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# Strategies and Pacemaker Algorithms for Avoidance of Unnecessary Right Ventricular Stimulation

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Additional information is available at the end of the chapter

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## 1. Introduction

Since the first implantation of a pacemaker (PM) was performed in 1958, this effective form of antibradycardia therapy has evolved in an amazing way. Besides ensuring the survival of patients with asystole or complete AV block who lack a sufficient intrinsic escape rhythm, today there is a wide range of further indications including advanced therapy strategies for pacing therapy. After it was shown that frequent right ventricular (RV) stimulation (especially in the RV apex (RVA)) can be associated with clinical deterioration in patients with implanted cardioverter-defibrillators (ICD) the avoidance of unnecessary RV pacing (RVP) has become one of the cornerstones of modern ICD- and PM-therapy.

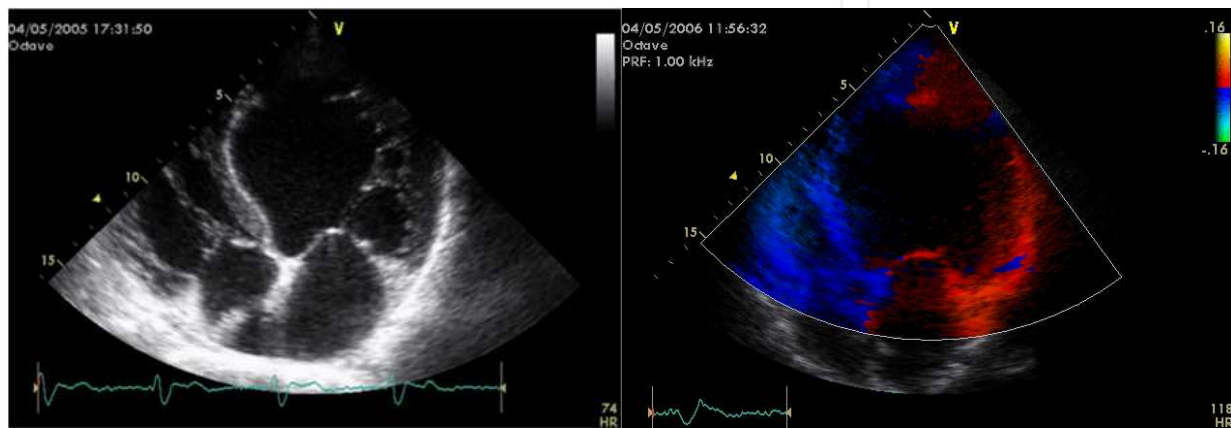
## 2. Pathophysiology of right ventricular stimulation

With intact cardiac conduction, the physiological excitation of the ventricles occurs with high velocity (3-4m/s) via the His-Purkinje-system (HPS) nearly synchronously. This is the basis for an optimum hemodynamic contraction sequence in all heart chambers.

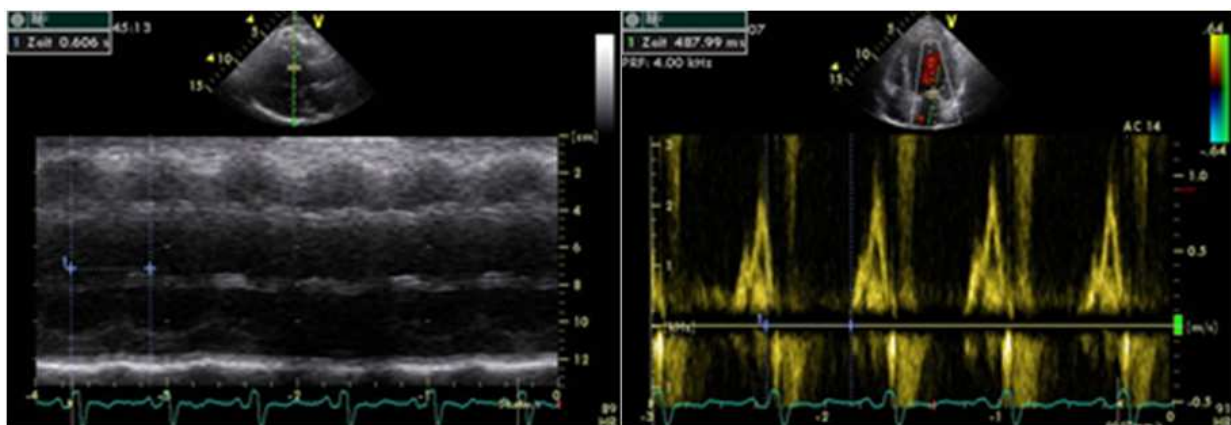
Similar to the excitation in a premature ventricular contraction (PVC) or following conduction through an antegrade conducting bypass tract, ectopic ventricular stimulation will result in a more or less non-physiologic activation and therefore non-physiologic contraction sequence of the ventricles. For example, the conduction after stimulation in the RV apex (RVA) will occur mostly in the working myocardium with a significantly lower velocity  $\leq 1$  m/s in an apico-basal direction from the RV via the interventricular septum to the left ventricle (LV). The exact individual sequence of excitation and contraction will be influenced by stimulus location, activation of parts of the specific conduction system and electroanatomical characteristics of the myocardium (fibrosis, scars). The dyssynchronous

contraction resulting from atypical excitation due to pacing can be compared to the situation in patients with conduction delay or block in the left Tawara-bundle (left bundle branch block (LBBB)).

At the start of systole (isovolumetric phase) the myocardial fibers near the RVA-pacing site will be the first ones to shorten, whereas the more remote left lateral ventricular areas will go into passive stretching, as they are lacking electrical excitation at this point. In the ejection phase the early activated areas will be able to contract only a little further, whereas the later activated areas will contract 1) delayed and 2) increased due to the previous stretching (Fig. 1 and 4).



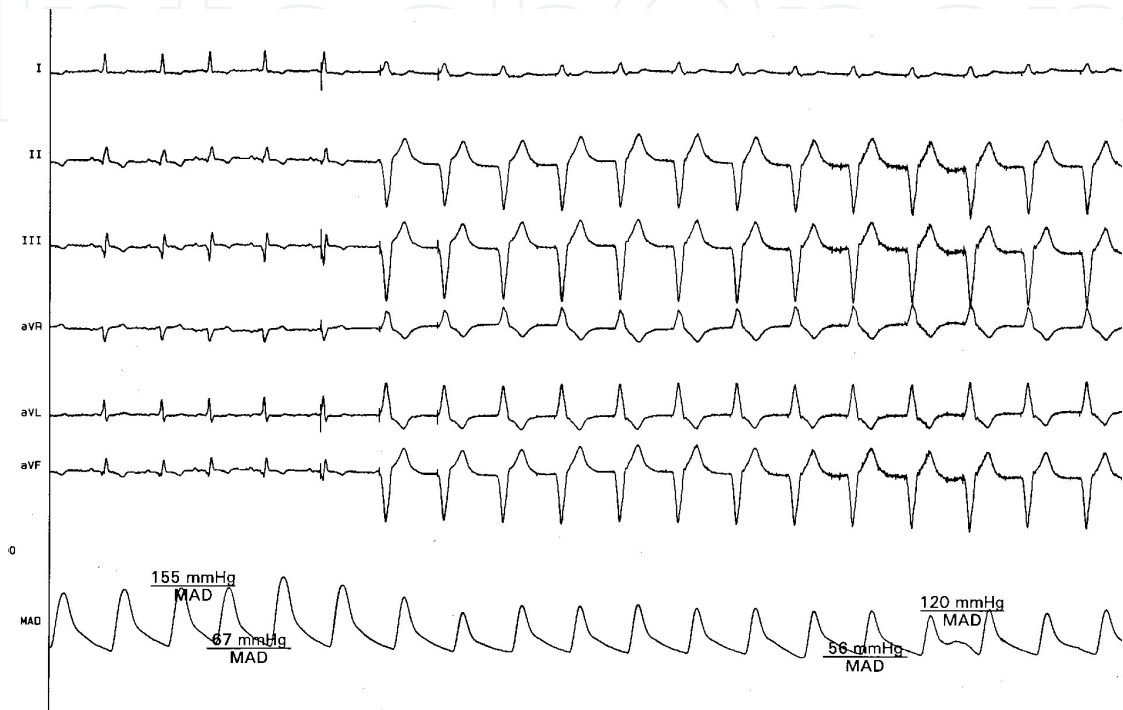
**Figure 1.** a. Transthoracic echocardiogram (TTE, apical 4-chamber view (A4CH)); 2b. Tissue Doppler. There is preserved global systolic LV-function but longstanding left ventricular dyssynchrony (here resulting from LBBB) causes a typical hypertrophy of the left lateral wall compared to the interventricular septum. This is due to the delayed systolic LV lateral wall activation and the increased contraction after the preceding passive stretching. The different colors in the Tissue Doppler demonstrate the dyssynchronous wall motion.



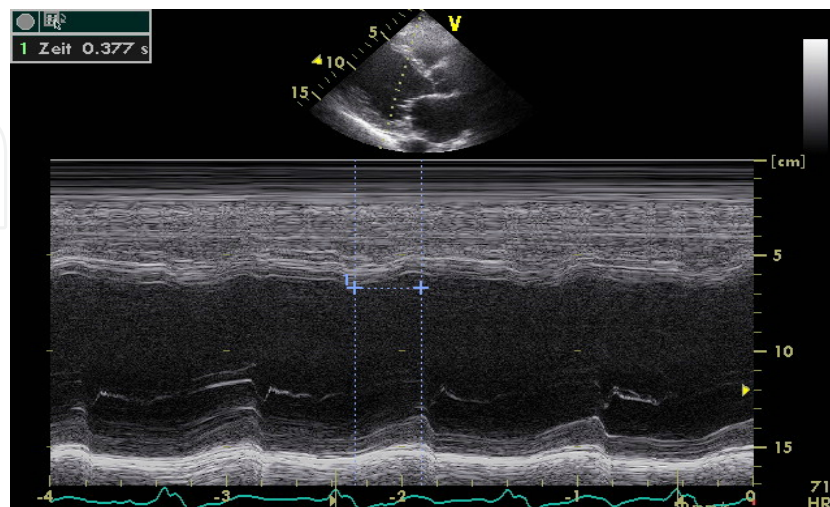
**Figure 2.** a. TTE, m-mode, parasternal long axis (PLAX); 2b. Doppler at mitral inflow, A4CH. Demonstration of systolic contraction of the left posterolateral ventricular wall (LV-PLW) while there is already left ventricular filling. The time interval  $\Delta t_1$  from the beginning of the QRS complex to the end of anterior movement of the LV-PLW (fig. 2a) is longer than  $\Delta t_2$ : from the beginning of the QRS complex to the start of transmitral filling (fig. 2b). Transmitral Doppler shows fusion of E- and A-wave, representing an overlap of the passive and active LV filling, which is therefore shortened and reduced.

The electromechanical dyssynchrony influences the diastole as well. Whereas the first activated areas of myocardium already enter the relaxation cycle, the delayed activated ones can still be in systolic contraction. This late systolic contraction delays the passive ventricular filling and thereby shortens the effective duration of diastole (Fig. 2) [1].

The delayed dyssynchronous activation of the ventricles with RV stimulation is visible in the ECG by a more or less deformed and widened QRS complex (Fig. 3).

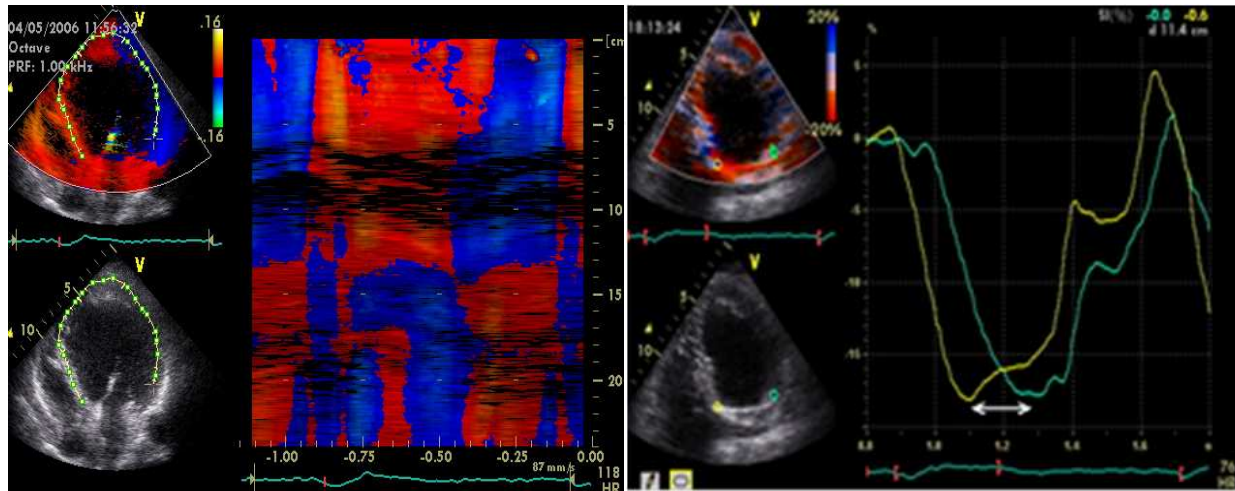


**Figure 3.** 12 Lead-ECG of VVI pacemaker stimulation in the right ventricular apex. The stimulated QRS complex is visibly widened, shows a negative deflection in the inferior leads (II, III, aVF) and LBBB-like deformation. Note the fall of aortic pressure with VVI stimulation here in a patient with sinus rhythm.



**Figure 4.** TTE, m-mode, PLAX. Demonstration of the different times for maximum systolic contraction of the interventricular septum and the LV posterolateral wall. The "septal to posterior wall motion delay" (SPWMD) is measured as 377 ms in this case. Values > 130 (140) ms are considered pathological.

Echocardiography allows excellent noninvasive estimation of global and regional electromechanical dyssynchrony and hemodynamic consequences. Examples are shown in Fig. 1, 2 as well as 4 and 5. For more detailed information further specialized reading is recommended [2-5].



**Figure 5.** Visible shift of the contraction phases of interventricular septum and lateral LV wall, color-m-mode (5a) and Tissue Doppler/ strain (5b).

### 3. Clinical consequences of unnecessary right ventricular pacing

The first evidence for clinically relevant negative effects of a high percentage of RV pacing was found interestingly in studies that were originally intended to show benefits of “physiologic” AV sequential DDD stimulation compared to VVI stimulation.

The original intention of the DAVID trial (Dual Chamber and VVI Implantable Defibrillator) was to show a survival benefit of dual chamber ICD systems compared to single chamber ICDs. Patients with an ejection fraction <40% and chronic heart failure were enrolled, who didn’t have an indication for antibradycardia stimulation. The study was stopped early after enrollment of 506 patients: the patients with the supposedly “physiological” AV sequential DDD pacing (at least 70/min) had a 1.61 increased risk for mortality or hospitalization because of new onset or deteriorated heart failure compared to patients with VVI backup stimulation (40/min) only [1,6,7]. The proportion of ventricular stimulation was 55.7% in the DDD group compared to 2.9% in the VVI patients.

In a sub-study of the MOST trial (Mode selection Trial) it was shown that patients with DDD(R) stimulation for sick sinus syndrome / sinus node dysfunction (SSS / SND) and normal QRS duration (<120 ms) had a significant increase of their risk for heart failure hospitalization (HFH) associated with an increase of cumulative percentage RVP (cum%RVP) up to 40% [1,8].

Interestingly the correlation between the percentage of RV stimulation and the risk for HFH was different for patients with DDDR versus VVIR stimulation.



After detailed review it seemed that the risk for HFH stayed nearly constant for percentages of VP >40% in the DDDR mode. It was therefore speculated that the risk of HFH in the DDDR mode would not increase with further increases in cum%RVP above 40%, but a further risk reduction to about 2% could be achieved with minimization of unnecessary RV pacing (VP <10%).

Overall the relative risk for hospitalization due to heart failure was always higher for VVIR patients compared to DDDR patients who had a comparable percentage of cumulative right ventricular stimulation.

Furthermore a linear relationship, between RV pacing and the incidence of atrial fibrillation (AF), was found up to a right ventricular stimulation percentage of 85% [8].

This observation was confirmed in a prospective randomized study including 177 patients with SSS, by demonstrating that AAIR stimulation was associated with a significantly lower incidence of AF compared to DDD stimulation with a short ( $\leq 150$  ms) or a long (300 ms) AV interval [9]. Furthermore no significant changes were observed for left atrial (LA) or left ventricular diameters in the AAI(R) population, whereas in both DDD(R) groups the LA diameter increased significantly.

A sub-analysis of the MADIT II study (Multicenter automatic defibrillator trial II) was also able to show a clear correlation between more frequent RV stimulation and increasing morbidity and mortality for the included collective of ICD patients [10]. With increased RV stimulation the percentage of VT episodes was higher. If there was a cum%RVP of  $\geq 50\%$  a significant increase of the risk for HFH was observed ( $p < 0.001$ ).

Gardiwal et al. showed that apart from an LV ejection fraction (EF) <40% a cum%RVP >2% is an independent predictor for the occurrence of ventricular tachyarrhythmias, mortality and episodes of heart failure in ICD patients (who had predominantly secondary prophylactic ICD indications) [11].

Since the implementation of specific algorithms for avoidance of unnecessary RV stimulation in modern PM and ICD systems several studies have shown the clinical relevance and necessity of this approach. The details of these studies will be shown in the following sections respectively.

## **4. Strategies and algorithms for avoiding unnecessary right ventricular stimulation**

### **4.1. Single-chamber AAI(R) pacing**

In patients with single SND and completely intact AV conduction, the implantation of an AAI(R) system theoretically appears to be the best form of pacemaker therapy especially considering the - here 100% - avoidance of RV stimulation [12]. It has to be emphasized, that this pacing modality is so far the only one with a prognostic benefit (overall and cardiovascular mortality of 225 PM patients with SND) that was proven in a study: in the

DANISH trial the AAI(R) stimulated patients had a higher survival rate, less deaths due to heart failure (HF) and other cardiac causes, less AF and fewer thromboembolic complications compared to the group with VVI(R) stimulation [7,12-14].

Indication:

In principle all AAI systems can be indicated in single SND without evidence of impaired AV conduction or concern over development of AV block in the future.

The following conditions have to be present:

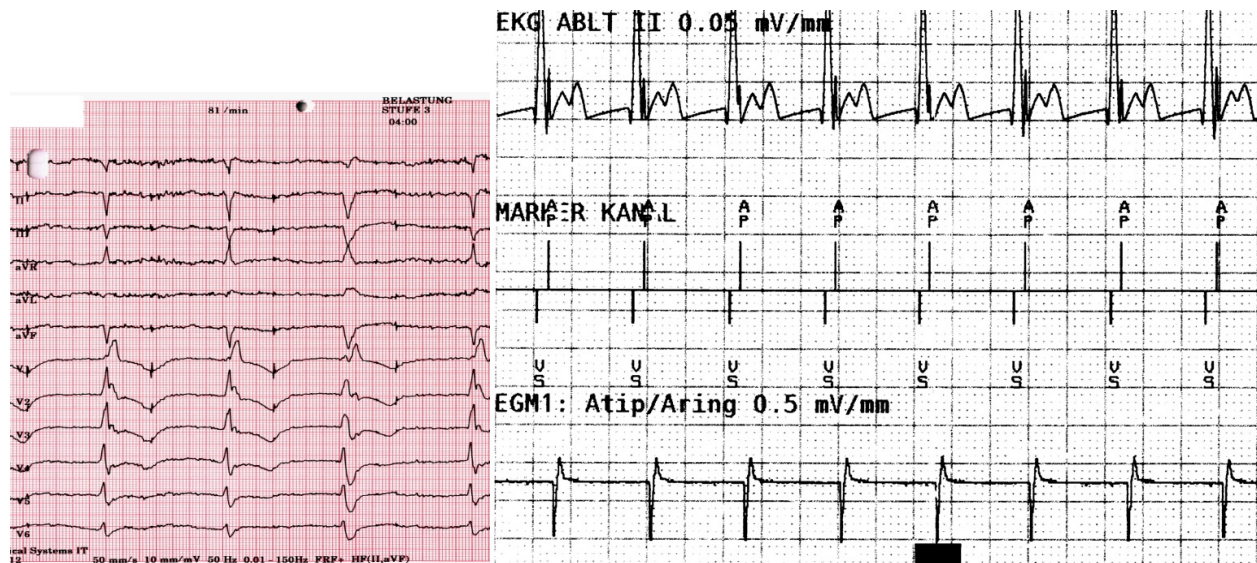
- No AV block of any degree (including  $^{\circ}1$ )
- Narrow QRS complex
- Antegrade 1:1 conduction / Wenckebach point  $>120$  (130)/min
- No need for any medication causing conduction delay
- No carotid sinus syndrome
- No loss of consciousness as primary indication for pacing therapy.

Patients with carotid sinus syndrome or vasovagal syncope are not suitable for AAI systems, because apart from the inhibition of the sinus node intermittent AV block is encountered. [14].

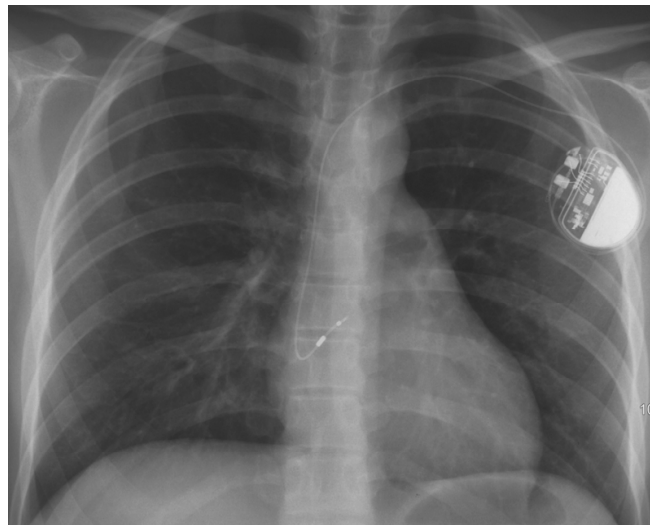
Whereas the overall percentage of AAI(R) pacemaker systems is about 9-10% in Scandinavian countries [1,7], atrial single-chamber pacemakers are only implanted in selected cases in other countries. The German PM register lists for the year 2009 a nearly constant low implantation rate of 0.5% AAI systems [15]. The reasoning behind it is, that relevant AV conduction disturbances are often not detectable or foreseeable at the time of implantation, however a later manifestation cannot be predicted or excluded for the individual patient. The incidence of new onset AV block is overall low and is reported to be approximately between 0.65% and 1.8% per year [1,12,16]. In studies on atrial pacing for SND a median annual incidence of third-degree AV block of 0.6% (0%-4.5%) with a total prevalence of 2.1% (0-11.9%) was revealed. Potential clinical manifestations include

- Clinical symptoms due to AV block associated bradycardia, pauses or asystole, if there is no sufficient intrinsic escape rhythm. The incidence of syncope or near-syncope is high within the group of patients with onset of higher degree AV block.
- AAI pacemaker syndrome with non-physiologic long intrinsic, hemodynamically unfavorable AV delay (Fig. 6)

The fixation of the atrial lead in the appendage usually provides a stable position and good results for sensing and pacing threshold. Relevant ventricular far field signals should be ruled out carefully. Alternatively septal atrial (active) lead placement in the area of Bachmann's bundle (Fig. 7) can provide a more synchronous atrial activation resulting in a shorter P wave duration. There is some evidence that septal atrial pacing might have preventive effects on the incidence and progression of atrial fibrillation [51,52].



**Figure 6.** a. 12-lead stress test ECG: Unlike the normal physiologic response there can be a lack of shortening or even an increase of the intrinsic AV conduction delay during AAI stimulation with exercising in some patients with SND: the atrial stimulation can appear in extreme cases within the preceding systole (atrial stimulus shortly after or even within the QRS complex), the (nearly) simultaneous contraction of atria and ventricles can be the consequence, resulting in an AAI PM syndrome (6b).



**Figure 7.** Chest x ray. Single-chamber AAI PM implanted on the right side in a young female patient with symptomatic idiopathic sinus bradycardia. The active atrial electrode is placed at the septum, resulting in a narrow P wave indicating better synchronized activation of the atria.

If there is impaired AV conduction, a dual- or triple-chamber pacemaker system should be implanted. This should be considered in patients with advanced cardiac disease as well [14].

The indication for implantation of single-chamber AAI PM in patients with SND is currently questioned even more after the results of the DANPACE trial (The Danish multicenter randomised trial on AAIR versus DDDR pacing in sick sinus syndrome) [Nielsen, ESC Congress 2010]. The aim of this study was to compare AAIR with DDDR stimulation (lower



rate 60/min, upper rate 130/min, paced/sensed AV-interval  $\leq 220$  /  $\leq 200$  ms). As main finding there was no survival difference for the 1415 patients in the two groups after follow up over  $5.4 \pm 2.6$  years. The mortality of all causes was 29.6% in the AAIR group versus 27.3% in the DDDR group ( $p=0.53$ ). There was a doubling of reoperation risk with AAIR pacing. After correction for baseline variables, the patients in the AAIR group had a 27% risk increase for the development of atrial fibrillation. This contradicts the results of previous studies and therefore was not expected. However there was no monitoring regarding atrial fibrillation before enrollment, which means that a preexisting difference between the groups in AF prevalence already at baseline cannot be excluded. Additionally, monitoring in the follow up was not very sensitive for recognizing of AF episodes. The conclusion of the DANPACE authors was, that single-chamber (AAIR) pacing should be avoided in patients with SND and that DDDR stimulation using an AV interval  $\leq 220$  ms should be the pacing modality of choice for SND.

In his guest editorial for PACE in 2001 S. Barold concluded that permanent single-chamber atrial pacing is *obsolete*: "Proponents of AAI(R) pacing claim it is safe but dual-chamber pacing is *safer* than AAI(R) pacing and more suitable for the overall care of SSS patients." [17].

#### 4.2. VVI stimulation with low intervention rate („VVI backup“)

The guidelines of the German society of cardiology state that VVI stimulation with a low intervention rate (e.g.  $<45$ /min) can be indicated, if there is rare disturbance of AV conduction (occurrence  $<5\%$ ) [indication class I B]. [14,18,19].

Fröhlig justifies the indication for implantation of a simple „VVI backup“-PM system in patients with recurrent syncope due to paroxysmal AV block, BBB and normal HV interval [1]. These patients have a high risk for further syncopal episodes. If there is no need for antibradycardia pacing apart from the short phases of paroxysmal AV block, this subgroup can be fitted adequately with a sole VVI „backup“ stimulation of 40/min.

Compared to pacemaker patients the situation looks different in patients with an ICD indication only, without need for antibradycardia pacing. The above mentioned DAVID study showed superiority of single-chamber ICD systems with a programming of VVI 40/min to a dual-chamber mode [1,6,7].

In 2007 the INTRINSIC RV trial enrolling 988 ICD patients showed that the group with DDD pacing (60-130/min) with AV search hysteresis (AVSH, Boston Scientific) was not inferior to the VVI backup pacing group (40/min) in terms of all-cause mortality and heart failure hospitalization after 10 months follow up [20]. In the DDDR AVSH group the mean cum%RVP was 10% compared to 3% in the VVI pacing group. It has to be emphasized however, that prior to randomization only patients that had  $<20\%$  ventricular stimulation in the first week after implantation in DDDR AV search hysteresis mode were selected and therefore would be regarded as likely "responders" to AVSH.

The MVP trial was a prospective, multicenter, randomized, single-blind, parallel, controlled clinical trial which didn't succeed in showing that atrial-based dual-chamber managed ventricular pacing mode (MVP™) is equivalent or superior to backup only ventricular pacing (VVI 40/min) with regard to time to death, heart failure hospitalization and heart failure-related urgent care in patients with standard indication for ICD therapy and no indication for antibradycardia pacing. The overall HF event rate was found to be slightly higher during AAI pacing and was mainly seen in patients with a PR interval  $\geq 230$  ms in the MVP-60 group compared to VVI-40. There were no differences between the two compared ICD pacing modes for atrial fibrillation, ventricular tachyarrhythmias, quality of life, or echocardiographic measurements. [21].

There is an ongoing discussion with regard to a possible improvement of discrimination between supraventricular and ventricular tachyarrhythmias due to additional atrial information in dual-chamber ICD compared to VVI systems as this could avoid inadequate therapy deliveries by the ICD.

The DATAS trial found a reduction of clinically significant adverse events (CSAE) in dual-chamber ICD versus single-chamber devices or simulated single-chamber mode in implanted dual-chamber systems [22]. It was possible to reduce the occurrence of inadequate ICD shocks for atrial fibrillation in dual-chamber ICDs. Procedure related complications were more frequent with dual-chamber devices.

A meta-analysis from 2008 (748 patients) found less inappropriate treated episodes with dual-chamber discrimination but the number of patients experiencing inadequate therapies was not reduced [23]. It has to be known that the programmed criteria for differentiation of supraventricular and ventricular tachyarrhythmias in the VVI ICD in this study were most commonly "onset" and "stability". Modern single-chamber ICDs offer markedly improved discrimination algorithms as standard today.

In summary the majority of patients with ICD indication only, i.e. lacking foreseeable demand for antibradycardia pacing or indication for CRT at the time of implantation, can be fitted adequately with a modern VVI ICD system and a backup-rate of 30-40/min. Advantages include avoidance of unnecessary RV stimulation, less expensive and less complex systems, less complications at implantation and in the long term course by using just a single lead. Most of the time in current single-chamber ICDs using modern algorithms there isn't worse SVT/VT discrimination compared to dual-chamber ICDs.

The disadvantage of this strategy is: If the need for regular antibradycardia pacing arises in the clinical course of patients with single-chamber ICDs the upgrade to a dual-chamber or CRT system is often a more complex procedure.

Therefore, dual-chamber ICD systems should be preferred in the following situations (of course unnecessary RVP should still be avoided when possible):

- Conventional PM indication (especially SND; with permanent AV block II ° or III ° consider CRT-system)
- Long-QT-Syndrome

- History of (frequent) atrial tachyarrhythmias.

### 4.3. DDD stimulation with fixed long AV delay

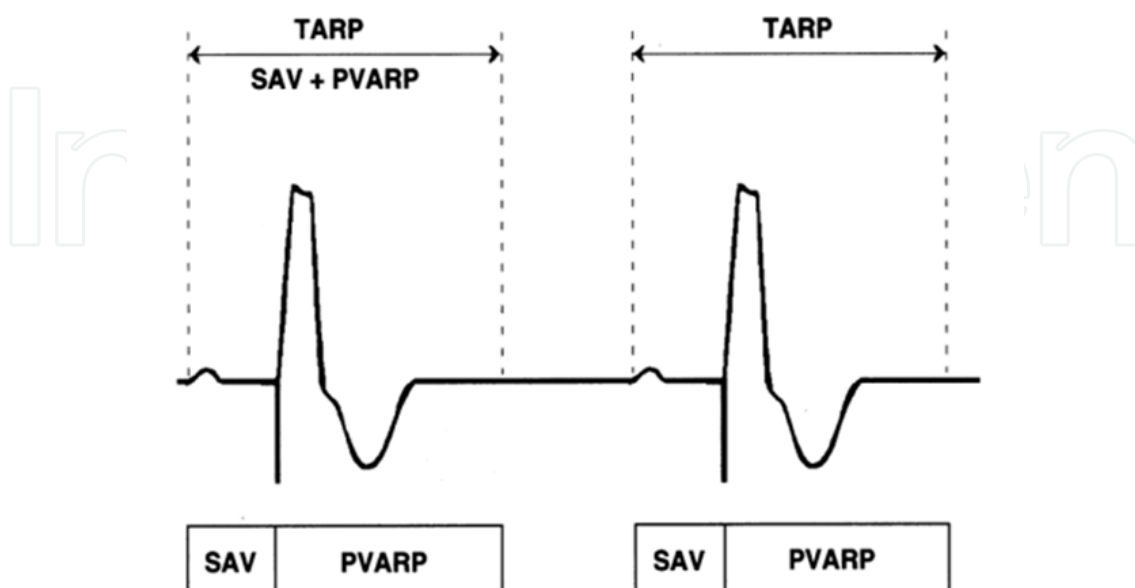
Programming of a fixed long atrioventricular delay (AVD) supports intrinsic conduction in patients with largely intact or only mildly impaired atrial and atrioventricular conduction and thereby avoids unnecessary RV stimulation.

However, even in patients with isolated disease of the sinus node and a programmed fixed AVD of 300 ms, a percentage of >10% RV stimulation is found in about every third patient [1,24]. It has to be kept in mind that the IEGM determined AVD of the PM is not identical with the PQ interval measured in the surface ECG. The relevant AV interval for the timing of the PM in atrial stimulation consists of: conduction time from the stimulus to the atrium, intra- and interatrial conduction times, AV conduction and the time to the expected actual detection of ventricular activation, which sometimes can be markedly delayed up to the S wave of the chamber complex [25].

In clinical practice the following problems have to be considered with fixed long AVD programming [25]:

- A prolonged AVD results in an extension of the total atrial refractory period (TARP, fig. 8). Depending on the programmed postventricular atrial refractory period (PVARP) a limitation of the upper rate behavior can be the consequence, i.e. respectively lower limitation of the upper 1:1 AV conduction rate (upper tracking rate, 2:1-block rate), which can lead to problems with higher degree AV block on exercising.

Example: with an AVD of 300 ms plus a PVARP of 300 ms, the PM is not able to detect atrial rates above 100/min 1:1 anymore and if there is a higher degree AV block to track AV sequentially 1:1.



**Figure 8.** TARP = AV Delay + PVARP

- If as compensation the PVARP is programmed shorter in patients with preserved VA conduction, the occurrence of pacemaker mediated tachycardias (PMT) is facilitated.
- With an extremely long AVD the frame for detection of intrinsic atrial activities is limited, which sometimes - depending on the postventricular atrial blanking period (PVAB) - can possibly lead to an impairment of the mode switch reaction in atrial tachyarrhythmias [26].
- In case of higher degree AV block with resulting need of ventricular stimulation the (ultra-) long fixed AVD may result in a less favorable hemodynamic situation.
- If there is intermittent atrial undersensing (typically in atrial fibrillation) a very long AVD may favor proarrhythmic pacemaker-induced R-on T-stimulation. To avoid this a short postatrial ventricular blanking period should be programmed and the ventricular safety stimulation (safety window pacing) should be activated [25].

With SND and preserved AV conduction DDIR mode is recommended if a long AV delay is programmed [25,27]. Unfortunately this is not really an option in patients with intermittent AV block, as intrinsic P waves (AS-events) can't trigger AV sequential response then.

In summary the programming of fixed long AVD is associated with numerous problems. Nielsen et al. entitled a publication in 1999: "Programming a fixed long atrioventricular delay is not effective in preventing ventricular pacing in patients with sick sinus syndrome" [24]. For the effective avoidance of unnecessary RV stimulation the following modern algorithms should be preferred, if the implanted DDD PM offers these options.

#### 4.4. AV hysteresis

To escape the problems associated with long fixed AVD the AV hysteresis was developed. The term "hysteresis" originates from the Greek *hysteros* = thereafter, later.

The algorithm distinguishes intact versus impaired / non-physiologically prolonged intrinsic AV conduction. A longer intrinsic AV conduction time is permitted ensuring stimulation with an optimized AV interval in case of a higher degree AV block.

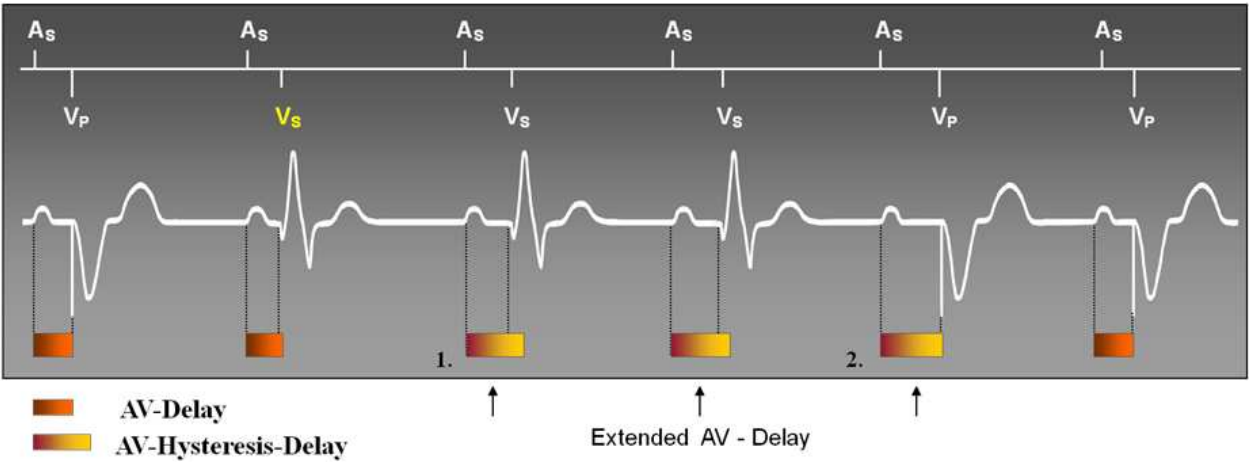
Basically there are 2 sets of sensed or paced (AV / PV) atrioventricular intervals:

- The shorter AV-/PV delay becomes active, if the conducted intrinsic ventricular sensed (VS) event is missing.
- The longer (hysteresis) AVD will be switched to after VS events or when there is a search for intrinsic conduction [28].

The AV sequential cycle is mandatory for every beat.

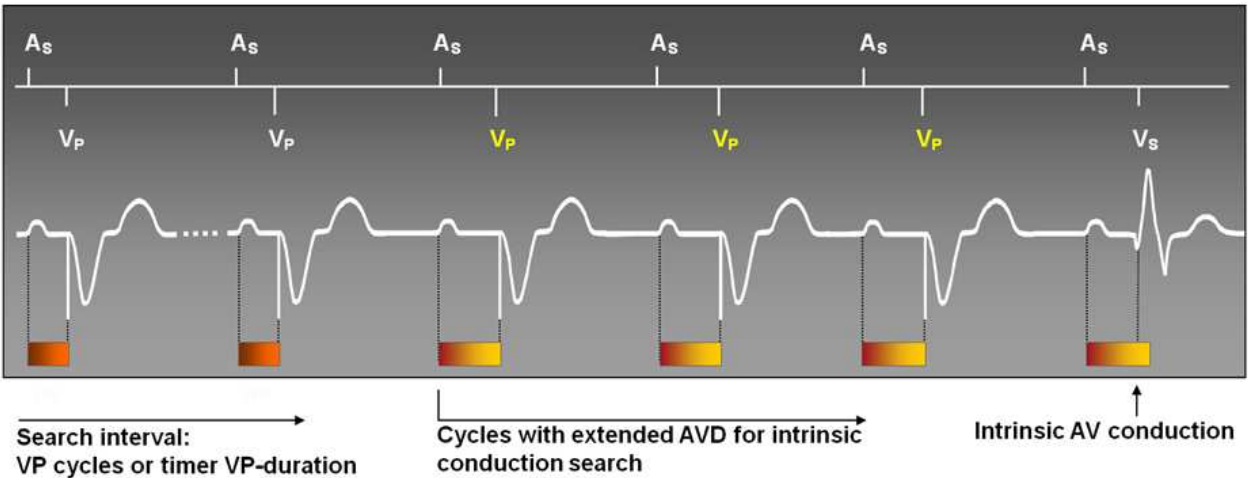
- If AV hysteresis is activated the stimulated or sensed (short base) AV time will be extended by a programmable amount of time after a spontaneous VS event. This now long AV interval remains unchanged, as long as there is intrinsic AV conduction within this interval (VS). After ventricular stimulation (VP) the shorter AV interval becomes active. (fig. 9).





**Figure 9.** AV hysteresis: 1. After ventricular sensing (VS) the short AVD is extended by the programmed hysteresis interval. 2. A ventricular stimulation (VP) after the active long AVD deactivates the hysteresis and stimulation continues with the programmed short AV/PV delay.

- If an *AV repetitive hysteresis* is activated, a single VP event will not immediately result in switching to the short base AV interval, but the long AV hysteresis interval will remain for a programmed number of cycles. The set back to the short AVD will come if there is no intrinsic conduction during these cycles.
- The *AV search hysteresis* looks actively for preserved intrinsic conduction: In determined intervals the short base AV interval will be prolonged actively by the hysteresis duration for a set number of cycles (fig. 10).



**Figure 10.** AV search and repetitive hysteresis.

Generally in modern devices these 3 algorithms can be activated combined in 1 function. The exact criteria that can be programmed (maximum AV time extension, search intervals) vary between the device manufacturers and models.

As examples available algorithms of 4 manufacturers are explained:

- a. AV search hysteresis (AVSH (+)), Boston Scientific



- The function becomes inactive in the following situations:
  - DDD(R) or VDD(R) mode + base rate  $\geq 90/\text{min}$  + active rate dependent AVD
  - Intrinsic atrial rate or sensor rate  $\geq 90/\text{min}$
  - During rate search hysteresis.
- c. Intrinsic Rhythm Support (IRSplus), Biotronik
  - Example device: Philos II DR.
  - When the IRSplus is activated, the following features are set:
    - AV hysteresis is at a fixed length of 300 ms. The long AV interval stays active if an intrinsic ventricular signal is sensed (VS).
    - In AV repetitive hysteresis there are five cycles with the prolonged AV / PV interval after a VS event has occurred. The AV hysteresis remains active, if intrinsic ventricular activity is sensed during one of these five cycles. However after five repetitive cycles without spontaneous AV conduction the device changes back to the short AV / PV interval.
    - In AV scan hysteresis there is extension of the AV delay for five cycles after 180 consecutive ventricular paced cycles. If in these five cycles a spontaneous AV conduction is detected, the AV hysteresis stays active. If no ventricular event has been detected within these five cycles the device switches back to the short AV delay interval and the cycles end with ventricular stimulation. The cycle counter is reset and commences counting the consecutive paced cycles.
- d. Search AV<sup>TM</sup>/Search AV<sup>TM+</sup>, Medtronic
  - Example devices: Kappa 700 DR, EnPulse<sup>TM</sup>
  - The PM will try to detect intrinsic conducted events in an “AV delay window” that precedes scheduled VP events by -55 to -15 ms.
  - If the device classifies 8 out of 16 AV conduction sequences as too long / “late” ( $\leq 15$  ms before scheduled VP), it prolongs the operating SAV and PAV intervals by 31 / 62 ms for the next 16 pacing cycles to facilitate intrinsic conduction until the maximum AVD. If the previous 8/16 AV intervals are defined as too short ( $> 55$  ms before scheduled VP), the device will shorten the operating SAV and PAV intervals by 8 ms for the next 16 pacing cycles.
  - In the case of inadequate AV conduction (8/16 VP with maximum AVD) the search will be repeated after 15 and 30 minutes and then after 1, 2 ... 16 hours. The algorithm is deactivated after 10 unsuccessful searching attempts / 16 hours until the next device interrogation.
  - With the help of this algorithm intrinsic conduction is promoted even in cases with slightly changing AV conduction times and unnecessary long AV delay intervals are avoided.
  - The maximum AVD is 350 (Search AV<sup>TM</sup>) respectively 600 ms (Search AV<sup>TM+</sup>).

Melzer et al. compared the above mentioned algorithms Search AV<sup>TM</sup> (max. AVD sensed 230 / paced 260 ms) versus Search AV<sup>TM+</sup> (max. AVD 300 / 360 ms) in a randomized study with 30 PM patients [29]. They showed that prolonging the AV interval above 300 ms results in an additional significant reduction of the percentage of ventricular stimulation ( $19 \pm 28\%$  versus  $70 \pm 40\%$ ,  $p < 0.001$ ).

A larger prospective non randomized multi-center study enrolling 197 patients with a dual-chamber PM (EnPulse) demonstrated a reduction of cum%RVP from 97.2% without AV interval extension to 23.1% with Search AV+™ [30]. There were no adverse events reported under Search AV+™.

#### 4.5. AAI(R)↔DDD(R) mode switch

This strategy is currently considered the most effective form of reducing unnecessary RV stimulation. A dual-chamber system (PM or ICD) is implanted in the usual way with conventional atrial and ventricular leads. The programming follows a special AAI(R) mode, by which the device controls AV conduction with every beat. If intrinsic conduction is preserved, the stimulation will be in a functional AAI(R) mode. However, as the algorithm still maintains ventricular sensing to assess AV conduction, it acts technically like ADI(R) mode. In contrast to conventional dual-chamber systems with e.g. AV hysteresis these devices are allowed to accept even single non conducted p waves, e.g. as in second-degree AV block type Wenckebach (fig. 12).



**Figure 12.** A dual-chamber PM with AAI↔DDD mode switch (Reply DR, AAISafeR2™) accepts a single non conducted p wave in second-degree AV block type Wenckebach.

If a higher degree AV block occurs the device switches automatically to a dual-chamber mode according to defined criteria and keeps this up until improvement of intrinsic conduction.

This strategy thereby is thought to combine the advantages of the AAI(R) mode in avoiding unnecessary RV stimulation with the safety of DDD(R) backup.

To show examples 4 currently available systems will be explained.

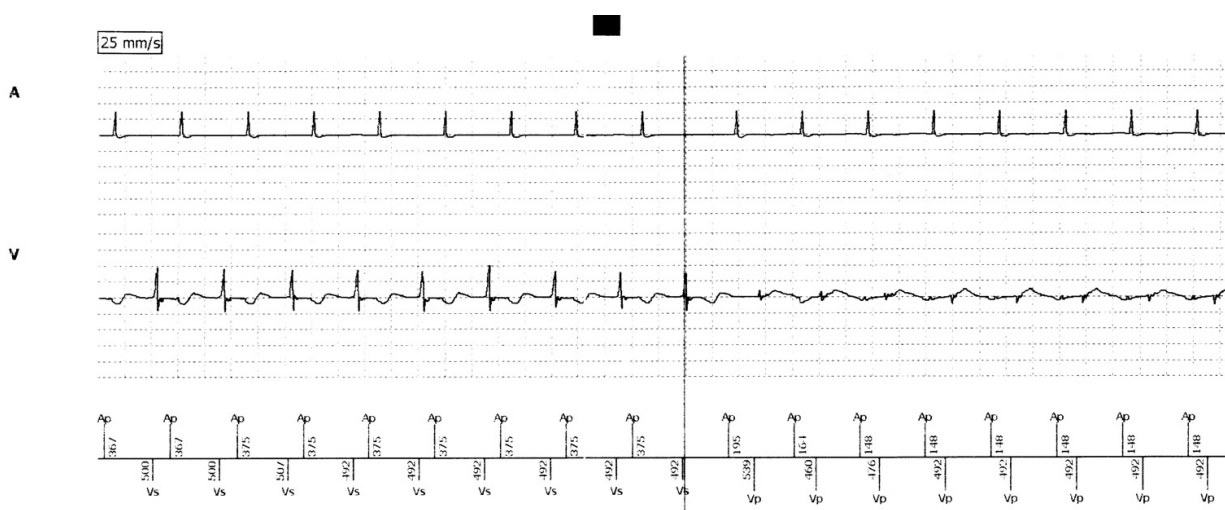
- a. AAISafeR™, AAISafeR2™, ELA Medical, Sorin Group
- Example devices: Symphony™ DR, Reply™ DR.



- AAISafeR™: loss of sufficient intrinsic AV conduction:

The switch to dual-chamber mode occurs following a defined pattern, by which the AV conduction is classified:

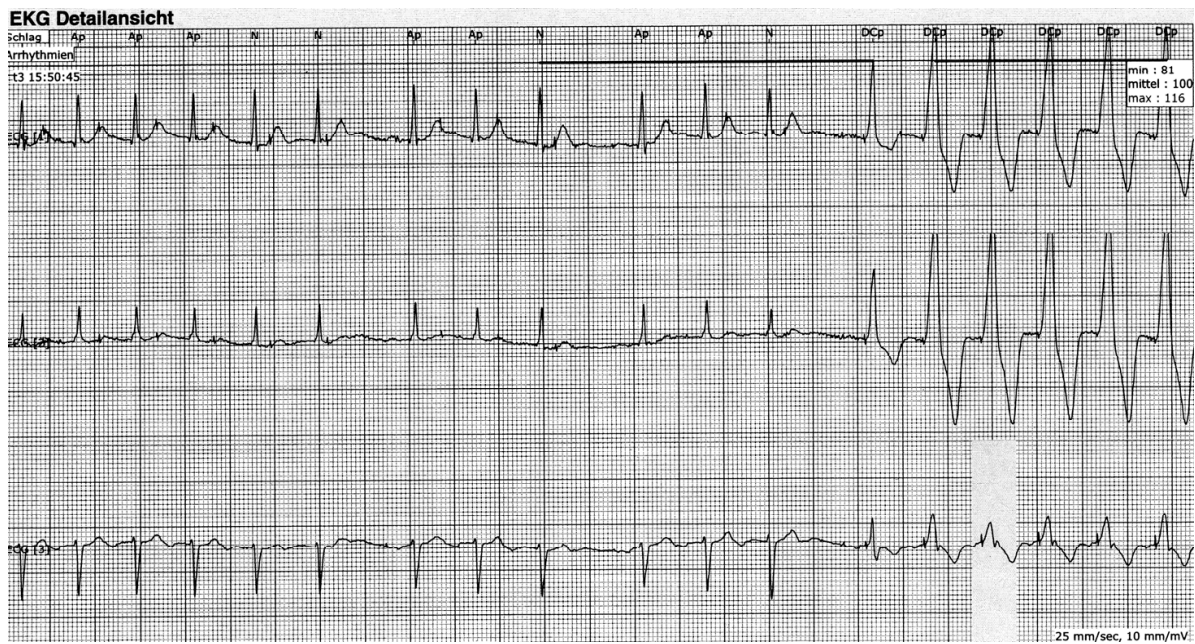
- 7 consecutive AV / PV intervals, that are too long (programmable for rest and exercise “first-degree AV block” criterion, fig. 13)
- 3 AS / AP events without VS within the last 12 atrial cycles (“second-degree AV block” criterion, fig. 14,15)
- 2 consecutive AS / AP without VS (“high degree AV block” criterion, fig. 16)
- Ventricular pause >2 up to 4 sec. (length of pause programmable, fig. 20)



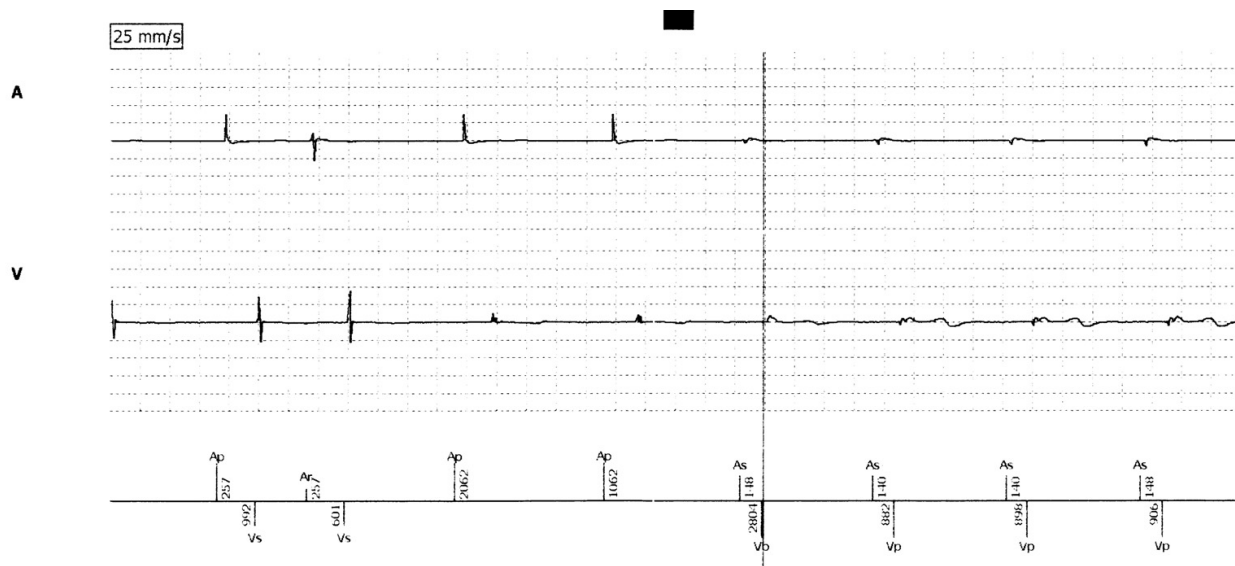
**Figure 13.** AAISafeR2™, Reply™ DR: pacing mode switch with consecutive long stimulated AVD.



**Figure 14.** AAISafeR2™, Reply™ DR: mode switch after 3 of 12 consecutive sensed or stimulated atrial events without VS. (In this particular case the pacing mode switch is triggered by a frequency-dependent AV block caused by a short run of an atrial tachycardia, atrial CL about 450 ms).



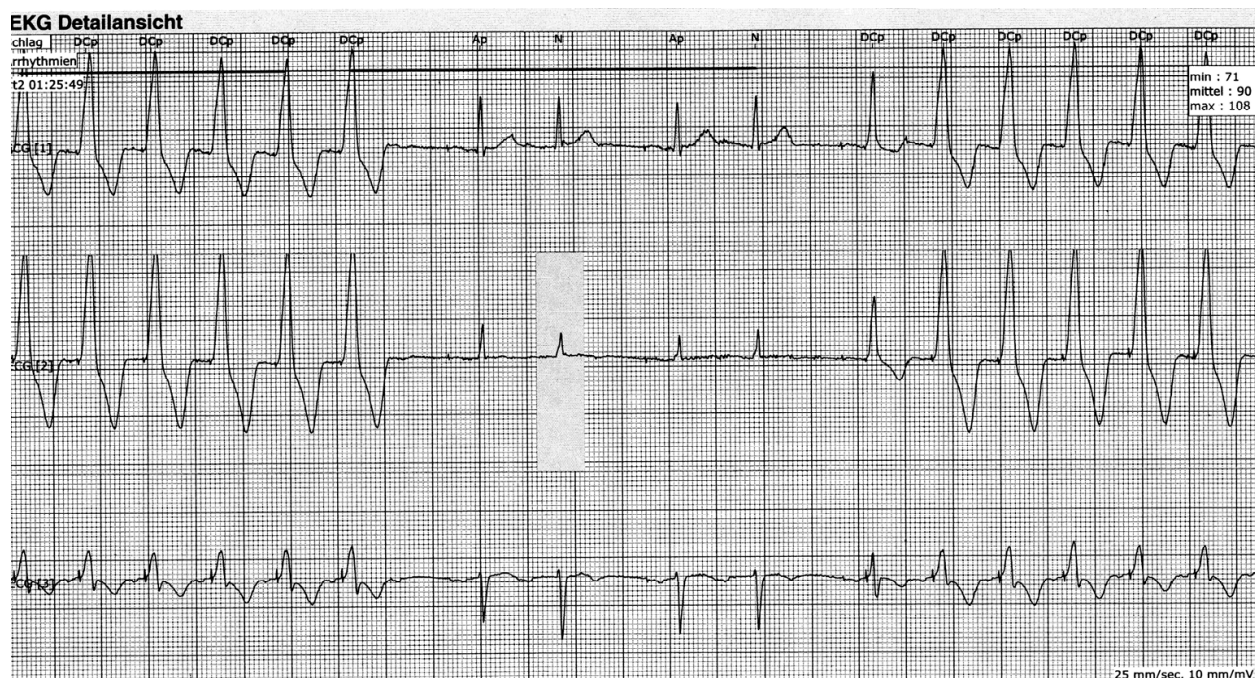
**Figure 15.** AAISafeR2™, Reply DR, Holter-monitoring: switch from AAI(R) to DDD(R) after 3 (in this case stimulated) atrial events without intrinsic conduction within the last 12 AA intervals.



**Figure 16.** AAISafeR2™, Reply™ DR: paroxysmal AV block, possibly phase 4 block caused by critical prolongation of the PP interval after a conducted atrial premature beat ("Ar"). Switch from AAI to DDD after 2 consecutive atrial stimulated events (AP) without intrinsic conduction.

- AAISafeR™: Recurrence of sufficient intrinsic AV conduction

After 100 ventricular stimulations (VP) the device checks intrinsic AV conduction (fig. 17, 18, 20). A switch back from DDD(R) to AAI(R) takes place after 12 cycles of spontaneous conduction.



**Figure 17.** AAI-SafeR2™: After unsuccessful search for sufficient intrinsic conduction DDD(R) stimulation is continued.

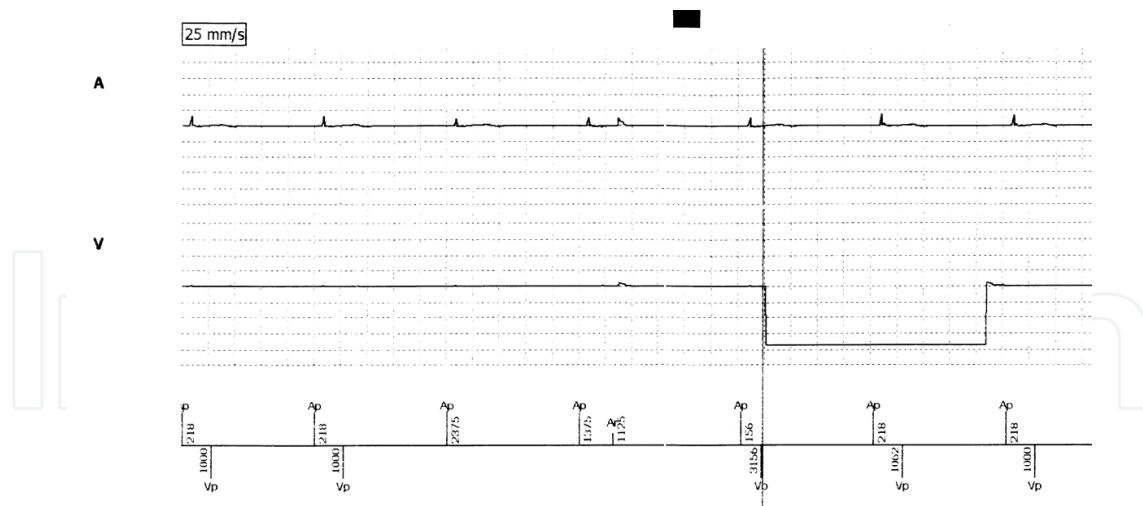


**Figure 18.** AAI-SafeR2™, Symphony™ DR: Successful mode switch from AV sequential DDD pacing with ventricular fusion to AAI mode resulting in intrinsic AV conduction (APace/VSense).

In contrast to MVP® the AAI-SafeR™ is programmed for a permanent switch to DDD(R) mode in case of persisting AV conduction disturbance:







**Figure 20.** AAISafeR2™, Reply: Unsuccessful search for intrinsic conduction in a patient with third-degree AV block, resulting in a long pause > 3 sec. DDD mode is maintained.

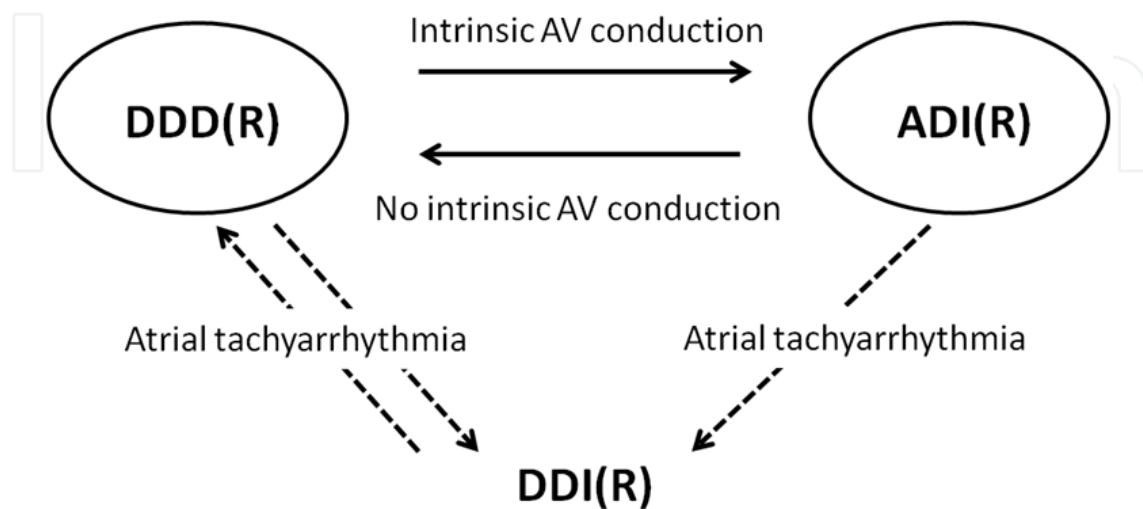
The majority of publications about AAISafeR2™ didn't report any adverse events [32-35].

Thibault et al. observed 2 SafeR related adverse events among 208 PM patients:

1 patient with SND and second-degree AV block complained of dizziness. 24-hour electrocardiogram revealed ventricular pauses as cause, another patient with SND and first-degree AV block presented with unexplained syncope. In both of these cases the device was reprogrammed to DDD [36].

- b. Ventricular pace suppression (Vp Suppression®), Biotronik.
- Example devices: Evia / Entovis, Estella series

Depending on evaluation of intrinsic AV conduction the device works either in DDD(R) or ADI(R) mode. Independent of that the system offers a mode switch to DDI(R) for atrial tachyarrhythmias (fig. 21).



**Figure 21.** Stimulation forms of the Vp Suppression® algorithm, Biotronik

- Vp Suppression®: DDD(R) mode

With Vp Suppression® activated the system stimulates first in the DDD(R)-mode with a programmed AVD. A VS search is started after a VS event or if there is no intrinsic conduction within 0.5 min. AVD is then extended to 450 ms to search over 8 cycles for intrinsic conduction. The device switches to ADI(R), if the programmable criterion “x consecutive VS” is met. It is possible to program 1, 2...8 consecutive VS events in individual steps, default 6. If the criterion isn’t met within the VS search period, the device continues to work in the DDD(R) mode with the programmed AVD and the searching interval is doubled up to maximum of 128 min. Thereafter the next search is initiated every 20 h, as long as Vp Suppression® is activated.

- Vp Suppression®: ADI(R) mode

A cycle without intrinsic conduction / VS within 450 ms triggers an observation period of 8 repetitive cycles, to make the decision about switching back to DDD(R) mode according to the following criteria:

- x/8 cycles without VS (programmable)
- 2 consecutive cycles without VS
- No VS for at least 2 sec.

- c. RYTHMIQ™, Boston Scientific

- Example devices: ADVANTIO™, INGENIO™, ENERGEN™, INCEPTA™

The algorithm is automatically activated, if the indication-based programming (IBP) is used.

- RYTHMIQ™: Intact intrinsic AV conduction

If there is preserved intrinsic AV conduction, the system works in the AAI(R) mode at the lower rate limit (LRL) or sensor rate (SIR) with backup VVI stimulation at a rate which is 15/min below the programmed LRL [37]. The VVI backup can be provided between a rate not slower than 30/min but not faster than 60/min. During AAI(R) mode the device continuously checks AV synchrony.

- RYTHMIQ™: Loss of sufficient intrinsic AV conduction

The device automatically switches to DDD(R) mode, if three blocked or “slow ventricular beats” are documented within a rolling detection window of 11 beats. RYTHMIQ™ defines a “slow ventricular beat” as a ventricular event (VS or VP) occurring at least 150 ms slower than the atrial pacing rate (LRL or SIR) [37].

- RYTHMIQ™: Reoccurrence of sufficient intrinsic AV conduction

From DDD(R) mode a regular search for intrinsic conduction is carried out by using the AV Search+ algorithm. The pacing mode is switched back to AAI(R) with VVI backup, if AV Search+ 1) can remain in AV hysteresis for a minimum of 25 intervals and 2) less than two out of the last ten cycles are VP events [37].

- RYTHMIQ™: Mode switch for atrial tachyarrhythmias

The algorithm is able to detect atrial tachyarrhythmias from either AAI(R) with VVI backup or DDD(R). In the case of detection of atrial tachyarrhythmias the system immediately changes to the ATR mode switch.

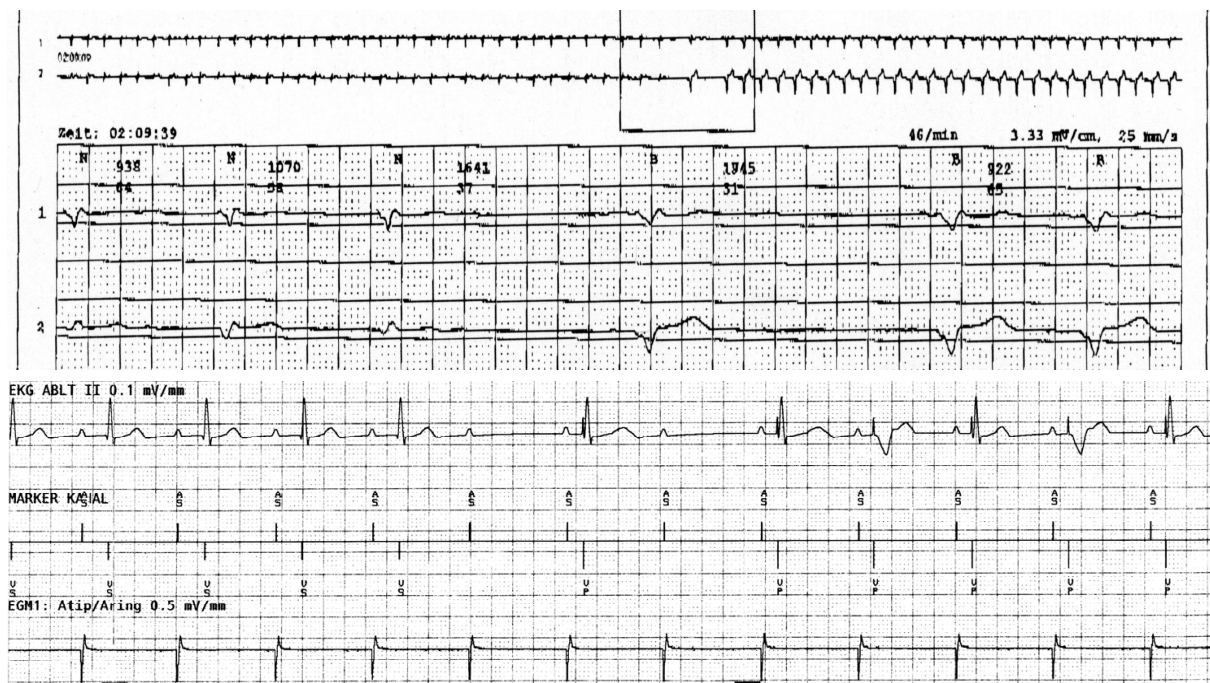
d. Managed Ventricular Pacing® (MVP®), Medtronic

- Example devices: Adapta L ADDRL, Ensura DR MRI™, Protecta DR.
- MVP®: Intact intrinsic AV conduction [38]

The device works in the AAI(R) mode with programming and timing for atrial single-chamber stimulation. At the same time there is active surveillance of AV conduction.

The atrial refractory period (ARP) cannot be programmed. It is set to 600 ms for rates <75/min respectively 75% of ventricular cycle length (CL) for rates ≥75/min. This dynamic ARP is intended to stop unnecessary switch episodes with singular non conducted atrial extra beats (PAC) or R wave far-field sensing.

If there are fast intrinsic ventricular events (e.g. PVC, VT) the atrial stimulation is inhibited. This is done to avoid unnecessary atrial stimulation, if the intrinsic ventricular rate is higher than the stimulation rate. Additionally the recognition of tachyarrhythmias is facilitated, if there is no interference by the blanking periods after atrial stimulation.



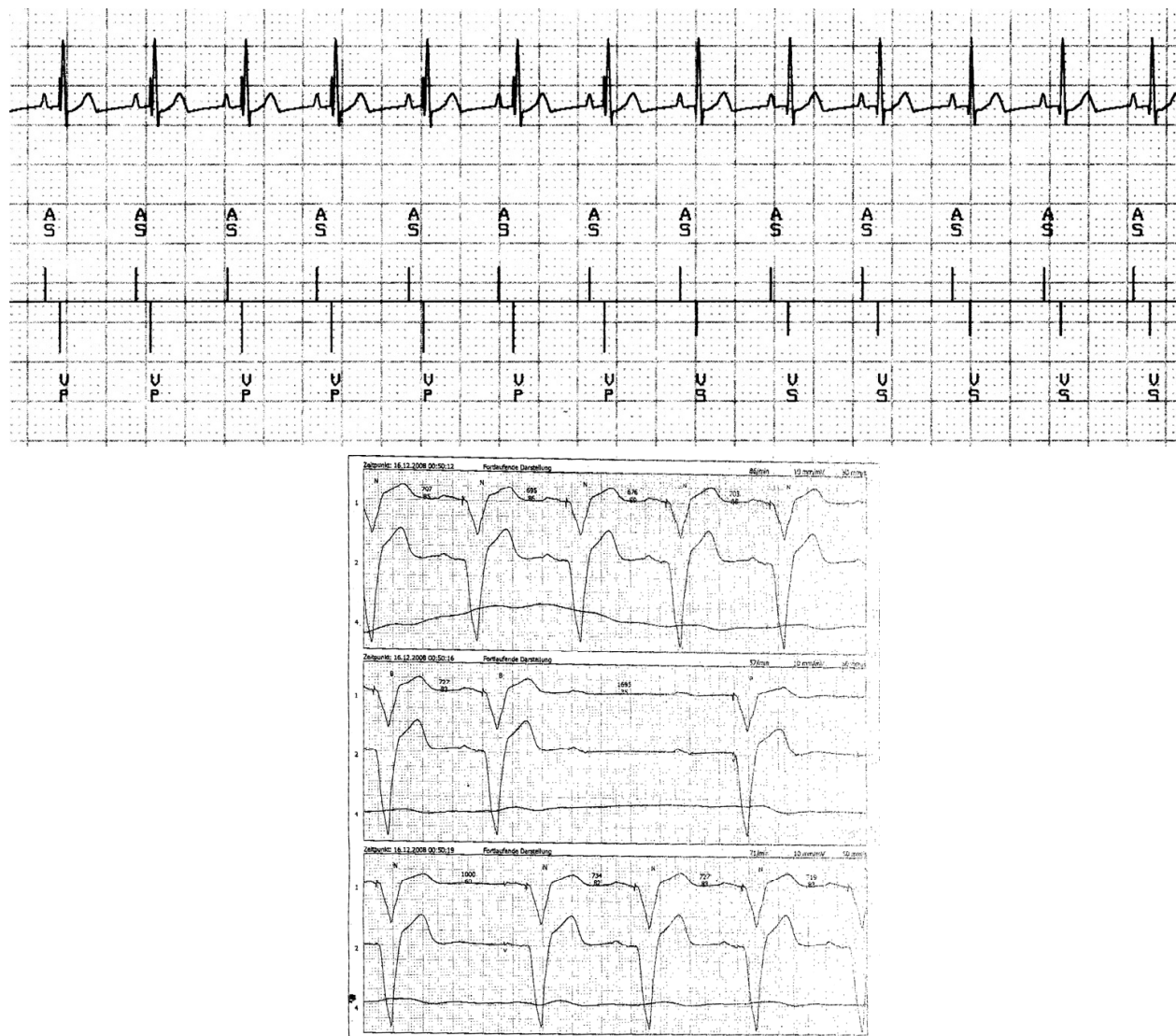
**Figure 22.a.** MVP® (EnTrust): Switch from AAI(R) to DDD(R) after intrinsic AV conduction was missing during 2 of the last 4 AA intervals. Special attention has to be paid to the fact, that the ventricular backup stimulation fires 80 ms after the intended (actually given or inhibited!) atrial stimulus after each AA interval without ventricular sensing (VS). (This ECG was sent to us per emergency fax as suspected ICD dysfunction: the specifics of AAI ↔ DDD mode switch can lead to substantial uncertainties).

b. MVP® (Protecta DR): Switch from AAI(R) to DDD(R) due to sudden second-degree AV block with 2:1 AV conduction.





the ventricular backup-stimulus is here 1280 ms. Because the following intrinsic AV conduction was intact again, the device stayed in the AAI(R) mode.



**Figure 25.** a. MVP® (Protecta DR): Successful test for intrinsic AV conduction, switch from DDD (AS/VP, ventricular fusion) to AAI (AS/VS).

b. MVP®: Negative test for intrinsic AV conduction in a patient with third-degree AV block.

There is no automatic switch over to a permanent DDD(R) mode.

- MVP®: Reoccurrence of sufficient intrinsic AV conduction

After switching to DDD(R), the device checks the intrinsic conduction in regular intervals and thereby checks the possibility for return to AAI(R). This starts already one minute after change to DDD(R) with a switch to AAI(R) for one cycle.

- If there is a VS event following the next AA interval, the device remains in AAI(R) (fig 25a).
- If there is no VS event following the next AA interval, the conduction test was negative and the device remains in DDD(R) (fig. 25b).

After each negative test the time interval doubles to the next control (1 => 2 => 4 => 8 =>...min). The maximum time interval is 16 hours.

As a consequence of this periodic check, patients with permanent complete AV block will have a single missing ventricular beat every 16 hours.

- MVP®: Mode switch for atrial tachyarrhythmias

The device switches to DDIR both from AAI(R) and DDD(R) on the onset of an atrial tachyarrhythmia to avoid fast atrial 1:1 triggering. The mode switch to DDIR for atrial tachyarrhythmias is given a higher priority than MVP®. Once the termination of the atrial tachyarrhythmia is recognized, there is a change to DDD(R) no matter which mode was active before that episode. Then an AV conduction test (1 beat) is performed and the device returns to functional AAI(R), if AV conduction is verified. If not, the DDD(R) mode is maintained and regular conduction tests are carried out (1, 2, 4, 8 min ... 16 h), as described above.

The MVP® algorithm is highly effective in avoiding unnecessary RV stimulation.

In a randomized pilot study including 30 patients with dual-chamber ICDs without history of AV block MVP® “dramatically” reduced cum%RVP from  $80.6 \pm 33.8\%$  to  $3.79 \pm 16.3\%$  ( $p < 0.0001$ ) [39]. 15% of AV intervals under MVP® were longer than 300 ms. There were no relevant symptoms or adverse effects with MVP®.

In 181 ICD patients, that were randomized in a prospective manner, a 99% relative reduction of the cumulative ventricular pacing percentage (cum%VP  $4.1 \pm 16.3$  vs.  $73.8 \pm 32.5$ ,  $p < 0.0001$ ) by application of the MVP®-algorithm versus DDD(R) was found, again without adverse events [40].

In principle it is possible to reduce cum%RVP in all patients with SND and intermittent impairment of AV conduction. According to an investigation by Gillis et al. the reduction of ventricular stimulation percentage is higher in PM patients with SND than in patients with AV block (median relative reduction 99.1% vs. 60.1%) [41]. In a mixed PM population it was possible to reduce cum%VP to  $\leq 40\%$  with the MVP® algorithm in 72% of patients [42]. Compared to AV search hysteresis Search AV+™ there was a significantly lower median percent VP by application of MVP® with the exception of the patients with persisting third-degree AV block [43]. Of the 322 PM patients in this study the best VP reduction was found in mildly impaired AV conduction.

The safe and effective use of MVP® was shown for pediatric patients and grown up patients with congenital heart disease as well [44]. In this study it was necessary to change the programming to DDD in one case of symptomatic intermittent AV block.

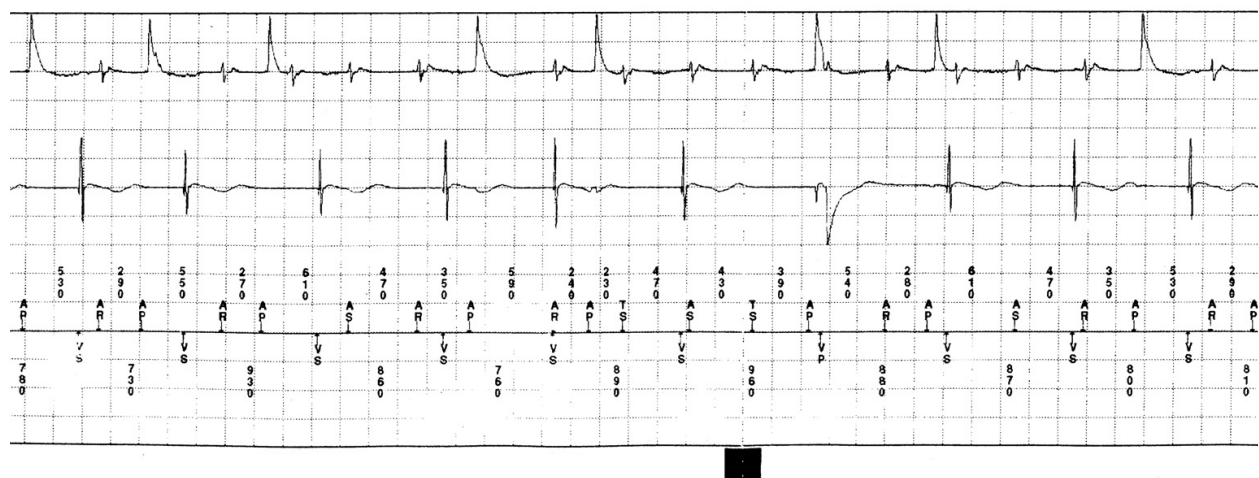
The (hemodynamically) optimal form of stimulation for patients with a long AV conduction time (“long AV-block °1”) remains still unclear and has to be tested in the individual patient. Especially for these patients one has to consider that MVP® depending on the intervention rate will tolerate any length of AV conduction time, as long as there is a ventricular sensed event (VS) before the next atrial sensing (AS) or atrial stimulation (AP).

This can lead to hemodynamically unfavorable (ultra-) long intrinsic AV times (Fig. 6). In this clinical scenario permanent DDD(R) stimulation with a fixed AV delay optimized e.g. by echocardiography may be more favorable [45].

As already mentioned before, the effective ventricular rate can drop to half of the intervention rate before switch to DDD(R), if there is a sudden loss of intrinsic conduction. Therefore it is recommended to program the basic rate of patients with sinus bradycardia or frequent AV block to a minimum of 50/min.

When the available literature is reviewed, only few cases concerning clinical problems with MVP® are to be found. Mostly the algorithm worked as specified; the most common findings were:

- Atrial events, in which functional undersensing occurred due to the long atrial refractory period (Fig. 26)
- Ventricular events, in which functional undersensing occurred during the ventricular blanking time following the next atrial stimulation
- Major variations in AV delays
- Ultra long AV delays being accepted with the result of short VA intervals
- Long atrial pauses
- Occurrence of unnecessary RV pacing because of “linking”, i.e. repetitive retrograde invasion of ventricular depolarization into the AV junction resulting in non-conducted P waves



**Figure 26.** MVP®, EnRhythm DR: Functional undersensing of atrial events due to the long atrial refractory period in a patient with a fast atrial rhythm (sinus or atrial tachycardia), CL about 480 ms.

Murakami et al. reported 2 out of 127 Patients suffering from chest discomfort and one case with mild dizziness due to 2<sup>nd</sup> or 3<sup>rd</sup> degree AV block with frequent non-conducted atrial events in MVP mode [46]

A serious potentially proarrhythmic effect of MVP was observed by van Mechelen and Schoonderwoerd. In a patient with implanted PM for complete AV block a polymorphic VT

degenerated to ventricular fibrillation which was successfully terminated by external defibrillation. Pacemaker interrogation showed correct device function in AAI mode (MVP) before the VT episode with irregular ventricular events (slow escape rhythm with frequent PVCs) and no AV synchronicity. The slow ventricular escape rhythm together with short coupled PVCs constituted proarrhythmogenic short-long-short cycles. Combined with documented hypokalemia, this caused the VT. As a consequence the MVP algorithm was switched off [47].

#### Clinical Benefit of Ventricular Pacing Reduction by AAI(R)⇌DDD(R) mode switch

Meanwhile, first study results became available showing the clinical benefit of reducing unnecessary RV-stimulation by AAI(R)⇌DDD(R) mode switch algorithms.

In the SAVE PACe trial patients with symptomatic bradycardia due to sinus node disease were evaluated for the primary endpoint “time to persistent atrial fibrillation” [48]. Excluded were patients with persistent atrial fibrillation or cardioversion for atrial fibrillation in the preceding 6 months, second- or third-degree AV block and wide QRS complex. The 1065 enrolled pacemaker patients were randomized to either DDD(R) pacing mode (AVD 120 to 180 ms) or to a dual-chamber pacing mode with a minimal ventricular pacing algorithm (MVP or SAV+). The study was stopped when in the interim analysis the pre-specified efficacy boundary ( $P=0.007$ ) for difference in persistent atrial fibrillation between the two groups was reached (after  $1.7 \pm 1.0$  years). The difference in the median cum%RVP was substantial: 99 % in the DDD group vs. 9.1 % in the MVP group ( $P<0.001$ ). The reduction of the risk for development of persistent atrial fibrillation was significant: 40% relative risk reduction ( $P=0.009$ ) and 4.8% absolute risk reduction in the SAV+/MVP group. As clinical outcome there was a trend towards more strokes in patients who developed persistent atrial fibrillation, compared to those who did not (n.s.,  $P=0.18$ ). There was no significant difference for mortality between the two groups. The conclusion of the authors was that in their examined group of patients with SND dual-chamber pacing with the use of a minimal ventricular pacing feature (MVP or SAV+) prevents ventricular desynchronization and is of advantage in reducing risk of persistent atrial fibrillation.

A single center randomized clinical trial done by Xue-Jun et al. compared follow up results after 3 months of pacing in DDD mode (AV delay 250 ms with 30 ms extension) with AAISafeR mode. 30 patients with sick sinus syndrome were randomized to one of the two modes for 3 months and then switched over to the other mode for another 3 months. After 3 months in DDD mode echocardiographic analysis showed that left atrial diameter, left ventricular end-diastolic diameter and left ventricular end-systolic diameter had increased significantly and left ventricular ejection fraction had decreased. However after 3 months of pacing in the AAISafeR mode no obvious changes were noted. In the AAISafeR mode cum%RVP was significantly reduced compared to the DDD mode. The authors of this randomized trial using echocardiographic follow up concluded that AAISafeR mode is not only effective in reducing the amount of unnecessary RV pacing in sick sinus syndrome substantially, but also prevents harmful effects on cardiac performance [49].



## 5. Conclusion

Recently the importance of reducing unnecessary RV stimulation has been recognized widely. This is reflected in the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, which for the first time includes a separate chapter regarding this topic ("Importance of Minimizing Unnecessary Ventricular Pacing") [50].

Today we have several options available for this task. Which one to use has to be considered individually for each patient with an indication for a device - at the time of implantation and during follow-up.

The use of atrial single-chamber systems will stay limited to singular cases even in patients with SND, because of the missing ventricular backup if impairment of AV conduction occurs. Apart from the indication for bradycardia in permanent atrial fibrillation, single-chamber VVI PM systems as "backup" can be used as an option for patients with rare paroxysmal AV block. The other major application of single-chamber VVI backup devices with low intervention rate is in ICD therapy, if there is no need for concomitant antibradycardia pacing.

In dual-chamber systems the programming of a fixed long AVD offers a "makeshift-programming", if there is no other specific algorithm available. AV search hysteresis permits markedly longer intrinsic AV conduction times with stimulation with optimized AV interval in the event of higher degree AV block. An effective reduction of unnecessary RV stimulation is possible with the new AAI⇌DDD mode switch algorithms. The clinical effects of wider use of these new functions need to be further evaluated in ongoing trials.

## Author details

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