Non-Fluoroscopic Catheter-Based Mapping Systems in Cardiac Electrophysiology--from Approved Clinical Indications to Novel Research Usage.

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Non-fluoroscopic Catheter-based Mapping Systems

in Cardiac Electrophysiology:

From Approved Clinical Indications to the Novel Research Use

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Abstract

During 20 years of development of catheter-based technologies in the management of cardiac arrhythmias, the electrophysiological mapping/ablation systems have evolved from the single-plane fluoroscopic mapping to the 3-dimensional non-fluoroscopic computer-based mapping systems. Based on magnetic technology, the electro-anatomic CARTO® mapping system can accurately correlate the local electrograms with recording sites, by which the system can reconstruct 3-D maps with color-coded electrophysiological information superimposed on the anatomy. Whereas the CARTO® system is primarily designed for studying cardiac activation and not repolarization, the system has been widely used in the diagnosis and ablation of cardiac arrhythmias, and in the research of basic arrhythmic mechanisms. In order to study cardiac repolarization *in vivo*, an innovative method, the *monophasic action potential* (MAP) mapping technique that integrates the MAP recording with the electroanatomical mapping, has recently been developed in our center. Using the MAP technique, global sequence and dispersion of atrial/ventricular repolarization have been evaluated *in vivo* both in experimental and clinical settings. This innovative technique provides unique research opportunities for *in vivo* studies of basic electrophysiological mechanisms.

INTRODUCTION

Twenty years of technological progress in electrophysiology

About 20 years ago, introduction of catheter-based radiofrequency (RF) ablation techniques in the management of cardiac arrhythmias dramatically changed approaches to the management of large patient populations suffering from rhythm disorders which could only to a limited extent be treated with medications. The ablation method not only gave cure to patients with arrhythmias caused by accessory pathways, AV nodal, focal atrial and ventricular tachycardias, atrial flutter and atrial fibrillation but also demanded more and more precise mapping technologies allowing visualization of activation spread over cardiac tissues.

Introduction of user-friendly non-fluoroscopic computer-based visual systems in the late ’90s, which allowed coupling between the catheter tip position in three-dimensional space and the timing of the cardiac signal became an important step in the development of catheter-based electrophysiological systems. By providing higher precision of catheter positioning, introduction of these systems allowed substantial reduction in number of RF applications thus minimizing size of lesion on the endocardial surface and improving patient safety. Three major systems (LocaLisa®, Medtronic[(1)]; EnSite®, Endocardial Solutions Inc.[(2)]; CARTO®, Biosense Webster Inc.[(3)]) have been developed with first reports published almost simultaneously in the end of ’90s, each of them being based on different physical principles.

Electro-anatomical CARTO mapping system

The CARTO® system (Biosense Webster Inc.) with applications described in this review is a catheter-based non-fluoroscopic cardiac mapping system that is composed of miniature passive-magnetic field sensors, an external ultra-low magnetic field emitter (or location pad) and a CARTO processing unit. The miniature magnetic field sensors are located at the tip of

a combined mapping/ablation catheter (NAVI-STAR®) and a reference catheter (REF-STAR®). The location reference patch is fixed on the back of the subject, while a mapping/ablation catheter navigates within the cardiac chambers or on the surface of the heart (Fig. 1).

Three magnetic fields emitters are situated under the catheterization table and emit fields of different frequencies. The sensors receive the emitted low-intensity magnetic fields and transmit them along the catheter to the main processing unit. The processing unit collects and analyses data on the amplitude, frequency, and phase of the magnetic fields to determine the precise location of the mapping/ablation catheter tip and its orientation (roll, pitch and yaw) within the fields. The accuracy of spatial localization has been verified to be 0.7 mm *in vivo*[4]. The three-dimensional geometry of the cardiac chamber is generated, and the system displays the real-time location of the catheter and reference patch relative to each other. The electrophysiological information is color coded and superimposed over an electro-anatomical map.

Established Approach: Activation Sequence and Conduction Velocity in Research and Clinical Applications of Electro-anatomical Mapping

Initially, the system was developed in the later ’90s and clinically first used in Europe in 1997. It was approved by the US Food and Drug Administration (FDA) in 2000 for ablation of accessory atrioventricular (AV) conduction pathways (WPW syndrome), AV nodal reentrant tachycardia and creation of complete AV nodal block in patients with a difficult to control ventricular response to an atrial arrhythmia. Clinical applications of the system in the real world went far beyond this and the system has found widespread use in a variety of tachyarrhythmias. The built-in possibility to reconstruct cardiac activation maps on a color-

coded display has made the system a useful tool in diagnostics and ablation of focal atrial or ventricular tachycardias[5,6] where ablation success depends on the accuracy of identification of the abnormally firing focus.

Pulmonary veins ablation in the management of atrial fibrillation has become facilitated by the ability of the CARTO™ system to tag the crucial anatomical landmarks such as the veins ostia in the left atrium[7]. The ability to register the location of individual RF application points facilitates creation of complex linear lesions such as during the pulmonary vein isolation or ablation of ventricular tachycardias.

The wide spectrum of diagnostic options offered by the electro-anatomical mapping made it an exceptionally useful tool in the research of cardiac activation and basic arrhythmic mechanisms. Firstly, the technique allowed reconstruction of the left atrial anatomy and its activation sequence thus leading to development of a novel curative technique of ablation of atrial fibrillation by creating complex linear lesions in the left atrium[8]. Local conduction disturbance associated with development of atrial fibrillation has recently been documented by our group using electro-anatomical mapping of the right atrium and the coronary sinus[9] (Fig. 2).

NOVEL RESEARCH APPLICATIONS

Monophasic Action Potential Mapping in Evaluation of Global Cardiac Repolarization

Disturbances in myocardial conduction and repolarization play important roles in initiation and perpetuation of tachyarrhythmias[10-12]. However, in contrast to the extensive explorations on cardiac activation, little is known about the global repolarization.

Global sequence and dispersion are two of the important features for assessment of global repolarization. To evaluate these features, one needs A) a sufficient number of recordings reflecting local repolarization time[13]; and B) an accurate correlation of the

recordings with the anatomic locations of the recording sites. The difficulties consist in obtaining localized information on repolarization from numerous sites throughout the heart. To resolve this problem, we successfully integrated the monophasic action potential (MAP) recording technique with the CARTO electro-anatomical mapping technique for evaluation of the global cardiac repolarization [11, 13-15].

INTEGRATION OF MAP RECORDING AND CARTO ELECTRO-ANATOMICAL MAPPING

The MAP can accurately reproduce the time course of the local repolarization and is generally accepted as the method of choice in *in vivo* evaluation of myocardial repolarization[16, 17]. From the MAP recordings, three main time intervals can be obtained: the local activation time (AT), defined as the time interval from the earliest recorded atrial activation to the local activation; MAP duration, the time interval from the local activation to the local repolarization point and the local end of repolarization time (EOR), the time interval from the earliest activation to the local repolarization point, which is equal to the sum of the local AT and MAP duration at that recording site. As both the activation and the repolarization constitute spatiotemporal processes, the EOR, rather than the APD/MAPd, should be more directly related to the sequence and dispersion of global repolarization.

The CARTO system allows an accurate correlation between recording signals and recording sites in the construction of three-dimensional maps, which provided the possibility of rapid cardiac activation assessment with high spatial accuracy. It is not necessary to follow any anatomical scheme since the system accurately memorizes the recording sites and the acquired signals. Note, however, that the CARTO system was designed for evaluation of cardiac activation and that information on cardiac repolarization previously was not widely available. Whereas the CARTO system was designed for studies of cardiac activation sequences, it actively contributed to knowledge acquisition on cardiac repolarization.

A prerequisite for the use of the CARTO system as a means to evaluate repolarization is that the MAP recording catheter must be locatable by the system. We first validated the possibility of recording MAPs using a conventional platinum electrode ablation catheter[18] and then verified the feasibility of recording MAPs using a CARTO sensor-equipped catheter. To improve the quality of the MAP recording and to facilitate the mapping procedure, a special Navi-star catheter with a modified tip was developed for MAP mapping using the CARTO system[19] (Fig. 3). Based on these developments, the MAP mapping technique, which integrates the MAP recording technique and the CARTO electro-anatomical mapping technique, is ideally set up.

MONOPHASIC ACTION POTENTIAL MAPPING AND ANALYSIS

Using the CARTO system, the MAPs are recorded using a modified-tip 7 F NaviStar catheter, which has a contact ball of 0.5 mm length and 1 mm diameter at the end of the tip electrode (Fig. 3), in atria and/or ventricles. The MAP signal is recorded between the tip and the ring electrode proximal to the tip at a filter bandwidth of 0.01–400 Hz. When the amplitude and morphology of the MAP appeared satisfactory, the signals are captured into a sampling window for further inspection.

The MAP analysis can be performed off-line using the feature of double annotations of the CARTO system (Fig. 4). The first annotation line is set at the onset of the MAP upstroke, representing the local activation, the second at the intersection between the baseline and the tangent to the steepest slope on phase 3 of the MAP, representing the local EOR[14]. Taking the peak of the QRS complex on the reference ECG as the time reference, the AT, MAP duration and EOR time can be calculated (Fig. 5). Based on these values, three-dimensional maps of the atria and/or ventricular activation sequence, EOR sequence and the spatial distribution of MAP durations can be reconstructed (Figs. 5). The maximum differences in

the AT, EOR time, and MAP duration, *i.e.,* the total ranges of the scales of these maps, represent the total magnitude of the disparity between the measurement values, are called the maximal dispersion of these parameters[13]. Thus, the global sequence and dispersion of atria and/or ventricular repolarization are obtained and can be evaluated, and our experimental and clinical studies have verified the feasibility and reliability of this novel technique for evaluation of global cardiac repolarization[11, 13-15].

DISCUSSION

The new approach presented has grown out of clinical experience of currently available non-fluoroscopic cardia mapping technology. The Medtronic LocaLisa® system uses three skin electrode pairs, positioned in x,y,z directions around the heart to track catheters. Using a reference electrode, three separate low-power radiofrequency fields are generated to create three orthogonal fields. This electrical field creates a voltage gradient along its axis, allowing the LocaLisa® system to calculate the catheter position[1]. By giving an opportunity to mark locations of critical points in the heart and to precisely position the ablation catheter introduction of this system allowed to reduce fluoroscopic time and RF energy required for safe ablation of a number of cardiac arrhythmias including atrial flutter, atrial fibrillation and ventricular and AV re-entry tachycardias[2].

The EnSite® mapping system (Endocardial Solutions Inc.) was developed during the same period. This is a non-contact system that allows simultaneous mapping of an entire heart chamber. Using a catheter containing 64 electrodes on a balloon placed in the patient's heart chamber the instrument receives electrical impulses from over 3,000 points within the chamber and without having to touch the cardiac walls. It then produces a display of a three-dimensional view of the heart, showing its electrical activity and activation spread[3]. The unique ability to simultaneously record activation from the number of points gave an

opportunity to map arrhythmias with irregular activation spread such atrial fibrillation[4]. It has also simplified studying activation patterns in heart chambers which were difficult to access and map using conventional techniques. Thus, the non-contact mapping system was the first that allowed assessment of the activation of the left atrium in humans[5].

The CARTO® system (Biosense Webster Inc.) with applications described in this review is based on a principle of interpolated magnetic fields of different frequencies which allow not only registration of activation sequence coupled to a points in an orthogonal coordinate system but also offers a possibility to reconstruct endocardial surface of cardiac chambers[6]. The complexity of cardiac structures such as atrial appendages or coronary sinus demands a high precision tool, which in addition to established clinical tasks such as ablation of common arrhythmias allows detailed high-density mapping of endocardial surface aimed at investigating fundamental arrhythmic mechanisms.

Initially, the catheter ablation was guided by a single-plane fluoroscopic monitoring and electrical signals from stable positioned or movable catheters placed in the heart with surface ECG being a reference for estimating of the earliest activation point during tachycardia or assessment of accessory pathway location. It has soon become obvious that simultaneous registration of signals from different cardiac regions is required. Development went towards introduction of multipolar diagnostic tools with electrodes placed either along the catheter, such as 20-polar HALO XP catheter (Biosense Webster Inc.), or multipolar basket catheters when 64 electrodes were mounted on several flexible, self-expanding nitinol splines (Constellation® EPT, Boston Scientific Corp.). After introduction into a cardiac chamber, such multipolar basket catheters could be shaped so that the electrodes were brought in contact with cardiac walls and allowed reconstruction of activation sequence and location of the earliest activation point, such as an arrhythmic focus. An important limitation of such

systems was that they were lacking visualization capabilities and did not allow to memorize with a required precision location of the point of interest on the endocardial surface which is especially important in treatment of certain arrhythmias (*e.g.*, atrial flutter or atrial fibrillation) where uninterrupted lines of conduction block are required in order to achieve definitive cure—*c.f*. Fig. 6.

SUMMARY

Non-fluoroscopic endocardial mapping system introduced in electrocardiology during recent years has dramatically changed the practice of diagnostics and management of cardiac arrhythmias. These systems offered useful clinical tools allowing delivering of therapeutic energy with high precision thus improving patient safety. As demonstrated by our experience of creative using inbuilt system capacities, the new techniques may also provide unique research opportunities allowing *in vivo* studies of basic electrophysiological phenomena such as global cardiac repolarization that earlier were beyond reach.

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Figures and Figure Legends

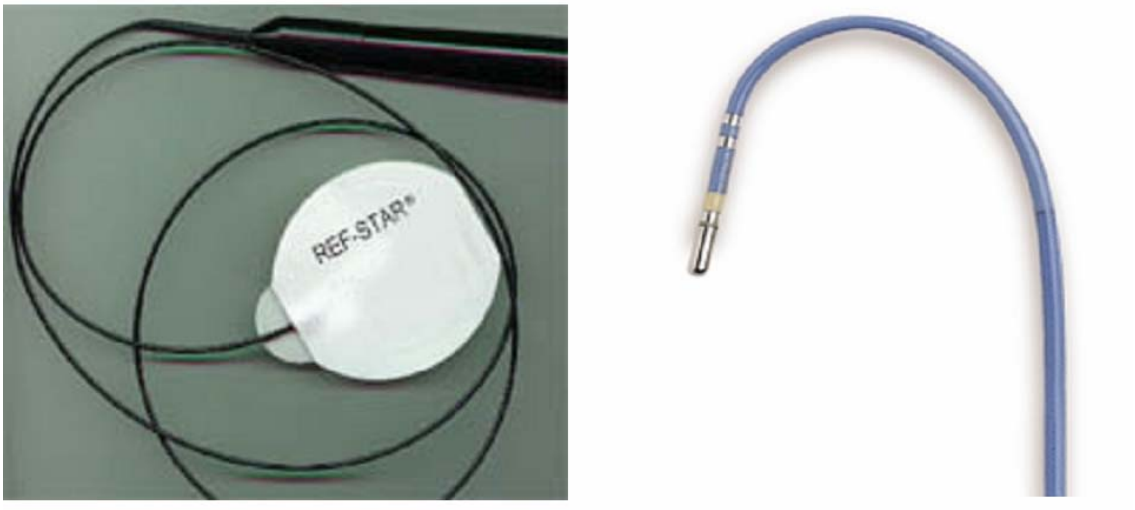

Figure 1. Location reference catheter REF-STAR® (left) which is fixed on the back of the subject and the tip of the active mapping/ablation catheter NAVI-STAR® (right).

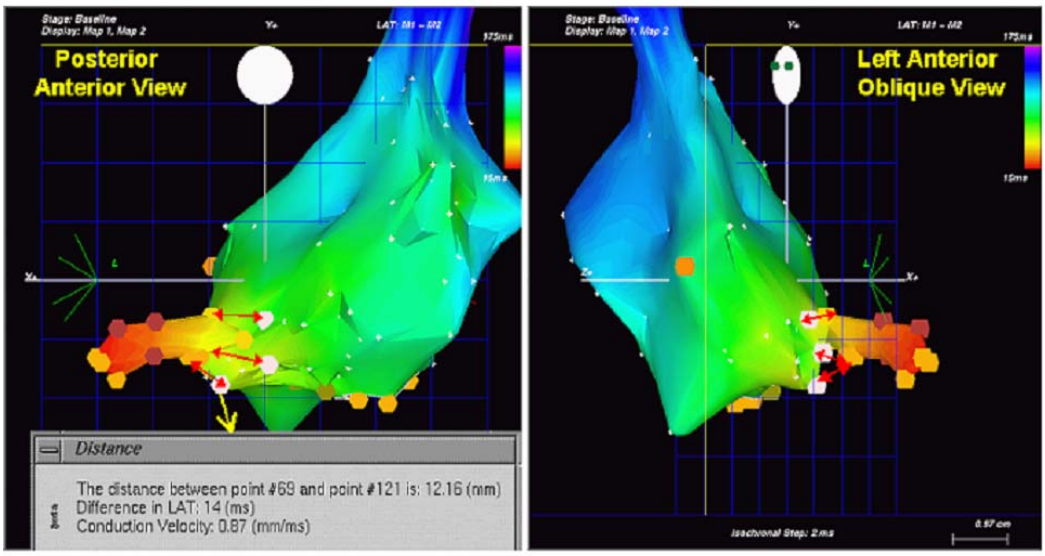

Figure 2: Right atrium and coronary sinus (CS) maps during distal CS pacing in a patient with paroxysmal atrial fibrillation. The mean velocity across the CS ostium was 0.7 m/s, which was calculated from 8-paired sites between the posteroseptal right atrium and proximal CS. Left. Posterior-anterior view, showing 3 paired sites (double-arrow lines) between the posteroseptal right atrium and posteroinferior proximal CS. The distance, conduction time and velocity between one of the paired sites were automatically measured as 12.16 mm, 14 ms and 0.87 mm/ms, respectively, using the CARTO system. Right. Left anterior oblique view, showing additional paired sites across the CS ostium (Reproduced with permission from Ref. 9).

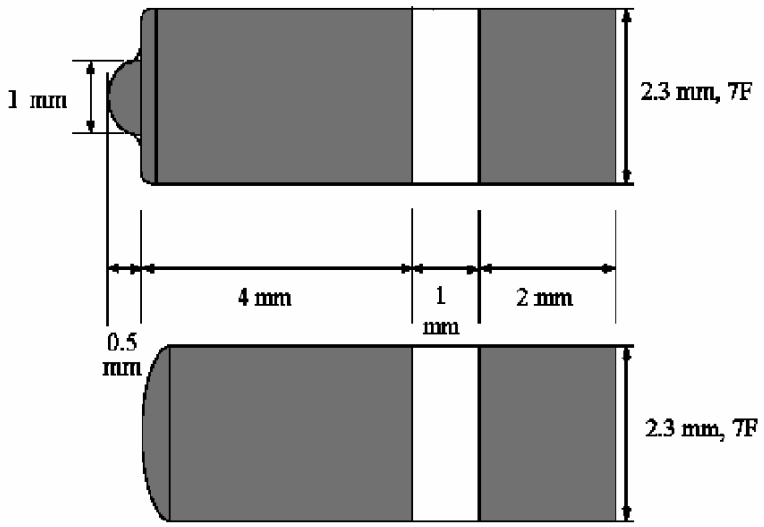

Figure 3. Schematic comparison of the modified-tip electrode and the ordinary tip electrode of the Navi-Star catheter. Modified-tip electrode is 7F, quadripolar and has a contact ball 1 mm in diameter and about 1.2 mm^2 in contact area on the end surface of the tip electrode (upper). An ordinary Navi-Star catheter has a tip electrode 4 mm long, 2.3 mm in diameter and 4.2 mm^2 contact area on its end surface. (lower) (Reproduced with permission from Ref. 19).

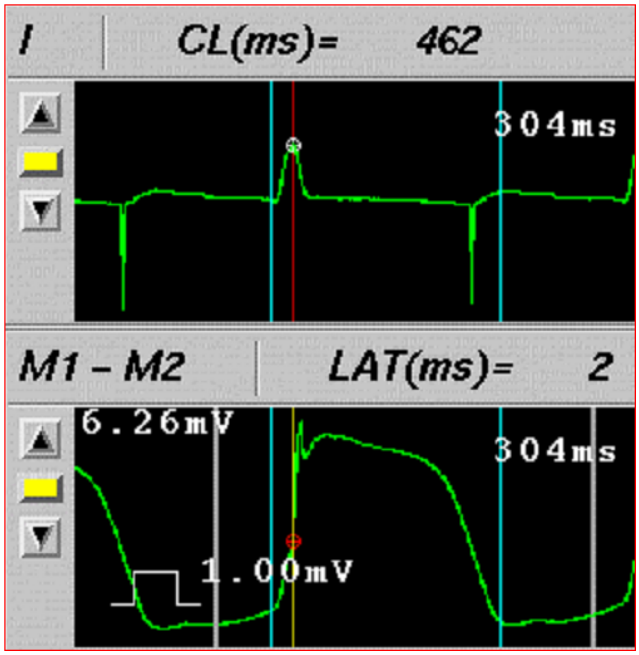

Figure 4: Recordings of MAP from the left ventricle during sinus rhythm in the sampling window of the CARTO system. On the ECG (upper tracing), the time reference line is set on the peak of the QRS complex (red line). On the MAP (lower tracing), MAP duration is measured as the interval between the two annotation lines, the yellow and the second blue one. The first blue line denotes the earliest recorded activation and thus the interval between this blue line and the yellow line represents the local activation time. Between the two blue lines is the end of repolarization time. Time scale is 100 mm/s.

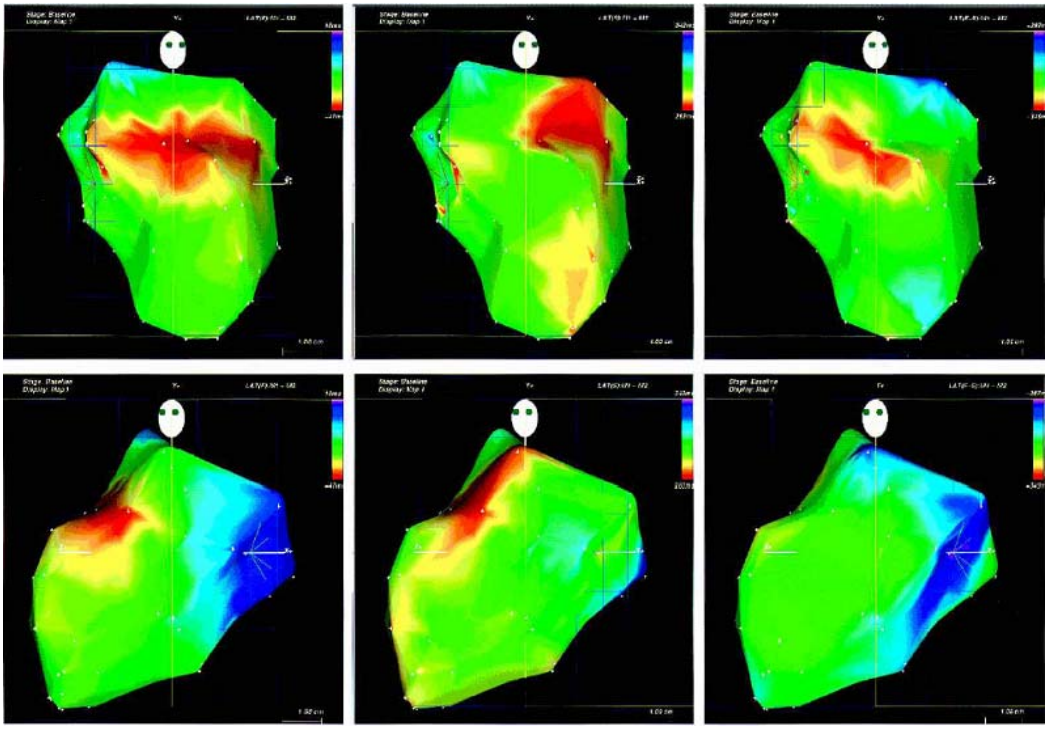

Figure 5: Left ventricular maps from a pig during sinus rhythm: right anterior oblique (upper panel) and left anterior oblique views (lower panel). (Left) Activation started from the upper midseptum (red area), proceeded eccentrically towards the superior septum, antero- and posteroparaseptal and apical areas, and then passed through the free walls (yellow and green areas) to end in the posterolateral basal (blue and purple) area. (Middle) The end-of-repolarization sequence was similar to the activation sequence. (Right) The longest monophasic action potentials (MAPs) (red area) were recorded in the area activated earliest, and the shortest (blue and purple) near the area activated latest. Note that the MAP duration map was reconstructed using the negative values of the MAP durations in this figure, so that the red area represents the longest MAPs and the purple one the shortest. (Reproduced with permission from Ref. 14)

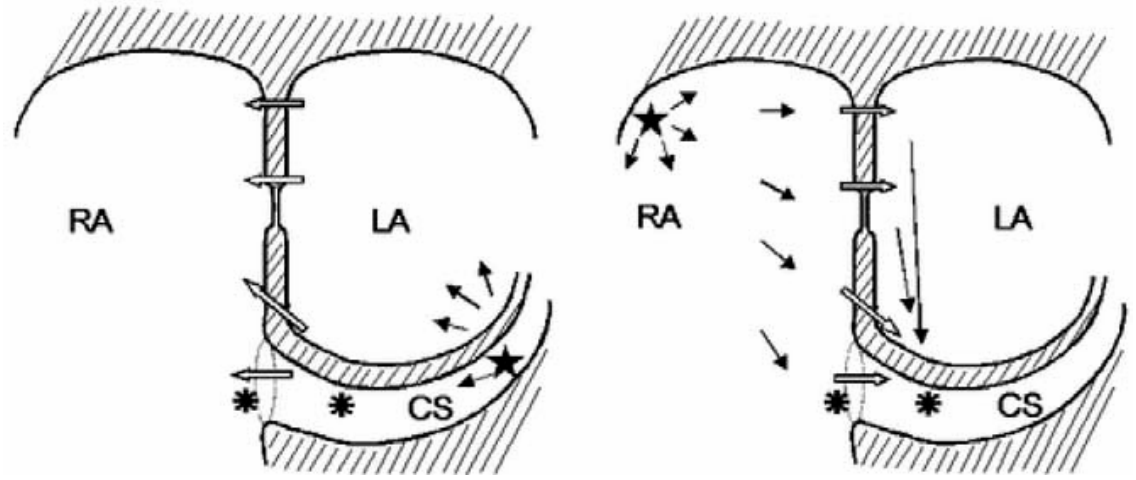

Figure 6. Schematic diagram of activation velocity measurements. Open arrows indicate possible interatrial conduction routes. Solid arrows indicate propagation of activation wavefronts. ***Left:*** *During distal coronary sinus (CS) pacing, conduction across the CS ostium is along the long axis of the CS. Thus, the calculated activation velocity between the two stars (*)—with left one indicating a right atrial site and the right one indicating a proximal CS site—may represent true conduction velocity across the CS ostium.* ***Right:*** *During sinus rhythm, when conduction is across the CS ostium along the long axis of the CS, the measured activation velocity between the two stars (*)—with the left one indicating a right atrial site and the right one indicating a proximal CS site—represents true interatrial conduction through the CS ostium. However, when the interatrial conduction is produced via other routes, the conduction route across the CS ostium is not a preferential route. As a result, the right atrial site by the CS ostium and the site at the proximal CS may be activated by different wavefronts.*