EP Tips & Techniques

Closed Loop Stimulation for Rate-Responsive Pacing: Single-Center Experience

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BACKGROUND

For patients with an absolute or relative pacing dependence, rate-response algorithms attempt to provide heart rates appropriate for the associated physiologic demand. Accelerometer-based rate-responsive pacing is the most widely used. Accelerometers rely on the translational motion of the patient, where pacing occurs at the lower rate limit (LRL) until movement of the pulse generator occurs. Accelerometers are most sensitive to perturbations around the rest state, with less discrimination between changing requirements at high workload and during recovery from exercise. Minute ventilation sensors perform best at high workloads, with sustained rate support during recovery, yet miss modest heart rate changes that may normally occur during a single respiratory cycle and are prone to oversensing (Figure 1).

In general, traditional sensors fail to account for subtle physiologic fluctuations during activities of daily living (ADLs), which involve inconsistent translational motion and little change in respiration. Furthermore, ADLs require an appropriate heart rate response to changes in mental activity or mental stress, which traditional sensors fail to account for (Figure 2). There is good rationale for blended sensors, which combine minute ventilation with an accelerometer; however, these lack the finesse of a normal chronotropic response and have not been widely adopted. Although various adjustments and scaling are available to modulate an accelerometer response (i.e., activity thresholds and slope, exertion response, ADL response, recovery time, etc.), considerable frustration can be experienced when tinkering with settings in an attempt to achieve a satisfactory heart rate profile for patients.

MECHANICS OF CLS

Closed Loop Stimulation (CLS) is a contractility-based rate-adaptive algorithm that accounts for subtle physiologic variation. A proprietary algorithm of BIOTRONIK, CLS first appeared in 2003. Catecholamine release is exquisitely sensitive to changing states including exercise, postprandial, and mental activity, with near-instantaneous changes in myocardial contractility.[1] The CLS algorithm tracks contractility changes on a beat-to-beat basis by detecting associated lead impedance changes. Unipolar impedance is measured at the lead tip, where sampling occurs eight times during each cardiac cycle, between 50 and 300 msec of systole. These measures are used to establish a reference waveform at rest (when no motion is detected by the accelerometer), and subsequently with regular updates whenever the patient is in a resting state. Increasing contractility changes the dynamics of the tissue/blood ratio at the lead tip during systole, with associated changes in the impedance profile. The pacing rate is instantaneously adjusted based on the impedance difference relative to the reference waveform.

Closed loop negative feedback refers to the higher contractility that is present prior to a rate increase, which attenuates as the heart rate rises. The rate response gain is then scaled so 20% of all beats will be above the exertional threshold rate

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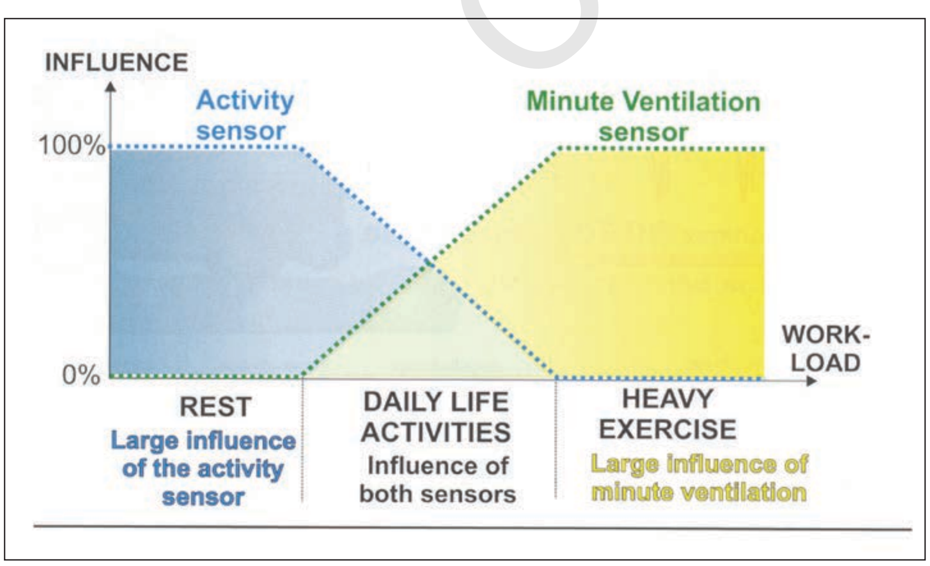

Figure 1: Performance of rate-responsive pacing sensors. Accelerometer-based (activity) sensors are most sensitive to changes from the rest state, and perform poorly at high exertion levels. Minute ventilation sensors perform well during heavy exercise, yet fail to account for minor activity. Neither sensor performs optimally for activities of daily living (ADLs), for which CLS is most appropriate. *Image courtesy of BIOTRONIK.*

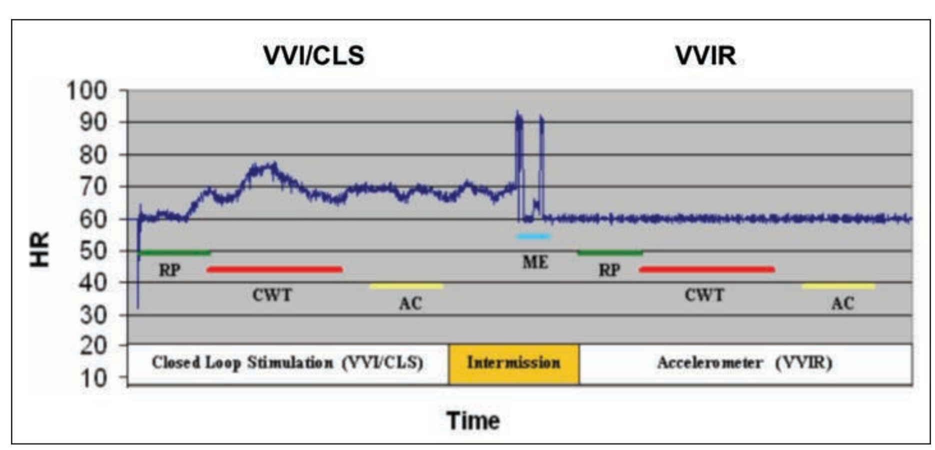

Figure 2: Sensitivity of CLS to mental activity. In pacer-dependent patients with single-chamber ventricular pacemakers, CLS provided physiologic heart rate variability during mental challenges including color word testing (CWT) and arithmetic challenge (AC), while VVIR programming failed to respond to the changing physiologic demand. A resting period (RP) and magnet effect (ME) were defined. *Image courtesy of BIOTRONIK.*

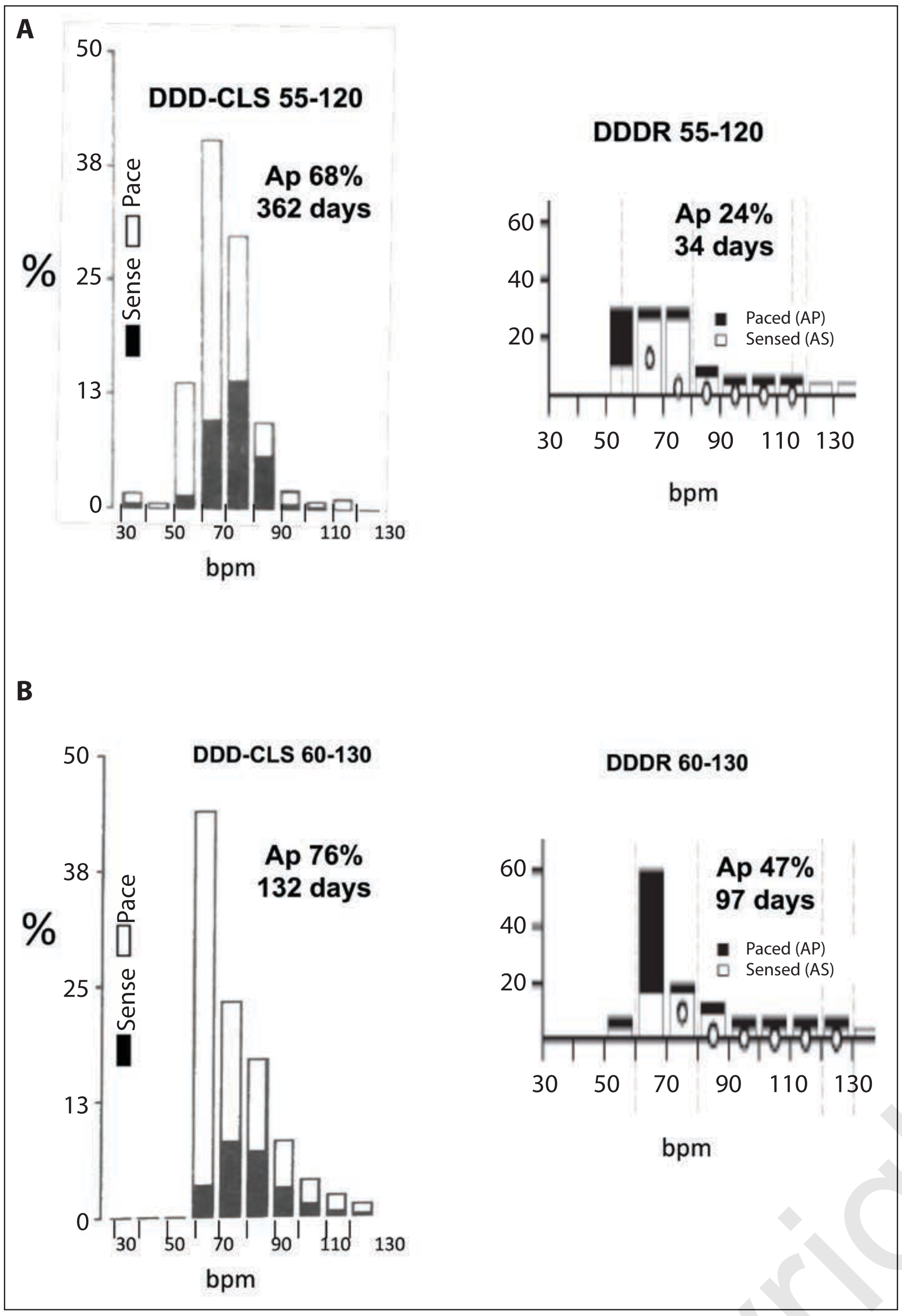

Figure 3: Comparison of CLS with accelerometer-based programming for chronotropic incompetence. (A) These data are from an 86-year-old male who underwent change-out from a DDD-CLS pacemaker to a DDDR pacing system; rate histograms over 362 days prior and 34 days following change-out are shown. (B) These data are from a 62-year-old male who underwent change-out from a DDD-CLS pacemaker to a DDDR system; rate histograms over 132 days prior and 97 days following change-out are shown.

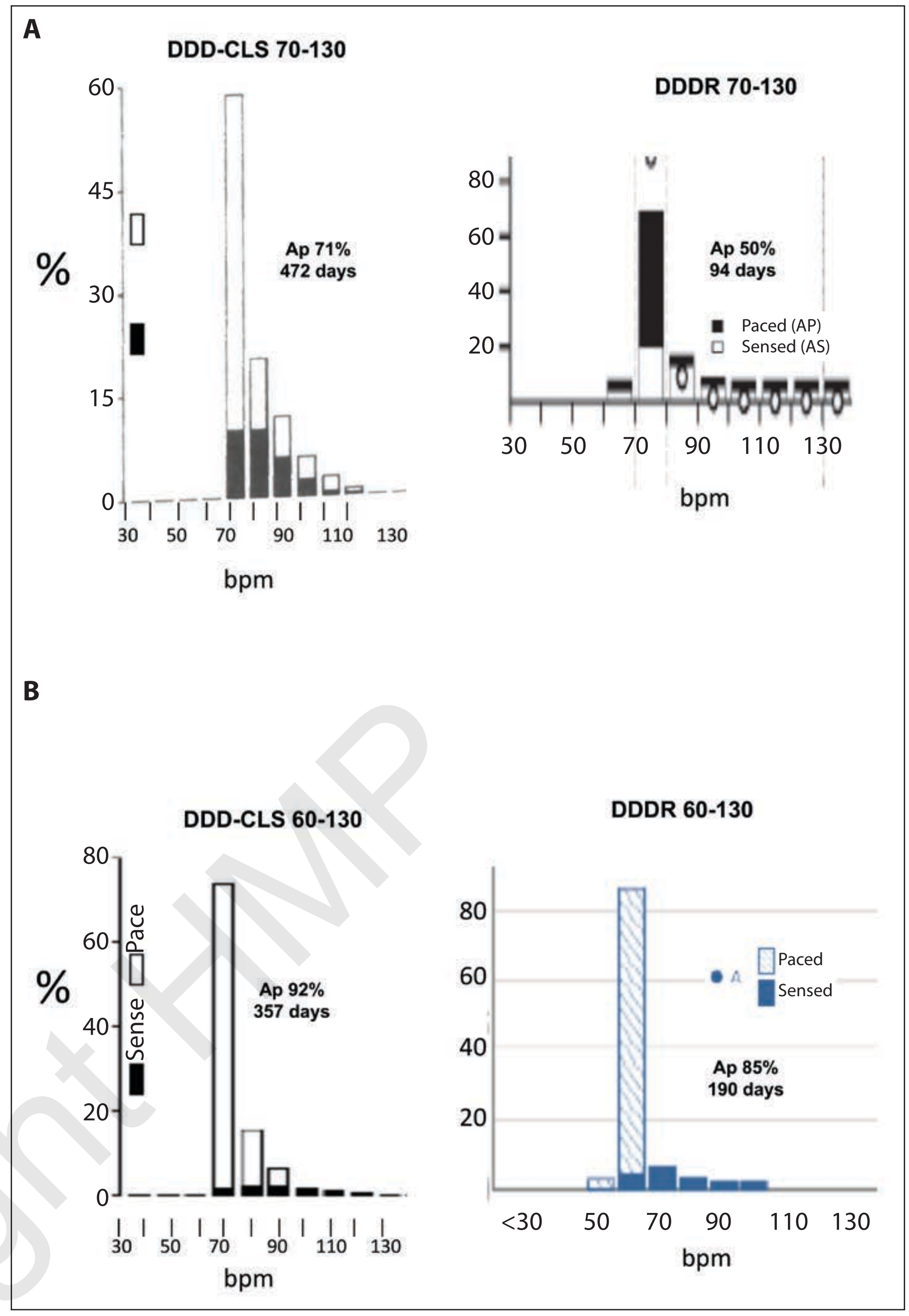

Figure 4: Comparison of CLS with accelerometer-based programming for chronotropic incompetence. (A) These data are from a 63-year-old male who underwent change-out from a DDD-CLS pacemaker to a DDDR pacing system; rate histograms over 472 days prior and 94 days following change-out are shown. (B) These data are from an 89-year-old female who underwent change-out from a DDD-CLS pacemaker to a DDDR pacing system; rate histograms over 357 days prior and 190 days following change-out are shown.

(ETR) over time.[2] While nominal settings work best for the majority of patients, CLS can be scaled to low, medium, or high by defining an ETR of 73, 80, or 92 bpm, respectively.

COMPARISON WITH COMPETITIVE CHANGE-OUTS

Advantages of CLS may be best appreciated by comparing accelerometer-based performance. The following are several representative cases that may give insight into applying this algorithm. As a first example, an 86-year-old male with chronotropic incompetence and a DDD-CLS pacemaker since 2009 underwent change-out to a DDDR pacemaker in 2016 (Figure 3A). Initial programming was DDD-CLS 55-120 bpm, followed by DDDR 55-120 bpm, both with nominal settings. Over 362 days prior to change-out, CLS provided 68% atrial pacing, with only 10% pacing at the lower rate limit (LRL), and the majority of pacing within the ADL range of 60-80 bpm. Over 34 days following change-out, DDDR provided only 24% atrial pacing, with the majority at the LRL, and unvaried rate support from 60-80 bpm.

In a second example, a 62-year-old male with chronotropic incompetence and a DDD-CLS pacemaker since 2009 underwent change-out to a DDDR pacemaker in 2016 (Figure 3B). Initial programming was DDD-CLS 60-130 bpm, followed by DDDR 60-130 bpm, both with nominal settings. Over 132 days prior to change-out, CLS provided 76% atrial pacing with good rate support within the ADL range of 70-100 bpm, appropriate for an active individual seeking to maintain a high level of function. Over the subsequent 97 days, DDDR provided only 47% atrial pacing with substantially less rate support from 70-100 bpm.

In the next case, a 63-year-old male with chronotropic incompetence and a DDD-CLS pacemaker since 2001 underwent change-out to a DDDR pacemaker in 2016 (Figure 4A). Initial settings were DDD-CLS 70-130 bpm, followed by DDDR 70-130 bpm, both with nominal settings. Over 472 days prior to change-out, CLS provided 71% atrial pacing. Over the subsequent 94 days, DDDR provided only 50% atrial pacing. As with the previous cases (Figure 3), DDDR gave considerably less pacing support over the ADL range of 80-110 bpm relative to pacing at the LRL (Figure 4A).

In a final case, an 89-year-old female with chronotropic incompetence and a DDD-CLS pacemaker since 2009 underwent change-out to a DDDR pacemaker in 2016 (Figure 4B). Initial settings were DDD-CLS 60-130 bpm, followed by DDDR 60-130 bpm, both with nominal settings. Over 357 days prior to change-out, CLS provided 92% atrial pacing. Over the subsequent 190 days, DDDR provided 85% atrial pacing. For both CLS and DDDR, the majority of pacing occurred at the LRL. As before (Figure 3, 4A), CLS provided considerably more pacing support in the

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CLS Experience

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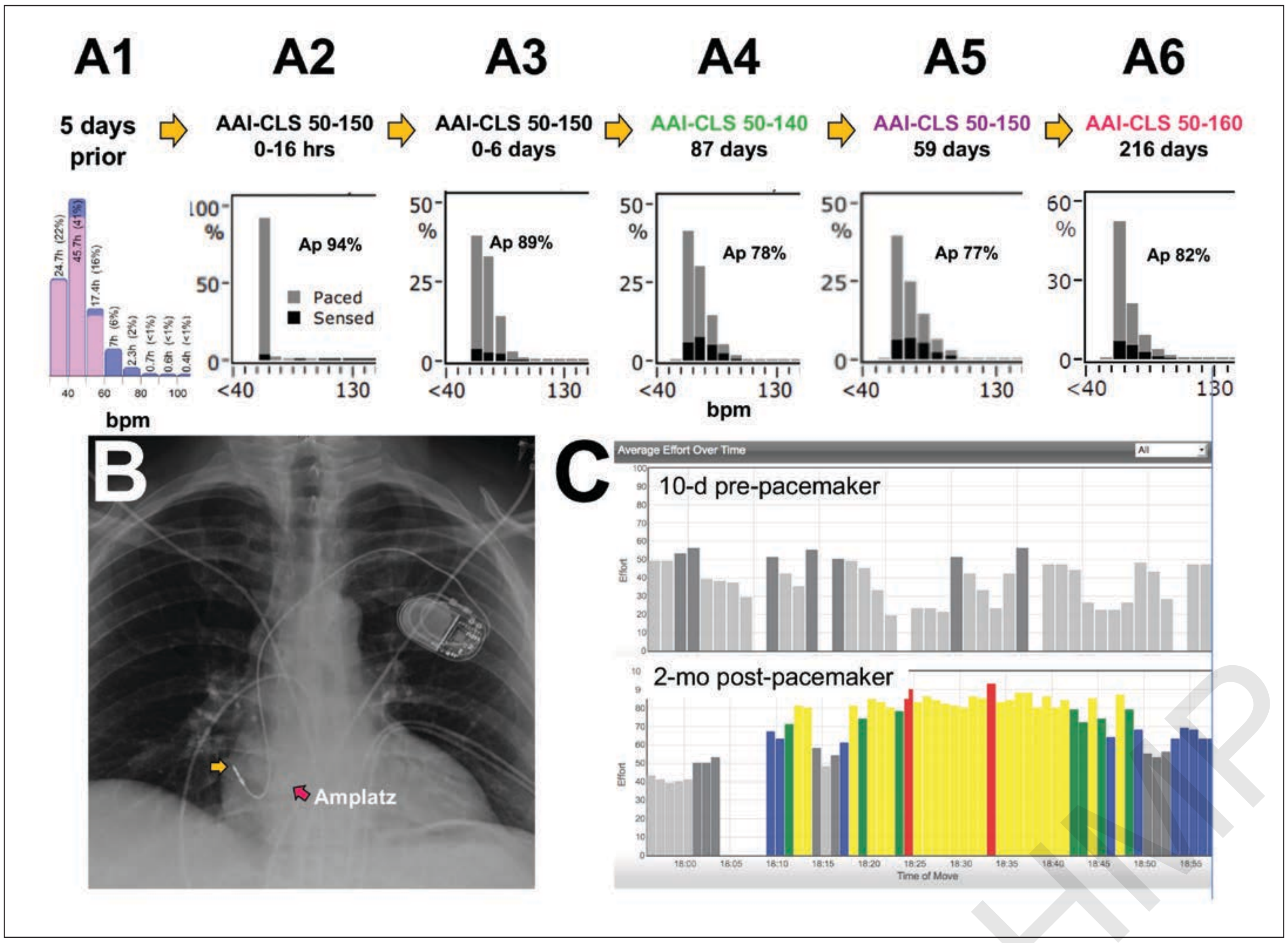

Figure 5: Representative case of a single-chamber atrial pacemaker with CLS (B). Five-day ambulatory monitor prior to the pacemaker (A1), AAI-CLS 50-150 bpm programming over first 16 hours (A2) and one-week (A3) post implant. Heart rate response with URL 140 bpm (A4), then URL 150 bpm (A5), and finally 160 bpm (A6). Improvement in sustained exertion is demonstrated 2 months post implant (C).

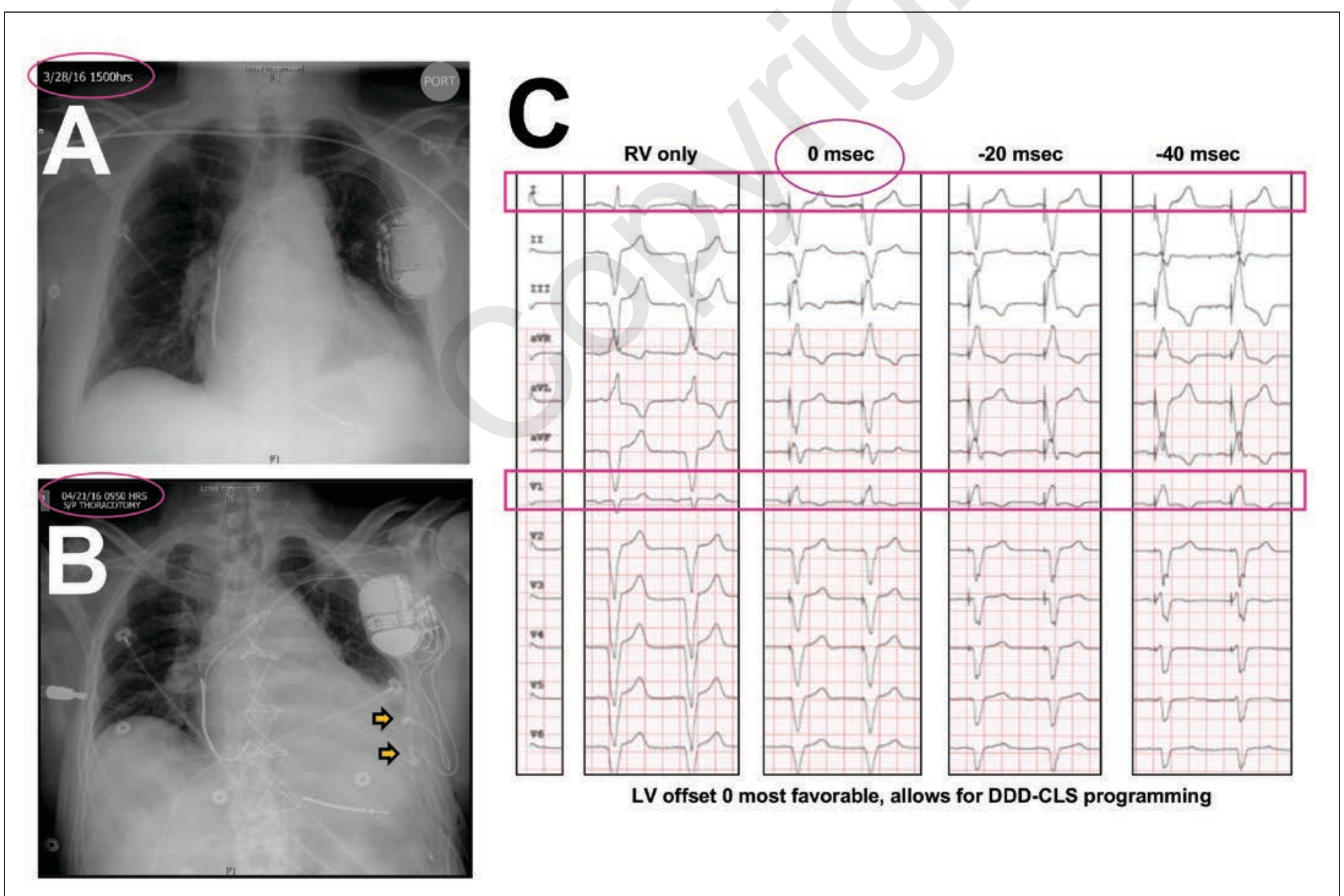

Figure 6: ECG-guided CRT optimization. CXR before (A) and after (B) CRT upgrade with epicardial lead placement. Twelve-lead ECG performed for RV-only pacing, and biventricular pacing with LV offset 0 msec, -20 msec, and -40 msec (C). With 0 msec offset, the QRS morphology became steeply negative in lead I and positive in V1. This pattern persisted for LV offset -20 and -40 msec, but with undesirable QRS widening. Therefore, LV offset of 0 msec was considered optimal and selected for initial programming. CLS presently requires an LV offset 0 msec in CRT systems.

ADL range of 70-90 bpm relative to pacing at the LRL (Figure 4B).

In summary, sinus node dysfunction (i.e., chronotropic incompetence or sick sinus syndrome) is the most common indication for pacemaker implantation.[3] In this setting, atrial pacing should be applied liberally for complete symptom resolution, as atrial pacing does not adversely affect myocardial function.[4] In the representative cases shown (Figures 3 and 4), we see that CLS consistently provided more overall atrial pacing, with considerably better rate support within the ADL range. Patients consistently reported improved energy and exercise tolerance with CLS. In our experience, it is all but impossible to reproduce the results of CLS by adjusting accelerometer settings in non-CLS pacemakers (i.e., activity threshold/slope, exertion response, ADL response, recovery time, etc.). CLS can be disabled at any time, with a return to accelerometer-based programming if desired. In my opinion, there is no substantive disadvantage in implanting a pacing system with CLS capability, from which patients may benefit substantially. It is difficult to justify withholding the option of CLS when choosing the best device to treat patients in need of rate-responsive pacing.

CLS FROM THE RA AND HB POSITIONS

By design, CLS derives contractility dynamics from a pacing lead positioned in the RV apex. Since even 20% pacing from the RV apex predicts the development of pacing-induced cardiomyopathy,[5] associated pacing is best applied in the RA with any ventricular pacing occurring in the His-bundle (HB) position.[6] Numerous operators have stopped implanting brady leads in the RV apex since HB pacing is now widely available, and this trend is expected to continue. In light of this shift away from the RV apex, there is renewed interest in whether CLS performs adequately when contractility measures are obtained from the RA and HB positions.

In May 2014, the FDA approved the Entovis Single-Chamber Pacemaker with ProMRI Technology (BIOTRONIK), with the first implant in the U.S. performed in our lab on May 13, 2014. Learning from the example of our European colleagues, we frequently implant single-chamber atrial pacemakers for chronotropic incompetence. While the Entovis platform assumes the lead is positioned in the RV (VVI-CLS is the only programming option), we find no discernable compromise in CLS performance when contractility dynamics are derived from the RA.

A representative case of a RA-only CLS pacemaker is shown (Figure 5). The patient is a 53-year-old male, with an unmistakable limitation in his ability to perform strenuous exercise since childhood. He underwent Amplatz closure of a large PFO six months prior, without symptom improvement. His heart is otherwise structurally normal with no CAD. A five-day ambulatory monitor (Medi-Lynx) demonstrated marked chronotropic incompetence, with heart rates <50 bpm over 60% of the time (Figure 5A1). Given there was no indication for ventricular pacing and the patient's desire for minimal hardware, a BIOTRONIK single-chamber atrial pacemaker was implanted in December 2014 (Figure 5B). Initial programming was AAI-CLS 50-150 bpm (Figure 5A2–A3), with CLS pacing derived from and delivered to the RA. Following an initially exuberant response to CLS, an upper rate limit (URL) of 140 bpm was needed temporarily (Figure 5A4) before returning to an URL of 150 bpm (Figure 5A5), with eventual progression to 160 bpm for complete restoration of functional capacity (Figure 5A6). Two months post pacemaker implant, the patient's ability to perform sustained strenuous exercise was restored (Figure 5C).

CLS FOR ICD AND CRT PATIENTS

CLS first appeared in BIOTRONIK's ICD platform in 2016, extending benefit to heart failure patients with chronotropic incompetence. An example case of CLS in a CRT-D system is shown in Figures 6 and 7. The patient is a 76-year-old male who remains mentally alert and active. He is status-post CABGx6 in 2005 complicated by an embolic CVA, with residual R-sided weakness that keeps him wheelchair bound. He experienced dissection of a thoracic aortic aneurysm in 2008, requiring AVR complicated by complete heart block. With LVEF 35% at that time, he underwent implantation of a dual-chamber ICD with failed endovascular LV lead placement for CRT. LVEF declined to 20-25% (2016) in the setting of 100% RV pacing (DDDR 60-130 bpm), and the patient underwent epicardial LV lead placement (Figure 6B).

ECG-guided CRT optimization was performed (Figure 6C), with an LV offset of 0 msec giving the most favorable QRS (QS in lead I, R in lead V1 with the least QRS widening).[7] CLS programming was initiated post-op with immediate benefit (Figure 7). Over 236 days of DDDR programming pre-op, there was 6% atrial pacing at the LRL of 60 bpm. Over the initial 26 days post-op with CLS, atrial pacing increased to 35% overall, with the majority of pacing at the 70 bpm range, with significant pacing at 80 and even 90 bpm. Ongoing progress was observed over 200 days post-op, with atrial pacing increasing to 49% as the patient responded to CRT therapy, and with the majority of

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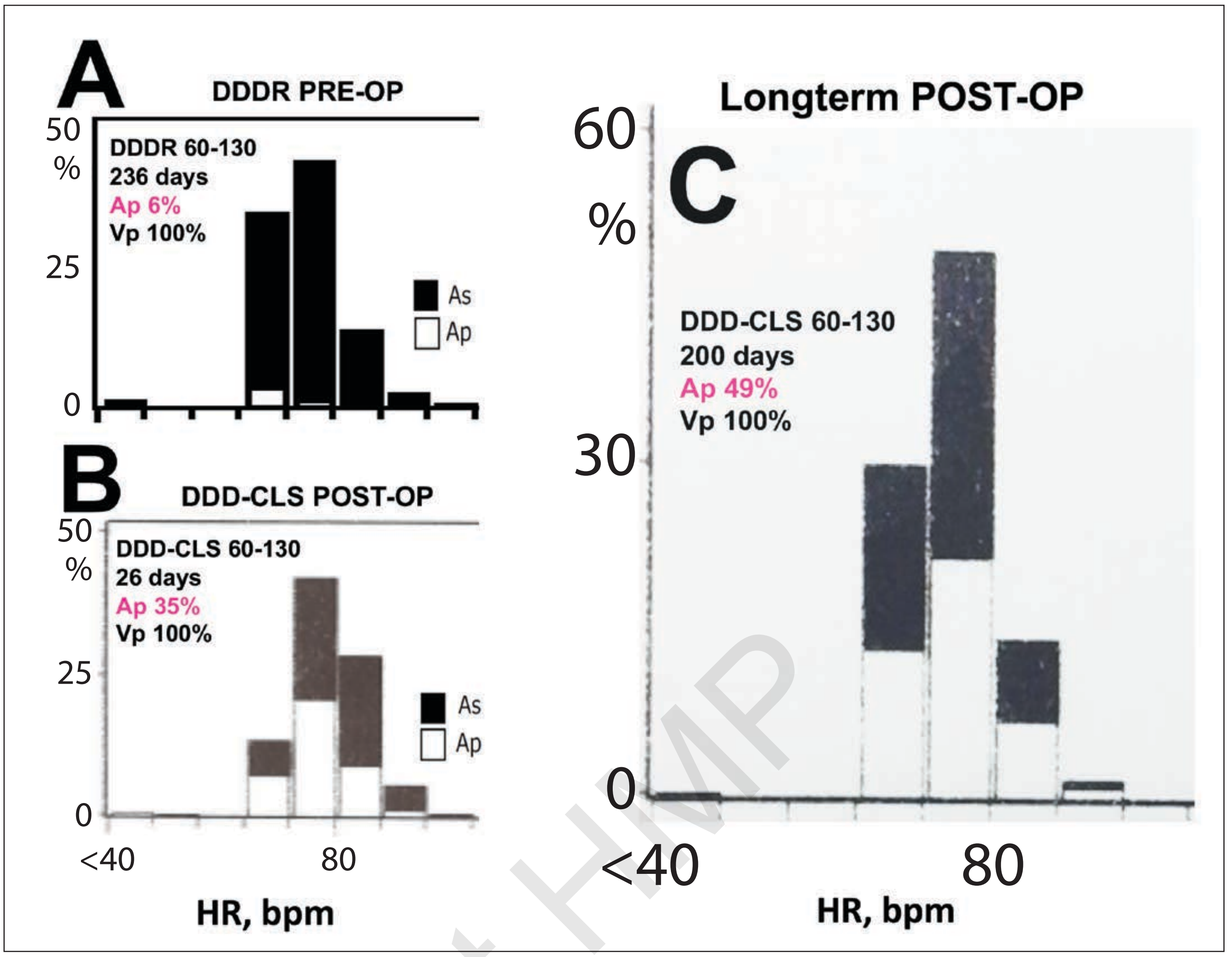

Figure 7: **CLS performance in a CRT-D system.** Rate histogram prior to CRT upgrade with DDDR programming (A). Enhanced rate histogram early (B) and late (C) following CRT upgrade with CLS programming.[8]

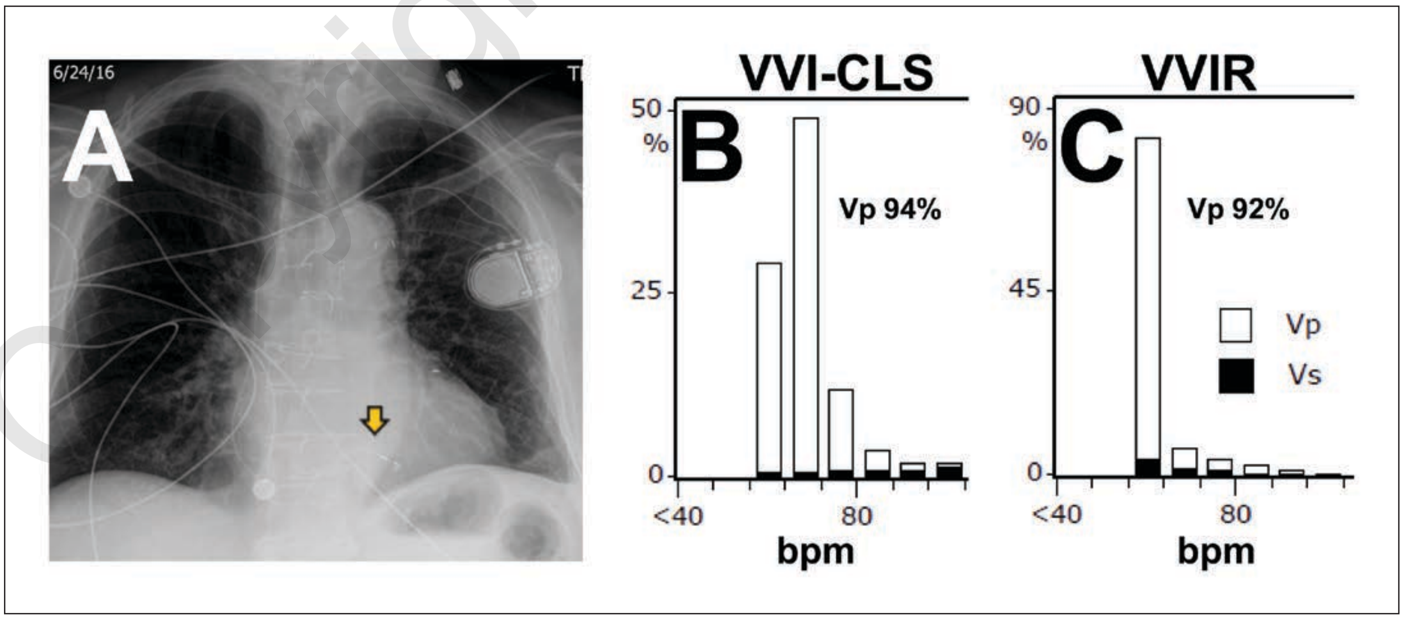

Figure 8: **CLS derived from the HB position in a single-chamber ventricular pacemaker** (A). Heart rate histograms were brisk with CLS (B) compared to VVIR (C). There was no discernable compromise in contractility dynamics and CLS from the HB position.

It is important to recognize the unique role that CLS may play in averting reflex vasovagal syncope. Following spontaneous vasodilation, a compensatory forceful systolic contraction may follow. This sudden increase in contractility is immediately detected by CLS, which provides a rate increase within a single beat.

CLS Experience

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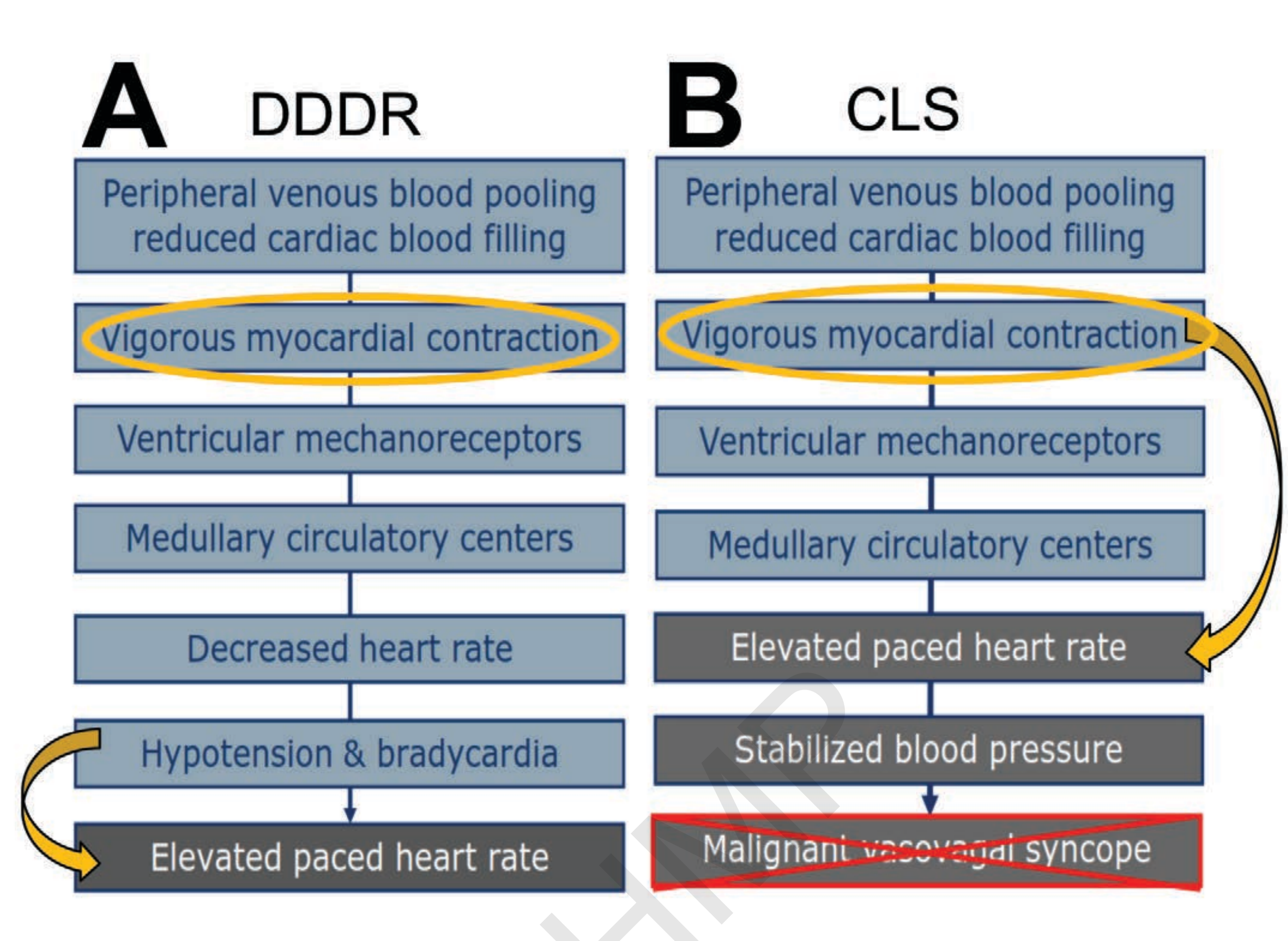

Figure 9: Treatment of vasovagal syncope with CLS. A vasovagal episode may result in venodilation and venous pooling, which is followed by a compensatory escalation in contractility. An autonomic imbalance may then occur, resulting in bradycardia rather than tachycardia to compensate for venous pooling, resulting in a faint (*Schematics courtesy of BIOTRONIK*). CLS may respond to upstream contractility changes to preserve cardiac output and prevent a faint (A). Other algorithms compensate after bradycardia occurs (Panel B), which may be too late to prevent a fainting episode.

pacing occurring above the LRL, within the ADL range of 70-90 bpm. There was 100% ventricular pacing throughout due to complete heart block.

The CLASS trial (NCT02693262) is systematically evaluating the potential role for CLS as heart failure therapy, comparing CLS versus accelerometer settings in heart failure patients with BIOTRONIK CRT-D systems. As the case shown in Figures 6 and 7 illustrates, we have observed a meaningful benefit with CLS in our heart failure patients. It is important to note that CLS is only available in CRT devices when the LV offset is set to 0. We routinely perform ECG-guided CRT optimization at the time of implant and during follow-up, and frequently identify a non-zero LV offset, giving the most favorable QRS morphology.[7] In these cases, we prioritize an optimized LV offset over CLS to maximize heart failure therapy. This restriction on CRT optimization is anticipated to limit the CRT response in the CLASS trial, and highlights the need for CLS capability for all CRT settings.

CLS WITH HIS-BUNDLE PACING (HBP)

It is uncertain how contractility dynamics compare between the RV and HB positions, and how differences may influence CLS. We performed the first-known case of HBP with CLS on June 23, 2016, combining what may be the most physiologic algorithm for rate-responsive pacing with the most physiologic pacing site (Figure 8A).[8] The patient was an 89-year-old male with limited mobility, permanent atrial fibrillation, moderate cardiomyopathy with LVEF 45-50%, LBBB, and profound bradycardia. With VVIR, the majority of pacing occurred at the LRL (50 bpm), with a blunted, linear response of the accelerometer (Figure 8C). VVI-CLS produced a brisk chronotropic response, with the majority of pacing occurring in the 60-69 bpm range, and considerably more pacing from 70-90 bpm (Figure 8B), consistent with an improved ADL response as demonstrated previously (Figures 3 and 4). Improved QOL quantified with CLS was demonstrated using the Minnesota Living with Heart Failure Questionnaire (MLHFQ).[8]

In a series of patients with BIOTRONIK pacemakers and ventricular pacing dependence (n=8), we have upgraded to HBP due to concerns for pacing-induced cardiomyopathy, allowing direct comparison of CLS dynamics from the HB and RV positions. Preliminary analysis suggests a loss of ~10 bpm rate response from the HB position; however, this is not consistently observed.

CLS FOR REFLEX VASOVAGAL SYNCOPE

Lastly, it is important to recognize the unique role that CLS may play in averting reflex vasovagal syncope. Following spontaneous vasodilation, a compensatory forceful systolic contraction may follow. This sudden increase in contractility is immediately detected by CLS, which provides a rate increase within a single beat (Figure 9B). In such cases, it is important to disable the "resting rate control", which nominally limits a sudden rate change to 20 bpm, as a large instantaneous rate increase (100 bpm) may be necessary to prevent a faint. In contrast, other algorithms for vasovagal syncope only compensate following a decrease in heart rate, which occurs downstream from contractility changes, and may be too late to prevent a faint (Figure 9A). The utility of CLS in recurrent reflex vasovagal syncope was recently evaluated in the SPAIN study.[9] This randomized, double-blind, controlled study included 46 patients with high burden syncope (≥5 episodes, ≥2 episodes in the past year) and a cardioinhibitory head-up tilt test (bradycardia <40 beats/min for 10 s or asystole >3 s). The proportion of patients with ≥50% reduction in the number of syncopal episodes was 72% (95% confidence interval [CI]: 47% to 90%) with DDD-CLS compared with 28% (95% CI: 9.7% to 53.5%) with sham DDI mode ($P = 0.017$). Overall, DDD-CLS pacing significantly reduced syncope burden and time to first recurrence by 7-fold, prolonging time to first syncope recurrence in patients age ≥40 years with head-up tilt test-induced vasovagal syncope compared with sham pacing. ■

Disclosures: The author has no conflicts of interest to report regarding the content herein. Outside the submitted work, Dr. Kneller reports minor honoraria and non-financial support from BIOTRONIK for research work.

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