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EDITORIAL COMMENT

Adverse Effects of Ventricular Desynchronization Induced by Long-Term Right Ventricular Pacing*

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In this issue of the *Journal*, Nielsen et al. (1) report the results of the first randomized trial comparing the AAIR and DDDR modes of pacing in 177 consecutive patients who received a first pacemaker for sick sinus syndrome. The patients were followed for 2.9 ± 1.1 years and had normal atrioventricular (AV) conduction (according to previously used arbitrary criteria by these workers) and no bundle branch block. The primary end points were changes from baseline to last follow-up in left atrial (LA) size and left ventricular (LV) function, as determined by M-mode echocardiography. The patients were randomized to three arms: AAIR, DDDR-s (short, rate-adaptive AV delay 110 to 150 ms) and DDDR-l (fixed, long AV delay ≥250 ms) modes.

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The AV delay was not optimized because the study was designed to evaluate the effect of cumulative right ventricular (RV) pacing. The AAIR group exhibited no significant change in the LA and LV diameters or LV fractional shortening (LVFS). However, the LA diameter increased significantly in both DDDR groups (more marked in the DDDR-s group), whereas LVFS decreased significantly in the DDDR-s group but not in the DDDR-l group.

The AAIR versus DDDR trial clearly documents the detrimental effects of ventricular desynchronization or LV dyssynchrony produced by long-term, nonphysiologic RV pacing (1). The DDDR-s group with 90% proportion of RV pacing developed LA dilation and decreased LVFS, but the DDDR-l group with 17% proportion of RV pacing developed LA dilation but no change in LVFS. Atrial fibrillation, which was diagnosed on the basis of a 12-lead electrocardiogram at planned follow-up visits, was more common in the DDDR group, indicating that ventricular desynchronization promotes atrial fibrillation, probably by causing LA dilation.

Comparison of the AAIR versus DDDR trial with VVI(R) versus DDD(R) trials. The lack of ventricular desynchronization in the AAI mode may explain the remarkable benefit of AAI compared with VVI pacing obtained by the Danish group in patients with the sick sinus syndrome, in a protocol where the investigation focused only on the role of AV synchrony (2). In contrast, studies comparing the DDD(R) with the VVI(R) modes of pacing have yielded less impressive and somewhat inconsistent results, probably because the benefit of AV synchrony was attenuated by the depressant effect of ventricular desynchronization in patients using the DDD(R) mode (3,4).

Impact of ventricular desynchronization. The results of the AAIR versus DDDR study are in accordance with the recent data from the Dual Chamber and VVI Implantable Defibrillator (DAVID) and Mode Selection Trial (MOST) trials, where the end point was hospitalization for congestive heart failure (CHF) (5–8). Sequential LV function was not evaluated in these two trials. The DAVID trial compared the clinical effectiveness of dual-chamber implantable cardioverter-difibrillators (ICDs) programmed to the DDDR pacing mode at 70 beats/min versus the VVI mode at 40 beats/min (5). The AV delay was programmed according to the clinical judgment of the investigators and was commonly set at 180 ms, thereby favoring ventricular pacing in the majority of patients. The study revealed a strong trend toward higher mortality and hospitalization for new or worsened CHF in the DDDR group (with nearly 60% of ventricular beats being paced). The DAVID study suggested that unnecessary RV apical pacing delivered as part of the DDDR arm produced ventricular desynchronization with impaired LV hemodynamic performance that was ultimately harmful. The VVI group fared better because the programmed rate of 40 beats/min minimized RV apical pacing (with 1% of ventricular beats being paced). The depression of LV function by RV apical pacing may be more important in ICD patients with poor LV function and/or a history of heart failure. The MOST study also demonstrated an association between the percentage of RV pacing in the DDDR mode (with maintenance of AV synchrony) and CHF in patients with sick sinus syndrome and a QRS duration <120 ms (7,8). The harmful consequences of RV pacing in the MOST trial also appeared related to nonphysiologic LV contraction. A cumulative percentage of the ventricular pacing index <10% was associated with lower rates of CHF hospital admissions, and an index >90% was associated with higher rates of hospitalization for CHF. For DDDR pacing, the risk of CHF increased linearly until the aforementioned percentage index reached 60%, and then it formed a plateau. As in the study by Nielsen et al. (1), the MOST study found a correlation between the cumulative percentage of ventricular pacing index and the development of atrial fibrillation (8). Interestingly, in the Multicenter Automatic Defibrillator Trial II (MADIT II) study, in which ICD programming was not standardized, the development of new or worsened CHF was more common in the ICD arm (19.9%) compared with the conventionally treated patients (14.9%) (9). The higher incidence of CHF in the ICD group was in all likelihood due to ventricular desyn-

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chronization rather than myocardial injury from ICD shocks.

Mitral regurgitation induced by ventricular desynchronization. Ventricular desynchronization itself may occasionally cause severe mitral regurgitation that may precipitate atrial fibrillation and CHF. Left ventricular contraction initiated by apical RV pacing alters papillary muscle function, with resultant derangement of the time sequence of activation of the mitral valve apparatus. Mitral annular movement, which influences mitral valve function, is also affected by LV dyssynchrony. Pacemaker-induced mitral regurgitation may be largely reversible or attenuated in many cases by restoration of LV synchrony either by spontaneous beats or LV/biventricular pacing, thus avoiding mitral valve replacement, even in patients with a normal ejection fraction (10,11).

Are the abnormalities induced by long-term ventricular desynchronization reversible? Long-term, nonphysiologic or RV pacing in dogs induces adverse cellular changes with myofibrillar disarray, asymmetric myocardial hypertrophy, and LV dilation (12–14). The reversibility of these changes has not been studied. In humans, RV pacing produces alterations in local myocardial blood flow that are more pronounced during pacing of the RV apex than of the outflow tract (15,16). Furthermore, after 18 months of long-term stimulation, RV apical pacing, but not RV outflow tract pacing, was found to depress the LV ejection fraction (16). Nielsen et al. (17) also found reversible alterations in regional myocardial blood flow upon switching temporarily from long-term RV apical pacing to the AAI mode, suggesting that perfusion defects are related to the altered pattern of ventricular depolarization. In their myocardial blood flow study, Nielsen et al. (17) programmed their DDD patients (the same as those in the DDDR-s group) to the AAI mode at the time of myocardial blood flow measurement. The LV ejection fraction measured during temporary AAI pacing was significantly higher than that during DDD-s pacing and not different from the LV ejection fraction measured at the time of implantation about 22 months previously. These intriguing results were not reproduced in the AAIR versus DDDR study of Nielsen et al. (1), where the DDDR-s mode was programmed to the AAI mode and an echocardiographic comparison was performed only 5 min after programming the AAI mode. The very short duration of pacing in the AAI mode may probably explain the persistence of LA and LV abnormalities in the AAI mode, so that no firm conclusions can be drawn from these observations. Obviously, more work is needed to determine the reversibility of the LA and LV abnormalities engendered by ventricular desynchronization. The reversibility of mechanical LA remodeling caused by long-term VVI pacing upon the establishment of DDD pacing (18) suggests that AAI(R) pacing for a longer time than 5 min might also have reversed mechanical LA remodeling associated with DDDR pacing in the AAIR versus DDDR trial (1).

Is the long-term benefit of AAIR pacing worth the small risk of AV block? The development of spontaneous, complete heart block during AAI pacing in carefully selected patients is unusual and generally not considered a potentially life-threatening situation in reports advocating the use of single- lead atrial pacing. Although complete AV block during AAI(R) pacing often seems to be tolerated without a ventricular lead in place, it can obviously be devastating, especially when accompanied by syncope. The incidence of syncope related to AV block is not negligible during AAI pacing, and its occurrence, no matter how infrequent, is difficult to accept considering that the fundamental purpose of antibradycardia pacing is to prevent it.

The best of both worlds. Perhaps it is time to reconsider the generally held view in the U.S. that AAIR as a primary mode of pacing is obsolete and to examine how the risk of AV block can be eliminated. Theoretically, in patients with normal AV conduction, functional AAIR pacing should occur with virtual elimination of ventricular pacing by using the DDDR mode with a long AV delay (250 to 300 ms). The AAIR versus DDDR trial showed this was not possible, at least with an AV delay of 250 ms (17% RV pacing), confirming data from a small number of studies that used AV delays as long as 300 ms or AV search hysteresis (1,19–21). The causes of the 17% incidence of ventricular pacing in the DDDR-l group was not studied and may involve many mechanism such as ventricular fusion and pseudofusion beats. Such data would help in the design of pacemakers capable of withholding RV stimulation in a variety of circumstances where pacing is not warranted.

In 1997, Andersen (22), an obvious proponent of AAI pacing, wrote that "in the future, another technical solution may be available with modern units, i.e., automatic mode switching from AAI to DDD. . ." for patients with sick sinus syndrome. Such devices became available some time ago, but their performance in minimizing RV pacing has not been studied in detail. The results of the AAIR versus DDDR, DAVID, and MOST trials have highlighted the importance of developing sophisticated pacemakers and ICDs capable of minimizing RV pacing more efficiently than the present devices (which work primarily on the basis of a relatively long AV delay) in patients without AV block (1,5–8). With such new devices, we will be able to give patients without AV block or bundle branch block the best of both worlds—almost continuous physiologic ventricular depolarization through the His-Purkinje system without the risk of AV block.

Finally, the results of the AAIR versus DDDR, DAVID, and MOST trials should be considered as a wake-up call to investigate the use cardiac resynchronization not for the treatment of existing LV dyssynchrony in patients with CHF and left bundle branch block but for "primary prevention" in the first place in selected patients who require ventricular pacing most of the time.

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