Ganglia modulation in atrial fibrillation

Leonardo Calo'

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cause of the relatively benign nature of the arthmia, therapeutic failures or mistakes are tolble. A reliable image of the vagosympathetic ance is provided by studying the cardiac freency and variability of the prevailing sinus thm. Since experimental models of AF probashare many features with the arrhythmia ob-





they do not have an identical distribution. Stimulation of the sympathetic system may affect vagal function and vice versa. For example, acetylcholine released from vagal nerve endings diminishes norepinephrine release from neighboring sympathetic nerve endings. The functional responses to cholin ments to suggest that atrial vulnerabilit stimulation mainly depends on the sho the wavelength of the atrial impulse, w favors the formation of macroreentrant cit as flutter (Fig. 2). Microreentries and and triggered activities are more likely t

Laboratory Electrophysiology

There are many experimental methods used to induce AF,¹ an ECG aspect that forms the final stage of various arrhythmias. In animals, rapid stimulation of the atrium, local application of acetylcholine, or aconitine can produce the surface ECG pattern of AF. In humans, aggressive endocavitary

> Adenosine-induced atrial tachyarrhylhmia. ADENOSIN bolus -> extremely rapid atrial activity which reflect the duration of refractoriness in the small recorded atriat area

J Cardiovasc Electrophysiol, Vol. 7, pp. 999-1007. October 1996)



Effect of vagal cardiac stimulation in basic and clinical studies



Circ Res. 2014;114:1500-1515

Adrenergic and Cholinergic Contributions to AF Mechanisms



SINUS RHYTHM ----->Paroxysmal AF

VNA: vagal nerve activity SGNA: stellate ganglion nerve activity



the elevated vagal nerve activity (VNA) accelerated atrial rate, leading to paroxysmal reduction of ventricular rate (prolonged RR interval) before conversion from paroxysmal atrial tachycardia (PAT) to PAF.



Differences in the Atrial Electrophysiological Properties Between Vagal and Sympathetic Types of Atrial Fibrillation

LI-WEI LO, M.D.,*,† CHUEN-WANG CHIOU, M.D.,†,‡ YENN-JIANG LIN, M.D.,*,† SHIH-LIN CHANG, M.D.,*,† YU-FENG HU, M.D.,*,† HSUAN-MING TSAO, M.D.,†,§ TZE-FAN CHAO, M.D.,*,† CHENG-HUNG LI, M.D.,*,† HUNG-YU CHANG, M.D.,*,† FA-PO CHUNG, M.D.,*,† and SHIH-ANN CHEN, MD.*,†

The left atrial area was smaller in the patient with the vagal-type AF, compared to the patient with the sympathetic-type AF.



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Electroanatomic bipolar voltage mapping. In the patient with the vagal-type AF, the low-voltage areas were less extensive than those in the patient with the sympathetic- type AF.



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Huang JL, Wen ZC, Lee WL, Chang MS, Chen SA: Int J Cardiol 1998;66:275-283.

Ganglia ablation

Cardioneuroablation for AF Why a selective approach?



Cardiovascular Research (2009) 84, 245–252 doi:10.1093/ cvr/ cvp194

Autonomic mechanism for initiation of rapid firing from atria and pulmonary veins: evidence by ablation of ganglionated plexi

Zhibing Lu¹, Benjamin J. Scherlag², Jiaxiong Lin³, Lilei Yu¹, Ji-Hong Guo⁴, Guodong Niu², Warren M. Jackman², Ralph Lazzara², Hong Jiang¹, and Sunny S. Po²*





High Frequency stimulation: Prolongation of A–H interval and 2:1 AV conduction block were induced by HFS (1.5 V)

at the LSPV.

Selective Atrial Vagal Denervation Guided by Evoked Vagal Reflex to Treat Patients With Paroxysmal Atrial Fibrillation

Mauricio Scanavacca, Cristiano F. Pisani, Denise Hachul, Sissy Lara, Carina Hardy, Francisco Darrieux, Ivani Trombetta, Carlos Eduardo Negrão and Eduardo Sosa *Circulation* 2006;114;876-885; originally published online Aug 21, 2006; DOI: 10.1161/CIRCULATIONAHA.106.633560

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10 patients with episodes suggestive of vagal-induced paroxysmal AF and no heart disease were selected for percutaneous epicardial and endocardial mapping of the atria to search for sites in which highfrequency transcatheter stimulation (20 Hz,) induced vagal reflexes

Selective Atrial Vagal Denervation Guided by Evoked Vagal Reflex to Treat Patients With Paroxysmal Atrial Fibrillation

Mauricio Scanavacca, Cristiano F. Pisani, Denise Hachul, Sissy Lara, Carina Hardy, Francisco Darrieux, Ivani Trombetta, Carlos Eduardo Negrão and Eduardo Sosa *Circulation* 2006;114;876-885; originally published online Aug 21, 2006;

Conclusion

RF catheter ablation of selected atrial sites in which high-frequency stimulation induced vagal reflexes *may prevent AF recurrences in selected patients* with apparently vagal-induced paroxysmal AF.



Localization of Left Atrial Ganglionated Plexi in Patients with Atrial Fibrillation

SUNNY S. PO, M.D., PH.D., HIROSHI NAKAGAWA, M.D., PH.D., and WARREN M. JACKMAN, M.D.



Our preliminary results showed that all the four major atrial GP can be identified in the vast majority of patients. The parasympathetic response can be eliminated by applying radiofrequency current. In the first 83 patients, the percent of patients free of symptomatic AF or atrial tachycardia after a single ablation procedure was 80% at 12 months and 86% at a mean followup of 22 months.

J Cardiovasc Electrophysiol, Vol. 20, pp. 1186-1189, October 2009)

Anatomic Approach cardioneuroablationis in left atrium is all we need?

Anatomic Approach for Ganglionic Plexi Ablation in Patients With Paroxysmal Atrial Fibrillation

Demosthenes Katritsis, MD, PhD^{a,*}, Eleftherios Giazitzoglou, MD^a, Demetrios Sougiannis^a, Nicolaos Goumas^a, George Paxinos, MD^a, and A. John Camm, MD^b

Variable	Circumferential Ablation (n = 19)	GP Ablation $(n = 19)$
Age (yrs)	52.2 ± 9.4	51.2 ± 8.8
Men	16 (84%)	16 (84%)
Cause of AF		
Hypertension	13 (68%)	11 (58%)
Coronary artery disease	2 (10%)	2 (10%)
Lone atrial fibrillation	5 (26%)	6 (32%)
Medication		
β Blockers	18 (95%)	19 (100%)
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers	13 (68%)	11 (58%)
Diuretics	11 (58%)	10 (53%)



J Am Cardiol 2008;102:330-334

Selective ganglionated plexi ablation for paroxysmal atrial fibrillation

Evgeny Pokushalov, MD, PhD,* Alex Romanov, MD,* Pavel Shugayev, MD,* Sergey Artyomenko, MD,* Natalya Shirokova, MD,* Alex Turov, MD,* Demosthenes G. Katritsis, MD, PhD[†]



Selective ganglionated plexi ablation for paroxysmal atrial fibrillation

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Selective GP ablation directed by high-frequency stimulation does not eliminate paroxysmal AF in the majority of patients. An anatomic approach for regional ablation at the sites of GP confers better results.

The rationale of cardioneuroablation in the right atrium The anatomy

Autonomic tone modification after AFib TCA





Atrial Mapping and Radiofrequency Catheter Ablation in Patients With I diopathic Atrial Fibrillation: Electrophysiological Findings and Ablation Results

Fiorenzo Gaita, Riccardo Riccardi, Leonardo Calò, Marco Scaglione, Lucia Garberoglio, Renzo Antolini, Michele Kirchner, Filippo Lamberti and Elena Richiardi

Circulation. 1998;97:2136-2145.

Gaita, et al. Circulation. 1998;97:2136-2145.



The typical pattern of activity found in patients who underwent successful ablation is evident, showing more disorganized activity in the septum and more organized activity in the lateral wall with a craniocaudal activation sequence; after some cycles there is an inversion of the sequence with a caudocranial activation. The efficacy of this linear ablation approach in the RA can be caused by several factors such as conduction deterioration, increased nonuniform anisotropy, and disorganized electric activity. *Several mapping and ablation studies found the septum and posterior wall of the RA (regions with the largest prevalence of cardiac ganglia) as the areas with higher prevalence of complex fragmented atrial electrograms (CFAEs)*

Topography of cardiac ganglia in human heart



Sanjay Singh, MSc^a Patricia I. Johnson, PhD^a Robert E. Lee, MD, PhDb Emilo Orfei, MDb Vassyl A. Lonchyna, MDc Henry J. Sullivan, MD^c Alvaro Montoya, MDc Hoang Tran, BS^a William H. Wehrmacher, MD^a Robert D. Wurster, PhDa

TOPOGRAPHY OF CARDIAC GANGLIA IN THE ADULT HUMAN HEART Published descriptions of the topography of cardiac ganglia in the human heart are limited and present conflicting results. This study was carried out to determine the distribution of cardiac ganglia in adult human hearts and to address these conflicts. Hearts obtained from autopsies and heart transplant procedures were sectioned, stained, and examined. Results indicate that the largest populations of cardiac ganglia are near the sinoatrial and atrioventricular nodes. Smaller collections of ganglia exist on the superior left atrial surface, the interatrial septum, and the atrial appendage-atrial junctions. Ganglia also exist at the base of the great vessels and the base of the ventricles. The right atrial free wall, atrial appendages, trunk of the great vessels, and most of the ventricular are devoid of cardiac ganglia. These findings suggest modifications to surgical procedures involving incisions through regions concentrated with ganglia to minimize arrhythmias and related complications. Repairs of septal defects, valvular procedures, and congenital reconstructions, such as the Senning and Fontan operations, involve incisions through areas densely populated with cardiac ganglia. The current standard areas ucusely populated with carolae ganglia. The current standard procedure for orthotopic heart transplantation seres cardiae ganglia and the standard transplantation seres and the mathematica of the standard transplantation of the standard procedure for orthotopic nearl transplantation severs cardiac ganglia and their projections to nodal and muscular tissue. One modification of the uren projections to notial and muscular tissue. Une modification of mediae condition procedure, involving bicaval anastomosis, current heart transplantation procedure, involving Decomposition of condition current transplantation procedure, involving Dicaval anastomosis, preserves atrial anatomy and the cardiac ganglia. Preservation of cardiac preserves atrial anatomy constrained constituent constrained constituent and const reserves atrial anatomy and the cardiac ganglia. rreservation or cardiac substrate additional neuronal substrate the donor heart may provide additional neuronal substrate to the donor heart may provide for recentrating nerve fibers to the

 \geq Para-SA nodal ganglia are concentrated primarily lateral to the right pulmonary veins.

- The para-AV nodal ganglia are on the epicardial surface superior to the coronary sulcus (CS) and within the interatrial septum.
- Smaller collections of ganglia are dispersed throughout both atria, including the region superior to coronary sinus, the superior left atrial surface, and lateral to the left pulmonary veins.
- The right atrial free wall (RA) and the adventitia of the aorta (Ao) and pulmonary artery (PA) do not contain cardiac ganglia

J Thorac Cardiovasc Surg 1996;112:943-53

Gross and Microscopic Anatomy of the Human Intrinsic Cardiac Nervous System

J. ANDREW ARMOUR,^{3,*} DAVID A. MURPHY,¹ BING-XIANG YUAN,³ SARA MACDONALD,² AND DAVID A. HOPKINS²

¹Departments of Surgery, ²Anatomy and Neurobiology, and ³Physiology and Biophysics, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada





Intrinsic atrial ganglia <u>placed in fat pad</u> are 5

- 1) the superior right atrial GP
- 2) the superior left atrial GP (ganglia identified on the posterior surface of the left atrium between the pulmonary veins);
- *3) the posterior right atrial GP* (on the posterior surface of the right atrium adjacent to the interatrial groove)
- 4) the posteromedial left atrial GP (on the posterior medial surface of the left atrium)
- 5) posterolateral left atrial GP (identified on the posterior lateral surface of the left atrial base on the atrial side of the atrioventricular groove.

The rationale of cardioneuroablation in the right atrium Eletrophysiology



SVC-aorta-GP in AF initiated by rapid firing from the SVC.

HFS of this anatomical structure slowed sinus rate and/or atrioventricular conduction and determined more significant shortening of ERP and a greater increase in window of vulnerability at the SVC than other sites

The role of IRGP (Inferior-right ganglionated plexi)



The role of IRGP (Inferior-right ganglionated plexi) and integration centers



- IRGP seems to be the integration center for the extrinsic ANS to innervate the AV node as ablation of IRGP completely eliminated the VR slowing response induced by vagosympathetic stimulation.
- ARGP and IRGP play a selective role in regulating SA and AV nodal function, respectively

The role of IRGP (Inferior-right ganglionated plexi)

GP function as "integration centers"



Modulation of sinus rate by vagosympathetic stimulation.



Modulation of ventricular rate during atrial fibrillation by vagosympathetic stimulation.





Learn and Live

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Catheter Ablation of Right Atrial Ganglionated Plexi in Patients With Vagal Paroxysmal Atrial Fibrillation

Leonardo Calò, Marco Rebecchi, Luigi Sciarra, Lucia De Luca, Alessandro Fagagnini, Lorenzo Maria Zuccaro, Pietro Pitrone, Serena Dottori, Maurizio Porfirio, Ermenegildo de Ruvo and Ernesto Lioy

Circ Arrhythm Electrophysiol 2012;5;22-31; originally published online December 6, 2011;

DOI: 10.1161/CIRCEP.111.964262

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The Year in Review of Clinical Cardiac Electrophysiology

Gregory M. Marcus, MD, MAS,* Edmund Keung, MD,† Melvin M. Scheinman, MD* San Francisco, California

> rigor in assessing outcomes. Although achieving pulmonary vein isolation remains the mainstay of curative AF ablation procedures (23), several adjunct approaches demonstrated evidence of additional benefit, including targeting areas with high dominant frequencies (defined as the frequency with the maximum power derived from spectral analysis and fast-Fourier transform of sinus rhythm bipolar electrograms) (24), <u>ablating ganglionated plexi in the right atrium</u> of vagal AF patients (25), and a combined endocardial and epicardial approach (26). In addition, although radiofre-

 Calo L, Rebecchi M, Sciarra L, et al. Catheter ablation of right atrial ganglionated plexi in patients with vagal paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol 2012;5:22–31.

	Overall (n=34)	Anatomic GP Abl (n=17)	Selective GP Abl (n=17)
Age, y*	48.6±4.6	49.5±4.8	47.7±4.4
Sex, males, n (%)	22 (64.7)	10 (58.8)	12 (70.6)
AF vagal triggers, n (%)			
During sleep	23 (67.6)	11 (64.7)	12 (70.6)
After meals	8 (23.6)	5 (29.4)	3 (17.6)
Coughing	3 (8.8)	1 (5.9)	2 (11.8)
AF history, y*	4.9±1.3	4.9±1.4	4.9±1.2
AF episodes/y*	83.6±22.3	85.4±25.6	81.8±23.3
Risk factors for cardiopathy, n (%)			
Hypertension	3 (8.8)	2 (11.8)	1 (5.9)
Dyslipidemia	3 (8.8)	1 (5.9)	2 (11.8)
Echocardiogram*			
Left atrium AP diameter, mm	37.2±0.8	37.1±0.6	37.3±0.9
LVEDD, mm	48.3±3.7	46.4±3.6	47.5±3.8
LVESD, mm	28.4 ± 3.6	27.7±3.4	28.2±3.4
EF, %	63.4 ± 5.3	63.3±5.1	63.5±5.2
Septal thickness, mm	9.7±0.4	9.4±0.6	9.6±0.5
Posterior wall thickness, mm	8.9±0.5	8.7±0.4	8.8±0.6

_

Table 1.Demographic Characteristics of theStudy Population

Selective approach



Figure 2. A, Parasympathetic response evoked during high-frequency stimulation (HFS) near coronary sinus ostium (I and V₃, surface ECG; CS1–CS10, distal and proximal coronary sinus; Abl d/p, bipolar distal and proximal mapping and ablation catheter). **B**, CARTO 3 Fast Anatomic Map of right atrium (RA) (lateral projection) in a case of selective ganglionated plexi (GP) ablation. **Red dots** represent sites of radiofrequency pulse near HFS-positive sites (**yellow dots**). White dots represent HFS-negative sites. HIS indicates proximal His bundle; CS, coronary sinus; IVC, inferior vena cava; SVC, superior vena cava; and AV, atrioventricular.

Autonomic Denervation Guided by high frequency stimulation (HFS)

HFS was performed at the posterior and septal surface of RA adjacent to the junction of the SVC and RA (superior RA GP), adjacent to the interatrial groove (posterior RA GP), between the inferior vena cava and septum near the coronary sinus ostium (inferior RA GP), and adjacent to the atrial ventricular groove.

Rectangular electric stimuli were delivered at a frequency of 20 Hz, amplitude of 12 V increasing to 15 V in the case of no vagal reflex evoked, and pulse duration of 10 ms (Stimulator TECS II, Medico, Italy).

A significant parasympathetic response was defined as prolongation of R-R interval by 50% during AF associated to a sudden 20 mm Hg decrease in blood pressure



Anatomic approach



Calò et al





Figure 3. A, Distribution of sites where radiofrequency applications evoked a parasympathetic response during anatomic ablation. B, Distribution of sites where high-frequency stimulation evoked a parasympathetic response during selective approach. PA indicates pulmonary artery; IVC, inferior vena cava; SVC, superior vena cava; RV, right ventricle; and LV, left ventricle. See text for further details. At a mean follow up of 19.7 \pm 5.2 months, AF recurred in 5 (29.4%) of 17 patients with anatomic ablation and in 13 (70.5%) of 17 patients with selective approach (*P*=0.01).



Calò, et al. Circ Arrhythm Electrophysiol. 2012;5:22-31.

CFAE and ganglia

CFAEs ablation as target of cardioneuroablation?



Selective ganglionated plexi ablation for paroxysmal atrial fibrillation Evgeny Pokushalov, MD, PhD,* Alex Romanov, MD,* Pavel Shugayev, MD,* Sergey Artyomenko, MD,* Matalya Shirokova, MD,* Alex Turov, MD,* Demosthenes G. Katritsis, MD, PhDt

>we observed **CFAEs** around each positive vagal site the posteroseptal region, particularly the posteroseptal space, showed the greatest prevalence of such electrograms. **GP** ablation **determined in 33 of the 34 patients studied the disappearance or the significant reduction of CFAEs.**

Nakagawa and Lemery suggested that areas close to ganglionated plexi, where the local vagal stimulation shortens the local effective refractory periods can cause the formation of CFAEs.



Why the reduced effectiveness of selective approach The octopus Hypotesis?



- An hyperactive state of the GP/head of octopus, may trigger local release of a gradient of excessive amounts of neurotransmitters and subsequently initiate AF
- the excitation of assons/tentacles can determines a retrograde activation of GP at distance, can provide an interesting explanation for the discrepancy between the sites of vagal response (which are also the sites of radiofrequency ablation) and real location of GP.

J Cardiovasc Electrophysiol, Vol. 18, pp. 83-90, January 2007



2-Map (381, 0) 👻

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Future perspectives





Atrial tissue characterization

"Cardioneuroablation" — new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation

Jose C. Pachon M^{*}, Enrique I. Pachon M, Juan C. Pachon M, Tasso J. Lobo, Maria Z. Pachon, Remy N.A. Vargas, Adib D. Jatene

Spectra obtained from four endocardial sites in the left and right atria



Europace (2005) 7, 1-13



The penetration of the nervous fibres changes myocardial conduction and the frequency spectrum of the endocardial potential which shifts from the compact conduction (A) pattern to the fibrillar (B).

Functional Characterization of Atrial Electrograms in Sinus Rhythm Delineates Sites of Parasympathetic Innervation in Patients With Paroxysmal Atrial Fibrillation

Nicolas Lellouche, MD, Eric Buch, MD, Andrew Celigoj, BS, Carin Siegerman, PHD, David Cesario, MD, PHD, Carlos De Diego, MD, Aman Mahajan, MD, PHD, Noel G. Boyle, MD, PHD, Isaac Wiener, MD, Alan Garfinkel, PHD, Kalyanam Shivkumar, MD, PHD



AH interval modification after ablation targeted on normal, LAFE and HAFE left atrial EGMs

J Am Coll Cardiol 2007;50:1324–31





A Vagal denervation guided by atrial identifications CFAEs could be particularly advantageous through the use of spectral analysis techniques and the future development of software that can really differentiate fragmented electrograms (HAFE) which are more closely indentifier of nervous tissue in the context of a healthy myocardium









Ganglionated plexi ablation in right atrium to treat cardioinhibitory neurocardiogenic syncope

Marco Rebecchi · Ermenegildo de Ruvo · Stefano Strano · Luigi Sciarra · Paolo Golia · Annamaria Martino · Leonardo Calò

Case 1	Pre-ablation	1 day post-ablation	2 months	8 months
HR/bpm	65	78	80	74
LF (ms ²)	235	7	78	201
HF (ms ²)	207	8	21	127
LF/HF	1.13	0.87	3.72	1.58
Case 2	Pre-ablation	1 day post-ablation	2 months	5 months
HR/bpm	58	87	78	62
LF (ms ²)	197	12	101	185
HF (ms ²)	184	14	42	176
LF/HF	1.08	0.83	2.41	1.03





J Interv Card Electrophysiol (2012) 34:231–235