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The knowns and unknowns of leadless pacing in 2022

1. Introduction

Since the development of the first cardiac pacemakers in the late 1950s, cardiovascular implantable electronic devices are commonly utilized and improved the quality of life and survival of patients with various heart diseases [1]. Leadless pacemakers are implanted in the right ventricle, and the Micra transcatheter pacing system (Medtronic) is the only leadless pacemaker currently available in clinical practice. Leadless pacemakers could provide benefit over conventional transvenous pacemakers by avoiding a subcutaneous pocket and leads traversing the tricuspid valve. As the experience with leadless pacemakers increases, outcome studies are important in understanding whether the leadless pacemakers measure up to these expectations.

In this issue of the Indian Journal of Pacing and Electrophysiology, Darlington et al. present a systematic review and meta-analysis of the safety, efficacy, and outcomes of leadless pacemakers [2]. After literature review, 18 studies were selected, including 4 studies comparing patients with leadless pacemaker implantation to transvenous pacemaker implantation. Among 2496 included patients, implant success rates were high (95.5–100%), but 1 in 3 patients required redeployment of the pacemaker during the implant. The mean age at implantation was 80 years. Procedure-related mortality was rare (0.29%), but the overall mortality was 6.1%. The mean age and overall mortality are reflective of the elderly population that receives single-chamber pacemakers. Any complication occurred in 3.1% cases, pericardial effusion, and cardiac tamponade in 0.96% and 1.47% patients respectively. The authors present a meta-analysis from four studies that included a transvenous pacemaker comparator group. There was no difference in hematoma, pericardial effusion, device dislodgement, any complication or death between leadless and transvenous pacemakers.

The study is a timely summary of the current published evidence surrounding leadless pacemakers. When considered together with another recent meta-analysis, and two recent reports from the Micra post-approval registry, we can appraise the “knowns” and the “unknowns” of leadless pacing in 2022 [3–5]. While the origins of the “knowns” and “unknowns” lie beyond medicine, it can provide a useful analytical construct to appraise our current knowledge of leadless pacing or any topic.

2. Known knowns

The “known knowns” are information obtained from the best available evidence on a topic, such as controlled studies, systematic reviews, and meta-analyses.

2.1. Implant success and acute electrical performance

The implant success rate with leadless pacemaker implantation remains high at 95–100%, with most contemporary studies reporting >98% success rates [2]. The acute and mid-term electrical performance is satisfactory. The recent meta-analysis by Ngo et al. reported a capture threshold <2V in 98.9% and 91.5% patients at 1 and 2 year follow up respectively [3].

2.2. Safety

Procedure-related pericardial effusion and cardiac tamponade have been under focus since the pivotal studies of leadless pacing [6]. Changes in the implant technique were adopted, favoring a mid-septal location over conventional apical implant location, and using contrast injections in orthogonal fluoroscopy views to determine septal device location before deployment. In the subsequent Micra post-approval registry, septal implant was present in 64% of patients compared to 33% in the pivotal study, and this was associated with a 30% reduction in complications [7].

Despite optimization of implant technique, pericardial effusion and cardiac tamponade remain a concern for patients undergoing leadless pacemaker implantation. A study from the Manufacturer and User Facility Device Experience (MAUDE) database reported a relative increase in cardiac tamponade, cardiac surgery, circulatory shock, and death after Micra implantation compared to transvenous CapSureFix leads between 2016-20 [8]. A subsequent report from MAUDE characterized the consequences of cardiac perforation with leadless devices, with 26% of patients requiring cardiac surgery to repair perforation, and an attendant high rate of mortality (27%) [9]. Among reported cases with cardiac perforation, an operator or device-related issue was identified in half of the cases, with the remainder having no clear device or operator issue at the time of implant. These data have important limitations, including the lack of ascertainment, and inability to estimate an incidence of these complications.

Additional comparison of cardiac tamponade rates between leadless vs transvenous pacemakers was reported from the Longitudinal Coverage with Evidence Development Study on Micra Leadless Pacemakers (Micra CED). This study continuously enrolls Micra recipients from the US Medicare fee-for-service population. Among 5746 patients with leadless pacemakers and 9662 patients with transvenous pacemakers, there was a small but significant increase in pericardial effusion/perforation with leadless pacemakers compared to transvenous pacemakers (adjusted model: 0.8 vs 0.4%, $p = 0.004$).

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These studies highlight the importance of operator training and technique, continued development of the implantation tools, and the formulation of risk scores to risk stratify patients receiving leadless pacemakers [10]. Elderly, female patients, low body mass index and chronic obstructive pulmonary disease are at the greatest risk of cardiac perforation, and previous sternotomy appears to confer a benefit.

Despite the concerns surrounding cardiac tamponade, leadless pacing may confer an overall benefit in reducing acute complications, by complete avoidance of subcutaneous pocket and access complications such as hematoma and pneumothorax. Darlington et al. did not find any difference in the overall complications after leadless pacemaker implantation compared to transvenous pacemaker implantation, and the Micra CED study mirrored this observation. The best available data on chronic complications are from the 2-year follow-up from the Micra CED study, which did report a reduction in overall complications with leadless vs transvenous pacemaker (adjusted HR 0.69, $p < 0.0001$) [4].

2.3. Elderly and comorbid patient population

Data from the Micra CEP study demonstrate that leadless pacemakers are more frequently utilized in the elderly and patients with comorbidities compared to transvenous pacemakers [5]. This is particularly evident in end-stage renal disease patients undergoing dialysis, in whom preservation of upper extremity vascular access (or lack thereof) is a driver for leadless pacemaker implantation in clinical practice.

Since leadless pacemakers are implanted in a "sicker" population in the real world, these findings have implications when comparing leadless to transvenous pacemakers in observational studies. In the absence of randomization, careful adjustment and propensity matching is required to infer conclusions from these studies, since the baseline characteristics of leadless vs transvenous pacemaker recipients are different.

3. Known unknowns

The "known unknowns" represent the questions regarding leadless pacemakers that clinicians are aware of but remain unanswered.

3.1. Long term electrical performance

Leadless pacemakers are routinely implanted since their FDA approval in 2016, providing up to 6 years of follow-up data in 2022. The estimated longevity of leadless pacemakers is up to 12 years, with an improvement in estimated longevity partly due to the shorter pulse width at 0.24 ms, among other factors. Ongoing stability in pacing thresholds and superior battery longevity are expected but can only be realized over time.

3.2. Pacing-induced cardiomyopathy & physiological pacing

Frequent right ventricular pacing results in interventricular dyssynchrony and pacing-induced cardiomyopathy. Frequent right ventricular pacing is frequently encountered among single-chamber pacemaker recipients since atrioventricular node ablation for management of atrial fibrillation is a common indication. Little is known about the impact of single-chamber leadless pacing on the left ventricular ejection fraction, and the development of pacing-induced cardiomyopathy. One study of 131 patients with 100% right ventricular pacing demonstrated a 3% vs 14% incidence of pacing-induced cardiomyopathy in the leadless vs transvenous pacemaker groups [11]. Although the routine septal implantation of leadless pacemakers should reduce interventricular dyssynchrony compared to RV apical pacing, larger studies are required to ascertain the purported low incidence of pacing-induced cardiomyopathy with leadless pacemakers.

Pacing-induced cardiomyopathy usually responds well to the restoration of interventricular synchrony by the addition of a coronary sinus lead and upgrade to a cardiac resynchronization therapy device. Notably, "upgrade" to a CRT device is not possible with the current generation of leadless pacemakers, and pacing-induced cardiomyopathy necessitates the abandonment or extraction of the leadless pacemaker and implantation of a new pacing system.

Physiological pacing techniques, including His bundle pacing and left bundle branch area pacing, have emerged as options for cardiac resynchronization, or prevention of pacing-induced cardiomyopathy [12]. Whether a leadless pacemaker or a left bundle branch area pacemaker emerges as a superior option for patients requiring single-chamber pacing remains to be determined. As the utilization of leadless pacing extends to include younger patients, and those with pre-existing systolic dysfunction, this question of leadless pacemaker vs left bundle branch area pacing will become increasingly important.

3.3. Impact on valvular function

Transvenous pacemaker implantation is associated with an increase in tricuspid valve regurgitation, which is an independent risk factor for heart failure and mortality among these patients. By avoiding direct mechanical impingement on the tricuspid valve leaflets, leadless pacemakers were expected to reduce the incidence of worsening tricuspid valve regurgitation compared to transvenous pacing. Indeed, there was no worsening of tricuspid valve regurgitation among leadless pacemaker recipients in two studies [13,14].

A subsequent study of 53 patients with a leadless pacemaker included a comprehensive evaluation of mitral and tricuspid valve function and left and right ventricular function after leadless pacemaker implantation [15]. At 12-month follow-up, there were equivalent rates of worsening tricuspid valve regurgitation among leadless and transvenous pacemaker recipients. Leadless pacemaker implantation resulted in worsening right ventricular function, left ventricular ejection fraction, and mitral valve regurgitation.

These findings suggest that worsening tricuspid valve regurgitation after pacemaker implantation may be due to factors beyond simple mechanical interaction, such as right ventricular dyssynchrony, and tricuspid annular dilatation associated with permanent atrial fibrillation. However, since there was increased tricuspid valve regurgitation with septal vs apical leadless pacemaker, a contribution from mechanical disruption of the tricuspid subvalvular apparatus cannot be ruled out.

3.4. Cost-effectiveness

Cost-effectiveness is a major consideration in the care of patients in any health care system but is especially relevant in predominantly self-pay healthcare systems such as in India. Leadless pacing systems can be two to four times the cost of a transvenous single chamber pacemaker [16]. There are currently no cost-effectiveness studies that report or even estimate the differences between leadless pacemakers and transvenous pacemakers. In the long term, improved cost-effectiveness of leadless pacemakers could be anticipated considering the expected longer battery life, and possible reduction in overall complications, but this remains a "known unknown" at present.

Table 1
Comparison of leadless pacing vs transvenous pacing in 2022 and beyond.

Known Knowns	Known Unknowns
• High rate of implant success • Stable electrical parameters including threshold at 2 year follow up • Small increase in rate of pericardial effusion and cardiac tamponade • Comparable overall acute complication rate and procedure-related death **Unknown knowns** • Lower risk of device infection	• Long term electrical performance • Pacing-induced cardiomyopathy and impact of left bundle branch pacing • Impact on valvular function including tricuspid valve regurgitation • Cost-effectiveness **Unknown unknowns** • Recalls and malfunctions • Impact of multiple devices within the RV

4. Unknown knowns

The “unknown knowns” represent information that is known and probably accurate but remains understudied, unrecognized, or underappreciated. Regarding leadless pacemakers, infection risk is one such “unknown known”. Cardiovascular implantable electronic device infection carries a significant risk of morbidity and mortality, and often requires lead extraction for management of infections. The risk of infection increases over time and with repeat interventions on the device pocket [17].

There is a dearth of controlled studies comparing infection risk between leadless and transvenous pacemakers, and Darlington et al. report no differences in any infection or infective endocarditis between these groups. Data demonstrating lower infection rates with leadless pacemakers are limited to small retrospective studies [13]. Despite the lack of controlled studies on the topic, it is telling that with over 50,000 leadless pacemakers implanted worldwide, there are only case reports of leadless pacemaker endocarditis in the literature [18].

Reduced risk of infection with leadless pacemakers is biologically plausible. The absence of a subcutaneous pocket eliminates the chances of a pocket infection. The intravenous portion of the leadless pacemakers has a lower surface area compared to transvenous leads. Additional hypotheses of leadless pacemaker bacterial resistance include endothelialization of the device, minimal direct handling, and turbulent blood flow within the right ventricle.

5. Unknown unknowns

The “unknown unknowns” refer to risks (or benefits) of leadless pacing that we may not yet be aware of and will become apparent only with time. After the leadless pacemaker battery is exhausted, a new leadless pacemaker must the placed in the right ventricle. As alluded to by Darlington et al., the hemodynamic and other impacts of multiple devices in the RV remains unknown. With any cardiovascular implantable electronic device, device malfunction and recalls remain unknowns that may only become apparent over decades of experience with these devices.

6. Future directions

Leadless pacemakers have evolved from single-chamber pacing systems to those capable of atrioventricular synchronous pacing with the Micra AV device. Consistent AV synchrony with the current generation of devices remains elusive but is expected to improve, with the advent of dual-chamber leadless pacemakers which are currently in clinical trials (NCT04559945). Eventually, dual-chamber leadless pacemakers capable of synchronously pacing the atrial Bachman's bundle and the ventricular conduction system may offer optimal physiological pacing for patients, while avoiding the drawbacks of transvenous pacing systems.

7. Conclusions

Despite their utilization in elderly and comorbid populations, leadless pacemakers have a high rate of implant success, with a low risk of acute complications. Further studies are required to characterize their impact on left ventricular systolic function, valvular function, and long-term electrical performance. Leadless pacemaker utilization is anticipated to increase as the potential benefits such as the absence of device infection are realized. The next generation of leadless devices capable of dual-chamber pacing and communication with subcutaneous defibrillators are under evaluation and will expand the scope of leadless pacing beyond 2022. (see Table 1).

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