Up-righting Dual-Chamber Cardiac Pacing. The Story of Managed Ventricular Pacing

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Keywords: Managed Ventricular Pacing

Introduction:

Managed Ventricular Pacing (MVP) was conceived as a permanent pacing modality in 1999. This was nearly three decades after an atrial lead was added to permanent pacing and dual-chamber pacemaker was commercialized.[1] At the time, pacemakers were indicated in over two-thirds of paced patients to correct symptoms that result from abnormally slow origination of impulses in the sinoatrial (SA) node. Yet since pacemakers were developed from bottom-up starting with VOO, they incrementally evolved to pace in a way such that every cardiac cycle ended with a ventricular sensed or paced event. Prior to MVP, an important step towards physiologic cardiac pacing occurred upon adoption of A-A timing in 1990, whereby pacemaker sequencing was predominantly driven by the atrial channel. MVP went a step further by relaxing the requirement that all atrial events be followed by a ventricular event. In doing so, ventricular pacing was practically eliminated in all paced patients with the exception of those having persistent complete heart block.[2]

MVP FDA approval in August 2004 did not require a large, prospective randomized trial. It was approved following two relatively small, download trials involving a total of 211 patients (30 patients using Gem III DR and 181 using Marquis DR). Both proved MVP as safe and highly effective in reducing right ventricular (RV) pacing, with no clinical endpoints. Commercial release was bolstered by emerging and compelling evidence showing the harmful effect of RV overpacing. The most compelling trial findings came from the Dual Against Backup Ventricular Pacing ICD (DAVID) trial,[3] Mode Selection Trial (MOST) trial and substudy,[4] published in 2002-2003 timeframe. Combined, these trials provided incontrovertible evidence that ventricular overpacing contributed to heart failure and atrial fibrillation. Another important contemporaneous realization came from evidence that iatrogenic left bundle branch block (LBBB) created by RV pace activation, was equally harmful in non-LBBB patients with congestive heart failure. [5] As such, results from early CRT trial results further contributed to MVP's early adoption.[6, 7].

Facilitated Atrial Pacing Threshold Testing (FAPTT)

MVP's true origin traces back to 1995, when its predominant AAI+ operation was first described as a means safely facilitate attended atrial threshold determination (Figure 2). Prior to pacemaker systems with real-time, multichannel ECG and event marker display, assessment of atrial capture during attended follow-up was difficult, and virtually impossible in patients with sinus tachycardia or frequent premature atrial contractions (PAC) and complete heart block (Figure 1a). An innovation called Facilitated Atrial Pacing Threshold Testing (FAPTT) described a means to safely and more easily performing atrial threshold test by simply pacing 2:1. Doing so thereby extended isoelectric time and allowed visualization of atrial capture on alternating beats (Figure 1b). [8] As with MVP, the invention maintained atrial only pacing in the event of intrinsic conduction and thereby allowed atrial capture inference during sustained overdrive atrial pacing (Figure 1c).

a b — **LOAC***cFigure2:* a) ECG/Marker strip taken during 1:1 AV pacing at a rate of 120 ppm. Atrial capture verification was complicated by overlap of atrial pace and the terminal end of the ventricular paced complex. b) ECG/Marker strip taken during 2:1 AV pacing at a rate of 120 ppm. Note that by liberating isolelectric time, atrial capture assessment on alternating intervals is visually unhampered. c) sustained ADI pacing in the event of 1:1 AV conduction. Loss of atrial capture (LOAC) is indicated by an abrupt and sustained fallback in heart rate with the appearance of native p-waves on the ECG.

MVP Story

Recollections of significant changes often fall into comfortable narratives that bear little resemblance to actual events. These narratives often bury the controversy, nuance and important events that generally surround significant shifts in approach within a field, and so do a disservice to those who will try to innovate

in the future. Our purpose here is, in part, to establish the timeline and motivations for the development of MVP, highlighting the controversies and uncertainties that surrounded the conception of a feature which is now considered standard-of-care.

In the case of MVP, a common false narrative is that MVP was a response to multicenter trials, most notably the DAVID trial, which were designed to confirm the general understanding that excess ventricular pacing was harmful. When MVP was initially developed in 1999 and 2000, the idea of harm from ventricular pacing was a very small minority opinion. In fact, the original purpose of DAVID was to establish the *superiority* of dual-chamber pacing, and the results of DAVID (which was terminated early) represented only the beginning of a reevaluation of that idea.

We have decided to tell this story for the sake of posterity. Most pacing and cardiac electrophysiology practitioners do not appreciate that MVP was fully described well before significant multicenter clinical trials had been completed. MVP has been recognized as a disruptive innovation and was introduced well before its time. It continues to be prescribed as a mainline treatment for patients with sinus node dysfunction and paroxysmal heart block.

At the time of its conception in 1999, the most significant clinical evidence that AAI was superior to DDD was from the small (i.e. 177 patients),randomized, prospective (i.e. DANPACE I) trial performed in Denmark, which showed a significantly lower incidence of AF in patients paced in the AAI modality.[9] Although AAI was prescribed routinely in some European countries, atrial only pacing never obtained a foothold in the United States. Few U.S. device implanters were willing to risk the possibility of frank syncope in a pacemaker patient. At the time that evidence of AAI pacing's superiority in sick sinus syndrome (SSS) patients began to build, insertion of a right ventricular pacing lead had already become established practice. In a country having a robust healthcare system and a degree of litigousness, single-lead ventricular pacing simply evolved directly to dual-lead atrioventricular pacing systems. In the U.S., little consideration was ever given to atrial-only pacing. AAI pacing was declared extinct in 2001. [10] The best option for SSS patients at the time was programming DDD/R or DDI/R with a long AV (e.g. 350 ms) delay, but static, long AV delays introduced the potential for retrograde conduction and resultant arrhythmias including pacemaker mediated tachycardia (PMT) and repetitive non-reentrant ventriculoatrial synchrony (RNRVAS).

MVP was fully described before the DAVID trial was publicly announced,[11] and before the compelling (mode selection trial) MOST substudy results were published.[4]Interestingly, the MOST and DAVID trials hypothesized that dual-chamber DDD pacing, then considered the universal pacing mode, was going to prove superior. Ultimately, MOST demonstrated that DDD pacing was superior, but pacemakers programmed to both DDD and VVIR increased heart failure (HF) hospitalizations and atrial fibrillation. However, DAVID showed that DDD pacing increased the combined endpoint of death or heart failure hospitalization compared to backup VVVI pacing in ICD patients having compromised left ventricular function. It was ultimately the combined results from the DANPACE I, MOST substudy and DAVID, and the realization of the harmful effects of dysynchronous ventricular activation gained from early CRT trials,[6, 7, 12-16]that cinched MVP's destiny.

Although dual-chamber pacing had become widely accepted as the "physiologic" or "universal" pacing modality in the mid-late 1990's, excessive ventricular pacing was troubling to two Medtronic biomedical engineers: David Casavant, a Boston based field clinical engineer and Paul Belk, a newly hired Medtronic field scientist working at Boston's Beth Israel Hospital.

Casavant had worked extensively with Dr. Pramod Deshmukh, widely recognized as the electrophysiologist who pioneered permanent His bundle pacing (PHBP). In the early 1990's, Deshmukh had realized that pacemaker implantation in patients with compromised left ventricular function often seemed to exacerbate their heart failure and accelerate mortality. Combined with his extensive knowledge of the literature, he inferred that cardiac dyssynchrony imposed by sustained RV apical pacing was detrimental to cardiac function. More importantly, he understood why. Prior researchers had shown in 1968 that ventricles activated normally via temporary His bundle pacing functioned better.[17]As a collaborator and coauthor of the landmark publication

describing first in man PHBP, Casavant learned the paramount importance of preserving normal activation whenever possible in pacemaker indicated patients with failing hearts.[18] Published studies suggesting adverse consequences from use of conventional DDD/R pacemakers already existed but were largely ignored.[19-23] A particularly significant publication in 1993 from a large single center study involving 557 consecutive patients hospitalized for HF with 42 having pacemakers, showed the risk of non-sudden cardiac death at one year was 48% higher.[24]

Belk had done his PhD work in developing a finite-element model of ventricular arrhythmias and had concluded that abnormal ventricular activation increased ventricular tachyarrhythmia susceptibility in ICD indicated patients. Under the guidance of Josephson, he designed a simple protocol in patients being evaluated for ICDs and showed that VT was more readily induced when premature ventricular stimuli (i.e. S2, S3, S4) were delivered in the wake of a ventricular paced (S1) drive train than when premature ventricular stimuli were delivered at the same coupling intervals following a narrow QRS drive train produced by atrial pacing.[25]

Remarkably MVP was conceived in a clinical environment in Boston without substantial input from the vast array of Medtronic in-house engineers, scientists, marketing, and product planners. The widespread realization that ventricular pacing was not benign occurred following the presentation of the MOST results as a late breaking clinical trial at the North American Pacing and Electrophysiology (NASPE) Society Meeting in 2001. Thereafter, it became a priority for pacemaker practitioners to avoid ventricular pacing. Programming long AV delays within the constraints of DDD/R pacing, mainly to avoid pacemaker 2:1 block at elevated sinus rates, was often a difficult task. Although AV search hysteresis DDD/R mode algorithms pacing did prove to be quite effective in reducing ventricular pacing in pacemaker recipients,[26-28] they had not been implemented, nor tested, on a dual-chamber ICD platform. In fact, initial DDD ICDs introduced in the US in 1998 (Ventak AV, Guidant, St. Paul, MN), 1999 (Gem DR, Medtronic, Inc., Minneapolis, MN), and 2000 (Photon DR, St. Jude, St. Paul, MN) respectively, did not incorporate AV search algorithms.

The most important influence on MVP's "AV delay-less" design was a mandate imposed by Medtronic's initial dual-chamber (Gem DR) ICD designers that the VP-AP interval "fit" within the VT detection zone *at all times* as to not interfere with VT detection due to same-chamber and cross-chamber post pace blanking periods. Such a scenario could easily be demonstrated on a simulator (Figure 3). At the time, most EPs and industry experts maintained that the primary function of ICDs was to protect patients from malignant ventricular tachyarrhythmia and accepted that some degree of ventricular overpacing was acceptable.

MVP Development Effort:

To fully define MVP as a permanent pacing modality, multiple enhancements were added to the FAPTT algorithm. Firstly, an AV delay of 80 ms following a non-conducted atrial event was chosen as it was the shortest AV delay that was known to be asymptomatic during the clinical evaluation of Medtronic's non-competitive atrial pacing (NCAP) feature in the Thera DR pacemaker(Medtronic, Inc., Minneapolis, MN) . Secondly, a post-atrial refractory period of 600 ms for rates below 75 bpm and 75% of the ventricular interval for rates above 75 bpm; this was somewhat arbitrarily chosen to delineate PACs from "physiologic" atrial sensed events originating from the sinus node. Thirdly, reverse mode-switching (RMS) from AA/IR+ to DDD/R in the event of 2:1 block or rhythms having a ratio of A:V events below 4:3. Fourthly, mode-switching to DDI/R in the event of atrial fibrillation. Fifthly, periodic attempts to restore AAI/R+ operation following DDD/R reversion by withholding singular ventricular paced events at geometrically increasing intervals (i.e. 1 minute, 2 minute, 4 minutes, 8 minutes,up to 16 hours). And sixthly, a PVC response during AAI/R+ operation that suspends atrial pacing, to eliminate potential VT detection interference from post atrial, ventricular cross-blanking following PVCs and PVC runs. Figure 2 demonstrates basic MVP operation.

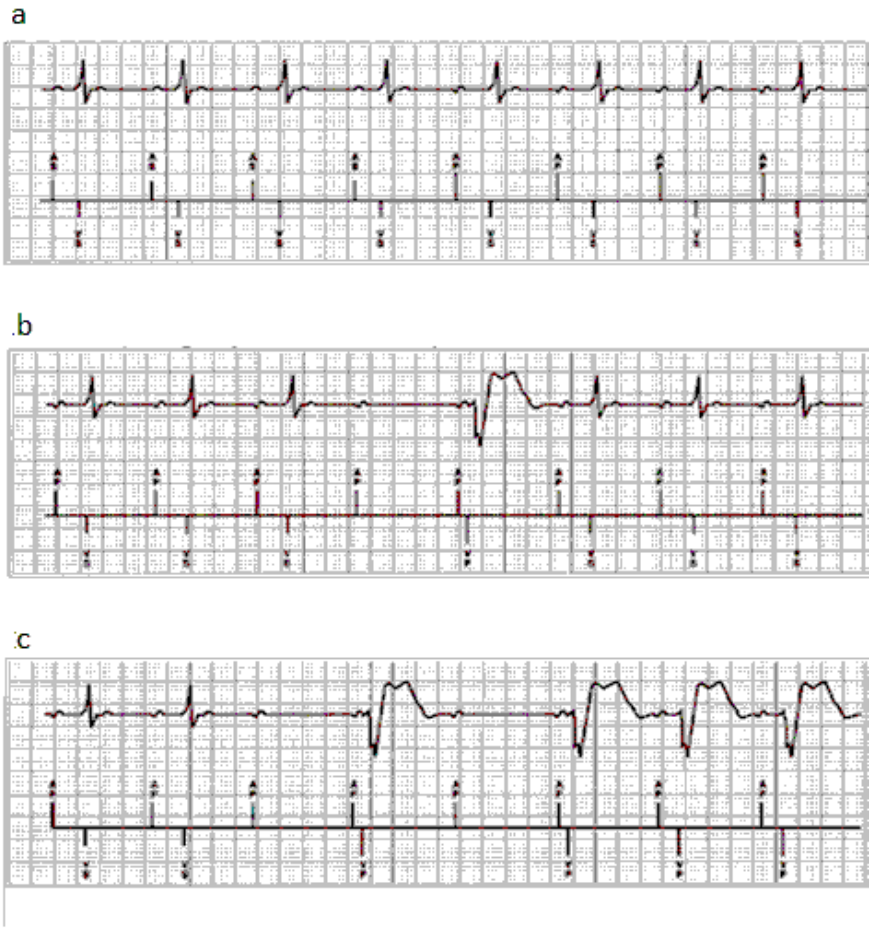

Figure 2: a) ECG and Marker Channel captured in AAI/R+ mode, MVP's predominant operating mode in patients with intact conduction. b) Example showing issuance of a backup ventricular pace following a singular non-conducted atrial event, c) conversion to temporary DDD/R mode in event of high degree HB (i.e. 2 of 4 intervals without a ventricular sense). Not shown is AAI/R+ restoration method, which involves dropping a ventricular pace periodically and deemed successful if a ventricular sense occurs prior to the next atrial event.

In the end, four engineers were credited as inventors of MVP.[29] Casavant and Belk were the primary architects. Tom Mullen, PhD, contributed solutions to several of the pace timing issues necessary to make the final MVP design reliable in the general pacing population. He was also instrumental in the design, data analysis and publication of the MVP Gem III DR download study.[30]The forth inventor, John Stroebel, a veteran Medtronic system engineer, contributed to MVP's final design and conceived a sophisticated "under the hood" method to implement MVP as a download algorithm in the Gem III ICD. His contribution expedited the clinical evaluation of the algorithm and hastened MVP's commercial approval.

The complete list of MVP contributors is vast of course includes*all* those that participated in the planning, design, development, and regulatory approval. The pacing and electrophysiology community as well as the patients who benefited owe a great deal. Medtronic's highly energized and creative culture engendered by a management philosophy borne from co- founder, Earl Bakken, represented an immensely critical, intangible components to MVP's conceptualization and huge commercial success.

MVP received regulatory approval based on 1 week data obtained in 30 of Dr. Sweeney's patients and on multicenter data from 206 patients having the MVP algorithm temporarily downloaded as "RAMware" into the Marquis DR ICD.[31] Commercial release came in 2004 with the launch of the Medtronic Intrinsic ICD.[32]

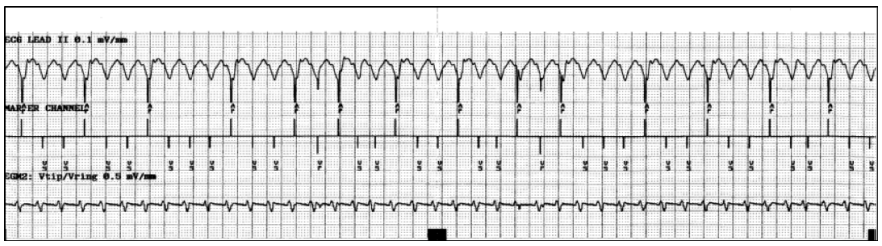

Figure 3: Simulated *failure to detect rapid VT due to long AV delay programming and interference from post Ap and post Vp ventricular blanking periods during sensor driven pacing at 100 bpm and during VT at a rate of 200 bpm. Programmed DDDR, LR=60 bpm, UR=130 bpm, PAV = 280 msec, TDI=280 ms, FDI=320 ms. (VS markers are* ***not*** *denoted as TS as the above could only be simulated).*

Dr. Michael O. Sweeney:

The story would not be complete without crediting Dr. Michael Sweeney, a Boston based electrophysiologist from Boston's Brigham and Women's Hospital (BWH), coincidentally came to the nearly simultaneous realization that RV overpacing was harmful. Dr. Sweeney's first recognition of the deleterious impact of RV pacing came during analyses of the results from the landmark MOST study, which unexpectedly failed to show a significant benefit of DDD over VVIR pacing.[33] Dr. Sweeney theorized that perhaps the common contributing factor was unnecessarily high ventricular pacing burden. Ultimately, his subanalyses showed that ventricular overpacing, either in the DDD or VVIR mode, contributed to a higher incidence of heart failure and atrial fibrillation and heart failure hospitalization in pacemaker patients.[4] After joining Medtronic as a consultant on the MVP, his relentless advocacy and teachings solidified his position as a MVP's primary advisor and investigator. Dr. Sweeney oversaw the first in man applications of MVP at BWH in late 2002. His pre-established authority as a key opinion leader greatly influenced MVP's expedited testing and commercial approval. Dr. Sweeney is primarily responsible for ultimately convincing the worldwide pacing community that MVP was a solution to DDD/R pacing and that maintained harmonious activation of an electrically intact heart via it's innate "infinite virtual electrode" is highly preferred over optimal AV timing.

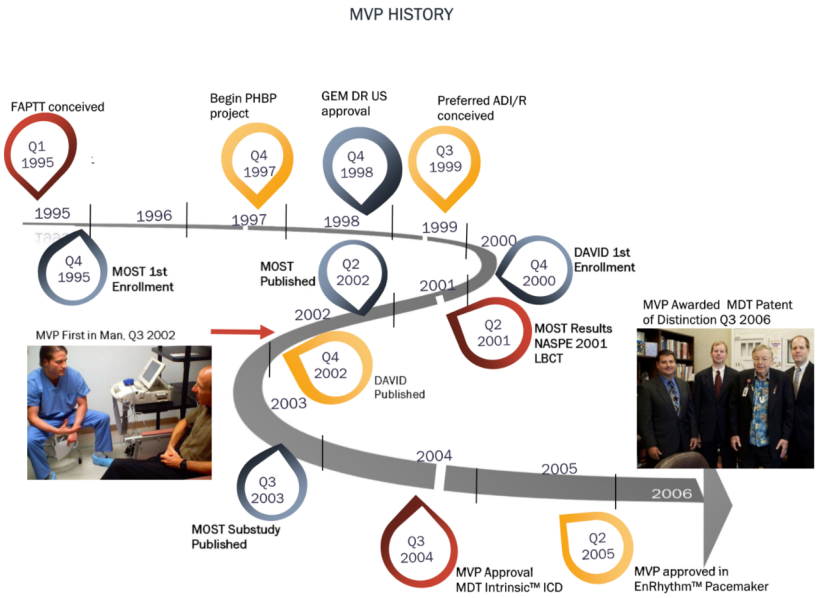

Figure 3: Timeline showing the evolution of MVP from pre-conception to final release. FAPTT refers to facilitated atrial threshold test. Preferred ADI/R was the original name for MVP. Pictured (L) Dr. Michael O. Sweeney with the first MVP patient during the Gem III DR download study. I David Casavant, Paul Belk, Medtronic founder Earl Bakken, and Tom Mullen upon receiving Medtronic Patent of Distinction Award, the 12th granted in Medtronic's 65+ year history recognizing disruptive innovation.

Final Perspectives :

Many agree that the rapid acceptance of MVP was largely due to its simplicity, in that it more closely mimicked normal activation of the heart, and allowed non-pacemaker indicated rhythms including 1'st Degree and 2nd Degree Mobitz I, Type I "Wenckebach" heart block. This simplicity was enhanced by its lack of programable parameters. MVP was introduced as an ON/OFF feature, a characteristic the inventors vehemently defended, thereby avoiding "feature creep" that often results from the desire to appease all. The naming of the mode was unique and is owed to Dr. Sweeney. Interestingly, the initial descriptor, "minimal" ventricular pacing was disallowed by FDA due to its implicit claim, thus requiring a frantic search of "M" words in Webster's dictionary.

In some ways, MVP can be viewed as a precursor to future permanent his bundle pacemaker modalities (e.g. sequential Atrial-His) since both favor normal ventricular activation. In fact, it is being employed on occasion for patients with intermittent heart block receiving Atrial-His (AH) pacing systems by programming short AV delays consistent with normal AH intervals.

Although the MVP mode significantly reduced ventricular pacing in the majority of patients, including those having a heart block indication,[2, 34] some criticized the mode for allowing occasional pauses that were excessively long. Sweeney et. al. debunked the notion that pauses were more significant than other modalities such as backup VVI pacing and showed that although (non-paced) short-long-short sequences (S-L-S) were permitted more frequently by MVP, S-L-S sequences terminating with a paced beat were not.[35]

MVP has seen very high levels of clinical success but has not seen unconditional patient acceptance. It has been implicated in ventricular tachycardias in prone patients, [36-39] and there have been some patients reported to have symptoms of pseudo pacemaker syndrome from with first degree heart block. Some patients

have reported vague symptoms from the extended pauses that are allowed following non-conducted atrial events. Experience has shown that only a small minority of MVP paced patients have been reprogrammed to conventional DDD/R pacing.

Despite its shortcomings, MVP has been a huge clinical success that resulted from hard work, research, and serendipity and a product of collaboration amongst engineers and physicians, a characteristic that is shared by so many important innovations in medicine.

MVP 2.0

The second generation of MVP was implemented in cardiac rhythm devices released in 2017 with slight modifications. These includes an optional programmable limit for longest allowed A-R intervals and an enhancement to lessen the duration of long V-V intervals and severity of S-L-S. MVP's 2nd version employs a dynamic, adjusting A-A interval and a programmable maximum AV interval limit such that switching to DDD/R occurs if 2 of 4 Ap-Vs or As-Vs intervals exceed this limit.[40, 41]

Future:

MVP is not the optimal solution: Clinical equipoise is imposed by the competing goals of optimizing AV synchrony while maintaining normal ventricular activation, particularly in patients having long PR and narrow QRS. In pacemaker indicated patients, optimizing AV interval using DDD pacing is only indicated in the event of symptoms due to severe AV decoupling (i.e. pseudo pacemaker syndrome).[42] In heart failure patients, physician sentiment continues to favor AAI/R (i.e. MVP) and other modes that limit RV pacing.[43-45] Ultimately, permanent his bundle and direct conduction system pacing will provide better solutions.

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"Don't be trapped by dogma – which is living with the results of other's people's thinking. Don't let the noise of others' opinions drown out your inner voice. And most importantly, have the courage to follow your heart and intuition."

–*S* teve Jobs

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