REVIEW

Past, present and future of cardiac resynchronization

Désynchronisation et resynchronisation cardiaque : passé, présent et avenir

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Summary  The growing interest in dyssynchrony and cardiac resynchronization therapy has opened the field of cardiac stimulation to new haemodynamic indications. French investigators have played a key role in the formulation of new concepts, all arising from clinical observations, and the development (in collaboration with industry) and clinical evaluation of resynchronization devices. This review summarizes recent knowledge and perspectives pertaining to atrial, atrioventricular and ventricular dyssynchrony and resynchronization. Some of these concepts have been validated by robust clinical evidence, on the basis of which scientific recommendations have been formulated. Other concepts have been less successful but probably merit further attention.
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Résumé  L'intérêt pour la désynchronisation et la resynchronisation cardiaque n'a cessé de croître, permettant d'élargir le champ de la stimulation à de nouvelles indications hémodynamiques. Les équipes françaises ont joué un rôle moteur dans la définition de ces concepts nouveaux, tous nés de l'observation clinique, dans la conception des outils de resynchronisation en lien avec l'industrie, et dans leur évaluation clinique. Cette revue se propose de faire la synthèse des connaissances récentes sur la désynchronisation et la resynchronisation cardiaque aux trois étages, atrial, atrioventriculaire et ventriculaire, et de dresser quelques perspectives d’avenir.
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Abbreviations: AV, atrioventricular; CRT, cardiac resynchronization therapy; HF, heart failure; LBBB, left bundle branch block; LV, left ventricular; NYHA, New York Heart Association.
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Atrioventricular dyssynchrony and resynchronization

The first cardiac pacemaker was implanted at Stockholm’s Karolinska hospital in 1958, for the treatment of syncope due to complete AV block. The 57-year-old recipient survived for 43 years thereafter, consumed 24 pulse generators, lived comfortably and remained active and free from HF, despite the ventricular dyssynchrony caused by single-chamber ventricular pacing. Other less fortunate patients have not tolerated the cardiac dyssynchrony due to ventricular pacing. Identification of patients prone to developing cardiac dysfunction after ventricular pacing remains an important challenge for clinical practice.

For a quarter of a century, the only indication for cardiac pacing was the management or prevention of symptoms due to bradycardia; its adverse effects on cardiac mechanical function, which could not be circumvented, were overlooked. At that time, the only pacing mode applicable was VVI, perpetuating AV dissociation and asynchronous ventricular contraction. The first attempts at cardiac resynchronization were made in the 1960s, with the advent of atrial synchronous pacemakers, followed, in 1981, by the first DDD pacing system. ‘Physiologic’ stimulation was born, which restored AV synchrony and chronotropic function.

Symptomatic, high-degree, atrioventricular block: the prime indication for cardiac pacing

Symptomatic, high-degree, AV block remains the most prevalent (>40%) of all pacing indications. The mean age of French patients paced for this indication, usually due to degenerative disease, is 80 years [1]. In the presence of normal sinus node function, a DDD pacemaker restores the atrial contribution to ventricular filling and preserves the physiological heart rate adaptation. An alternative choice is single-chamber VVIR pacing, which does not eliminate AV dyssynchrony, although it restores chronotropic function with rate-responsive sensors.

What is the true impact of atrioventricular resynchronization in clinical practice?

The long-debated question of clinical superiority of DDD pacing over VVIR pacing has been answered only recently. After a French controlled study failed because of lack of support from the medical community and its industrial partners, 20 years elapsed until the publication of the UK-PACE trial, which showed that, in older patients, ‘physiologic’ pacing conferred no benefit compared with VVI or VVIR pacing in terms of overall survival (primary criterion) or cardiovascular morbidity, including HF, cerebral vascular accidents, atrial fibrillation, etc. [2].

Figure 1. A. Long PR haemodynamic syndrome in a patient in NYHA functional class III. During sinus rhythm, with a 450 ms PR interval, the left ventricular (LV) filling time is markedly foreshortened and the transmitral flow is monophasic due to the lack of atrial contribution. B. DDD pacing with a standard 150 ms atrioventricular (AV) delay doubles the LV filling time, restores an effective atrial contribution and increases the aortic ejection flow velocity.
Cardiac resynchronization therapy

Figure 2. Representative example of atrial resynchronization in a patient with HF with a left ventricular (LV) ejection fraction of 60%. A. The surface electrocardiogram shows typical, high-degree, interatrial block, confirmed by (B) the endocardial electrograms showing a 140 ms delay between the right atrium (RA) and the left atrium (LA) during sinus rhythm. C. A DDD-biatrial pacing system was implanted, including an RA lead in the sinus node region, a lead advanced to the mid coronary sinus (CS) to pace the inferolateral LA and a lead at the right ventricular (RV) apex to synchronize the system. D. A specific algorithm synchronized LA pacing upon RA sensing, immediately normalizing the duration and morphology of the P wave.

Furthermore, the risk/benefit ratio was unfavourable to DDD pacing, which was associated with an 8% rate of major, procedure-related complications versus 4% with VVI or VVIR pacing. Despite being the land of Descartes, France paid little attention to these observations and the proportion of DDD/DDDR pacing systems continued to increase steadily, reaching 75% of implants in 2009 [1].

Patients with a symptomatic long PR interval may benefit from atrioventricular resynchronization

A subgroup of highly incapacitated patients owe their disability and symptoms to a markedly prolonged PR interval, which, as a result of non-adaptation to exercise, causes left heart mechanical AV dyssynchrony, which increases proportionally to heart rate acceleration [3]. A typical example at rest is illustrated in Fig. 1. When properly selected, these patients derive a major functional benefit from DDD pacing, despite the ventricular dyssynchrony it creates. This haemodynamic indication has been included as a class IIa recommendation in the practice guidelines issued by international professional societies [4].

Atrial dyssynchrony and resynchronization

Disorders that cause progressive left atrial dilatation, such as long-standing hypertrophic cardiomyopathy and hypertensive heart disease, are often associated, during sinus rhythm, with major intra-atrial conduction abnormalities. The most extreme form is complete interatrial block, with P waves more than 120 ms in duration, opposite axes of the initial vectors reflecting normal activation of the right atrium and late vectors reflecting retrograde and delayed activation of the left atrium (Fig. 2A). These patients are at high risk of atrial tachyarrhythmias—mainly left atrial flutter and HF [5]. LV ejection fraction in usually preserved or only slightly impaired in these patients. This atrial dyssynchrony can be remedied by bialtrial stimulation, which implies the implantation of a coronary sinus lead to stimulate the lateral or posterolateral wall of the left atrium [6]. Atrial resynchronization devices have been built, along with an algorithm, to sense sinus activity in the right atrium and trigger synchronous left atrial stimulation (Fig. 2C). It became readily apparent that atrial resynchronization improves AV synchrony in the left heart as well as the global mechanical performance of hypertrophied and non-compliant left ventricles (Fig. 3).
The clinical usefulness of atrial resynchronization has remained unproven despite results of long-term observational studies suggesting clinical benefit [7]. The negative results of SYNBIAPACE [8]—the only controlled, crossover study of atrial resynchronization conducted in the early 1990s—were never published. It should, however, probably be pursued. SYNBIAPACE was methodologically weak and used atrial fibrillation burden as a primary study endpoint, when the expected clinical benefit was haemodynamic instead of antiarrhythmic. We will follow with much interest the imminent revival of a controlled study by other French investigators, who will examine the effects of atrial resynchronization in HF in the presence of a preserved ejection fraction [9].

Ventricular dyssynchrony and resynchronization

Three different concepts will be discussed: prevention of ventricular dyssynchrony, deliberate ventricular dyssynchrony and ventricular resynchronization.

Prevention of ventricular dyssynchrony

Over 50% of approximately 60,000 pacemakers implanted annually in France are used to treat isolated sinus dysfunction or bradycardia-tachycardia syndrome [1]. Nearly all of these patients are paced incessantly at the atrial level, either in single-chamber AAI-AAIR mode, if AV conduction is preserved, or in dual-chamber DDD-DDDR mode, which is considered safer but is associated with a risk of unnecessary and deleterious asynchronous ventricular pacing. In the early 1990s, two mechanistic studies compared the effects of DDD pacing with ventricular capture versus atrial pacing alone, in recipients of dual-chamber pacemakers implanted for sinus node dysfunction [10,11]. These studies showed that asynchronous activation due to ventricular capture caused considerable degradation of global and septal LV function, accentuated by exercise.

Subsequent observational and controlled clinical studies confirmed the suspicion of long-term adverse effects and higher morbidity and mortality caused by ‘forced’ ventricular pacing [12,13]. To prevent unnecessary ventricular capture, state-of-the-art pacing systems incorporate specific algorithms that confine pacing to the atrial level, as long as intrinsic AV conduction is preserved. AAI SafeR, the first such algorithm, was developed in France. The clinical merit of one of these algorithms was confirmed in a large controlled trial, which revealed a decreased incidence of atrial fibrillation in particular [14].

Deliberate ventricular dyssynchrony: the particular case of obstructive, hypertrophic cardiomyopathy

Obstructive, hypertrophic cardiomyopathy is the only cardiac disorder that might benefit from ventricular dyssynchrony. Original clinical observations were made in France by Gilgenkrantz et al. in the 1960s [15]. Pre-excitation of the right ventricular apex reverses septal activation and delays the systolic thickening of the basal septum, decreasing or eliminating the systolic obstruction (Fig. 4). This effect requires the coexistence of complete ventricular capture, manifest on the electrocardiogram by the widest paced QRS, and the preservation of normal AV synchrony in the left heart to promote optimal atrial contribution.

In this disorder, ventricular filling is highly dependent on atrial function. The effective attainment of both conditions is challenging. In the majority of patients, particularly in the young, the PR interval during sinus rhythm is short, forcing the programming of an AV delay as short as 30–50 ms in order to capture the ventricles during DDD pacing. This might result in a loss of atrial contribution, negating the benefits expected from ventricular dyssynchrony and explaining its many apparent failures. Modulation of AV junctional conduction by the prescription of pharmaceuticals with negative dromotropic properties, or by catheter ablation, enables a lengthening of the PR interval and the conversion of apparent treatment failures to secondary therapeutic successes (Fig. 5) [16].

In contrast to septal surgical myectomy [17,18] and alcohol ablation [19–21], DDD pacing is the only treatment...
Figure 4. Immediate haemodynamic effects of VDD pacing in hypertrophic obstructive cardiomyopathy. The baseline left intraventricular gradient is 80 mmHg. As soon as pacing begins, the gradient decreases to 20 mmHg until an atrial extrasystole (APC) occurs, followed by a long cycle and ventricular paced escape. The postextrasystolic potentiation and transient atrioventricular (AV) dissociation bring the obstruction back with a gradient of 120 mmHg. The normal function of the pacemaker returns and the gradient gradually decreases over the following cycles. AV: atrioventricular.

Figure 5. Importance of optimal atrioventricular (AV) synchrony in the left heart, in hypertrophic obstructive cardiomyopathy treated with DDD pacing. In this 33-year-old patient, whose intrinsic PR was 80 ms in duration, a 30 ms AV delay had been programmed to completely capture the ventricle from the right ventricular apex. On the left, DDD pacing had no effect on the obstruction. The mitral flow is impaired, with a markedly delayed and barely visible atrial contribution. The images on the right were obtained after modulation of AV junctional conduction by radiofrequency energy, lengthening the intrinsic PR interval to 220 ms and allowing the reprogramming of the pacemaker AV delay (AVD) to 150 ms. The return of a biphasic mitral flow is associated with an effective atrial contribution and disappearance of the subaortic gradient. LVOT: left ventricular outflow tract.
of obstructive, hypertrophic cardiomyopathy that has been compared with medical management in controlled studies [22,23]. While a significant decrease in transaortic gradient was measured, along with the alleviation of symptoms and improved quality of life, the maximal duration of exercise (the primary study endpoint) did not change significantly and a placebo effect of device implantation was strongly suspected (Fig. 6) [24].

Consequently, this treatment has been assigned a class IIb/level of evidence B recommendation in the practice guidelines issued by international professional societies [4]. Should it be abandoned altogether? We believe not and recommend its re-evaluation, using robust methodology and optimal delivery of individual therapy, which was far from the case in the PIC and M-Pathy trials. Furthermore, by adding a cardioverter defibrillator, a comprehensive electrical treatment can be offered, which relieves the subaortic obstruction and prevents arrhythmic sudden death, unlike isolated myectomy or septal ablation [25].

**Ventricular resynchronization in heart failure**

The idea of ventricular resynchronization as a treatment for HF, arising from clinical and epidemiological observations available in the early 1990s, is attributed to Cazeau et al. [26]. LBBB is present in up to 30% of patients presenting with systolic cardiac dysfunction, and QRS and PR duration both increase as LV dysfunction and HF progress. LBBB is an independent predictor of death. In addition, echocardiographic observations by Grines et al. revealed an alteration of systolic performance and LV filling due to isolated LBBB, which causes dyssynchrony of contraction and relaxation (Fig. 7) [27].

The results of the first short-term, haemodynamic studies of biventricular or LV stimulation were highly encouraging [28–30]. Compared with baseline, stimulation immediately lowered the pulmonary pressures and increased cardiac output and pulse pressure. Subsequently, more detailed investigations revealed that biventricular stimulation increases contractile function and improves overall LV performance without increasing energetic demand, in contrast to the administration of inotropes [31–33]. At the same time, the implantation of permanent CRT systems began in humans, to stimulate the left ventricle via a transthoracic, epicardial approach [26,34] or via the coronary venous system [35]. Observational studies conducted throughout the 1990s confirmed the feasibility and relative safety of the technique despite the use of rudimentary instrumentation.

**Figure 6.** Ventricular resynchronization by DDD-biventricular stimulation. This patient was in New York Heart Association (NYHA) heart failure (HF) functional class III despite optimal medical management. A. He was in sinus rhythm, with a left ventricular (LV) ejection fraction of 25%, a QRS complex duration of 170 ms and typical left bundle branch block (LBBB) morphology; a 190 ms delay was measured between the onset at the right ventricular (RV) septum and the end of ventricular activation at the lateral LV wall. B. A triple-chamber pulse generator was implanted and interfaced with a right atrial lead to synchronize biventricular stimulation with sinus activity, an RV lead placed at the free wall and an LV lead placed in a posterolateral tributary of the coronary sinus (CS). C. When stimulation was turned on (arrow) the QRS duration immediately shortened to 120 ms. IEGM: intracardiac electrogram channel; RA: right atrium.
The proof of concept was finally obtained in 2001, in the multicentre, crossover, controlled MUSTIC trial, which showed that, compared with no stimulation, biventricular stimulation significantly increased the distance covered during a hall walk test, improved quality of life and lowered the mean NYHA functional class in a population of patients presenting in HF functional class III or IV [36]. Since then, clinical evidence has continued to accumulate, with the publication between 2001 and 2010 of remarkably concordant results from over a dozen controlled clinical trials that included more than 8000 patients.

The main investigative steps have been: the confirmation of a decrease, conferred by CRT alone, in long-term cardiovascular morbidity and mortality, all-cause mortality and rate of sudden death in patients in NYHA functional class III [37,38]; and the confirmation, in the recent REVERSE, MADIT and RAFT trials, of the prevention of progression of HF and of ventricular remodelling in patients in NYHA functional class II [38–42]. This robust evidence prompted the European Society of Cardiology to assign, in 2006, a class I/level of evidence A to CRT for patients presenting in NYHA functional classes III or IV and, in 2010, for patients presenting in NYHA functional class II after unsuccessful optimal medical management and with an LV ejection fraction less than 35% and a QRS complex more than 150 ms [43].

With respect to the electrocardiographic criteria, it is noteworthy that the REVERSE, MADIT-CRT and RAFT trials underscored the importance of the duration and morphology of the QRS complex. In all three trials, the benefit conferred by CRT was limited to patients with LBBB or whose QRS duration was more than 150 ms. Although these were subgroup analyses, the level of evidence was sufficient to limit the clinical indication to these populations who were highly likely to respond to treatment. These are probably the first treatment recommendations made by an international professional society that were not strictly based on primary study endpoints and the inclusion criteria applied in the studies that were used for their formulation – probably an important stage in the history of clinical guidelines.

Future endeavours

Much has been accomplished, although much remains to be done. Important issues that remain unsettled, such as atrial resynchronization and electrical treatment of hypertrophic, obstructive cardiomyopathy, must be revisited using new tools and more rigorous methodologies. Despite a strict selection of a small proportion of patients with HF, the rate of response to CRT does not exceed 70%, illustrating the current limitations of the patient selection criteria as well as of the techniques of stimulation. While the potential power of the electrocardiogram remains underestimated, it is not the only tool available. Imaging techniques, which have lost momentum since the inconclusive results of the PROSPECT trial [44], will likely return with new, more sensitive, more reproducible and less operator-dependent techniques, along with a more global perspective of mechanical dyssynchrony. These new instruments will need to be rigorously evaluated.
Today’s CRT is based on a simple (perhaps even simplistic) concept, which might be the key to its success. Dual-point, right to LV stimulation lacks power and is unlikely to provide optimal resynchronization in the majority of patients. New configurations and technological progress must be tested, leaving aside individual and poorly reproducible options. After the resolution of several technical challenges, LV endocardial stimulation should logically replace the electrically and mechanically less effective epicardial stimulation. It remains to be shown, however, whether more complex configurations will yield better results. We must keep in mind that the merit of a technique is not strictly gauged by its therapeutic efficacy but also by its feasibility and the risks incurred by the patients.

Finally, new clinical indications for CRT will be evaluated, although might not be validated. Prior experience has shown that casting a wider and wider net tends to decrease the benefits conferred by a given technique. Prospective indications include NYHA functional class I, echocardiographic dyssynchrony in the absence of a wide QRS, the so-called ‘Narrow QRS’, standard pacing with a presumed high percentage of ventricular capture, HF with LBBB but no severe LV dysfunction and HF with a preserved LV ejection fraction, although the last of these seems less likely.

We wish much success to all who will pursue this trail of adventures.

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