Basic Properties And Clinical Applications Of The Intracardiac

Francesco Zanon,¹ Lina Marcantoni,¹ Gianni Pastore,¹ Enrico Baracca,¹ Silvio Aggio,² Franco Di Gregorio,³ Biol.Sc D, Alberto Barbeta,³ Mauro Carraro,² Claudio Picariello,² Luca Conte,² Loris Roncon²

¹Arrhythmia and Electrophysiology Unit. ²Dept of Cardiology, Santa Maria della Misericordia General Hospital, Rovigo, Italy. ³Clinical Research Unit, Medico Spa, Rubano (Padova), Italy.

Abstract

The electric signals detected by intracardiac electrodes provide information on the occurrence and timing of myocardial depolarization, but are not generally helpful to characterize the nature and origin of the sensed event. A novel recording technique referred to as intracardiac ECG (iECG) has overcome this limitation. The iECG is a multipolar signal, which combines the input from both atrial and ventricular electrodes of a dual-chamber pacing system in order to assess the global electric activity of the heart. The tracing resembles a surface ECG lead, featuring P, QRS and T waves. The time-course of the waveform representing ventricular depolarization (iQRS) does correspond to the time-course of the surface QRS with any ventricular activation modality. Morphological variants of the iQRS waveform are specifically associated with each activity pattern, which can therefore be diagnosed by evaluation of the iECG tracing. In the event of tachycardia, SVTs with narrow QRS can be distinguished from other arrhythmia forms based upon the preservation of the same iQRS waveform recorded in sinus rhythm. In ventricular capture surveillance, real pacing failure can be reliably discriminated from fusion beats by the analysis of the area delimited by the iQRS signal. Assessing the iQRS waveform correspondence with a reference template could be a way to check the effectiveness of biventricular pacing, and to discriminate myocardial capture alone from additional His bundle recruitment in para-Hisian stimulation.

The iECG is not intended as an alternative to conventional intracavitary sensing, which remains the only tool suitable to drive the sensing function of a pacing device. Nevertheless, this new electric signal can add the benefits of morphological data processing, which might have important implications on the quality of the pacing therapy.

Introduction

The intracardiac electrograms recorded in right atrium and ventricle (AEGM, VEGM) play a pivotal role in permanent cardiac pacing and defibrillation, as pacing inhibition or shock administration fully rely on the detection of myocardial intrinsic depolarization. To maximize sensing specificity, bipolar lead technology has been developed and suitable band-pass filtering is applied. As a result, conventional AEGM and VEGM are mostly sensitive to local activity, restricted to the area surrounding the tip electrode, and the provided information is limited to the occurrence and timing of a sensing event¹. With this approach, indeed, any activation pattern gives rise to similar signals and no discrimination is possible between AV conduction and ectopic generation of the sensed beat.

Although the electric therapy regulation still remains the most important task, electrogram recording has become, in addition, a source of diagnostic information on the incidence and nature of cardiac arrhythmias. In dual-chamber devices, supraventricular and ventricular tachycardias (SVTs, VTs) can be distinguished from the presence or absence of a relationship between atrial and ventricular

signals.²⁻⁴ However, the morphological evaluation of ventricular waveforms can add further insight, and is feasible even with a single-chamber stimulator. To this purpose, the electrogram filter bandwidth must be enlarged and the sensitivity to remote phenomena increased, at the expense of specificity. Normally, the electrograms used by the sensing algorithms are high-pass filtered, while those recorded for diagnostic applications include lower frequency components. Some ICDs offer in addition the possibility to record “far-field electrograms” between the defibrillation coil and the stimulator can, besides the standard “near-field signals” derived by the pacing electrodes, in the aim to better recognize wide and narrow QRS complexes, which in turn would orient the diagnosis toward a VT or SVT, respectively^{5,6}.

An alternative approach to far-field sensing, which can be accomplished in pacemakers and ICDs as well, has recently been developed and referred to as intracardiac ECG (iECG)⁷⁻¹⁰. The iECG tracing closely resembles a surface ECG lead, featuring striking different waveforms in case of physiological AV conduction along the His-Purkinje pathway, left or right bundle branch block (LBBB, RBBB), idioventricular rhythm or ectopic ventricular beats (PVC). If the ventricle is paced, the ventricular component of the iECG depends on the stimulation target, which can therefore be identified. In the event of a tachycardia, the iECG allows reliable discrimination of VTs and SVTs, providing in addition detailed information on pre-excitation and retrograde AV conduction^{7,8}.

The main properties of the iECG and its actual and potential applications in the clinical setting are reviewed in the present paper.

Key Words

Cardiac electrograms, Fusion detection, Hisian pacing, CRT

Corresponding Author:

Francesco Zanon*,
Dept of Cardiology,
Santa Maria della Misericordia General Hospital,
Rovigo,
Italy.

The intrinsic intracardiac ECG

The iECG is a multipolar electric signal derived by the set of electrodes used in bipolar dual-chamber pacing. It is available in the most recent DDD, single-lead VDD, and CRT-P devices by Medico (Padova, Italy). The voltage detected by each electrode is weighted by an impedance network in order to balance the near and far field

Figure 1:

From top to bottom: surface ECG leads I, II, III, pacemaker event markers (As: atrial sensing; Vs: right ventricular sensing), intracardiac ECG (iECG, scaled in arbitrary units). The same tracings are displayed in the next figures. Sinus rhythm with intrinsic AV conduction and narrow QRS. Surface QRS and iQRS feature a similar time-course (iQRS onset and trailing edge are marked by dashed vertical lines). Full description in the main text.

components and summed to provide a waveform which reflects the global electric activity of the heart. The information reported in the literature so far, as well as our Center experience, refer to pacing systems where the atrial lead was positioned in right appendage and the right ventricular lead was either in the apex, mid to high septum, or para-Hisian region^{9,10}. In addition, the iECG was recorded in the presence of different tachycardias during EP studies, by means of temporary leads positioned in ventricular apex and high right atrium, connected with an external device.^{7,8}

Figure 2:

Sinus rhythm and intrinsic AV conduction with (A) LBBB and (B) RBBB. The iQRS onset and trailing edge are marked by dashed vertical lines. Note the prolonged latency between the iQRS onset and the ventricular sensing marker (*) in the presence of RBBB.

Figure 3:

First degree AVB ($PQ = 304 \pm 2$ ms). The iQRS features different specific morphology in case of AV conduction (*) or each of two PVC types (**, ***). Note the overlapping of PVCs and previous iP waveforms

In all tested conditions, the iECG signal typically comprises the 3 components of a surface ECG lead, i.e.: atrial depolarization (iP) and ventricular depolarization (iQRS) and repolarization (iT). Figures 1 and 2 compare the iECG with the corresponding surface ECG in different patients with RV apical (Fig. 1 and 2B)

Figure 4:

Linear relationship between surface QRS and iQRS duration in 13 patients. Ventricular pacing and different kinds of intrinsic activity (AV conduction with narrow QRS, LBBB, RBBB, PVCs) are pooled in the same plot, for a total of 30 paired determinations. The global least square line demonstrates a high correlation, with slope and intercept close to 1 and 0, respectively, indicating that the two variables are equivalent.

or septal implantation (Fig. 2A). All recordings refer to intrinsic AV conduction in sinus rhythm. In such conditions, discrimination of iP and iQRS is easy, as iP is the first deflection and generally corresponds to a biphasic or negative waveform. With cardiac rate increase and especially in case of a re-entry tachycardia, the iP-iQRS temporal sequence might result no more apparent and the iP shape can change. In such instances, cross-matching with the near-field event markers is advisable for prompt iP and iQRS recognition. Combining iECG and event markers evaluation is also helpful in bundle branch diagnosis. Fig. 1 shows a case with narrow QRS (98 ± 5 ms; mean $\pm$ SD in five consecutive beats) and iQRS (97 ± 5 ms), where the iQRS onset precedes the ventricular sensing marker by 45 ± 3 ms. The iQRS peak occurs close to the marker, which indicates

Figure 5:

Para-Hisian pacing with myocardial capture only. The emission of a pacing pulse is marked as Vp. A: threshold test in VVI (90 bpm). The third spike is ineffective and no electric signal but the stimulation artifact is detected on the iECG tracing. The fourth spike is ineffective as well, though it falls right at the onset of a QRS complex, as both the surface ECG and the iECG feature their intrinsic conduction pattern and the ventricular activity is preceded by a sinus P-wave (*). The iECG ventricular signal is different in the presence of capture (1st and 2nd cycles; note the iQRS peak saturation with the applied gain) and in this patient it shows a fast deflection at the beginning of the iT-wave, indicating pacing-induced retroconduction (). B: VDD pacing with 200 ms AV delay. This interval is quite similar to the intrinsic PR detected by the pacemaker, so that pacing inhibition takes place in the 2nd and 3rd cycle. In contrast, a pacing pulse is released in the 1st and 4th cycles, resulting in pseudofusion. The intrinsic iQRS is detected in all instances. In addition, it is noteworthy that the P-wave recorded in the 2nd cycle (***) is different from the sinus P-waves (*) both on the iECG and the surface ECG leads.**

the time of RV apex activation. Conduction with LBBB (Fig. 2A) is characterized by a wide iQRS (150 ± 7 ms) featuring a short latency (35 ± 5 ms) from its onset to the sensing marker (representing septal activation in this case). The opposite is observed with RBBB (Fig. 2B), where both the onset and main peak of a wide iQRS (130 ± 2 ms) precede the sensing marker (70 ± 4 and 30 ± 3 ms latency,

Figure 6:

Same case as in Fig. 5. VDD pacing with AV delay of 150 ms (A), 100 ms (B) and 50 ms (C), with correspondingly lower degree of fusion. Sequential atrium-driven pacing removed the fast deflection following the paced iQRS in VVI (Fig. 5), confirming that it actually was a retrograde P-wave.

respectively, in the reported example).

The iQRS waveform is highly sensitive to the pattern of ventricular activity. The signal shape, amplitude and duration are substantially modified when the intrinsic AV conduction is interrupted by ectopic ventricular beats. In the presence of PVCs originating from more than one site, correspondingly different iQRS subtypes are noticed (Fig. 3). With any ventricular activation modality (AV conduction with or without bundle branch block, idioventricular rhythm, or PVCs), the iQRS width closely reflects the duration of the surface QRS (Fig. 4). Relying on these properties, the iECG has been proposed as a tool to discriminate SVTs with narrow QRS from other tachyarrhythmias (VTs or wide complex SVTs). During EP studies, all SVT episodes with narrow QRS exhibited a iQRS waveform similar to the signal recorded in sinus rhythm, while all VTs were characterized by a widened iQRS, morphologically different from the sinus rhythm reference.⁷ The information gained from the analysis of either the iECG or the surface ECG tracings had a comparable diagnostic value.

The paced intracardiac ECG

Myocardial ventricular pacing entails electromechanical desynchronization, which can lead to detrimental effects on ventricular function.¹¹⁻¹⁴ Though careful selection of the best stimulation site in each patient can reduce these adverse effects, QRS axis and duration are unavoidably affected by ventricular pacing, unless a substantial fusion of paced and intrinsic conduction occurs.¹⁵⁻¹⁹ Since the iECG is sensitive to any change in the electric activity of the heart, the signal can be applied as a surrogate of the surface ECG to distinguish fully evoked beats from fusions or capture failure in implanted devices.

Single-site myocardial pacing

A comparison of the iECG waveform recorded with ventricular pacing or intrinsic AV conduction is provided in Fig. 5, which refers to a case of para-Hisian implantation where only septal-myocardial stimulation was achieved. Panel A shows a ventricular threshold test with two paced beats, followed by two ineffective spikes. Capture or pacing failure are promptly recognized, either in absence or presence of spontaneous activity. In the former case, no electric activity but the pacing artifact is recorded (3rd pulse); in the latter, the spike is associated with a different iQRS waveform, featuring the typical intrinsic conduction pattern.

If a threshold assessment routine is in progress, the capture loss can be diagnosed with the same morphological approach usually applied to the surface ECG. Panel B shows VDD pacing in the same patient, with the AV delay set very close to the intrinsic PR interval (200 ms). Ventricular stimulation was inhibited in some cycles and not in others, where the spike was delivered in the late portion of the intrinsic QRS, just preceding the expected sensing. A condition of this type would easily produce false alarms of pacing failure in most capture surveillance systems relying on the detection of intracavitary evoked potentials, as the residual signal after the end of the stimulation artifact is very small. The iQRS, in contrast, is detected since the beginning of the QRS complex, even before the spike release.

The effect of progressive AV delay shortening, with corresponding reduction in fusion degree, is shown in Fig. 6. Morphological modifications in the iQRS were described as changes in the area under the waveform, measured by off-line data processing in the attempt to simulate a potential pacemaker algorithm. The iQRS area was assessed in the interval from 30 ms before to 70 ms after

Figure 7:

Same case as in Fig. 5. VDD pacing with AV delay set at 200 ms (A) and 100 ms (B, C). In panel A, ventricular sensing (Vs) and pseudofusion (Vp) alternates in two consecutive cycles. Panel B and C show, respectively, effective stimulation with fully evoked QRS and capture loss, followed by intrinsic conduction. The area delimited by the iQRS waveform was measured in the interval from 30 ms before to 70 ms after the ventricular marker (dashed lines), considering the absolute value of the voltage and removing the stimulation artifact by a 20 ms blanking triggered by the spike (lowest tracing). Note that the iQRS area is much smaller in C than in any other condition, pseudofusion included.

a sensing or pacing marker, blanking the signal to 0 in the 20 ms following a spike to exclude the stimulation artifact (Fig. 7). The results were finally expressed as the ratio between the average areas of paced and intrinsic waveforms, at various AV delays (Fig. 8). The paced waveform area exceeded that measured with intrinsic AV conduction (ratio > 1) in case of fusion (150 ms AV delay) or fully evoked QRS (100 ms AV delay). In the presence of pseudofusion (200 ms AV delay ending with spike emission), the area was lower with pacing than with intrinsic conduction (ratio < 1), since the 20

Figure 8:

The histogram represents the area under the iQRS signal measured with different AV delays in VDD pacing mode. Data derived from the tracings shown in Fig. 5 and 6 are expressed as the ratio between the average area of the paced and sensed waveforms, $\pm$ the standard error of the quotient according to the error propagation theory. Both effective and ineffective stimulation (with pulse amplitude set just below the threshold) were performed at 100 ms AV delay.

Figure 9:

Pacing lead in the Hisian region in a patient with 2:1 AV block. A: VVI mode with basic rate of 30 bpm (A), resulting in pacing inhibition. Though ventricular markers only are displayed, iP-waves are easily recognized on the iECG (*). In addition, hidden IP-signals are likely fused with the iT waveform, which shows remarkable beat-to-beat variability (**). B: VVI pacing at 60 bpm, with capture of the His bundle. Both the iECG and the surface ECG feature the same ventricular complex as in panel A, demonstrating that the physiological conduction pattern was maintained.

ms blanking triggered by the spike removed part of the ventricular signal. Nevertheless, the iQRS area was about 10-times higher in case of pseudofusion than with real pacing failure independent of tissue refractoriness (to assess the effects of capture loss in the absence of intrinsic activity, the AV delay was set at 100 ms and the ventricular pulse amplitude was temporarily reprogrammed just below the threshold). As all types of ventricular activity, including fusion and pseudofusion, entail a iQRS signal featuring a wide safety margin

Figure 10:

Pacing lead in the para-Hisian region. Ventricular threshold test in VVI: all the spikes are effective, but the QRS complex suddenly changes during the energy scan, when Hisian capture is lost and fusion is replaced by pure myocardial stimulation. The iQRS waveform is consistently modified (duration 95 ± 3 ms and 110 ± 5 ms, respectively, in presence or absence of Hisian recruitment). At the same time, the sinus P-waves (*) are replaced by retroconduction (**).

Figure 11:

DDD pacing with (A): bipolar right ventricular stimulation; (B): unipolar left ventricular stimulation; (C): biventricular stimulation; in a chronic biventricular implant. The iQRS waveform is different in each ventricular activation modality, featuring a duration of 248, 256, and 170 ms in panel A, B and C, respectively.

versus the “no response” condition, the iECG can be proposed as an alternative tool in capture monitoring, preventing the undue increase in pacing energy caused by fusion-related false alarms²⁰⁻²³.

His bundle pacing

The only pacing technique which can preserve the physiological ventricular activation pattern is the stimulation of the His bundle^{24,25}. When this approach is fully successful and direct His bundle pacing is achieved, the paced QRS complex is unaltered with respect to intrinsic conduction in every surface ECG lead. This principle applies to the iECG as well (Fig. 9), which can provide therefore valuable insight on the actual effects of a stimulation performed in the Hisian region. Indeed, in case of para-Hisian capture, only the myocardium is paced at low energy and both the QRS and iQRS complexes are wide, with no latency between the spike and the Q-wave. At increased output, the additional recruitment of the His bundle is achieved, with corresponding QRS and iQRS narrowing and more physiological axis orientation^{26,27}. In this case, the issue is not the presence or absence of an electric response, but its nature and quality. Standard capture recognition methods are useless, as they are designed to detect any signal representing active myocardial depolarization, independent of the paced substrate. The iQRS waveform, in contrast, changes in shape, amplitude and duration according to the kind of ventricular activity, and is therefore much better suited to the discrimination of myocardial stimulation from the fusion of myocardial and Hisian responses (Fig. 10). This might have a relevant impact in the clinical setting, as the safety margin applied to ensure myocardial capture could be too small for reliable Hisian pacing. On the other hand, permanent high energy stimulation would strongly reduce the stimulator expected life. The analysis of the iECG represents an intriguing alternative, allowing His-bundle capture monitoring either beat by beat or at proper time interval, in the aim of keeping the pulse amplitude just above the Hisian threshold.

Biventricular pacing and CRT

Similar considerations apply to biventricular pacing, where reliable

dual-side capture should be achieved with the lowest possible energy expense. As quite different iQRS waveforms are recorded in the presence of right-, left-, or bi-ventricular stimulation (Fig. 11), a device could regulate the pacing parameters in both ventricles in order to maintain the electric evoked response close to the reference template, representing actual and properly timed biventricular activity. This strategy would allow checking the stimulation effectiveness in both right and left ventricle, as well as managing the AV and VV delays according to the intrinsic conduction timing. If fully evoked biventricular activity is the clinical goal, the iECG-based information could be useful to prevent fusions, which might alter the interventricular relationship and reduce the therapy effect in non-responding patients.²⁸ Conversely, in other instances fusion is the aim, as for single-side left ventricular stimulation synchronized to right ventricular intrinsic conduction in LBBB patients.²⁹⁻³² Significant synchronization impairment would modify the iQRS waveform, thereby prompting the necessary AV delay adjustment.

Clinical Implications

The iECG properties make it suitable to morphological characterization, similarly to a surface ECG lead. At present, the tracing interpretation requires the evaluation of an observer, who must compare the recorded signal with the reference stored in the pacemaker memory. In the event of tachycardia, the iECG is automatically acquired and can help exclude a VT, provided that the iQRS waveforms are similar in sinus rhythm and tachycardia as well. The reliability of this approach has been confirmed by previous studies, which suggested in addition a possible application in the automatic control of shock delivery by an ICD.^{7,8}

The iECG has proved a valuable diagnostic tool in the analysis of the patient's rhythm, which can complement the surface ECG by emphasizing the relationship between atrial and ventricular events, with special regard to retroconduction.^{9,10} The potential applications in capture surveillance (with fine discrimination of fusion beats from real failure), in para-Hisian pacing (to recognize true Hisian capture from myocardial stimulation), and in biventricular pacing (to check the suitability of stimulation energy and timing) still require the development of dedicated algorithms of waveform processing, which should be run by the device during independent routine operation. This is a realistic goal, since clear-cut waveform changes are expected on the basis of the available preliminary evidence. Such autoregulation mechanisms would have a great impact in the clinical setting, ensuring the stimulation of the appropriate target and reducing the incidence of false alarms of capture loss, which still affect the performance of most capture monitoring systems by inducing a useless increase in energy consumption.²¹⁻²³ As the care for the quality of the pacing therapy is progressively rising, the strategic relevance of advanced control tools like the iECG correspondingly grows.

Conclusion

The iECG is a method of multipolar recording of the electric cardiac activity, which provides a tracing with properties similar to a surface ECG lead by means of the implanted electrodes used in dual-chamber pacing. The waveform changes according to the ventricular activation pattern, allowing to distinguish intrinsic AV conduction from ectopic beats, as well as evoked responses induced by different pacing modalities. This new cardiac signal can discriminate VT from SVT episodes and could drive the automatic recognition of ventricular pacing failure with special sensitivity to fusion and pseudofusion. It

might be applied, in addition, to the autoregulation of Hisian/para-Hisian and biventricular stimulation, substantially contributing to the progress of the pacing technology.

Disclosures

None.

References

1. Irnich W. Intracardiac electrograms and sensing test signals: Electrophysiological, physical, and technical considerations. *Pacing Clin Electrophysiol.* 1985; 8: 870-888.
2. Glikson M, Swerdlow CD, Gurevitz OT, Daoud E, Shivkumar K, Wilkoff B, Shipman T, Friedman PA. Optimal combination of discriminators for differentiating ventricular from supraventricular tachycardia by dual-chamber defibrillators. *J Cardiovasc Electrophysiol.* 2005; 16: 732-739.
3. Francia P, Balla C, Uccellini A, Cappato R. Arrhythmia detection in single- and dual-chamber implantable cardioverter defibrillators: The more leads, the better? *J Cardiovasc Electrophysiol.* 2009; 20: 1077-1082.
4. Stambler BS. ICD arrhythmia detection and discrimination algorithms: whose is best? *J Cardiovasc Electrophysiol.* 2012; 23: 367-369.
5. Theuns DA, Rivero-Ayerza M, Goedhart DM, Miltenburg M, Jordaens LJ. Morphology discrimination in implantable cardioverter-defibrillators: Consistency of template match percentage during atrial tachyarrhythmias at different heart rates. *Europace.* 2008; 10: 1060-1066.
6. Jiménez-Candil J, Anguera I, Ledesma C, Fernández-Portales J, Morínigo JL, Dallaglio P, Martín A, Cano T, Hernández J, Sabaté X, Martín-Luengo C. Morphology of far-field electrograms and antitachycardia pacing effectiveness among fast ventricular tachycardias occurring in ICD patients: A multicenter study. *J Cardiovasc Electrophysiol.* 2013; 24: 1375-1382.
7. Pandozi C, Di Gregorio F, Lavallo C, Ricci RP, Ficili S, Galeazzi M, Russo M, Pandozi A, Colivicchi F, Santini M. Electrical and hemodynamic evaluation of ventricular and supraventricular tachycardias with an implantable dual-chamber pacemaker. *JAFIB.* 2014; 7: 17-22.
8. Pandozi C, Ricci R, Lavallo C, Ficili S, Galeazzi M, Russo M, Pandozi A, Di Gregorio F, Biasiolo M, Santini M, Colivicchi F. Tachyarrhythmia assessment with an implantable cardiac stimulator (Abs). *Cardiostim 2014 - EHRA Europace.* Nice, France, June 18-21, 2014. *Europace.* 2014; 16 Suppl. 2: 56P/38.
9. Zanon F, Baracca E, China P, Corrado A, Pastore G, Gasparini G, Barbetta A, Di Gregorio F. Benefits of iECG application in the assessment of pacing effectiveness (Abs). *XVI International Symposium on Progress in Clinical Pacing.* Rome, Italy, December 2-5, 2014. Abstract book. 2014: 105.
10. Zanon F, Gasparini G, Baracca E, Pastore G, Corrado A, China P, Barbetta A, Di Gregorio F. The intracardiac ECG: a new approach to the assessment of electrical cardiac activity by an implantable pacing device. *Venice Arrhythmias 2015.* Venice, Italy, October 16-18, 2015. *JAFIB.* 2015; October Special Issue: Section "Pacemaker: Technical, Procedural and Clinical Issues".
11. Thambo JB, Bordachar P, Garrigue S, Lafitte S, Sanders P, Reuter S, Girardot R, Crepin D, Reant P, Roudaut R, Jais P, Haissaguerre M, Clementy J, Jimenez M. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation.* 2004; 110: 3766-3772.
12. O'Keefe JH Jr, Abuissa H, Jones PG, Thompson RC, Bateman TM, McGhie AI, Ramza BM, Steinhaus DM. Effect of chronic right ventricular apical pacing on left ventricular function. *Am J Cardiol.* 2005; 95: 771-773.
13. Manolis AS. The deleterious consequences of right ventricular apical pacing: time to seek alternate site pacing. *Pacing Clin Electrophysiol.* 2006; 29: 298-315.
14. Zhang XH, Chen H, Siu CW, Yiu KH, Chan WS, Lee KL, Chan HW, Lee SW, Fu GS, Lau CP, Tse HF. New-onset heart failure after permanent right ventricular apical pacing in patients with acquired high-grade atrioventricular block and normal left ventricular function. *J Cardiovasc Electrophysiol.* 2008; 19: 136-141.
15. Kypta A, Steinwender C, Kammier J, Leisch F, Hofmann R. Long-term outcomes in patients with atrioventricular block undergoing septal ventricular lead implantation compared with standard apical pacing. *Europace.* 2008; 10: 574-579.
16. Ng AC, Allman C, Vidaic J, Tie H, Hopkins AP, Leung DY. Long-term impact of right ventricular septal versus apical pacing on left ventricular synchrony and function in patients with second- or third-degree heart block. *Am J Cardiology.* 2009; 103: 1096-1101.
17. Cano O, Osca J, Sancho-Tello MJ, Sánchez JM, Ortiz V, Castro JE, Salvador A, Olague J. Comparison of effectiveness of right ventricular septal pacing versus right ventricular apical pacing. *Am J Cardiology.* 2010; 105: 1426-1432.
18. Alhous MHA, Small GR, Hannah A, Hillis GS, Broadhurst P. Impact of temporary right ventricular pacing from different sites on echocardiographic indices of cardiac function. *Europace.* 2011; 13: 1738-1746.
19. Shimony A, Eisenberg MJ, Filion KB, Amit G. Beneficial effects of right ventricular non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials. *Europace.* 2012; 14: 81-91.
20. Lau C, Cameron DA, Nishimura SC, Ahern T, Freedman RA, Ellenbogen K, Greenberg S, Baker J, Meacham D. A cardiac evoked response algorithm providing threshold tracking: a North American multicenter study. *Pacing Clin Electrophysiol.* 2000; 23: 953-959.
21. Candinas R, Liu B, Leal J, Sperzel J, Fröhlig G, Scharf C, Duru F, Schüller H. Impact of fusion avoidance on performance of the automatic threshold tracking feature in dual chamber pacemakers: A multicenter prospective randomized study. *Pacing Clin Electrophysiol.* 2002; 25: 1540-1545.
22. Sperzel J, Kennergren C, Biffi M, Smith M, Knops M, Gill J, Boland J. Clinical performance of a ventricular automatic capture verification algorithm. *Pacing Clin Electrophysiol.* 2005; 28: 933-937.
23. Biffi M, Sperzel J, Martignani C, Branzi A, Boriani G. Evolution of pacing for bradycardia: Autocapture. *European Heart Journal Supplements.* 2007; 9: I23-I32.
24. Zanon F, Baracca E, Aggio S, Pastore G, Boaretto G, Cardano P, Marotta T, Rigatelli G, Galasso M, Carraro M, Zonzin P. A feasible approach for direct His bundle pacing using a new steerable catheter to facilitate precise lead placement. *J Cardiovasc Electrophysiol.* 2006; 17: 29-33.
25. Zanon F, Svetlich C, Occhetta E, Catanzariti D, Cantù F, Padeletti L, Santini M, Senatore G, Comisso J, Varbaro A, Denaro A, Sagone A. Safety and performance of a system specifically designed for selective site pacing. *Pacing Clin Electrophysiol.* 2011; 34: 339-347.
26. Zanon F, Barold SS. Direct His bundle and parahisian cardiac pacing. *Ann Noninvasive Electrocardiol.* 2012; 17(2): 70-78.
27. Sharma PS, Dandamudi G, Naperkowski A, Oren JW, Storm RH, Ellenbogen KA, Vijayaraman P. Permanent His-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. *Heart Rhythm.* 2015; 12: 305-312. <http://dx.doi.org/10.1016/j.hrthm.2014.10.021>
28. Hayes DL, Boehmer JP, Day JD, Gilliam FR III, Heidenreich PA, Seth M, Jones PW, Saxon LA. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm.* 2011; 8: 1469-1475. <http://dx.doi.org/10.1016/j.hrthm.2011.04.015>
29. van Gelder BM, Bracke FA, Meijer A, Pijls NHJ. The hemodynamic effect of intrinsic conduction during left ventricular pacing as compared to biventricular pacing. *J Am Coll Cardiol.* 2005; 46: 2305-2310.
30. Rao RK, Kumar UN, Schafer J, Vilorio E, De Lurgio D, Foster E. Reduced ventricular volumes and improved systolic function with cardiac resynchronization therapy: A randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing. *Circulation.* 2007; 115: 2136-2144.
31. Gage RM, Burns KV, Vatterott DB, Kubo SH, Bank AJ. Pacemaker optimization in nonresponders to cardiac resynchronization therapy: Left ventricular pacing as

- an available option. *Pacing Clin Electrophysiol.* 2012; 35: 685-694.
32. Boriani G, Gardini B, Diemberger I, Bacchi Reggiani ML, Biffi M, Martignani C, Ziacchi M, Valzania C, Gasparini M, Padeletti L, Branzi A. Meta-analysis of randomized controlled trials evaluating left ventricular vs. biventricular pacing in heart failure: effect on all-cause mortality and hospitalizations. *Eur J Heart Fail.* 2012; 14: 652-660.