

Technical Note

Cardiac Electrophysiology (EP)

Cardiac Electrophysiology is a method of capturing, diagnosing and treating deleterious electrical activities of the heart. The difference between the intra-cardiac ECG recording and body surface ECG electrodes is that the former collects signals from the pair of electrodes localized at the tip of the catheter while the surface ECG gives the electrical activity of whole heart.

Just as the innate SA node creates depolarization of the myocardium, a pacing electrode introduces premature electrical stimuli delivered at predetermined intervals known as programmed electrical stimulation (PES). Both the pacing and recording electrodes for PES are located on the same catheter and can be selected and adjusted during procedure based on necessities arising from specific procedure requirements and heart morphology. EP through PES provides a unique opportunity to explore mechanisms underlying conduction defects, evaluate electrophysiological properties of cardiac muscle including automaticity and conduction velocity, and examine abnormal electrocardiograms.

EP protocols include initiating, recording or monitoring:

- Electrical conductivity, automaticity (baselines)
- SA node (conductivity, automaticity)
- AV node and His bundle (conductivity, refractoriness)
- Atrial / ventricular arrhythmias
- Cardiovascular drug candidates

Representative results include:

- The baseline EP parameters for PR, PQ and QT intervals, QRS duration and its morphology.
- The PES parameters for sinus node (SNRT) for atrial (AERP) and nodal (AVNERP) refractory properties.

Types of PES pacing:

- incremental pacing (burst pacing) i.e. introducing train (usually sequence of 8 beats) of paced impulses with fixed cycle length
- extra-stimulus technique i.e. using premature impulses that usually follows the train

The advantage of positioning a pacing catheter inside of the cardiac chamber is in the precise assessment of conduction time from one location to another. Intra-cardiac depolarization using localized PES precisely reflects the immediate-adjacency myocardial response to depolarization.

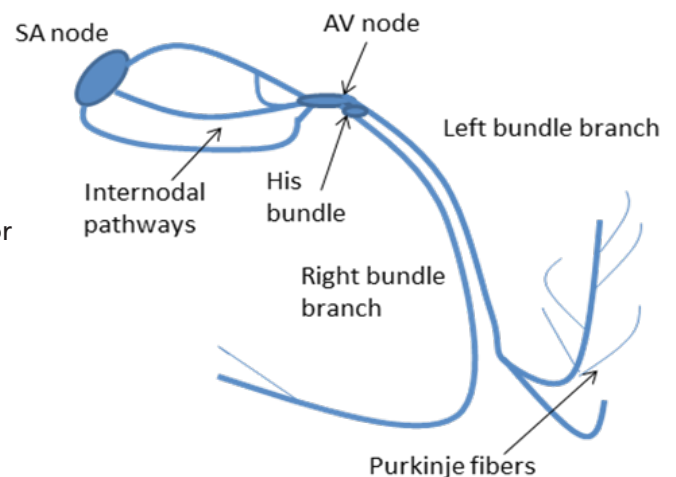


Fig. 1: Schematic picture of the internodal pathways present in the atria. It is claimed that specialized conduits exist within the atria with the ability to control the spread action potentials rather than action potentials being randomly spread through the atrial myocytes.

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Common position of pacing catheters include:

- The right atrium (RA) position or “high position” is used most commonly as it is close to the superior vena cava (SVC), approximating the SA node location. Pacing from this area produces P waves, similar to regular sinus beats.
- Left atrial (LA) pacing is pacing using the coronary sinus access. The catheter is usually positioned in the AV groove between the LA and LV.
- Newer EP methods are using pacing catheter entry into LV through transeptal puncture from the right ventricle (RV) or patent foramen ovale (fossa ovalis).
- AV conduction (His bundle recording) in Fig. 2 is accomplished by positioning the pacing catheter at the rear of the tricuspid valve. At that position electrical activity can be recorded from portions of the RA, AV node and RV.
- LV pacing is not usually performed. If pacing of the LV is necessary, usually the femoral artery access is selected due to concerns of introducing venous emboli (right to left). If it is performed, an arterial tree is used.

EP increasingly includes therapeutic methods (typically radio frequency ablation) in addition to diagnostic and prognostic procedures. Other therapeutic modalities used by EP

include monitoring of implantation of pacemakers (single or dual chamber), observation of long-term ECG recorders and automatic implantable cardioverter-defibrillators.

ACTION POTENTIALS & FIRING RATE

Intrinsically, for example, the SA node fires at a rate of 100-110 depolarizations per minute in adults as compared to a resting heart rate around 60 bpm. Vagal stimuli through action of acetylcholine slows down threshold action potentials of SA nodal cells (negative chronotropy) leading to a slower heart rate (HR). When HR increases positive sympathetic action (positive chronotropy) dominates over SA node firing potential, increasing the rate of depolarization of SA node cells.

Some drugs also influence SA nodal cells firing rate. For example, beta-blockers and similar beta adrenoceptor antagonists alter SA nodal activity causing bradycardia. While, digitalis alkaloid drugs causes inhibition of sodium/potassium ATPase pump slowing down the conduction in the AV node and increasing its refractory period.

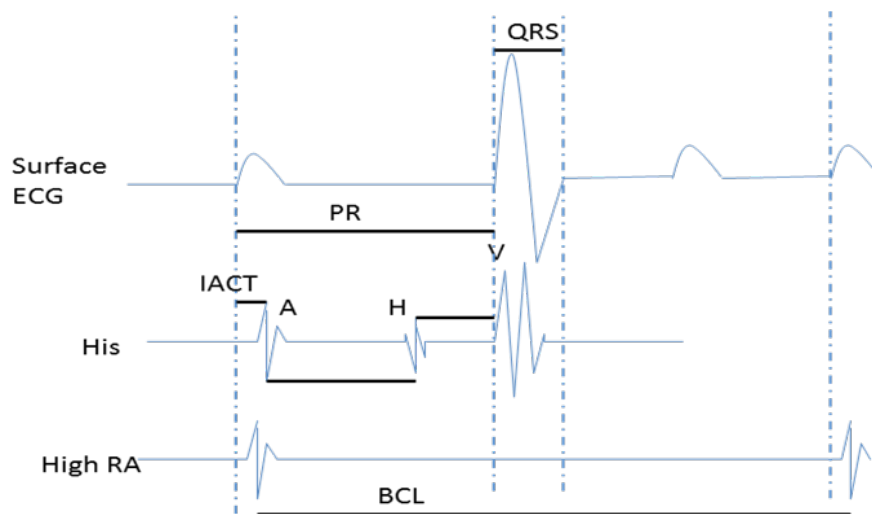


Fig. 2: Characteristics of baseline recordings of intracardiac electrogram with the reference to surface ECG (top) following by conduction intervals for His-bundle and basic cycle length interval (BCL). BCL is the interval between successive A waves; PR interval is the time from the start of the P wave until the beginning of the QRS complex; IACT (intraatrial conduction time) is the timing from the SA node to the AV node and is measured from the beginning of the P wave (surface ECG) to the A deflection on His electrogram. AH interval is characterized by slow depolarization of AV nodal tissue with no other high frequency signal, until H spike. The HV interval is characterized by the impulse spreading into ventricle myocardium until V deflection that is depolarization of ventricle muscle near the catheter.

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Electric potential precedes cardiac muscle tension development in time. As the frequency of cardiac contraction increases there is progressive reduction of action potential and cardiac contraction. Action potentials also vary within the heart and 2 main responses are recognized:

- Fast action potentials which rely on Purkinje fibers
- Slow action potentials which are found in SA-AV conduction system (Internodal pathway conduction).

AUTOMATICITY

Cardiac action potential of SA node delivers frequency firing at its intrinsic rate. Automaticity of SA node also known as pacemaker rate can be tested and recorded using pacing catheters. Its rate can be overridden by firing at a rate that is different (often faster) than the SA intrinsic rate. Electric impulse coming from pacing catheter before the SA node peacemaking potential threshold is reached will override but also suppress the SA node activity. In the lab the override is accomplished by rapidly pacing the RA (Transonic-Scisense EP catheter at high position) and then turning off the pacing catheter waiting to see how long it takes to recover the SA node pacing activity. In disease states this time of recovery will be longer as compared to healthy hearts.

Overdrive suppression is the method by which cells localized in SA node effectively suppress other cells localized within the AV node or within the ventricular conduction system. These cells also possess the pacemaker activity but become suppressed by more rapid firing of SA nodal pacemakers. On cellular level this is happening when sodium entry into these secondary pacemakers enters at high levels per unit of time as these cells are hyperpolarized when driven above their intrinsic firing rate. On the other hand, if secondary pacemakers take over the primary SA pacemaker, this situation is called ectopic foci. The SA node becomes suppressed as the secondary pacemakers takes over at their firing rate capacity.

CONDUCTION VELOCITY

Conduction velocity is related to the speed of conduction of an electric signal across the myocardium which, in turn, is directly related to depolarization phase of action potential of individual cardiac cell. By using a pacing catheter and its ability to capture localized electrical signals, measuring the time that it takes for an impulse to travel from one location of the myocardium to another (conduction interval) assessment of conduction velocities of innate portion of myocardium can be provided.

One of the conduction velocity measurements can be done by assessing the His bundle electrogram as it controls all AV conduction system components. Pacing catheter is localized posterior of tricuspid valve. His electrogram (Fig. 3) contains deflection (A) i.e. depolarization of low RA, and then impulse enters the His and AV node and slows down due to lack of rapid sodium channels. No high frequency conduction signal is captured as signals passes through His bundle and AV node and signals further passes into distant Purkinje fibers and through myocardium, producing final deflection (V) on His electrogram. The interval (H) to (V) corresponds to conduction time through His-Purkinje system and lasts 35-55 msec in humans. The conduction (A) deflection to (H) deflection is called AV node conduction velocity interval and lasts 50-120 msec. The highest velocities are recorded from Purkinje fibers and the lowest from the AV node.

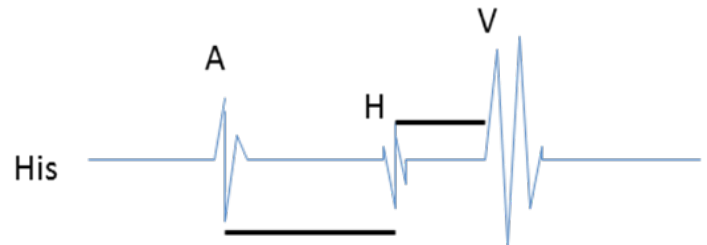


Fig. 3: His bundle electrogram has 3 characteristic deflections A spike, H spike and V deflection. A deflection characterizes low-RA area depolarization, H bundle deflection describes bundle branches depolarisation until Purkinje fibers and finally V deflection is created when impulse spreads into ventricular myocardium. For more information about conduction velocity intervals see ref (1).

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REFRACTORY PERIODS (RP)

The refractory period is time during which myocardial cells cannot be depolarized. The refractory period approximately corresponds with the duration of the action potential. There are several types of RP.

Effective RP (ERP) is a period of time that a new action potential cannot be initiated. It describes the situation: "if the premature impulse be any later, native myocardium would recover and propagate the impulse". This timing of refractoriness (un-excitability) to the new action potential is an innate cardiac trait. This refractoriness (resistance to propagate electrical signal) has at least two major functions: it allows the cardiac chambers adequate time to fill and prevents against development of titanic contractions (as known to occur in skeletal muscle).

Relative RP (RRP) describes the situation when a myocardial cell has the potential to be repolarized, but the stimuli must be stronger than what is normally needed when the myocardial cell is at rest. On a cellular level it is due to an incomplete recovery of ionic balance by the sodium channels to the final resting state. Resultant action potentials have slower conduction velocity due to the electrical potential that is progressively coming down to the resting state of polarization.

Both periods (ERP and RRP) can be related to the duration of action potential as oppose to the functional refractory periods (FRP) which relates to the smallest possible intervals in-between the action potentials (impulses conducted) through myocardium. FRP measures both the conductivity and refractoriness of myocardium.

Programmed Electrical Stimulation (PES) Pacing

Basic pacing techniques:

- Burst Pacing refers to short duration of pacing stimuli at constant rate. Generally used to terminate or induce arrhythmias.
- Overdrive pacing is delivered at the constant rate throughout all stimulation that is faster than baseline cardiac rhythm.
- Stepwise rate pacing is delivered in series (steps) at given rate with intervening breaks. Before increase to the next rate (next step), pacing has to be maintained at that step for at least 15 seconds to accommodate the tissue to conduct electrical impulse that is also affected by innate cardiac rate or preceding basic cycle length (BCL).
- Ramp pacing gradual decrease of BCL the without intervening pauses that is used in antitachycardial pacing. Block in the tissue conductivity can be found more precisely. Prolonged ramp pacing might induce hypotension.

EXPERIMENTAL PES IN RODENTS

In the animal setting, PES is sometimes performed as survival procedures using sterile surgeries, but increasingly rodent EP models are used in terminal setting. In rodent intracardiac PES set-up, the right atrium (RA) position is used most commonly (2, 3). At this setting the EP catheter is inserted into the RA through right jugular vein catheterization.

EP catheter delivers pacing stimulation by isolated constant current using output at twice the diastolic threshold. The threshold is determined by the lowest captured value in late diastole (1). Pacing threshold should be determined for each cycle length. Cardiac stimulation uses pulse of electrical current via the electrode catheter that becomes "the external pacemaker" to the myocardial tissue. This electrical impulse stimulates (depolarizes) the myocardium close to the pacing electrodes while propagates throughout the whole myocardium. Programmable stimulator ensures that these pacing impulses are precisely timed for each animal species.

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To demonstrate on the experimental example of pacing and captures, the typical stimulator has a stable current and is capable of pacing with wide variety of current strengths (0.1-10 mA) and pacing amplitude widths (0.1-10 milliseconds). Rodent RA pacing is usually first performed by 2 ms current at basic cycle length (BCL) of at least 50 stimuli to test consistency of the stimuli capture. A recovery period of at least 25-30 seconds is allowed between each stimulation protocol.

- Measure vulnerability to arterial arrhythmias by decreasing the intrinsic BCL (3,4).
- Measure sinus node recovery time (SNRT) using 15 second atrial pacing at BCL of 100 ms (5). The recovery time is based on last pacing stimulus train after which measurement of first spontaneous sinus beat occurs.
- Measure effective atrial refractory period (AERP) using a series of atrial pacing trains at fixed BCL (e.g. 100ms) coupled with premature extra stimulus. The inter-train interval is systematically reduced by 2 ms each time (e.g. from 70ms to 20ms). AERP is the longest atrial coupling interval that failed to generate a propagated extra-stimulus beat (5).
- Measure effective refractory period of the atrioventricular node (AVNERP) using a series of atrial pacing trains at fixed BCL (e.g. 100ms) coupled with premature extra stimulus. The inter-train interval is systematically reduced by 2 ms each time (e.g. from 70ms to 20ms). AVNREP is the longest train-extra stimulus coupling interval at which the premature beat delivered to atria is followed by His potential but not by QRS complex (5).

REFERENCES

- (1) Clinical Arrhythmology and Electrophysiology : A Companion to Braunwald's Heart Disease by Douglas P. Zipes, Ziad Issa and John M. Miller (2012, Hardcover) Author: John M. Miller, Douglas P. Zipes, Ziad Issa ISBN-10: 1455712744, ISBN-13: 9781455712748
- (2) Jiao KL, Li YG, Zhang PP, Chen RH, Yu Y. Effects of valsartan on ventricular arrhythmia induced by programmed electrical stimulation in rats with myocardial infarction. *J Cell Mol Med.* 2012 Jun;16(6):1342-51.
- (3) Luo X, Pan Z, Shan H, Xiao J, Sun X, Wang N, Lin H, Xiao L, Maguy A, Qi XY, Li Y, Gao X, Dong D, Zhang Y, Bai Y, Ai J, Sun L, Lu H, Luo XY, Wang Z, Lu Y, Yang B, Nattel S. MicroRNA-26 governs profibrillatory inward-rectifier potassium current changes in atrial fibrillation. *J Clin Invest.* 2013 May 1;123(5):1939-51.
- (4) Mathur N, Sood S, Wang S, van Oort RJ, Sarma S, Li N, Skapura DG, Bayle JH, Valderrábano M, Wehrens XH. Sudden infant death syndrome in mice with an inherited mutation in RyR2. *Circ Arrhythm Electrophysiol.* 2009 Dec;2(6):677-85.
- (5) Li N, Wehrens XH. Programmed electrical stimulation in mice. *J Vis Exp.* 2010 May 26;(39). 1730.



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