Physiologic Pacing: More Answers, More Questions

DAVID N. KENIGSBERG, M.D. and KENNETH A. ELLENBOGEN, M.D.

From the Department of Medicine, Virginia Commonwealth University Medical Center, Richmond, Virginia, USA

Editorial Comment

"Happy is the one who can know the cause of things"

-Virgil

Right ventricular apical (RVA) pacing is deleterious and may result in left ventricular dysfunction, heart failure, and increased mortality.[1-5] Pacing from the RVA results in a left bundle branch block morphology, due to depolarization of the right ventricle prior to the left ventricle and from the apex to the base.[6,7] It has been suggested that pacing the heart in a manner closer to the normal physiologic pattern of activation may reduce the incidence of these negative clinical outcomes.[8,9] The determination of the best site(s) to pace has been a question that remains unanswered. Before we abandon right ventricular pacing altogether, it seems worthwhile to consider if there are other RV sites that should be evaluated.

One of the potential sites that can be paced and results in near-normal depolarization of the heart is the septal aspect of the right ventricular outflow tract (RVOT).[10-12] Septal RVOT pacing results in a reduced QRS duration when compared with RVA pacing.[13-17] This translates into a shorter ventricular activation time and possibly less ventricular dyssynchrony. Furthermore, whereas RVA pacing has been shown to result in myofibrillar disarray and detrimental ultrastructural changes, septal pacing in canine hearts does not.[18] All of these findings suggest a potentially less harmful role of RVOT pacing than RVA pacing. However, in order to draw any clinical conclusions, a comparison between different pacing sites is needed.

In this issue of the *Journal*, Muto et al. report the results of the Effect of Pacing the Right Ventricular Mid-Septum tract in Patients with Permanent Atrial Fibrillation and Low Ejection Fraction study.[19] This *retrospective* analysis of single-chamber right ventricular mid-septal (RVMS) pacing compared with RVA pacing in patients with an ejection fraction (EF) of less than or equal to 30% and permanent atrial fibrillation (AF) is the *tipping point* and aids in our understanding of "physiologic pacing." In this study, patients with pacing of the RVMS experienced a significant improvement in NYHA class, EF, and quality of life measured at 18 months follow-up when compared with patients with RVA pacing.

This study's patient population, with over 100 subjects in each arm followed for 1.5 years, is an improvement from prior studies that have attempted to address this question with either smaller patient populations or relatively short-term follow-up. Furthermore, the body of prior work has resulted in conflicting conclusions. One potential reason for the differing results may be related to imprecise definition of RVOT pacing sites contrasted with the more strict definition of the RVMS as the area of the RV adjacent to the most anterior borders of the low and high septum and the most posterior border of the low and high free wall in this article. The RVMS was identified during the procedure by fluoroscopic and ECG criteria and confirmed postoperatively with echocardiography.

An example of a prospective trial that set out to evaluate the benefit of alternative RV septal pacing sites as investigated by Muto et al. is the ROVA (Right ventricular outflow versus apical) trial.[13] In this study, 103 patients with chronic AF and EF less than 40% were randomly assigned to RVA pacing, RVOT pacing, or both. Using a crossover design, patients were given each pacing mode for 3 months. After therapy, there was no difference in EF, hall walk distance, or quality of life measures between groups; there was, interestingly, a shorter QRS duration noted with RVOT pacing. In comparing these two similar studies with different results (i.e., Muto et al. and ROVA), the most notable difference is the length of follow-up. One must wonder if ROVA had longer follow-up, how different the results may have been. The differences between the RVA and RVMS groups became apparent only after 6 months in Muto's report.

Additional insight into a possible mechanistic explanation for these findings comes from a report from Lau et al. evaluating the long-term effects of alternative RV pacing sites on myocardial function and perfusion.[20] In this study, 24 patients with complete heart block were randomized to RVA or RVOT pacing. At 6 months, RVOT pacing resulted in shorter QRS duration, less myocardial perfusion defects, and regional wall motion abnormalities, but similar EF. However, at 18 months, EF was significantly higher, with RVOT pacing compared with RVA pacing, confirming the importance of long-term follow-up when evaluating the benefits of different pacing sites.

McGavigan and colleagues[15] have reported that a "true" septal RVOT lead placement is achieved only two-thirds of the time using standard techniques. In response to this problem, Mond et al. recently published their novel curved stylet shaping technique to position a lead in the low RVOT septum.[21] In Muto's report, it is not clear exactly how many times difficulty was encountered in positioning the lead in the RVMS, but a certain number of patients required the Locator^{Tm} system (St. Jude Medical, St. Paul, MN, USA) described in the methods section of the article.

Another pacing site of interest is the His bundle. His bundle pacing had been suggested to produce synchronous ventricular depolarization and improved cardiac function relative to RVA pacing acutely and in animal models. In 2000, Deshmukh and colleagues reported the results of permanent His bundle pacing in 18 patients with chronic AF, dilated

J Cardiovasc Electrophysiol, Vol. 18, pp. 1037-1038, October 2007.

Dr. Ellenbogen received significant honoraria as well as other compensation for participation on a speaker's bureau relevant to this topic.

Address for correspondence: Kenneth A. Ellenbogen, M.D., Virginia Commonwealth University Medical Center, PO Box 980053, Richmond, VA 23298-0053. Fax: 804.828.6082; E-mail: kellenbogen@pol.net or kaellenb@vcu.edu

doi: 10.1111/j.1540-8167.2007.00948.x

cardiomyopathy, and normal QRS duration undergoing implantation of a single-chamber rate-responsive pacemaker.[22] In 12 of these patients, the His bundle could be reliably stimulated using a fixed screw-in lead. Acute pacing thresholds were high at 2.4+/–1.0 V at 0.5 ms pulse duration and exit block and lead dislodgment occurred, as well. Long-term follow-up revealed a reduction of left ventricular dimensions and improved EF. In a study of 24 patients, Catanzariti et al. demonstrated the acute effects of permanent His Bundle pacing including the prevention of pacing-induced ventricular dyssynchrony, a decrease in the amount of mitral regurgitation, and an improvement in EF, as well.[23] These studies and others evaluating His bundle pacing, share the problem of elevated pacing thresholds making this alternative to RVA pacing a less attractive option.

When discussing physiologic pacing, biventricular pacing must be considered. In the PAVE study, Doshi and colleagues prospectively compared biventricular with RV pacing in 184 patients with cardiomyopathy (EF 46%) and NYHA class II/III heart failure symptoms undergoing AV nodal ablation for AF with rapid ventricular response.[24] At 6 months, patients in the biventricular pacing arm had a significant improvement in 6-minute walk distance and EF, compared with patients receiving RVA pacing with greater improvement in patients with lower EF or symptomatic heart failure. It should be pointed out that the magnitude of benefit reported by Muto et al. is similar to that demonstrated in the PAVE study. However, the excitement over the benefits of biventricular pacing as a better alternative than other forms of "physiologic" pacing must be tempered with the added resources, time, and expenses associated with the implantation of a left ventricular lead and device. If single-site RV septal pacing results are as good as biventricular pacing, the former would clearly be preferred. This issue still needs to be studied prospectively.

Many alternatives have been proposed in place of RVA pacing in order to achieve more physiologic pacing. At this point in time, there is no proof that RV septal pacing is the best RV pacing site. What is needed is a prospective large-scale study defining the benefits of RV septal pacing in terms of hard end points. Whereas Muto and colleagues have shown a benefit in RVMS pacing in comparison with RVA pacing in their retrospective analysis reported in this issue of the *Journal*, many questions still remain. Are there other sites in the RVOT that are as good as or better than the RVMS? In addition to answering this question, in our estimation, the next logical step that must be taken to clarify this question involves a prospective comparison of RV septal pacing to biventricular pacing. On the subject of RV pacing sites, despite the many answers, we are still left with many questions.

References

1. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A: 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.
2. Tantengco MV, Thomas RL, Karpawich P: Left ventricular dysfunction after long-term right ventricular apical pacing in the young. J Am Coll Cardiol 2001;37:2093-2100.
3. 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.
4. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK: Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997;350:1210-1216.
5. Nielsen JC, Andersen HR, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK: 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.
6. Rosenqvist M, Isaaz K, Botvinick EH, Dae MW, Cockrell J, Abbott JA, Schiller NB, Griffin JC: Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. Am J Cardiol 1991;67:148-156.
7. Prinzen FW, Peschar M: Relationship between the pacing induced sequence of activation and left ventricular pump function in animals. Pacing Clin Electrophysiol 2002;25:484-498.
8. Brady PA, Hammill SC: Ventricular-based pacing: One site fits all? J Cardiovasc Electrophysiol 2003;14:1187-1188.
9. Mond HG, Gammage MD: Selective site pacing: The future of cardiac pacing? Pacing Clin Electrophysiol 2004;27:835-836.
10. Durrer D, Van Dam RT, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC: Total excitation of the isolated human heart. Circulation 1970;41:899.
11. Ferrer MI: New concepts relating to the preexitation syndrome. JAMA 1967;201:1038.
12. Scher AM: The sequence of ventricular excitation. Am J Cardiol 1964;14:287.
13. Stambler BS, Ellenbogen K, Zhang X, Porter TR, Xie F, Malik R, Small R, Burke M, Kaplan A, Nair L, Belz M, Fuenzalida C, Gold M, Love C, Sharma A, Silverman R, Sogade F, Van Natta B, Wilkoff BL: ROVA Investigators. Right ventricular outflow versus apical pacing in pacemaker patients with congestive heart failure and atrial fibrillation. J Cardiovasc Electrophysiol 2003;14:1180-1186.
14. Mera F, Delurgio D, Patterson RE, Merlino JD, Wade ME, Leon AR: 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.
15. McGavigan AD, Roberts-Thomson KC, Hillock RJ, Stevenson IH, Mond HG: Right ventricular outflow tract pacing—Radiographic and electrocardiographic correlates of lead position. Pacing Clin Electrophysiol 2006;29:1063-1068.
16. Tse HF, Wong KK, Tsang V, Leung YL, Ho WY, Lau CP: Functional abnormalities in patients with permanent right ventricular pacing: The effects of sites of electrical stimulation. J Am Coll Cardiol 2002;40:1451-1458.
17. Victor F, Mabo P, Mansour H, Pavin D, Kabalu G, de Place C, Leclercq C, Daubert JC: A randomized comparison of permanent septal versus apical right ventricular pacing: Short-term results. J Cardiovasc Electrophysiol 2006;17:238-242.
18. Karpawich PP, Justice CD, Chang CH, Gause CY, Kuhns LR: Septal ventricular pacing in the immature canine heart: A new perspective. Am Heart J 1991;121:827-833.
19. Muto C, Ottaviano L, Canciello M, Carreras G, Calvanese R, Ascione L, Iengo R, Accadia M, Celentano E, Tuccillo B: Effect of pacing the right ventricular mid-septum tract in patients with permanent atrial fibrillation and low ejection fraction. J Cardiovasc Electrophysiol 2007;18:1032-1036.
20. Tse HF, Yu C, Wong KK, Tsang V, Leung YL, Ho WY, Lau CP: Functional abnormalities in patients with permanent right ventricular pacing: The effect of sites of electrical stimulation. J Am Coll Cardiol 2002;40:1451-1458.
21. Mond HG, Hillock RJ, Stevenson IH, McGavigan AD: The right ventricular outflow tract: The road to septal pacing. Pacing Clin Electrophysiol 2007;30:482-491.
22. Deshmukh P, Casavant D, Romanyshyn M, Anderson K: Permanent: Direct His-bundle pacing. A novel approach to cardiac pacing in patients with normal His–Purkinje activation. Circulation 2000;101:869-877.
23. Catanzariti D, Maines M, Cemin C, Broso G, Marotta T, Vergara G: Permanent direct his bundle pacing does not induce ventricular dyssynchrony unlike conventional right ventricular apical pacing. An intrapatient acute comparison study. J Interv Card Electrophysiol 2006;16(2):81-92. Epub 2006 Nov 18.
24. Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA; PAVE Study Group. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 2005;16:1160-1165.