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REVIEW

Pacing the right ventricular outflow tract septum: time to embrace the future

Richard J. Hillock[1] and Harry G. Mond[2]*

[1]Department of Cardiology, The Royal Adelaide Hospital, Adelaide, Australia; and [2]Department of Cardiology, The Royal Melbourne Hospital, Melbourne, Australia

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Transvenous pacing has revolutionized the management of patients with potentially life-threatening bradycardias and at its most basic level ensures rate support to maintain cardiac output. However, we have known for at least a decade that pacing from the right ventricle (RV) apex can induce left ventricle (LV) dysfunction, atrial fibrillation, heart failure, and maybe an increased mortality. Although pacemaker manufacturers have developed successful pacing algorithms designed to minimize unnecessary ventricular pacing, it cannot be avoided in a substantial proportion of pacemaker-dependent patients. Just as there is undoubted evidence that RV apical pacing is injurious, there is emerging evidence that pacing from the RV septum is associated with a shorter duration of activation, improved haemodynamics, and less LV remodelling. The move from traditional RV apical pacing to RV septal pacing requires a change in mindset for many practitioners. The anatomical landmarks and electrocardiograph features of RV septal pacing are well described and easily recognized. While active fixation is required to place the lead on the septum, shaped stylets are now available to assist the implanter. In addition, concerns about the stability and longevity of steroid-eluting active fixation leads have proven to be unfounded. We therefore encourage all implanters to adopt RV septal pacing to minimize the potential of harm to their patients.

Keywords Selective-site pacing • Pacing lead • Pacemaker • Right ventricular septal pacing

Introduction

Since the dawn of transvenous cardiac pacing, almost 50 years ago,[1] the right ventricle (RV) apex has been the preferred site for endocardial transvenous ventricular lead implantation due to the ease of placement, stability, reliability, and lead design. Like a left bundle branch block, pacing from the RV apex produces an abnormal late activation of the lateral wall of the left ventricle (LV).[2] This induces a differential muscle strain[3] and fibre shortening, which in turn increases myocardial work[4] and oxygen consumption.[5] The resultant changes in cardiac haemodynamics[6,7] cause LV cellular abnormalities, both at a gross and ultrastructural level[8] and ultimately may lead to ventricular remodelling resultant from neuro-hormonal and electrophysiological changes. Clinically, there is a higher risk of development of LV systolic dysfunction,[9,10] heart failure,[11,12] and atrial fibrillation.[13] These LV dyssynchrony changes resultant from RV apical pacing have been addressed in a recent extensive review.[14]

The described changes in LV function have generated a search for selective non-apical RV pacing sites in order to achieve a less eccentric, more physiologic pattern of ventricular activation.[12,14–16] To date, the alternate sites for RV pacing have included the His bundle and para Hisian tissues,[17,18] the mid-septum,[19] the low interventricular septum or RV inflow tract,[20,21] the right ventricular outflow tract (RVOT),[22,23] and in particular, the RVOT septum.[24] The most studied of these selective sites has been the RVOT with increasing focus on the septal aspect of this structure.

True RV septal pacing has until recently been difficult to consistently achieve. Some of the difficulties encountered with lead placement in these areas relate to the lack of suitable lead technology, the non-standardized nomenclature, and difficulty with consistent, accurate, and reliable placement of leads in the selected position. We now have a much clearer understanding of the relationship between the anatomy of the RV chamber and the fluoroscopic appearances and ECG patterns, which in turn has allowed successful development of tools to reliably direct steroid-eluting active fixation leads onto the true RV septum.[24]

Right ventricle septal anatomy

The right side of the interventricular septum has been poorly defined in the pacing literature and the term RVOT has been

* Corresponding author: Cato Cardiology, Suite 303, 12 Cato St., Hawthorn East Victoria, 3123, Australia. Tel: +613 9832 2260; fax: +613 9832 2280, Email: hmond@bigpond.net.au

used to describe a variety of pacing sites including the true outflow tract, the mid-septum, and even the area adjacent to the apex. This confusion persists, despite recent attempts to standardize the nomenclature of non-apical pacing sites.[16,25] The anatomy of the RVOT is complex and includes the septum which lies behind or posterior, the free wall in front, and between them, the narrow anterior wall upon which the left anterior descending coronary artery traverses (*Figure 1A*).

For purposes of cardiac pacing, the RVOT is bounded by the pulmonic valve superiorly and the upper roof of the tricuspid apparatus inferiorly (*Figure 1B*). In fact, 'septal RVOT' is a misnomer as much of the superior aspect abuts the proximal ascending aorta rather than the LV and thus the upper part of the RVOT 'septum' often referred to as high septum or high RVOT septum, actually lies superior to the aortic valve.[16,26,27] The posterior wall of the conus arteriosus is high and smooth walled and its position makes it both anatomically and electrophysiologically unsuitable for the attachment of a pacing lead. Indeed, attempted pacing from this area often fails because of high-stimulation thresholds.[28] Consequently, only the lower or inferior portion of the RVOT septum can be considered as truly septal. Anatomically, this area lies at or below the supraventricular crest (crista supraventricularis) and is represented as a cul-de-sac filled with septoparietal trabeculations making it ideal for active fixation pacing lead attachment (*Figure 1B*). Below this area again lies the trabeculated mid-RV septum and it too is suitable for septal lead attachment. The boundary between the two sites can be represented by a His-bundle catheter passed adjacent to the roof of the tricuspid valve toward the lateral wall.

Why then, is it so difficult to consistently achieve RV septal positioning? On review of *Figure 1*, the RV septum lies posterior. A pacing lead implanted via the superior vena cava traverses the tricuspid valve and with a simple curved stylet will pass superior towards the pulmonary valve. Unless the tip of the lead is arching posterior at the time of screw deployment, the lead tip will more likely become attached to the anterior or free wall. In order to consistently position a lead on the septal aspect, the prepared stylet requires posterior angulation.

Radiographic anatomy of the right ventricle septal areas

For recognition of RV septal lead placement, three fluoroscopic views are essential (*Figure 2*). The *postero-anterior* view is best for guiding the lead into the RVOT and mid-RV, whereas the *40° right anterior oblique* is used to exclude inadvertent positioning in the coronary sinus and great cardiac vein.[24] Differentiation between the septal, anterior, and free wall aspects of the RV is best defined by the *40° left anterior oblique* (LAO) view (*Figure 3*). The septal position is characterized by a posterior orientation of the lead tip, while the free wall positioning is seen with the lead tip facing anterior.

A fourth view, the *90° left lateral* is also valuable, but can only be performed after the operative procedure. A posterior projection of the lead tip indicates septal placement and is 100% specific (*Figure 2*).[15] In comparison, a lead attached to the free wall passes anteriorly towards the sternum. Anterior lead placement should be avoided as the active fixation screw lies close to the left anterior descending coronary artery[29] and may even occlude it.[30]

In summary, therefore, the LAO fluoroscopic view appears to be the most desirable method to determine RV septal positioning. It can be very easily performed during lead implantation and 40° has been chosen as it is the near maximum orientation in the oblique position that can be achieved without compromising the sterile field. The view, however, has not been proven to be

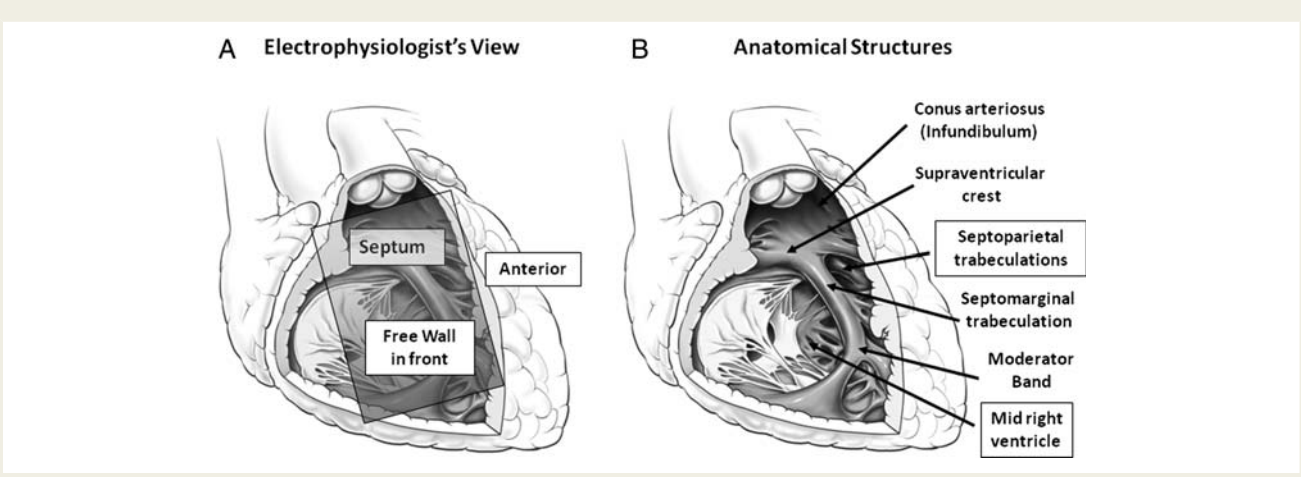

Figure 1 Illustrations of the heart, highlighting the right ventricle septal anatomy. Left A: Electrophysiologist's view. The right ventricle septum lies predominantly posterior. The free wall illustrated as a pink rectangle joins the septum at the anterior wall where the left anterior descending coronary artery lies. Right B: Anatomical structures. The upper part of the septal wall is the conus arteriosus, bordered below by the supraventricular crest and septomarginal trabeculation. To the anatomical left of the supraventricular crest are the septoparietal trabeculations which is a cul-de-sac suitable for active fixation lead fixation. Below the septoparietal trabeculations and the roof of the tricuspid valve lies the mid-right ventricle, which is also trabeculated and suitable for active fixation lead fixation.

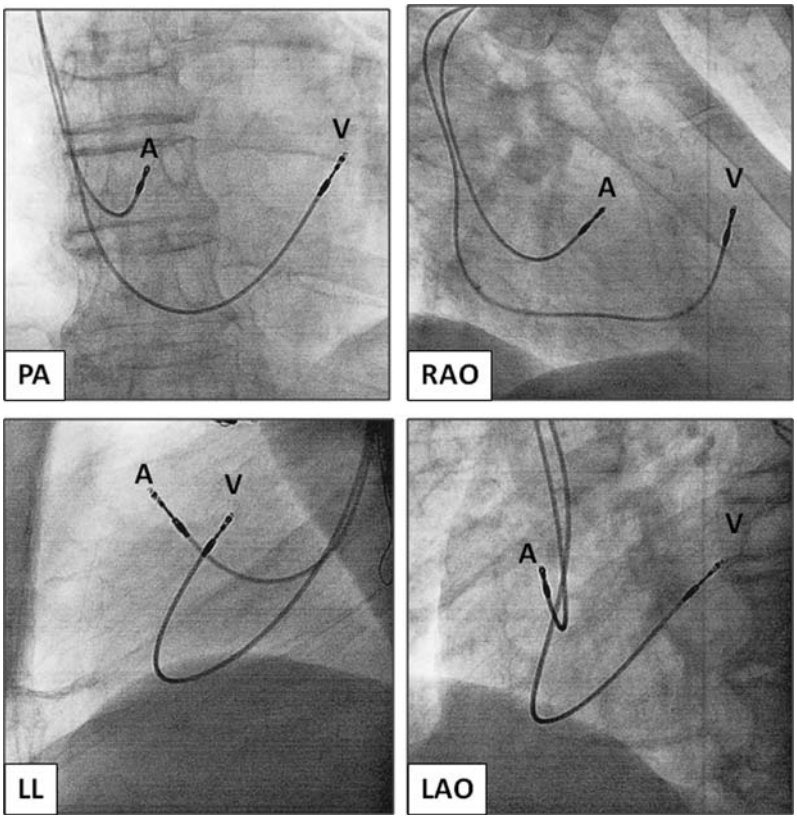

Figure 2 Postero-anterior (PA), 40° right anterior oblique (RAO), left lateral (LL), and 40° left anterior oblique (LAO) fluoroscopic chest images of a dual-chamber pacing system to demonstrate a ventricular lead attached to the right ventricular outflow tract septum. The left lateral and left anterior oblique views shows the lead pointing to the right which is posterior or septal. The leads are labelled; right atrial (A) and right ventricle (V).

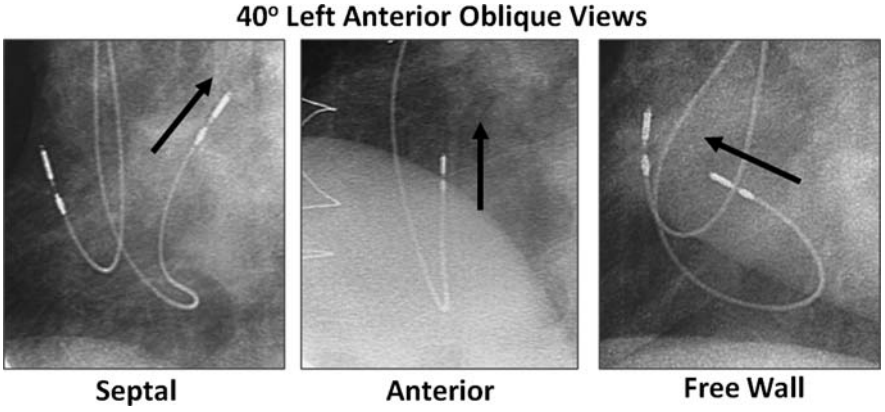

Figure 3 40° left anterior oblique fluoroscopic chest images to demonstrate lead positions in the right ventricle. Left: Right ventricular outflow tract septal with the lead tip pointing towards the vertebral column (black arrow). The atrial lead points anterior. Middle: Anterior mid-right ventricle with the red arrow pointing upwards. Right: Mid-right ventricle free wall with the lead tip pointing anterior away (red arrow) from the vertebral column. The atrial lead also points anterior.

the gold standard and like all potential clinical investigations is subject to patient anatomical variability. Other methods may include echocardiography, computerized tomography scanning, and in patients with compatible pacing systems even magnetic resonance imaging. However, such investigations are currently limited to post-operative evaluation.

Electrocardiograph correlates of lead position in the right ventricular outflow tract

Right ventricular outflow tract septal pacing is associated with shorter QRS durations than elsewhere in the RV outside the His bundle.[15] This suggests that pacing from the septal RVOT, although not as good as intrinsic conduction, may be the most desirable site for chronic RV pacing as a narrow QRS duration is associated with improved LV dynamics.[31] Pacing from the RVOT septum typically, but not consistently, produces a negative or isoelectric vector in lead I, as seen in *Figure 4*. Conversely, a free wall site is associated with a positive vector in lead I as well as a more prolonged QRS duration and notching of the inferior leads and in particular lead III.[15]

Clinical physiologic studies with right ventricular outflow tract pacing

Studies comparing RVOT with RV apical pacing have been available for more than a decade and include descriptive techniques for RVOT lead positioning.[32] Why then, has not RV septal pacing been widely accepted and utilized? One concern is that despite the perceived theoretical advantages of septal pacing, results to date have not been confirmatory. Both acute[6,31,33–41] and chronic[20,23,42–50] human studies have been undertaken utilizing a variety of alternate RV sites including the mid-RV and RVOT regions as well as patients with or without atrial fibrillation and LV dysfunction. Despite the paucity of robust data from these acute and chronic heterogeneous studies due to inconsistent experimental methods, the results do demonstrate a number of important findings:

- No studies suggest that RV alternate pacing sites are physiologically inferior to the RV apex.
- Although a number of studies refer to pacing site as RV septal, there has been to date, little instruction on how to either position leads or confirm septal sites. Consequently, most studies and in particular the earlier reports are potentially flawed in that the leads were positioned in the mid-RV or RVOT, but not necessarily septal. In a report of RVOT pacing using a simple curved stylet, probably similar to the tool used in many of the studies, only 61% of the leads was shown to be on the septum using the LAO fluoroscopic projection with the remainder on the anterior and free walls.[15] Why is it important to distinguish septal positioning from other RV sites? On review of the early work of Durrer *et al.*,[51] the septal regions of the LV were the first zones of the ventricle to depolarize, suggesting that initiating pacing from very close to these areas on the right side of the septum would achieve as normal a contraction pattern as possible. In contrast, the free wall of the RV was the last zone to be depolarized. When attempting to prove the physiologic and the haemodynamic benefits of septal pacing,

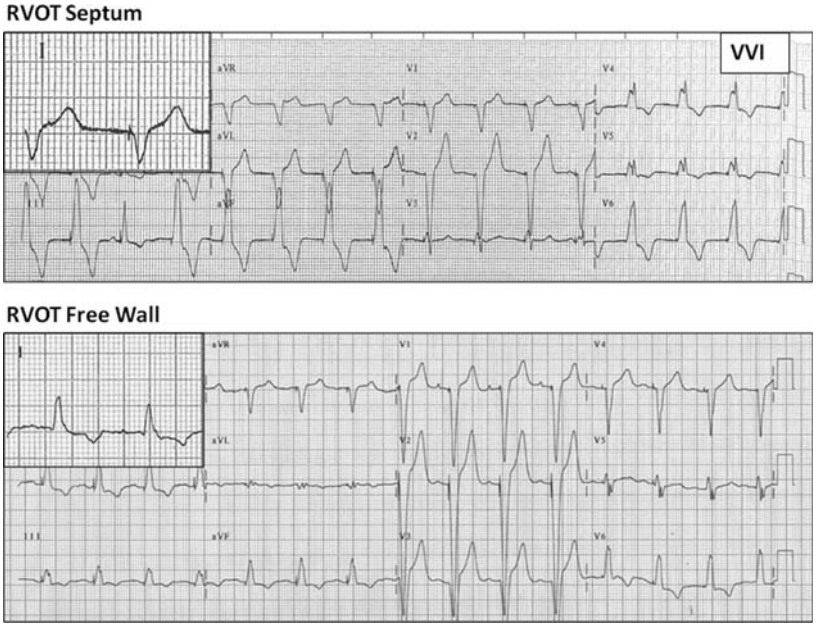

Figure 4 Twelve-lead electrocardiographs from the different patients, demonstrating forced ventricular pacing at 100 ppm from the right ventricular outflow tract. Above: Septal pacing (VVI). The frontal axis is vertical with a deep S wave in lead I (magnified insert). The horizontal axis shows a clockwise rotation with tall R waves from V4 to V6. Below: Free wall pacing. The frontal plane is more leftward with an R wave in lead I (magnified insert). The horizontal axis shows a clockwise rotation with smaller R waves only in V5 and V6. There is a notch in the R wave of Lead III.

Table 1 Long-term studies comparing pacing from the right ventricle apex and right ventricle alternate sites

Study/ reference	Year	No. pts.	Alternate pacing site	Study type	Physiologic investigation	EF	Length study	Result
AF studies								
Victor *et al.*[42]	1999	16	RVOT	Some ablation 4M wash-in period	NYHA, O_2 uptake, exercise time, EF radionuclide	Mixed	Cross-over 3M	O
Mera *et al.*[43]	1999	12	RVOT septal	All ablation No wash-in period	EF radionuclide Fractional shortening	Mixed	Cross-over 2M	+
Stambler *et al.*[23]	2002	80	RVOT	Some ablation 3M wash-in period	EF chocardiograph, quality of life, 6M Hall Walk	LV < 40%	Cross-over 3M	O
Bourke *et al.*[45]	2002	20	RVOT	All ablation 6W wash-in period	EF radionuclide	Mixed	Randomized 4M	O
Victor *et al.*[46]	2005	28	RV septum	All ablation 4M wash-in period	EF radionuclide	Mixed	Cross-over 3M	O
Muto *et al.*[47]	2007	233	RV mid-septum	Slow AF	EF echocardiograph	LV < 30%	Randomized 18M	+
Heart block studies								
Tse *et al.*[44]	2002	24	RVOT		EF radionuclide	Mixed	Randomized 18M	+
Vanerio *et al.*[49]	2008	150	RVOT	Some ablation AF	survival	_	9 to 2694 Days	+
Kypta *et al.*[48]	2008	98	RV septum		EF echocardiograph, exercise time, natriuetic peptide	Mixed	Randomized 18M	O
Tse *et al.*[50]	2009	12	RVOT septal	Upgrade RV apex to RVOT septal also RV apex control	EF radionuclide, 6M Hall Walk	Mixed	18M	+
Flevari *et al.*[20]	2009	31	Low mid-septum		EF echocardiograph, dyssynchrony	Mixed	Randomized 12M	+

AF, atrial fibrillation; No. Pts., number of patients; M, months; NYHA, New York Heart Association score; EF, ejection fraction.

it seems illogical to choose the RVOT with a mix of both septal and free wall pacing. The potential benefits of septal pacing would possibly be negated by free wall pacing and thus it is not surprising that there has been no consistent proven the physiologic benefit of RVOT pacing over RV apical pacing.

- The acute studies have utilized a variety of investigations to determine the potential benefits of RVOT lead positioning compared with the RV apex. About 50% of studies show a physiologic preference for RVOT pacing[6,31,34,35,40] with the remainder inconclusive. Because the negative remodelling effects of RV apical pacing may take years to manifest, it seems illogical to extrapolate acute physiologic conclusions particularly with normal or near-normal ventricles to chronic RV pacing sites.
- The question, therefore, is how long should chronic studies be conducted? *Table 1* reviews the 11 published studies since 1999. Five were conducted for up to 6 months[23,42–46] with only one positive,[43] whereas those conducted for 12–18 months were generally positive.[20,44,47,49,50] With only one study showing no physiologic benefit with alternate site pacing.[48] In particular, the study by Tse *et al.*[44] did not show significant physiologic differences between the two groups until 18-month post-implant. These data suggest that studies should probably be conducted for two or more years.
- Another criticism with chronic studies were protocols involving patients with established atrial fibrillation.[23,42,43,45–47] For a study to be meaningful, there should be at least 80% ventricular pacing and this was not always possible to determine accurately in earlier studies, whereas in those who had recently undergone AV node ablation,[43,45,46] there is often a gradual improvement in left ventricular performance with rate adaptive pacing and with short crossover periods, physiologic changes may not become evident unless there is a prolonged wash-in period.

From a critical review of these studies, long-term studies >12 months are almost invariably positive,[20,44,47,49,50] even if true septal pacing was not appropriately documented.

Lead selection and placement on the right ventricle septum

As previously stated, in order to achieve RV septal pacing, a conventional active fixation lead must be directed posterior once in the RV chamber. This can be consistently achieved using a septal stylet with posterior angulation (*Figure 5*). The lead loaded with the appropriately fashioned stylet is advanced through the right atrium into the right ventricle and from there into the pulmonary artery. The lead is then retracted and then secured to the septal wall. A detailed description of the implant procedure is now available.[28]

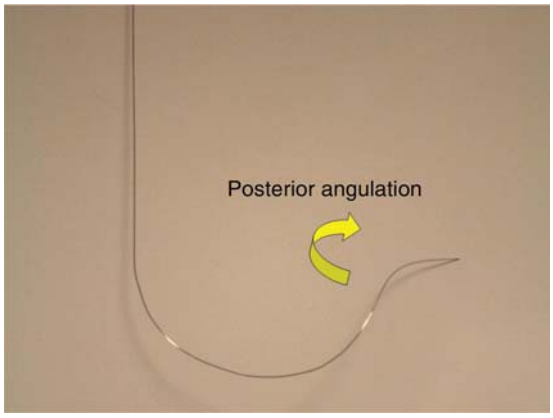

Figure 5 Hand-fashioned stylet with a generous curve and bent distal 2 cm with posterior angulation.

Similar implant techniques also apply to implantable cardioverter–defibrillator (ICD) leads. Because of their complicated and stiff terminal portion, it seems intuitive that all ICD leads have a greater potential to perforate the RV apex when compared with pacing leads.[52] In contrast, ICD leads secured to the more muscular RVOT septal or mid-RV septal walls are unlikely to perforate.[53–57] Septal positions also have the potential of physiologic and haemodynamic benefits if ventricular pacing is also required.[58] Furthermore, current evidence suggests that defibrillation thresholds are not adversely affected by septal positioning.[59–64] The techniques and the ease of insertion of ICD leads are identical to pacing leads and in the authors' experience, no lead complications have been documented. The concern about the heavier, stiffer, distal ICD lead segment and dislodgement appears unfounded. With current experience, mid-septal and even low septal positioning also appears satisfactory. Furthermore, current evidence suggests that defibrillation thresholds are not adversely affected by septal positioning.[60–64]

There is another described method for septal pacing lead implantation using the thin (4.1-French) lumenless fixed screw-in lead (Select Secure®, Medtronic Inc. Minneapolis, MN USA) which is passed through a steerable catheter delivery system (Select Site®, Medtronic Inc.). The procedure requires the use of a work station and a lead unfamiliar to most implanters.[65] Specialized training is required and there is a significant learning curve. The catheter, however, has no posterior angulation and it was not surprising that only 52% of leads positioned in the RVOT were found to be on the septum.[66]

Experience with right ventricle septal pacing

When correctly executed, the stylet with posterior angulation will position 90% of active fixation leads onto the RV septum.[67] Because the RVOT diameter is narrower, stylet positioning is more successful (97%) than in the wider mid-RV (89%), particularly when the chamber is enlarged.[63] With experience, there is ~2% failure to achieve septal pacing usually in cases with atrial fibrillation, gross enlargement of the RV and torrential tricuspid regurgitation.[63] In a reported consecutive series, the highest stimulation threshold at 1 year follow-up was 1.5 V and 94% of leads had a stimulation threshold of <1 V.[68]

In the experience of the authors with >600 cases of RV stylet driven active-fixation leads secured to all parts of the RVOT or mid-RV, one known dislodgement has occurred, which is similar to other reported series.[23,32,47] Unlike the RV apex, there are no other pacing complications associated with septal pacing. In contrast, traumatic occlusion of the left anterior descending coronary artery has been reported with anterior wall attachment[30] and similar to the RV apex, high stimulation threshold exit block, lead perforation, pericarditis, pericardial effusion, and tamponade can occur with free wall attachment.

Prospective, long-term physiologic studies comparing right ventricle apical and other alternate right ventricle pacing sites

Until recently, there have been neither implant techniques nor tools to reliably position active-fixation leads onto the RV septum. Now that such tools are available, it behoves us as physicians to design appropriate studies to demonstrate if chronic pacing from the RV septal areas is truly physiologically superior or not. Irrespective of the results of such studies, we now recognize that mechanically and electrophysiologically, the RV septal sites are equal or superior to the RV apex and thus pacemaker implanters should routinely consider abandoning the RV apex in preference to the RV septum for pacemaker implants and ICDs. More work, however, needs to done with RV lead positioning with cardiac resynchronization therapy.

There are two long-term randomized, prospective, multicentre clinical trials currently underway that hopefully may answer at least some of the physiologic and haemodynamic questions on RV septal pacing.[21] The most important difference these trials offer compared with previous studies is the strict fluoroscopic definition of septal sites. The first trial, *Protect Pace* (Right Ventricular Apical and High Septal Pacing to Preserve Left Ventricular Function), uses the steerable catheter and lumenless fixed screw in lead to achieve RVOT septal pacing. The second trial, *RASP* (Right Ventricular Apical versus Septal Pacing), uses either a conventional screw in lead or the lumenless fixed screw in lead for attachment to the RV septum at the level of the superior limit of the tricuspid annulus. Both trials will be conducted over at least 2 years and patient recruitment has been completed in the former. A third trial, *Optimize RV* (Optimize RV Selective Site Pacing Clinical Trial), used the steerable catheter and lumenless fixed active fixation lead to achieve mid-RV septal pacing. This trial was abandoned for a number of reasons, which may have included difficulties in achieving reliable septal pacing.

Other alternate sites for ventricular pacing

The least desirable alternate site for RV pacing is direct His bundle pacing. Although in theory, pacing the His bundle will preserve native ventricular activation and hence ventricular synchrony with narrow QRS durations, the implant techniques involved are complicated, time consuming, and currently there is only limited clinical success.[17,18] Lead complications and high stimulation threshold are unlikely to improve with current technology. The other undesirable factor with direct His bundle pacing is the limited number of indications for such lead positioning. Sick sinus syndrome is contraindicated because of potential damage to the conduction system. Equally, the technique cannot be used with distal conduction tissue disease and atrio-ventricular block. One option is atrial fibrillation, but because of high stimulation thresholds, this option cannot be exercised following AV node or His bundle ablation because of pacemaker dependency. It is unlikely that any large studies will be undertaken comparing direct His bundle pacing with any other ventricular sites.

Another ventricular alternate site often discussed is LV pacing. At this stage of our knowledge, LV pacing can only be recommended as therapy for severe LV dysfunction when combined with RV pacing for cardiac resynchronization. Its use with milder degrees of LV dysfunction or even normal cardiac function as a means of maintaining cardiac mechanical synchrony is controversial and unproven. The objective of RV septal pacing is quite different. It is hoped that by abandoning the RV apex, patients requiring RV pacing for bradyarrhythmic indications may be spared the deterioration of LV dysfunction created by RV apical dyssynchrony. Obviously, if a bradyarrhythmic patient has poor LV function with a low ejection fraction, then cardiac resynchronization therapy is at this stage of our knowledge, the more desirable therapeutic option.

It has been suggested that the true comparative study will be between LV pacing and RVOT septal pacing.[69] It is difficult to see how LV pacing via a coronary sinus/vein lead implantation can overcome the immutable obstacles in its way to supplant RV endocardial pacing therapy. The time, cost and experience required for LV lead placement, the high failure rates due to absent, unsuitable, unusable, or unattainable venous anatomy, coupled with operative and post-operative complications, all argue that at the moment RV septal lead placement is the option of choice.

It seems unfortunate that with the weight of evidence of harm from RV apical pacing and the evidence for benefit from RVOT septal pacing, that thousands of patients in the near future will be exposed to the adverse effects of RV apical pacing while we dally. We encourage all cardiologists to actively review their current right ventricular lead positioning preferences.

Conclusion

Although transvenous pacing has revolutionized the management of patients with potential life-threatening bradycardias, we now recognize that RV apical pacing can induce LV dysfunction, atrial fibrillation, heart failure, and maybe death. Although pacemaker manufacturers have developed successful pacing algorithms designed to minimize unnecessary ventricular pacing, it nevertheless frequently cannot be avoided in pacemaker-dependent patients. The move from traditional RV apical pacing to RV septal pacing requires a reluctant change in mindset for many practitioners, many of whom ironically espouse the merits of avoiding unnecessary ventricular pacing and also practice cardiac resynchronization therapy. The anatomical landmarks and electrocardiographic features of RV septal pacing are well described and easily recognized. Simple tools are readily available and reliable.

Conflict of interest: The senior author (H.M.) has designed a commercially available right ventricular septal stylet (St. Jude Medical, Sylmar, CA, USA), but has no financial interest in the product. There are no other conflict of interest.

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