicate low amplitude fragmanted electrogram and the arrows in below show high amplitude fragmanted electrograms, respectively. This figure provided by Dr Tolga Aksu from University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey.

system by Biosense Webster). Irrigated and non-irrigated catheters were used for cardioneuroablation in previous clinical studies. In the earliest published literature, Pachon et al [9] applied 4 mm non-irrigated catheter with the thermo-controlled system. The upper limit of power was set to 30 W. Radiofrequency energy were delivered in the targets near the pulmonary veins with maximum temperature of 60^{0}C and deliver time of 15 s, while delivered in other points with maximum temperature of 70^{0}C and deliver time of 30 s. With the development of technique, they chose two ablation models in further researches; the thermo-controlled radiofrequency was applied limited to 50 W/60^{0}C (non-irrigated) and 30 W/45^{0}C (irrigated) respectively.[11] In previous studies, our team used non-irrigated catheters with limitation set of 60 W/60°C and delivered at least 30 s until inhibition of the VR in each GP.[12, 14] Considering of the efficiency and safety of procedure, we tried to reduce the maximum temperature to 40 W and converted to the application of irrigated catheter (40 W/43^{0}C, irrigation flow of 17 mL/min). According to the experience of our team, a bi-directional catheter would be a better choice to guarantee optimal tissue contact essential factor to create transmural injury.[31] Aksu et al [15,25,32] consistently used irrigated catheter with power limit of 35 W, maximum temperature of 43^{0}C, and irrigation flow of 18 mL/min in their studies. Debruyne et al [20] furtherly chose contact force sensing catheter using a power of 40 W and a contact force > 8 g to ensure the ablation lesion.

During ablation of GPs, the most common response of each GP site is a vagal response such as transient ventricular asystole, atrioventricular block, or an increase of R-R interval. According to our previous research, among all the GPs ablated via LA, LSGP was the most frequent site demonstrating positive vagal response, while RAGP is the only target with heart rate increase during radiofrequency energy delivery.[14, 21]

The long-term clinical outcome of cardioneuroablation may be affected by incomplete ablation and consequent reinnervation by non-elimination of intramural parasympathetic postganglionic neurons. Repeat endocardial or epicardial pathway ablation may solve this problem in the future.

Endpoints of Cardioneuroablation

The simplest endpoint of cardioneuroablation is elimination of positive vagal response during ablation. Unfortunately, it is often difficult to evaluate the residual function of GPs by this rough method. Other endpoints usually depend on the approaches of GPs identification. We believe that the RAGP may need a different endpoint due to the unique response in most cases during the ablation, which often result in a rapid rise of sinus rhythm. In our lab, after completion of GP ablation, HFS is applied to recheck the vagal response status of each GP. In case of ongoing vagal response in any GP site, further ablation is performed up to complete elimination.[12, 14, 21] With this endpoint, we obtained excellent long-term clinical outcomes.[12, 14, 21] However, HFS may not necessarily predict long-term effects of cardioneuroablation; a negative HFS response after RF may be caused by the thermal effect of radiofrequency ablation.

Aksu et al [15, 22] performed electroanatomic mapping guided cardioneuroablation, the primary endpoints of their procedure is

Table 1: Techniques for cardioneuroablation in published clinical researches

Study	Enrolled patients	Included diseases	locations of targeted GPs	Approaches to identify GPs	Ablation catheter	Main endpoints
Pachon, et al.[9] 2005	21	NMS, AVB, SND	RA, LA	SA, AA	Non-irrigated	Elimination of the potentials according to SA; Persistent increase in the sinus rate and Wenckebach point.
Pachon, et al.[11] 2011	43	NMS	RA, LA	SA, AA	Non-irrigated, Irrigated	Elimination of the potentials according to SA; Atropine test.
Yao, et al.[12] 2012	10	VVS	LA	HFS	Non-irrigated	Elimination of the VR during ablation.
Pachon, et al.[33] 2015	47#	VRAF, NMS	NG	SA, AA	NG	Vagal stimulation; Atropine test.
Zhao, et al.[13] 2015	11	symptomatic SB	RA, LA	HFS, AA	Irrigated	Elimination of the VR during ablation; HFS after ablation.
Sun, et al.[14] 2016	57	VVS	LA	HFS, AA	Non-irrigated	Elimination of the VR during ablation; HFS after ablation.
Aksu, et al.[15] 2016	22	NMS, AVB, SND	RA, LA	SA, HFS, AA	Irrigated	Elimination of fractionated potentials; Elimination of parasympathetic response to HFS; Persistent increase in the sinus rate AND Wenckebach point; Completely elimination of AV block.
Qin, et al.[18] 2017	62	symptomatic SB	RA, LA	AA	Irrigated	Ablation of atrial electrical activity (peak-to-peak bipolar electrogram <0.1 mV); Elimination of the VR during ablation.
Rivarola et al.[19] 2017	14	NMS, AVB, SND	RA, LA	AA	Irrigated	The R-R interval, Wenckebach cycle length, and AH interval shortening, associated with a negative response to atropine.
Debruyne et al.20 2018	20	NMS, SND	RA	AA	Irrigated	P-P interval was < 70% of the baseline procedural P-P interval, was < 600 ms after 5 minutes of waiting time; Atropine test.
Aksu, et al.[22] 2019	20	VVS	RA, LA	SA, HFS, AA	Irrigated	Near complete elimination of all targeted atrial electrograms; Elimination of positive VR to ablation; Elimination of positive VR to HFS.
Hu et al.[21] 2019	115	VVS	LA	HFS, AA	Non-irrigated	Elimination of the VR during ablation; HFS after ablation.
Aksu, et al.[28] 2019	49	VVS, AVB, SND	RA, LA	SA, HFS, AA	Irrigated	Near complete elimination of all targeted atrial electrograms; Atropine test; Achievement of 75% of final sinus rate detected before procedure in patients with VVS and SND; Decrease > 25% in PR interval in patients with AVB.
Aksu, et al.[32] 2020	65	VVS, AVB, SND	RA+LA vs. RA	SA, HFS, AA	Irrigated	Near complete elimination of all targeted atrial electrograms; Atropine test; Achievement of 75% of final sinus rate detected before procedure in patients with VVS and SND; Decrease > 25% in PR interval in patients with AVB.

NMS: neurally mediated syncope; AVB: atrioventricular block; SND: sinus node dysfunction; RA: right atrium; LA: left atrium; SA: spectral analysis; AA: anatomical approach; VVS: vasovagal syncope; HFS: high-frequency stimulation; VR: vagal response; VRAF: vagal-related atrial fibrillation; NG: not given; SB: sinus bradycardia.
Only patients in denervation group were included in the evaluation.

near complete elimination of all targeted fragmented electrograms, and elimination of positive vagal response during ablation. They also applied atropine 30 minutes after cardioneuroablation to detect an acute anticholinergic response. Achievement of 75% of final sinus rate detected before procedure was accepted as clinical endpoint in patients with VVS and sinus node dysfunction. Decrease of >25% in PR interval was accepted as clinical endpoint for patients with atrioventricular block.[28, 32] Pachon et al [33] invented a neurostimulator to directly stimulate the vagal trunks during procedure and achieved stepwise strict control of the vagal denervation grade. The extracardiac vagal stimulation would be a reasonable technique to assess the endpoint of cardioneuroablation in the future.

In the end, we summarized the techniques of cardioneuroablation including locations of targeted GPs, approaches to identify GPs, ablation catheters, and main procedural endpoints from published clinical researches (case reports excluded) in Table 1.

Conclusions:

Cardioneuroablation is an emerging and apparently promising therapy. A few clinical trials have revealed the efficiency of this innovative strategy for VVS and autonomic related bradycardias. However, there are still many underlying questions need to be answered by more controlled clinical trials, which may also change the guidelines for the treatment of syncope and arrhythmia in the future.

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