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EDITORIALS

Interventricular septal or standard apical pacing in pacing dependent patients: still a dilemma?

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BACKGROUND

Permanent ventricular pacing for symptomatic bradycardia is one of those treatments proved to change the lives of numerous patients faced with a disease with high morbidity and mortality. Because of the important benefits of cardiac pacing in these patients, possible disadvantageous effects on cardiac function have only recently been recognized. Among possible ventricular pacing sites, right ventricular apex (RVA) has been selected as the conventional site. RVA site is easy accessible, allow safe and stable long-term pacing (1). More than 80 years ago, in 1925, Wiggers showed that RV pacing was associated with a reduction in left ventricular (LV) function (2,3,4).

Despite of important advantages, RVA pacing generates LV dyssynchrony, hemodynamic impairment, diastolic and systolic dysfunction with or without heart failure, especially for pacing dependent patients (5). This pacing site determines an abnormal contraction pattern bypassing normal conduction tissue (6).

LV dyssynchrony has important hemodynamic impact on LV function, with increased morbidity, mortality, risk of heart failure, and atrial fibrillation (7). This high risk of heart failure was observed even in patients with normal cardiac function before pacing (8).

The most important goal in cardiac pacing is to achieve a less eccentric, more physiological activation and timing patterns. In order to keep a normal cardiac function in patients with permanent ventricular pacing, an alternative pacing site might be superior to RVA (9). Septal RV pacing (IVS) might be an alternative site, because it is associated with shorter QRS duration than anywhere else in the RV (10) (Figure 1). ❑

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ANATOMIC CHANGES IN RVA PACING

RVA pacing bypasses the His-Purkinje system resulting in a LBBB like pattern on the surface ECG. In LBBB the activation of the RV precedes the LV, but on the normal way (11). During ventricular pacing, the impulse conduction occurs predominantly through the working myocardium. RV is first activated antero-apical, followed by trans-septal activation of the LV. The remaining part of the LV is activated slowly (12,13). The resulting electrical asynchrony generates a prolonged QRS duration due to slow myocardial conduction, greater then in the LBBB. The LV contraction is altered, and a significant inter- and intraventricular dyssynchrony may occur (14). The impact of pacing on ventricular activation pattern depends also on intrinsec conduction disturbance (15,16).

Ventricular dyssynchrony due to RVA pacing results in abnormal late activation of lateral wall, LV remodeling, asymmetric hypertrophy and redistribution of cardiac mass (17, 18), delayed papillary muscle activation with valvular insufficiency (19-21), increased left atrial diameter (22), and reduced myocardial perfusion and EF (23,24).

There are important redistribution of strain and coronary blood flow with RVA pacing. Early activated regions have ≈ 60% blood flow of late activated regions. The regions activated via the Purkinje system have greater fiber strain and blood flow (25,26). All these myocardial changes were observed to be present after more than 3 years (27). All important changes generated from RV pacing and the relationships between them are summarized in Table 1 and Figure 2. ❑

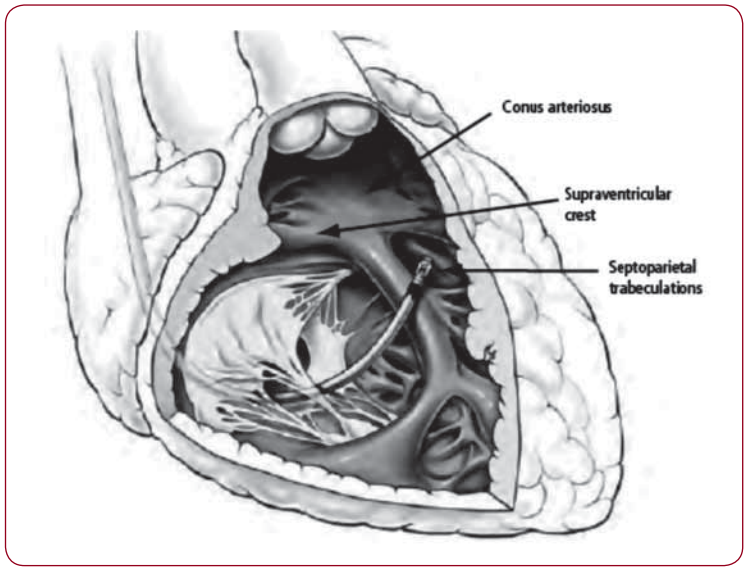

FIGURE 1. Illustration of the Right Ventricular Septal Anatomy. An active-fixation lead in the septal area is seen (adapted from McGavigan AD et al – *Curr Opin Cardiol* 2006; 21:7-14)

DEFINITION OF THE SEPTAL SITE

The RV septum is a relatively large area. Thus, the IVS pacing consists of a heterogeneous group of different pacing sites.

Giudici and Karpawich (28) defined the location of ventricular lead and the ECG generated patterns:

- RV Inlet Septum: "Above, on, or beneath the annulus of the septal/anterior tricuspid valve leaflets. Relatively normal QRS morphology and axis."
- RV Infundibular Septum: "Proximal to the pulmonic valve distal to, or near, the crista supraventricularis. Left bundle branch, vertical axis."
- RV Outflow Septum: "Near the septal/moderator band insertion at the mid-position on the right ventricular septum. Left bundle branch, vertical axis."
- RV Apical Septum: "Proximal to the septal/moderator band continuity that does not typically produce a vertical QRS axis."

By using the 2D echocardiography as the "gold standard" to visualize the exact pacing lead, Ng et al. defined different locations for IVS pacing sites.

The insertion sites for the RV pacing were visualized in the parasternal short-axis views, and were confirmed in the sub costal and apical views.

Septal anterior pacing was considered achieved if the tip of the pacing wire was seen inserting at the septoparietal trabeculations in the high ventricular or midventricular anterior segments.

RV septal pacing sites other than the anterior septoparietal trabeculations (i.e., midseptal, posteroseptal, RV free wall, or true RV outflow tract) were defined as septal nonanterior pacing.

RV apical pacing was considered if the pacing wire was seen inserting into the RV apex, as visualized in the short-axis view at the LV apical level. ❑

Remodeling
– Modified regional blood flow patterns – Increased oxygen consumption without increase in blood flow – 60% change in blood flow early - later activated regions – Abnormal/asimetric thickening of LV wall – Increased tissue catecolamine at the level of pacing site – Redistribution of cardiac mass – Functional mitral regurgitation
Increased Cellular disarray
– Degenerative fibrosis (away from pacing lead location) – Fatty deposits – Calcification – Mitochondrial abnormalities – Myofibril hypertrophy – Intracellular vacuolation – Down-regulation of proteins involved in calcium homeostasis

TABLE 1. Anatomic changes in the paced-heart

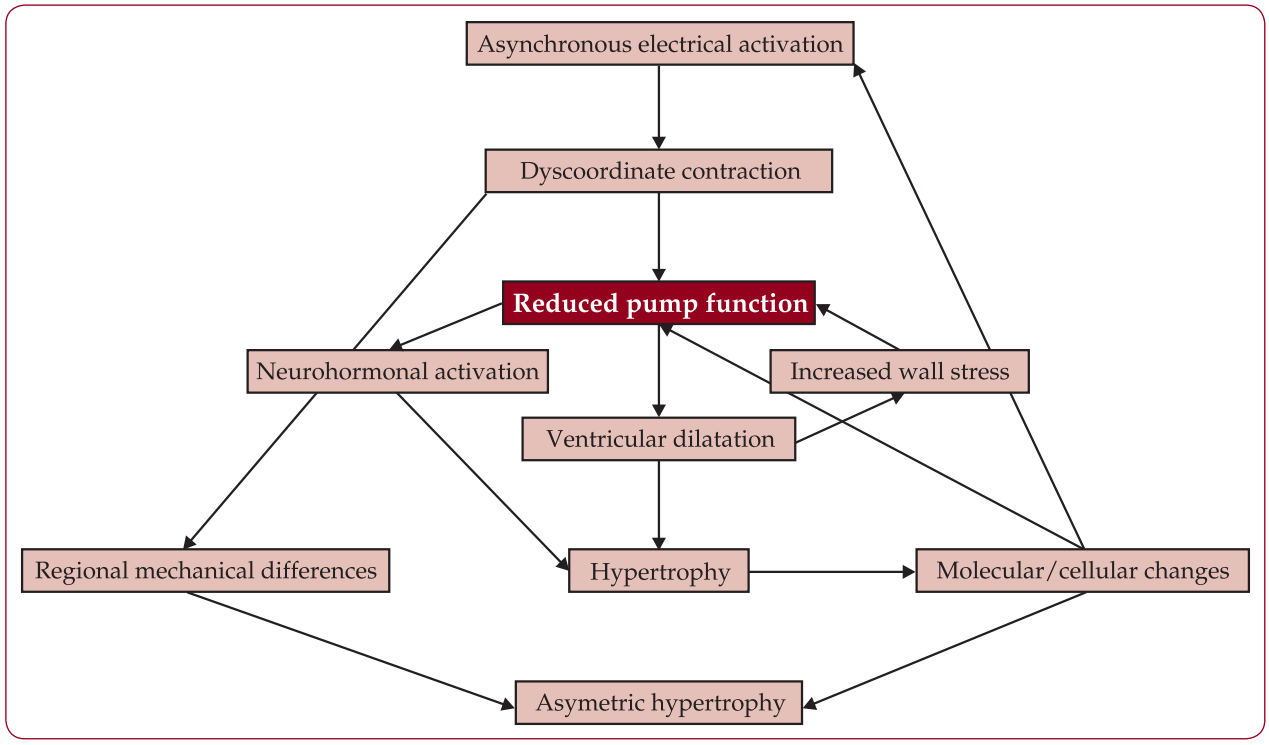

FIGURE 2. Mechanisms of remodeling of left ventricle in RVA pacing

SITE SELECTION – AN IMPORTANT DILEMMA

Clinical impact

There are limited data on the long term clinical outcome after RV pacing in patients with acquired AV block. In UKPACE (29) the annual incidence of HF was low, with 3.2% in the single-chamber pacing group, and 3.3% in the dual chamber pacing group, after a mean of 3 years of follow-up. The optimal RV pacing lead location for patients with standard indication for ventricular pacing is still controversial.

In a study of all factors that predict high mortality in permanent pacing patients, effect of chronic RVA pacing on left ventricular function was found to be the strongest predictor of LVEF decrease (5).

To prevent the detrimental hemodynamic effects of long-term RV pacing, alternative pacing sites have been studied. There is often a debate whether LV dysfunction after long term ventricular pacing is real or is dependent on pre-existing disease. A wide QRS complex before implantation may carry a higher risk of developing HF with right ventricular pacing (30).

The adverse effects on ventricular structure explain the association of RVA pacing, with increased risks of AF, heart failure (4, 9), and death in randomized clinical trials (22-32).

Recent studies have shown that up to 31-53% of pacemaker patients had LV dysfunction, and RVA pacing can lead to adverse outcome (5,32). The DAVID trial provided additional evidence that right ventricular pacing was associated with an increased risk of death and heart failure hospitalization in patients with an impaired LV function selected for ICD therapy (4). New or worsened heart failure or death during 3 years of follow-up was seen in 50% of patients with RVA pacing with >50% ventricular pacing (3).

Freudenberger et al. analyzed 11.246 patients with apical pacing. After a long follow up, a significantly higher hospital admission rates and cardiac death were observed compared to a control group.

Pacing from the IVS has been studied extensively, considered to have better hemodynamic effects and less harmful influence. This site of pacing generates an activation pattern very different, not as good as intrinsic conduction, who seems to improved outcomes, both acutely (39,40) and medium term (41,42).

A retrospective analysis of 150 consecutive patients, who underwent pacemaker for symptomatic bradycardia, showed that IVS pacing improve medium- and long-term survival. Vlay found, in a 9 year experience of 460 consecutive implants, an overall success rate of 84% in the IVS group, with excellent lead performance.

However, long-term clinical data are limited to nonrandomized studies or investigations including relatively few patients, heterogeneous groups, and different methods of evaluation (1,37). Furthermore, most studies that compared RV septal with apical pacing used echocardiographic or radionuclide determination of LVEF or acute invasive hemodynamic parameters. Follow up periods in these studies ranged from acute effects to up to 18 months. ❑

HISTOLOGICAL AND ECHOCARDIOGRAPHIC CHANGES

In a quantitative review of 9 studies, on alternative RV pacing sites, a modest but significant hemodynamic benefit was observed for IVS pacing as compared with conventional pacing (Table 2) (1).

Speckle-tracking analysis revealed that permanent RV pacing induced heterogeneity in time-to-peak radial strain, resulting in LV dyssynchrony in 57% of patients. A short time-to-peak radial strain of the anteroseptal segments and a long time-to-peak radial strain of the posterolateral segments were found. These findings were associated with deterioration of LV systolic function, and NYHA functional class (32).

After a mean of 3.8 years of follow up, in patients with normal LV function and no evidence of intraventricular or interventricular dysssynchrony at baseline, Tops et. al (34) found that 50% of these patients have developed new-onset echocardiographic evidences of dyssynchronism. Similar to these findings, other long-term studies (35, 36) concluded that RVA pacing induced ≈ 5-10% absolute reduction in LVEF, in patients with baseline preserved LV function.

RVA pacing impairs cardiac output, stoke work, EF, LV relaxation in patients with or without LV dysfunction (36). The decrease in LV systolic function and NYHA functional class is directly related to the presence of LV dyssynchrony (32). The effects of RVA pacing were found to be greater in patients with impaired LV function (33).

There are some studies that suggested the benefic role of the alternative ventricular pacing site. Karpawich et al. in a histological study compared RV apical with mid-septal site. He shown prevention of remodeling with IVS pacing after 4 months follow-up. No calcification, degenerative changes, or altered mitochondrial morphology were observed in the septal paced group (Figure 3).

Tse et al. (35) revealed that the mean QRS duration was significantly longer during RVA than IVS pacing. At 6 and 18 months after pacing, the incidence of myocardial perfusion defects and regional abnormalities were higher, and LVEF was lower (47±3 vs. 56±1%) during RVA than IVS pacing. He concluded that preserved synchrous ventricular activation during

Author	Publication/year	No. of patients	Parameter	Results
Benchimol[8]	Circulation/1966	6	CO[T]	±
Barold[9]	Am J Cardiol/1969	52	CO[T]	±
Raichlen[23]	Circulation/1984	18	CO[T]	–
Cowell[10]	PACE/1994	15	CO[T]	+
Giudici[11]	Am J Cardiol/1997	89	CO[E]	+
Gold[13]	Am J Cardiol/1997	13	CO[T]	±
Karpawich[24]	PACE/1997	22	LVEDP	+
Blanc[12]	Circulation/1997	14	PCWP	±
Buckingham[14]	PACE/1997	11	CO[E]	±
De Cock[15]	PACE/1998	17	CO[E]	+
Saxon[17]	J Card Electr/1998	11	FAC[E]	+
Buckingham[16]	PACE/1998	14	CO[T]	±
Mera[18]	PACE/1999	12	EF[N]	+
Buckingham[21]	PACE/1999	37	CO[T]	±
Schwaab[19]	JACC/1999	14	EF[N]	+
Victor[20]	JACC/1999	16	CO[T]	±
Kolettis[22]	Chest/2000	20	CO[E]	+

CO, cardiac output; T, thermodilution; E, Echo-Doppler study; N, nuclear study; FAC, fractional area change; PACE, Pacing Clin Electrophysiol; JACC, Journal of the American College of Cardiology. For details of publications see reference list. Results: +, positive effect; –, negative effect; ±, no effect of right ventricular outflow-tract pacing as compared with apex pacing.

TABLE 2. Haemodynamic variable from different studies, identified by comprehensive search; De Cock, CC et al. *Europace* 2003; 5:275-278

IVS pacing prevented the long-term deleterious effects of RVA pacing on myocardial perfusion and function in patients with permanent pacemakers.

The exactly time course of development of LV dyssynchrony, LV dysfunction, and heart failure is still unclear. The dysfunction of right ventricle is the first abnormality that occurs in RVA paced patients, which manifests by 1 week. This is followed by LV dysfunction which starts by 1 month. The diastolic dysfunction precedes the systolic dysfunction in both ventricles (43).

Despite the theoretical advantage of the IVS pacing, numerous reports did not show convincing data of the superiority of IVS over RVA pacing.

Kypta et al. (37) analyzed 98 pacing dependent patients regarding LVEF, BNP levels, and exercise capacity at 3 days, 3 months, and 18 months after the implantation. All changes from baseline to 18 months were statistically not different between septal and apical stimulation.

Riedlbauchova et al. (44) found a significant beneficial effect in positioning the RV lead in the mid ventricular septum, especially in the patients with non-ischemic cardiomyopathy.

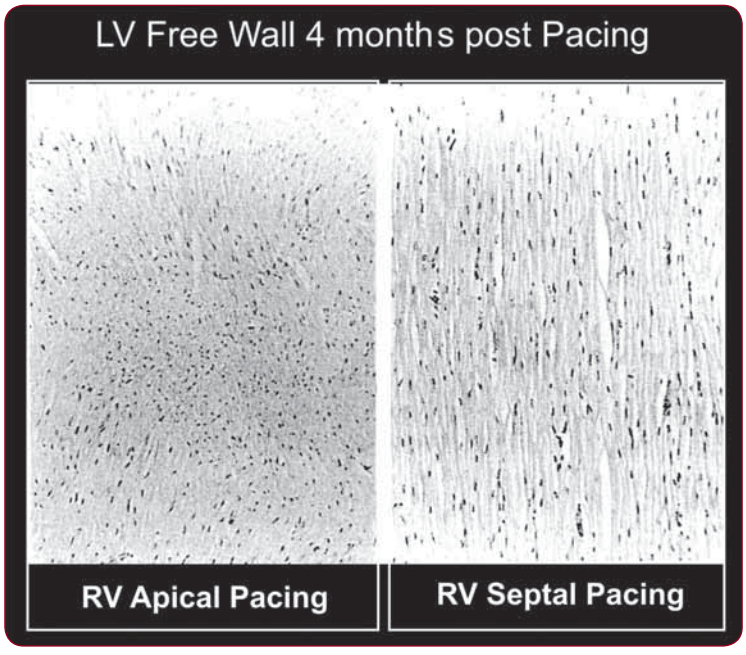

FIGURE 3. Histological differences after 4 months, between apical and septal site. No morphological changes were observed in the septal group (adapted from Karpawich PP et al. *Am Heart J* 1991; 121:827-833)

These results were not confirmed by other investigators who did not observe similar results in comparable study cohorts (45).

Cate et al. (46), in an acute study of patients with normal EF and without other cardiac abnormalities, concluded that both RVA and IVS pacing increase in the same way electromechanical delay compared to no pacing. Both can negatively affect regional longitudinal LV strain and timings without differences. Ng et al. (47), in a long-term study demonstrated more impaired circumferential strain and worse LV dyssynchrony in septal than in apical pacing and control. Liu et al. (48) revealed an acute increase of the LV systolic dyssynchrony index assessed with real-time 3D echocardiography during RVA pacing in a group of patients with sinus sick syndrome.

Occhetta et al. used a stimulation site which we consider the most proximal to the HIS bundle of all cited studies. He reported excellent results showing a similar QRS complex during intrinsic ventricular activation (52).

An important point is the specific position in the IVS pacing. Lieberman et al. (36), pointed out that the different positions of the septal lead could explain the different results reported in the literature. Ng et al. confirmed that RV septal pacing consists of a heterogeneous group of different pacing sites.

Another interesting point is that, there is no evidence to suggest that LV function will be reduced by non-RVA pacing. The non-inferiority of septal pacing could become an argument for the use of this pacing site. ❑

CONCLUSION

The optimal RV pacing in patients with a standard indication for ventricular pacing is still controversial. Different positions in the septum, and different evaluated parameters might explain the conflicting data about hemodynamic impact of this site when comparing to apical pacing. The effects of RV pacing could be attenuated by considering the importance of underlying cardiac disease. It is conceivable that patients with a significant LV activation delay may be at risk of developing LV dysfunction.

Echocardiography offers a remarkable variety of techniques and measurements with no clear gold standard for the characterization of LV dyssynchrony or for prediction of clinical response.

We think that larger studies and longer follow up, including selected patients, and comparing only specific septal sites to conventional pacing, might reveal more clear differences between these pacing sites, with clinical implications. We also suggest that a "gold standard" method for the evaluation of these patients is also important. ❑

References

1. **De Cock CC, Giudici MC, Twisk JW** – Comparison of the hemodynamic effects of right ventricular outflow-tract pacing with right ventricular apex pacing: a quantitative review. *Europace* 2003; 5:275-278
2. **Wiggers CJ** – The muscular reactions of the mammalian ventricles to artificial surface stimuli. *Am J Physiol* 1925; 37:275-282
3. **Steinberg JS, Fischer A, Wang P et al** – The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. *J Cardiovasc Electrophysiol* 2005; 16:359-365
4. **Wilkoff BL, Cook JR, Epstein AE et al** – Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002; 288:3115-3123
5. **O'keefe JH, Abuissa H, Jones PG et al** – Effect of chronic right ventricular apical pacing on left ventricular function. *Am J Cardiol* 2005; 95:771-773
6. **Torok TS, Thornton A** – The Effects Of Right Ventricular Apical Pacing On Left Ventricular Function. Stimulation Of The Right Ventricular Apex: Should It Still Be The Gold Standard? *Indian Pacing Electrophysiol J* 2003; 3:74-80
7. **McGavigan AD, Mond HG** – Selective site ventricular pacing. *Curr Opin Cardiol* 2006; 21:7-14
8. **Shukla HH, Hellkamp AS, James EA et al, for the Mode Selection Trial (MOST) Investigators** – Heart failure hospitalization is more common in pacemaker patients with a prolonged paced QRS duration. *Heart Rhythm* 2005; 2:245-251
9. **Sweeney MO, Hellkamp AS** – Heart failure during cardiac pacing. *Circulation* 2006; 113:2082-2088
10. **Schwaab B, Frohlig G, Alexander C et al** – Influence of right ventricular stimulation site on left ventricular function in atrial synchronous ventricular pacing. *J Am Coll Cardiol* 1999; 33:317-323
11. **Vassalo JA, Cassidy DM, Miller JM et al** – Left ventricular endocardial activation during right ventricular pacing: effect of underlying heart disease. *J Am Coll Cardiol* 1986; 7:1228-1233
12. **Baldasseroni S, Opasich C, Gorini M et al** – Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian

network on congestive heart failure. *Am Heart J* 2002; 143:398-405

13. **Verbeek XA, Vernooy K, Peschar M et al** – Quantification of interventricular asynchrony during LBBB and ventricular pacing. *Am J Physiol Heart Circ Physiol* 2002; 283:1370-1378
14. **Prinzen FW, Peschar M** – Relation between the pacing induced sequence of activation and left ventricular pump function in animals. *Pacing Clin Electrophysiol* 2002; 25:484-498
15. **Prinzen FW, Van Oosterhout MF, Vanagt WY et al** – Optimization of ventricular function by improving the activation sequence during ventricular pacing. *Pacing Clin Electrophysiol* 1998; 21:2256-2260
16. **Schwaab B, Kindermann M, Frohlig G et al** – Septal lead implantation for the reduction of paced QRS duration using passive-fixation leads. *Pacing Clin Electrophysiol* 2001; 24:28-33
17. **Prinzen FW, Augustijn CH, Arts T et al** – Redistribution of myocardial fiber strain and blood flow by asynchronous activation. *Am J Physiol* 1990; 259:300-308
18. **Thambo J-B, Bordachar P, Garrigue S et al** – Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation* 2004; 110:3766 -3772
19. **Kanzaki H, Bazaz R, Schwartzman D et al** – A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: insights from mechanical activation strain mapping. *J Am Coll Cardiol* 2004; 44:1619-1625
20. **Maurer G, Torres MAR, Corday E et al** – Twodimensional echocardiographic contrast assessment of pacing-induced mitral regurgitation: relation to altered regional left ventricular function. *J Am Coll Cardiol* 1984; 3:986-991
21. **Vanderheyden M, Goethals M, Anguera I et al** – Hemodynamic deterioration following radiofrequency ablation of the atrioventricular conduction system. *Pacing Clin Electrophysiol* 1997; 20:2422-2228
22. **Nielsen JC, Kristensen L, Andersen HR et al** – A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. *J Am Coll Cardiol* 2003; 42:614-623
23. **Nielsen JC, Andersen HR, Thomsen PEB et al** – Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single-chamber atrial or ventricular pacing. *Circulation* 1998; 97:987-995
24. **Nahlawi M, Waligora M, Spies SM et al** – Left ventricular function during and after right ventricular pacing. *J Am Coll Cardiol* 2004; 44:1883-1888
25. **Tse HF, Lau CP** – Long-term effect of right ventricular pacing on myocardial perfusion and function. *J Am Coll Cardiol* 1997; 29:744-779
26. **Tantengco MV,Thomas RL, Karpawich PP** – Left ventricular dysfunction after long-term right ventricular apical pacing in the young. *J Am Coll Cardiol* 2001; 37:2093-2100
27. **Skalidis EI, Kochiadakis GE, Koukouraki SI** – Myocardial Perfusion in Patients with permanent Ventricular Pacing and Normal Conary Arteries. *J Am Coll Cardiol* 2001; 37:124-129
28. **Giudici MC, Karpawich PP** – Alternative site pacing: it's time to define terms. *Pacing Clin Electrophysiol* 1999; 22:551-553
29. **Toff WD, Skehan JD, De Bono DP et al** – The United Kingdom Pacing And Cardiovascular Events (UKPACE) trial. United Kingdom Pacing and Cardiovascular Events. *Heart* 1997; 78:221-223
30. **Pap R, Fürge P, Bencsik G et al** – Native QRS complex duration predicts paced QRS width in patients with normal left ventricular function and right ventricular pacing for atrioventricular block. *Journal of Electrocardiology* 2007; 40:360-364
31. **Sweeney MO, Hellkamp AS, Ellenbogen KA et al** – Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRSd in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003; 23:2932-2937
32. **Tops LF, Suffoletto MS, Bleeker GB et al** – Speckle-Tracking Radial Strain Reveals Left Ventricular Dyssynchrony in Patients With Permanent Right Ventricular Pacing. *J Am Coll Cardiol* 2007; 50:1180-1188
33. **Zhang XH, Chen H** – New onset heart failure after permanent RV apical pacing in patients with acquired high-grade atrioventricular block and normal left ventricular function. *Journal of Cardiovascular Electrophysiology* 2007; 19:136-141
34. **Tops LF, Schalij MJ, Holman ER et al** – Right Ventricular Pacing Can Induce Ventricular Dyssynchrony in Patients With Atrial Fibrillation After Atrioventricular Node Ablation. *J Am Coll Cardiol* 2006; 48:1642-1648
35. **Tse HF, Yu C, Wong KK et al** – Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. *J Am Coll Cardiol* 2002; 40:1451-1458
36. **Lieberman R, Padeletti L, Schreuder J et al** – Ventricular pacing lead location alters systemic hemodynamics and left ventricular function in patients with and without reduced ejection fraction. *J Am Coll Cardiol* 2006; 48:1634-1641
37. **Kypta A, Steinwender C, Kammler J et al** – Long-term outcomes in patients with atrioventricular block undergoing septal ventricular lead implantation compared with standard apical pacing. *Europace* 2008; 10:574-579
38. **Wyman BT, Hunter WC, Prinzen FW et al** – Mapping propagation of mechanical activation in the paced heart with MRI tagging. *Am J Physiol* 1999; 276:881-891
39. **Cowell R, Morris-Thurgood J, Ilsley C et al** – Septal short atrioventricular delay pacing: additional haemodynamic improvements in heart failure. *Pacing Clin Electrophysiol* 1994 17:1980-1983
40. **Karpawich PP, Mital S** – Comparative left ventricular function following atrial, septal and apical single chamber heart pacing in the young. *Pacing Clin Electrophysiol* 1997; 20:1983-1988
41. **Mera F, DeLurgio DB, Patterson RE et al** – A comparison of ventricular function during high right ventricular septal and apical pacing after His-bundle ablation for refractory atrial fibrillation. *Pacing Clin Electrophysiol* 1999; 22:1234-1239
42. **Victor F, Mabo P, Mansour H et al** – A randomised comparison of permanent septal versus apical right ventricular pacing: short-term results. *J Cardiovasc Electrophysiol* 2006; 17:238-242
43. **Dwivedi SK, Sandeep B, Aniket P et al** – Diastolic And Systolic Right Ventricular Dysfunction Precedes Left Ventricular Dysfunction In Patients Paced From Right Ventricular Apex. *Indian Pacing Electrophysiol J* 2006; 6:142-152
44. **Riedlbauchová L, Cihák R, Bytesník J et al** – Optimization of right ventricular lead position in cardiac resynchronisation therapy. *Eur J Heart Fail* 2006; 8:609-614
45. **Shimano M, Inden Y, Yoshida Y et al** – Does RV lead positioning provide additional benefit to cardiac resynchronization therapy in patients with advanced heart failure? *Pacing Clin Electrophysiol* 2006; 29:1069-1074
46. **Ten Cate TJF, Scheffer MG, Sutherland GR et al** – Right ventricular outflow and apical pacing comparably worsen the echocardioghraphic normal left ventricle. *Eur J Echocardiogr* 2008; 9:672-677
47. **Ng AC, Aliman C, Vidaic J et al** – 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 Cardiol* 2009; 103:1096-1101
48. **Liu WH, Chen MC, Chen YL et al** – Right ventricular apical pacing acutely impairs left ventricular function and induces mechanical dyssynchrony in patients with sick sinus syndrome: a real-time three-dimensional

echocardiographic study. *J Am Soc Echocardiogr* 2008; 21:224-229

49. **Vanerio G, Vidal JL, Banizi PF et al** – Medium- and long-term survival after pacemaker implant: Improved survival with right ventricular outflow tract pacing. *J Interv Card Electrophysiol* 2008; 21:195-201
50. **Freudenberger R, Wilson A, Lawrence-Nelson J et al** – Permanent pacing is a risk factor for the development of heart failure. *Am J Cardiol* 2005; 95:671-674
51. **Vlay SC** – Right ventricular outflow tract pacing: practical and beneficial. A 9-year experience of 460 consecutive implants. *Pacing Clin Electrophysiol* 2006; 29:1055-1062
52. **Occhetta E, Bortnik M, Magnani A et al** – Prevention of ventricular desynchronization by permanent paraHisian pacing after atriovebrain natriuetic peptidentricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. *J Am Coll Cardiol* 2006; 47:1938-1945