Atrioventricular dromotropathy: evidence for a distinctive entity in heart failure with prolonged PR interval?

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REVIEW

Atrioventricular dromotropathy: evidence for a distinctive entity in heart failure with prolonged PR interval?

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Heart failure (HF) is often accompanied by atrioventricular (AV) conduction disturbance, represented by prolongation of the PR interval on the electrocardiogram. Studies suggest that PR prolongation exists in at least 10% of HF patients, and it seems more prevalent in the presence of prolonged QRS duration. A prolonged PR interval may result in elevated left ventricular (LV) end-diastolic pressure, diastolic mitral regurgitation, and reduced LV pump function. This seems especially the case in patients with heart disease, in whom it is associated with an increased risk for atrial fibrillation, advanced AV heart block, HF, and death. These findings point towards the importance of proper AV coupling in HF patients. A few studies, strongly differing in design, suggest that restoration of AV coupling in patients with PR prolongation by pacing improves cardiac function and clinical outcomes. These observations argue for AV-dromotropathy as a potential target for pacing therapy, but other studies show inconsistent results. Given its potential clinical implications, restoration of AV coupling by pacing warrants further investigation. Additional possible future research goals include assessing different techniques to measure compromised AV coupling, determine the best site(s) of ventricular pacing, and assess a potential influence of diastolic mitral regurgitation in the efficacy of such therapy.

Keywords Atrioventricular coupling • Cardiac resynchronization therapy • Biventricular pacing • Prolonged PR interval

Introduction

Chronic heart failure (HF) is a major cause of morbidity and mortality worldwide. Currently, approximately 26 million people worldwide are diagnosed with HF.[1–3] A variety of diseases and conditions, including various electrical conduction abnormalities, can contribute to the development and worsening of HF. Atrioventricular (AV) conduction disturbance may be one of these conduction abnormalities. The electrocardiographic PR interval represents conduction of the electrical impulse from the sinus node to the Purkinje fibres and reflects the time required for atrial activation and for crossing the AV node. A PR interval of more than 200 ms is defined as a prolonged PR interval. Such a prolonged PR interval is rare (0.5–2%) in the healthy population, but becomes increasingly prevalent with age (prevalence of 2–6% by the age of 4–60 years).[3–5] The prevalence of PR prolongation in HF patients has not been thoroughly investigated, but the incidence is probably high. Studies in patients with HF and cardiac resynchronization therapy (CRT) showed a prevalence of 18–52%.[6–9] Notably, an implantable cardioverter defibrillator (ICD) registry containing 50 000 patients showed that 15% of patients eligible for CRT had prolonged PR interval.[10]

A prolonged PR interval is frequently considered a harmless conduction disturbance. However, prolongation of the PR interval often represents advanced underlying cardiac pathology with significant fibrosis at times. Pathological causes include ischaemic heart disease, inflammatory and infiltrative diseases, degenerative conduction system diseases, and neuromuscular diseases.[5,11] Furthermore, as we will describe below, there is increasing evidence that a prolonged

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What's new?

- Heart failure is often accompanied by atrioventricular (AV) conduction disturbance, represented by prolongation of the PR interval on the electrocardiogram.
- PR prolongation is associated with poor hemodynamic performance and may contribute to worsening heart failure.
- Some studies indicate the importance of atrioventricular coupling, arguing for AV-dromotropathy as a distinctive entity in heart failure patients, whereas others show inconsistent results.
- However, it seems too early to abandon the idea that pacing-induced restoration of AV coupling in patients with PR prolongation can become an adjunct therapy in heart failure.
- Given its potential clinical implications, restoration of AV coupling in heart failure patients by pacing warrants further investigation.
- Additional possible future research goals include assessing different techniques to measure compromised AV coupling, determine the best site(s) of ventricular pacing and assess a potential influence of diastolic mitral regurgitation in the efficacy of such therapy.

PR interval results in poor haemodynamic performance and worse outcomes, especially in patients with HF. This review will evaluate the current evidence for AV-dromotropathy, i.e. the possible negative effects of a prolonged PR interval, especially in HF patients.

Haemodynamic implications of prolonged PR interval

In case of PR prolongation, atrial systole occurs too early in diastole, resulting in atrial contraction superimposed on the early left ventricular (LV) filling phase, and much earlier than the onset of LV systole. This leads to fusion of the E- and A-waves (*Figure 1A*)[12], as observed in echocardiographic studies.[13,14] Fusion of the E- and A-waves shortens the effective LV diastolic filling time, resulting in a lower cardiac output.[13]

Another important mechanical implication of PR prolongation is diastolic mitral regurgitation (*Figure 1A* and *B*). In a normal heart abrupt termination of forward flow at the end of atrial systole initiates a closing motion of the mitral valve. In PR prolongation, atrial systole is not followed by properly timed ventricular systole. The mitral valve remains open in mid or late diastole after the A-wave, whilst the LV end-diastolic pressure rises and exceeds left atrial (LA) pressure, thereby producing diastolic mitral regurgitation between the end of atrial contraction and the onset of ventricular contraction (*Figure 1B*).[15,16] As a consequence, a decrease in preload at the onset of LV systole occurs, ultimately decreasing LV systolic function and forward stroke volume. This phenomenon seems to be especially present in patients with HF (with elevated diastolic filling pressures).[13,17] Nevertheless, PR prolongation can also lead to diastolic mitral regurgitation in patients with DDD pacemakers and normal cardiac pump function.[16]

Furthermore, PR prolongation may be accompanied by an increased inter-atrial conduction time or inter-atrial block.[11] Increase of inter-atrial conduction time can induce inter-atrial dyssynchrony with different inter-atrial septal compliance and can disrupt optimal left-sided AV coupling. Under these conditions, LA contraction is delayed and happens against an already closing mitral valve. This causes increased LA pressures, retrograde flow in the pulmonary veins and a clinical condition similar to that of the pacemaker syndrome.[18,19]

Marked PR prolongation (PR interval > 300 ms) can also directly produce this pseudo-pacemaker syndrome. During markedly prolonged AV conduction, the close proximity of atrial systole to the preceding ventricular systole leads to atrial contraction when the AV valves are closed. Compromised ventricular filling can result in an increased pulmonary capillary wedge pressure and decreased cardiac output. Accordingly, PR prolongation shares the same pathophysiology as VVI pacing with retrograde VA conduction or an AAI induced pacemaker syndrome.[13,17,20] Such an increase of pulmonary capillary wedge pressure may cause dyspnea and retrograde blood flow in the jugular veins, leading to a sensation of fullness in the neck and palpitations. This deleterious effect is more marked in patients with HF. Symptoms of prolonged PR interval occur especially during moderate or mild exercise, when PR interval does not shorten appropriately to the previous ventricular systole.[13,21]

Prolonged PR interval: a benign phenomenon?

In the normal population, a prolonged PR interval is considered as a benign phenomenon that does not require treatment. This is supported by a study in an 'apparently healthy' middle-aged population where PR prolongation was not associated with an increased risk of cardiovascular mortality. Furthermore, these investigators found that a prolonged PR interval was partially transient in many cases.[22] However, other studies suggested that PR prolongation is related to a poorer prognosis.[5,11,23–28] Interestingly, the studies with relatively healthy individuals and a prolonged PR interval found the lowest risk for worse outcomes (*Table 1*). Additionally, a meta-analysis by Kwok *et al.*[5] about PR prolongation and adverse outcomes, showed lower risks for HF in studies with a healthy population (HR 1.4) compared with studies including patients with cardiovascular diseases (HR 1.5). The risk for cardiovascular mortality was also lower in studies with a healthy population only (HR 0.9 vs. HR 1.1, respectively). Summarizing these studies, it seems that prolonged PR interval does barely influence prognosis in healthy individuals.

Clinical evidence for atrioventricular-dromotropathy in heart failure

In contrast to the above-mentioned studies in healthy individuals, PR prolongation may worsen prognosis in older individuals, patients with comorbidities and or cardiovascular disease(s) (*Table 1*). Prolonged PR interval is associated with a substantially increased risk of developing atrial fibrillation (AF) in such patients (*Figure 2A*). Two meta-analyses with large study populations (>300 000 participants, ranging from 'apparently healthy' to individuals with stable coronary

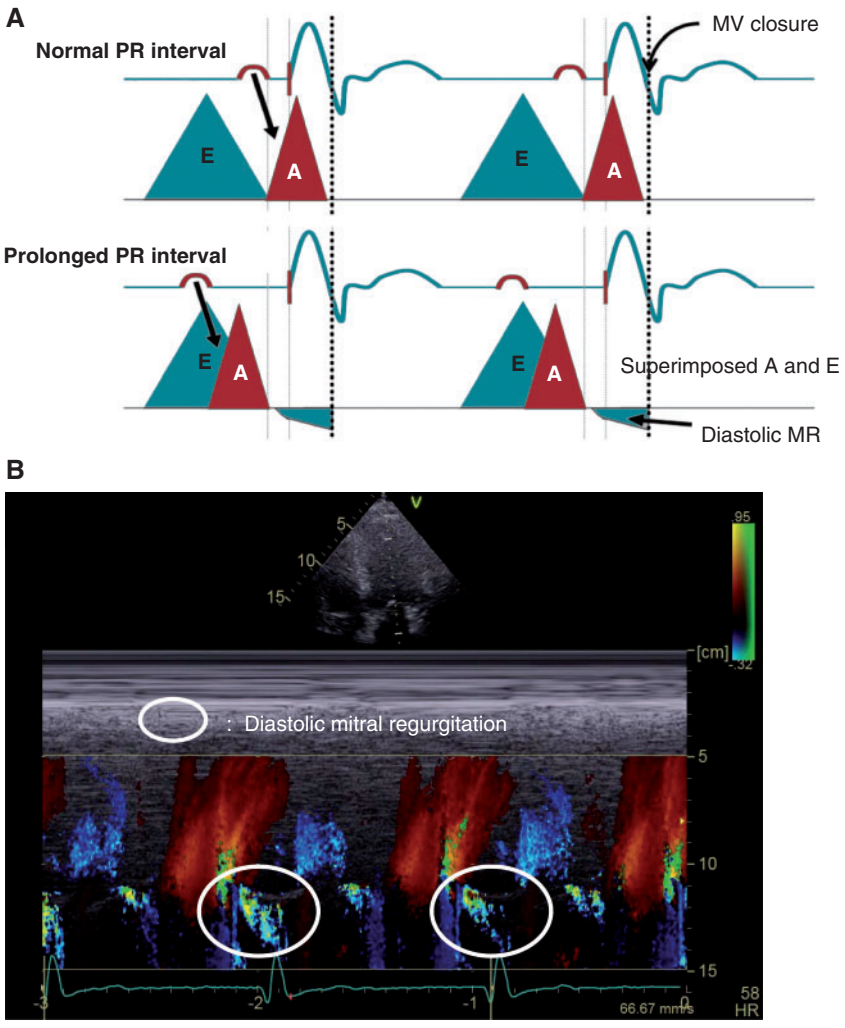

Figure 1 Haemodynamic implications of prolonged PR interval**.** (*A*) Schematic diagram of Barold *et al.*, showing the effect of PR interval on Doppler echocardiographic recordings of transmitral flow. With a normal PR interval, the MV closes at the end of the A-wave. In prolonged PR interval, the E- and A-waves become fused and the diastolic filling is shortened. Late diastolic MR may then occur.[12] (*B*) Echocardiographic image (apical view combined with color M-mode) of diastolic MR in a patient with a PR interval of 340 ms. MV, mitral valve; MR, mitral regurgitation.

artery disease and/or hypertension) showed a 30–47% higher risk of developing AF in patients with prolonged PR interval.[5,25] Two cohort studies (Health ABC and ARIC Study), with nearly 3000 and 15 000 participants, presented comparable results (HR 1.2–1.3).[23,24] Other studies found a two-fold risk to develop AF in patients with baseline PR prolongation compared with normal PR interval (*Table 1*).[11,26]

Several studies showed that a prolonged PR interval was associated with a higher risk of HF or LV dysfunction and HF hospitalization, compared with a normal PR interval. Studies showed a 39–51% increased risk of HF in patients with prolonged PR interval (*Figure 2B*).[5,23,26] The PR interval also significantly predicted LV dysfunction in patients with newly developed PR prolongation during the follow-up period.[26] In a prospective study of 938 patients with stable coronary heart disease from the Heart and Soul Study, a prolonged PR interval was associated with a higher risk of HF hospitalization (HR 2.3) compared with a normal AV conduction (*Table 1*).[27] Moreover, PR prolongation was a precursor of more severe degrees of AV conduction block (HR 2.7) with potential need for pacing.[26]

Furthermore, several studies showed a higher risk for all-cause mortality with a prolonged PR interval (HR 1.3–1.6) (*Figure 2C*).[5,11,27] In one of these studies, each 20 ms increment in PR interval was associated with 10% increase in all-cause mortality.[11] Crisel *et al.*[27] similarly showed a higher risk for cardiovascular mortality with prolonged PR interval (HR 2.3) (*Table 1*). In sub-analyses of two randomized CRT trials, patients with a prolonged PR interval in the control group had a higher risk of all-cause mortality or HF than those with a normal PR interval (HR 1.4–3.6) (*Table 2*).[6,8] However, Magnani *et al.*[23] did not find such association between PR interval and all-cause mortality. Participants of Magnani's study, however were

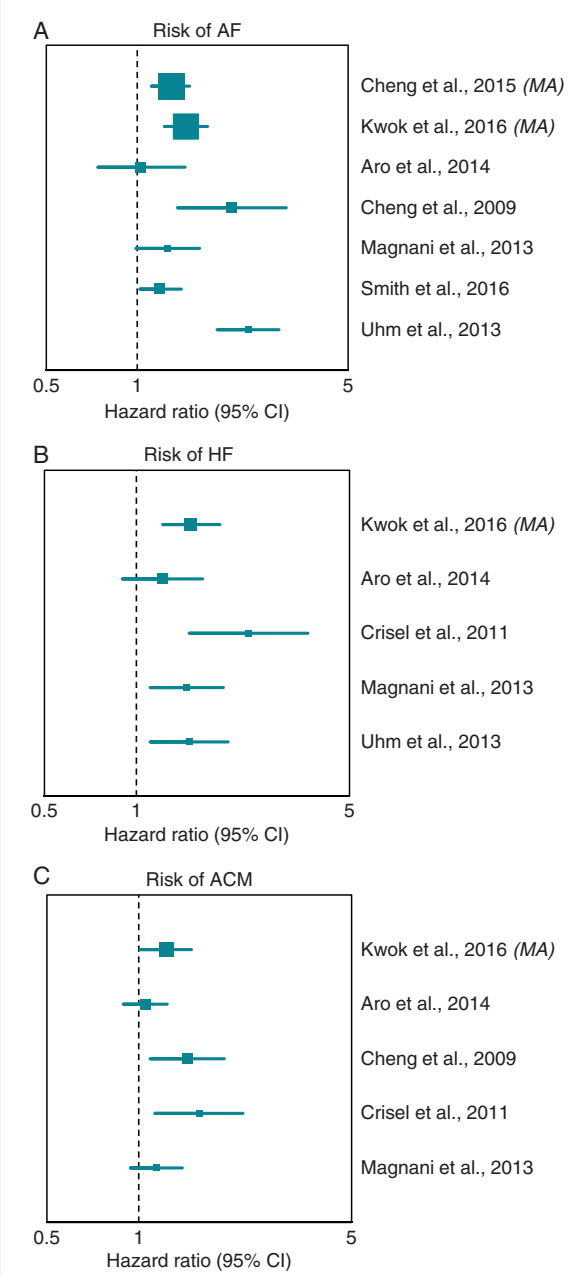

Figure 2 Risk of (*A*) AF, (*B*) HF and HF hospitalization, and (*C*) ACM in patients with prolonged PR interval by study.[4,5,11,23–27] MA, meta-analyses; AF, atrial fibrillation; HF, heart failure; ACM, all-cause mortality.

relatively old (mean age 74 years), and had a high burden of comorbidities, possibly overruling the impact of PR prolongation on mortality in this study.

It is important to note that while the studies mentioned above showed association between a prolonged PR interval and outcomes, they cannot distinguish between PR interval as a cause or a consequence of the underlying disease conditions, or as an innocent bystander. The most likely causal relationship appears to be the one between PR prolongation and third degree AV heart block, due to the progressive disease of the AV conduction system. Changes like fibrosis and calcification of the cardiac skeleton are dynamic with accumulating changes over time[5] and may favour the development of AF to intra-atrial conduction delay. Inter-atrial conduction delay leading to atrial dyssynchrony syndrome as mentioned above, may cause fibrosis and diastolic HF.[18] Similarly, fibrosis or other degenerative processes both in the AV node and in the ventricles may explain the relationship between PR prolongation and HF. Alternatively, the compromised filling and backward failure induced by a prolonged PR interval may make PR prolongation a direct causal factor in the origin of AF and HF. It is this latter option that is discussed below and for which pacemaker therapy may provide a useful therapy.

Restoring atrioventricular coupling in patients with prolonged PR interval

Rationale

Restoration of AV coupling may re-establish AV coordination improving diastolic filling and subsequently higher cardiac output. Part of this effect is established by abolishing premature closing of the mitral valve and the increase in diastolic filling time. Furthermore, PR interval normalization may eliminate diastolic mitral regurgitation, leading to a lower LA pressure and higher LV preload at the onset of ventricular contraction.[30] The restoration of AV coupling is especially important in patients with HF, considering the aforementioned haemodynamic and prognostic implications in these patients. According to current guidelines, permanent pacing may be considered for patients with persistent symptoms similar to those of pacemaker syndrome attributable to first-degree AV heart block (PR interval > 300 ms) (class IIa recommendation with level of evidence C).[21]

Ventricular pacing

These considerations about AV coupling led to the first studies on pacing in HF patients in the early 1990's. These studies utilized right ventricular (RV) pacing, and suggested significant functional and symptomatic improvement with restored AV coupling in patients with a prolonged PR interval. In a study of 16 patients with end-stage dilated cardiomyopathy, half of them with prolonged PR interval, AV sequential RV pacing at an AV delay of 100 ms increased LVEF from 16 to 26% in the total study group. Furthermore, the cardiothoracic ratio on chest X-ray decreased, systolic and diastolic blood pressure increased, and HF symptoms improved at follow-up (*Table 3*).[29] Brecker *et al.*[32] investigated AV sequential RV pacing in 12 HF patients of whom 5 had a prolonged PR interval, and selected the patients based on their reduced RV filling time. They optimized the AV delay, and found a significant reduction in the duration of mitral and tricuspid regurgitation, consequently increasing LV and RV filling times, and improving cardiac output (*Table 3*). Nishimura *et al.*[30] reported that AV sequential pacing at optimal AV interval in eight HF patients with prolonged PR interval increased cardiac output by 38%, but decreased cardiac output by 23% in seven patients with a normal baseline PR interval (*Table 3*). *Figure 3* shows another example of a

Table 1 Clinical implications of prolonged vs. normal PR interval at baseline

Study	Aro *et al.*[4] (*C*/*K*)	Magnani *et al.*[23] (*C*/*K*)	Smith *et al.*[24]	Cheng *et al.*[11] (*C*/*K*)	Uhm *et al.*[26] (*K*)	Crisel *et al.*[27]
Cohort name	Coronary Heart Disease Study	Health ABC	ARIC Study	Framingham Heart Study		The Heart and Soul Study
No. of patients	10 785	2722	14 924	7575	3816	938
Patient population	Community based	Community based	Community based	Community based	Hypertension	Stable CAD
Prolonged PR (%)	2.1 > 200 ms	12.5 > 200 ms	7.0 > 200 ms	1.6 > 200 ms	14.2 > 200 ms	9.3 ≥ 220 ms
Outcome (HR)						
AF	1.03 (0.74–1.44)	1.26 (0.99–1.61)	1.19 (1.02–1.40)	2.06 (1.36–3.12)	2.33 (1.84–2.95)	
HF	1.22 (0.90–1.65)	1.46 (1.11–1.93)			1.49 (1.11–2.00)	
CV mortality	0.94 (0.70–1.27)					2.33 (1.28–4.22)
SCD	1.16 (0.76–1.75)					
ACM	1.05 (0.89–1.24)	1.14 (0.94–1.39)		1.44 (1.09–1.91)		1.58 (1.13–2.20)
Others					Advanced AVB: 2.77 (1.38–5.59)	HF hosp.: 2.33 (1.49–3.65)
Follow-up (year)	30	10	21	Up to 35	9 ± 2	6 ± 2

Studies with '*C*' are included in the meta-analysis of Cheng *et al.*[25] and '*K*' in Kwok *et al.*[5] Hazard ratio's (HR) presented as mean value (95% CI).
ACM, all-cause mortality; AF, atrial fibrillation; AVB, atrioventricular heart block; CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; SCD, sudden cardiac death.

Table 2 Studies showing better CRT effect in patients with prolonged than with normal PR interval at baseline

Study	Lin *et al.*[7]	Olshansky *et al.*[8]	Gervais *et al.*[29]	Kutyifa *et al.*[6]	Stockburger *et al.*[9]
Cohort name	COMPANION	COMPANION	CARE-HF	MADIT-CRT	MADIT-CRT
No. of patients	903	1520	813	534	534
Design	CRT-D vs. OPT in prolonged and normal PR	CRT vs. OPT in prolonged and normal PR	CRT vs. OPT in PR at 3 months after randomization	CRT-D vs. ICD in prolonged and normal PR	CRT-D vs. ICD in prolonged and normal PR
Baseline					
Prolonged PR (%)	20.7 > 230 ms	52 ≥ 200 ms	48.7 ≥ 200 ms	18.0 ≥ 230 ms	18.0 ≥ 230 ms
QRS conf. (*n*)	LBBB: 143, RBBB/IVCD: 19	nr	LBBB: 730, RBBB: 35	Non-LBBB (RBBB/IVCD)	Non-LBBB (RBBB/IVCD)
Outcome (HR)					
HF				pPR: 0.25 (0.11–0.57) nPR: 1.31 (0.84–2.05)	pPR: 0.31 (0.14–0.68) nPR: 1.33 (0.85–2.07)
HF or ACM				pPR: 0.27 (0.13–0.57) nPR: 1.45 (0.96–2.19)	pPR: 0.33 (0.16–0.69) nPR: 1.49 (0.98–2.25)
ACM	pPR: 0.37 (0.21–0.67) nPR: 0.73 (0.52–1.03)			pPR: 0.19 (0.06–0.63) nPR: 2.14 (1.12–4.09)	pPR: 0.24 (0.07–0.80) nPR: 2.27 (1.16–4.44)
ACM or HF/AC hosp.	pPR: 0.60 (0.42–0.87) nPR: 0.81 (0.68–0.98)	pPR: 0.54* nPR: 0.71*	1.01/ms (1.00–1.01) (incl. HTx)		
Follow-up			30 months	30 ± 11 months	2 year (long-term follow-up 6)

All studies are randomized controlled trials. Hazard ratio's (HR) presented as mean value (95% CI). Outcomes with * are statistically significant.
AC(M), all-cause (mortality); HF, heart failure; HTx, heart transplantation; IVCD, interventricular conduction delay; LBBB, left bundle branch block; nPR, normal PR interval; nr, not reported; OPT, optimal pharmacological treatment; pPR, prolonged PR interval; RBBB, right bundle branch block.

Table 3 Effect of RV pacing in patients with baseline PR prolongation

Study	Hochleitner et al[31]	Brecker et al[32]	Nishimura et al[30]	Gold et al.[33]
No. of patients	16	12	15	12
Patient population	HF (end-stage) due to IDCM	HF due to DCM, CAD or muscular dystrophy	HF due CAD or IDCM	HF due CAD or IDCM
Paced AV delay	100 ms (DDD)	Optimal (DDD)	Optimal	Optimal (VDD)
Prolonged PR (%)	50	41.7	53.3	75
QRS duration (*n*)	nr	5/12 ≥ 120 ms	5/15 'wide' QRS	9/12 ≥ 110 ms
QRS conf. (*n*)	LBBB: 7/16	nr	LBBB: 4/15, RBBB: 1/15, Paced QRS: 2/15	nr
MR (*n*)	6/6	6/12	5/15 (all with pPR)	6/12
Outcome				
CO (l/min)		Δ = +1.1 (0.8–1.4)	pPR: 3.0 ± 1.0 vs. 3.9 ± 0.4 * nPR: 4.2 ± 1.8 vs. 3.4 ± 1.3 *	4.5±1.5 vs. 4.7±1.6 NS
SBP (mmHg)	108 ± 29 vs. 126 ± 21*			
DBP (mmHg)	67 ± 15 vs. 80 ± 11*			
LV filling time (ms)		Δ = +65 (35–95)	pPR: 215 ± 58 vs. 314 ± 102 * nPR: no change	
RV filling time (ms)		Δ = +90 (60–120)		
MR	2.0 ± 0.4 grade vs. 0.9 ± 0.4 *	Δ = -105 ms (85–125)	Abolishment MR 5/5	
Others	LVEF (%): 16 ± 8 vs. 26 ± 9 * Cardiothoracic ratio: 0.60 ± 0.06 vs. 0.56 ± 0.05 * NYHA (class): 3.6 ± 0.4 vs. 2.1 ± 0.5 *	Exercise duration (s): Δ = +104 (45–165) VO_2 max (ml/kg/min): Δ = +2.1 (1.5–2.7)		PCWP (mmHg): 16 ± 10 vs. 17 ± 8 NS

All studies are prospective studies. Acute measurements and short-term follow-up (max. 14 days) only are presented. Mean changes presented in values with 95% CI. Outcomes with * are statistically significant and 'NS' not significant.
CAD, coronary artery disease; CO, cardiac output; DBP, diastolic blood pressure; HF, heart failure; (I)DCM, (idiopathic) dilated cardiomyopathy; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; nPR, normal PR interval; nr, not reported; PCWP, pulmonary capillary wedge pressure; pPR, prolonged PR interval; RBBB, right bundle branch block; RV, right ventricular; SBP, systolic blood pressure.

HF patient with prolonged PR interval and the restoration of AV coupling by optimized atrial sensed ventricular pacing. These data are contradicted by the study of Gold *et al.*[33] who did not find acute haemodynamic benefit of dual chamber pacing at an optimal AV interval in patients with severe chronic congestive HF. However, in this study, no distinction was made between normal and prolonged PR intervals (*Table 3*). Therefore, there is some evidence that ventricular pacing with an optimal AV delay may improve pump function in HF patients with prolonged PR interval, but this has only been collected in small studies on acute haemodynamic effects.

Since these four studies were performed before the era of CRT, they all employed RV pacing, which likely creates intraventricular desynchronization, possibly offsetting the effect of AV coupling. Evidence for such interaction between AV coupling and interventricular synchrony also came from studies on the benefit of minimizing RV pacing by prolonging AV conduction times. Several pacemaker vendors provide an algorithm for minimizing ventricular pacing that gives preference to spontaneous ventricular conduction by allowing longer AV conduction times. However, studies in ICD patients on minimizing ventricular pacing mode showed slightly higher overall death and HF event rates using such algorithms as compared with ventricular backup pacing. In one study the impaired outcome was largely seen in the patients with a prolonged baseline PR interval. The risk of all-cause mortality and HF increased by 7.8% for every 10 ms increase in baseline PR interval.[34] Another study showed that the algorithm minimizing ventricular pacing may worsen or induce PR prolongation (>300 ms), predicted by the baseline PR interval.[35] Therefore, minimizing ventricular pacing by algorithms, that prolong the PR interval may replace one haemodynamic evil with another. While during the last two decades RV pacing-induced dyssynchrony has received much attention, PR prolongation induced inappropriate AV coupling has not.

Cardiac resynchronization therapy in prolonged PR interval

While the above-mentioned RV pacing studies can be considered as the start of pacing therapy for HF, it was quickly surpassed by CRT. Cardiac resynchronization therapy aims to restore inter- and intraventricular synchrony in HF patients with a wide QRS complex.[36,37] However, CRT restores not only inter- and intraventricular dyssynchrony, but also abolishes inappropriate AV coupling.[38,39] Using a combination of computer simulations and patient data, Jones *et al.*[40] showed that AV normalization and ventricular resynchronization

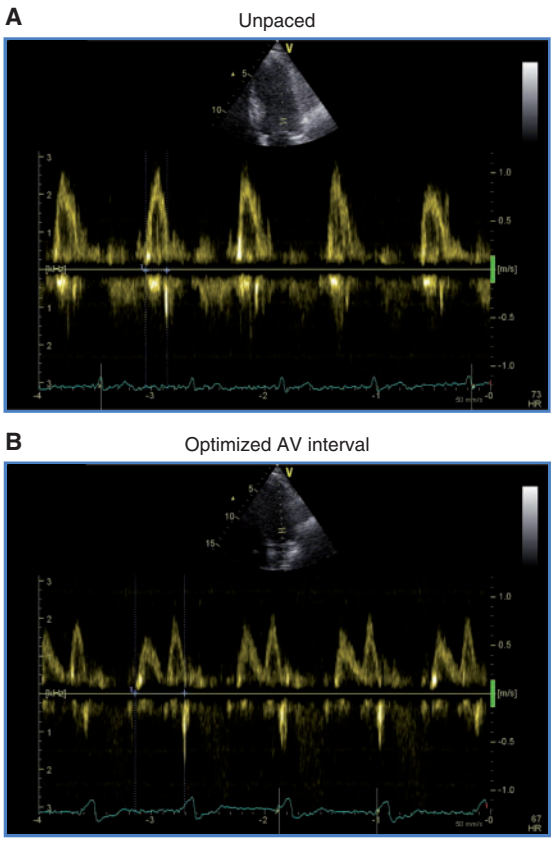

Figure 3 Echocardiographic images of (*A*) a patient with a PR interval of 380 ms without pacing and (*B*) restoration of AV coupling by optimized atrial sensed ventricular pacing (140 ms after atrial sense). (Unpublished by Stockburger). AV, atrioventricular.

may both contribute about half of the acute haemodynamic benefit of CRT. This observation is further supported by findings from the PATH-CHF study, in which 39 patients with HF and a mean baseline PR interval of 210 ms gained significant improvements in LV systolic function from restored AV coupling with RV pacing. Improvement of LV systolic function with RV pacing was 25–50% of the achievement compared with biventricular pacing.[41]

The beneficial effect of CRT in patients with left bundle branch block (LBBB) is well established, and it is mainly attributed to ventricular resynchronization. However, the effect of CRT in patients with wide QRS complex but no LBBB configuration is in debate, because it is unclear, to what extent ventricular resynchronization can be achieved in non-LBBB patients. Several studies investigated the value of restored AV coupling for clinical benefit in HF patients undergoing CRT implantation. Two sub-analyses of the COMPANION trial showed that the reduction in all-cause mortality and HF hospitalization, induced by CRT was more pronounced in patients with a prolonged than with a normal PR interval, irrespective of the bundle branch block pattern (*Table 2*). In these studies, CRT reduced the relative risk of all-cause mortality and hospitalization by 20–30% for patients with normal PR interval, and 40–50% for patients with prolonged PR interval.[7,8] A sub-analysis of the CARE-HF trial confirmed that shortening the PR interval by CRT was a stronger predictor of response than shortening the QRS duration (*Table 2*).[29] While the COMPANION and CARE-HF sub-studies analysed the results using data from all enrolled patients, two sub-analyses of the MADIT-CRT study limited their investigations to patients with a non-LBBB configuration only. In both sub-analyses of the MADIT-CRT, CRT was associated with a trend to adverse clinical outcomes in patients with a normal PR interval (*Table 2*). These results may be explained by some degree of ventricular desynchronization due to biventricular pacing (in the absence of a late-activated LV in non-LBBB patients). However, CRT reduced the risk of HF and all-cause mortality in patients with long PR interval (>230 ms) (*Figure 4*), suggesting that potentially unfavourable effects of biventricular pacing in these patients are overruled by restoration of AV coupling.[6,9] These results are further supported by a sub-analysis of the ReThinQ trial. This study investigated the effect of CRT in HF patients with a normal QRS duration (<130 ms) and showed a statistically significant improvement in VO_2 max and LVEF after 6 months of CRT in patients with a prolonged PR interval (>180 ms, $N = 46$), while there was no overall improvement in the total study population.[42]

Other, mainly non-randomized, studies showed results contrary to these findings. Data from a large medical registry of patients with an implanted ICD or CRT-D (CRT with ICD) devices showed that the beneficial effect of CRT was confined to patients with a normal PR interval, and was absent in patients with a prolonged PR interval, even in patients with LBBB (*Table 4*). This NCDR ICD Registry did not show an association between prolonged PR interval and a reduction in HF hospitalization or death in patients with an CRT-D and non-LBBB configuration.[10] Data from the Mayo Clinic, a retrospective study which included 403 patients who underwent CRT implantation, showed similar results. They found that CRT response rate (defined as improvement of LVEF > 5% and/or NYHA ≥ 1 class) was 88% in patients with normal PR interval and 74% in those prolonged PR interval. Furthermore, 5-year all-cause mortality was higher in patients with prolonged PR interval than with normal PR (40 vs. 27%). These data might have been confounded by a larger proportion of patients with LBBB in the normal PR group.[43] An observational, single-centre study also associated prolongation of the PR interval with a worse prognosis (HF hospitalization and reduced reverse remodelling) (*Table 4*).[44] The non-randomized nature of these studies hampers proper comparison of these results. Confounding factors in non-randomized studies cannot be ruled out. Furthermore, in the registry study by Friedman *et al.*, it is not known why certain individuals received a CRT.

Other studies seem to show a more favourable CRT response in patients with normal PR interval than with prolonged. In the MIRACLE trial, patients with a normal PR interval were over-represented in the responder group (73%, as compared with 58% in the non-responders) (*Table 4*). Unfortunately, this sub-analysis did not compare their results to the group randomized to standard medical therapy and the endpoint of this study was the (subjective) change in NYHA functional class. In addition, the MIRACLE-ICD study did not show similar findings, despite the fact that this trial had nearly identical enrolment criteria as MIRACLE.[45]

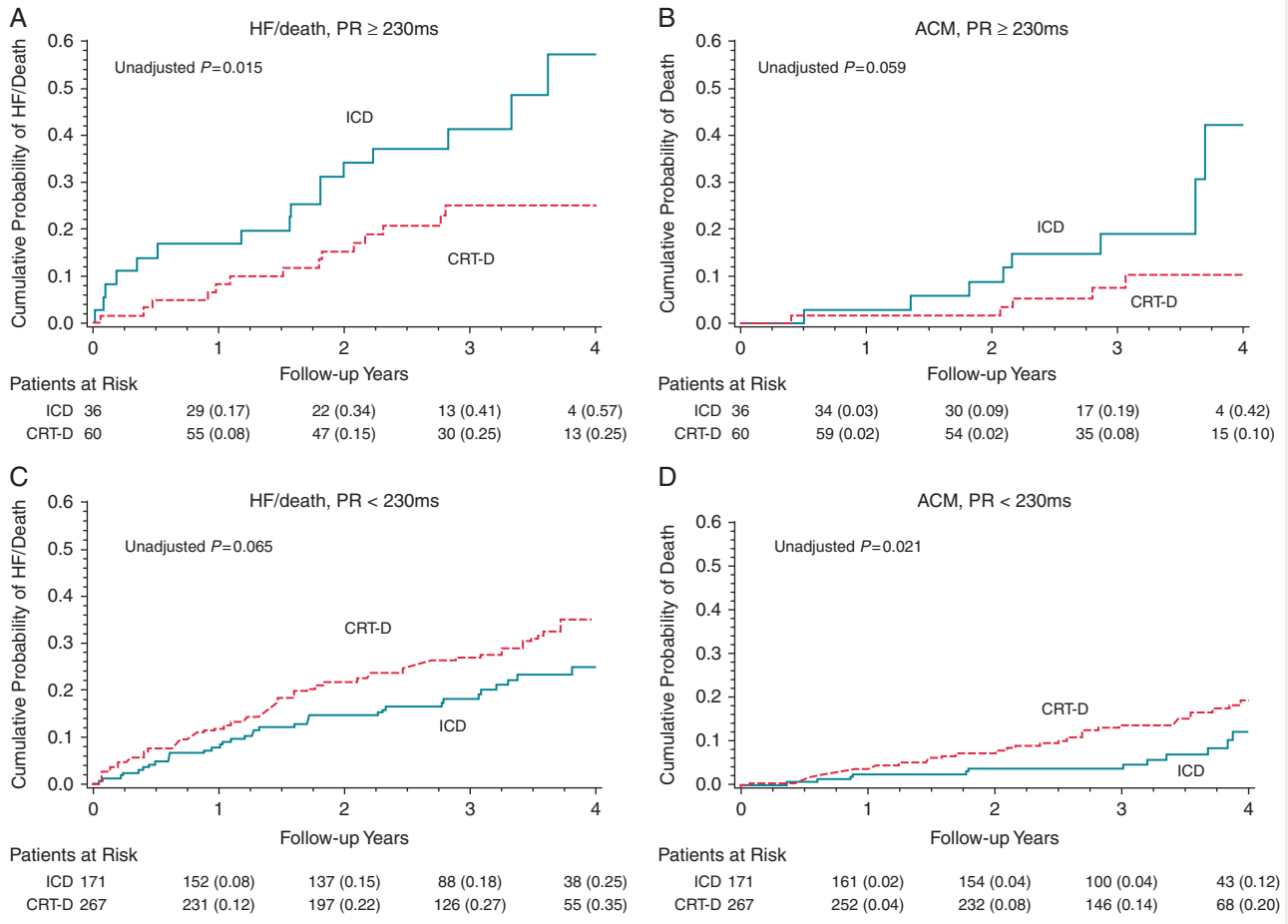

Figure 4 Figure from Kutyifa *et al.*[6] with (*A*) HF/death episodes in patients with non-LBBB and PR ≥ 230 ms, (*B*) ACM in patients with non-LBBB and PR ≥ 230 ms, (*C*) HF/death in patients with non-LBBB and PR < 230 ms, and (*D*) ACM in patients with non-LBBB with PR < 230 ms. HF, heart failure; ACM, all-cause mortality; LBBB, left bundle branch block.

In summary, in most of the above-mentioned, mainly non-randomized studies, patients with prolonged PR interval appeared to be sicker than patients with normal PR interval, suggesting that PR prolongation is a marker of a more advanced disease state associated with poor outcomes. Therefore, it is striking that this relatively sick patient group benefits from normalizing AV conduction times by CRT, as shown in nearly all sub-studies of randomized studies. However, the small number of studies in this field, the heterogeneity in the study populations and study designs and the sometimes controversial results warrant to further investigate the idea that biventricular pacing might be useful as an adjunct therapy for patients with HF and prolonged PR interval.

Additional considerations for atrioventricular-dromotropathy

All the above-mentioned studies used the intrinsic PR interval, assuming this expresses the delay in activation between atria and ventricles. However, the true inappropriate AV coupling may depend on the contribution of P-duration to the overall length of PR interval. The beginning of the normal sinus P-wave reflects RA depolarization, while LA depolarization contributes to the last 25–50% of the P-wave. Therefore, the true LA–LV interval, which is presumably relevant for proper LV filling, may be overestimated when measuring from beginning of the P-wave, especially in case of a long P-wave.[46] Soliman *et al.* observed that P-wave duration may range between 30 and 90% of the PR interval, indicating that P-wave duration might affect the analysis using PR interval. P-wave duration also has strong clinical implications. It is a surrogate of LA enlargement, which is a consequence of different upstream processes such as hypertension, obesity, atrial stiffness, and diastolic dysfunction. Most importantly, P-wave duration is strongly linked to the risk of AF, especially when using the P-wave onset to P-wave peak duration.[24] Probably as a consequence of the relation with AF, a long P-wave duration was associated with increased mortality, in both short and prolonged PR intervals (HR 1.46 and HR 2.00, respectively). In contrast, a low P-wave duration contribution did not show worse outcome in both

Table 4 Studies showing equal or worse CRT effect in patients with prolonged than with normal PR interval at baseline

Study	Friedman *et al.*[10]		Lee *et al.*[43]	Januszkiewicz *et al.*[44]	Pires *et al.*[45]
Cohort name	NCDR ICD Registry		Mayo Clinic	Massachusetts G.H.	MIRACLE and MIRACLE ICD
No. of patients	26 451		403	283	537
Design	Effect PR interval in CRT-D	Effect prolonged PR on CRT effect	Effect PR interval in CRT-D/P	Effect PR interval in CRT	Effect prolonged PR in CRT (Control: OPT, but not used in this sub-analyses)
Baseline					
Prolonged PR (%)	15.3 ≥ 230 ms		50.6 > 200 ms	44.2 ≥ 200 ms	40.3 ('1°AVB')
QRS conf. (*n*)	LBBB: 17 907, Non-LBBB: 8544		LBBB: 263	LBBB: 172, RBBB: 20	nr
MR (grade)	nr		pPR 1.6, nPR 1.4	nr	nr
Outcome					
LVEF			pPR Δ = +5.88% (±9.53) nPR Δ = +9.44% (±12.41)	pPR vs. nPR: OR 0.6 (0.3–1.0)	
HF hosp.	pPR vs. nPR: HR 1.28 (1.18–1.39)	CRT-D vs. ICD: HR 1.03 (0.85–1.25)		pPR vs. nPR: HR 1.6 (1.0–2.3)	
ACM	pPR vs. nPR: HR 1.12 (1.03–1.22)	CRT-D vs. ICD: HR 0.92 (0.78–1.09)	pPR vs. nPR: HR 1.45 (0.99–2.12)		
Others			LVEF > 5% and/or NYHA ≥ 1 class: pPR vs. nPR: OR 0.48 (0.25–0.93) MR grade: pPR Δ = −0.26 (±0.66) nPR Δ = -0.37 (±0.72)	ACM, HF hosp. or HTx: pPR vs. nPR: HR 1.2 (0.8–1.9)	NYHA ≥ 1 class: MIRACLE: 27% vs. 42% (in R vs. in non-R)* MIRACLE-ICD: 45% vs. 48% (in R vs. in non-R) NS
Follow-up	34 months		4 year	30 months	6 months

Friedman *et al.*, Januszkiewicz *et al.*, and Lee *et al.* are retrospective studies. Pires *et al.* used randomized data. Hazard ratio's (HR) and odds ratio's (OR) presented as mean value (95% CI), mean changes in values with standard deviation. Outcomes with * are statistically significant and 'NS' not significant.
ACM, all-cause mortality; AVB, atrioventricular heart block; HF, heart failure; HTx, heart transplantation; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; non-R, non-responders; nPR, normal PR interval; nr, not reported; R, responders; OPT, optimal pharmacological treatment; pPR, prolonged PR interval; RBBB, right bundle branch block.

short and prolonged PR interval (HR 1.53 and HR 0.99, respectively).[47]

A specific condition with prolonged P-wave duration is created by atrial pacing. Right atrial (RA) pacing, where the atrial lead is traditionally placed in the RA appendage, leads to a delayed electrical and mechanical activation of the LA by at least 60–100 ms.[48] In a study with CRT patients, RA-sensed pacing resulted in a higher degree of LV resynchronization and prolongation of the rate-corrected LV filling period, compared with RA-paced pacing. Right atrial pacing compromised passive and atrial transmitral inflow, which impedes LV preload compared with intrinsic LA activation.[48,49] An alternative to RA pacing may be biatrial pacing, since some small studies with AF patients and patients with bradycardia showed favourable acute haemodynamic effects. Compared to high RA pacing, P-wave duration decreased, left AV coupling improved and cardiac output increased.[50–52] Biatrial pacing increased the interval between the end of the atrial filling wave of transmitral flow and closure of the mitral valve. These improvements were especially remarkable in patients with a longer interatrial conduction delay.[51,52] Also, a study on 19 AF patients showed that bifocal RA pacing decreases the interatrial delay compared with unifocal RA pacing.[53] Altogether these small studies suggest that biatrial and bifocal RA pacing may be preferable to unifocal RA pacing in patients with prolonged PR interval.

Another additional consideration of CRT response may be diastolic mitral regurgitation. As previously mentioned, diastolic mitral regurgitation might be a mechanical consequence of PR prolongation (*Figure 1A* and *B*). It is unknown to what degree diastolic mitral regurgitation plays a role in HF patients with CRT. Panidis *et al.*[15] observed end-diastolic mitral regurgitation in 9 of the 16 patients with prolonged PR interval, but in none of the 20 patients with a normal PR interval. Schnittger *et al.*[54] observed diastolic mitral regurgitation in 20 of 22 patients with varying degrees of AV heart block (7 of 20 with a first-degree AV heart block). Nishimura *et al.*[30] found diastolic mitral regurgitation in the baseline state in five of eight patients with a

prolonged PR interval (*Table 3*). Clearly, this is still limited information regarding the relation between PR interval and diastolic mitral regurgitation, and further investigations are warranted.

Conclusions

There is evidence from different fields of research that in HF patients, a prolonged PR interval worsens outcome and that normalization of AV coupling can attenuate HF. However, the small number of studies, the heterogeneity between their design and partly between their outcome prevents us to firmly conclude that AV-dromotropathy is a distinctive entity in HF patients. However, it also seems too early to abandon the idea that pacing-induced restoration of AV coupling in patients with PR prolongation can become an adjunct therapy in HF. Clearly, further clinical studies are warranted to assess the benefits of CRT in HF patients with PR prolongation.

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References

1. Krum H, Abraham WT. Heart failure. *Lancet* 2009;**373**:941–55.
2. Zannad F, Jaarsma T, Anker SD, Fonseca C, Køber L, Rønnevik PK *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. *Eur Heart J* 2012;**33**:1787–847.
3. Holmqvist F, Daubert JP. First-degree AV block—an entirely benign finding or a potentially curable cause of cardiac disease? *Ann Noninvasive Electrocardiol* 2013;**18**:215–24.
4. Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA *et al.* Prognostic significance of prolonged PR interval in the general population. *Eur Heart J* 2014;**35**:123–9.
5. Kwok CS, Rashid M, Beynon R, Barker D, Patwala A, Morley-Davies A *et al.* Prolonged PR interval, first-degree heart block and adverse cardiovascular outcomes: a systematic review and meta-analysis. *Heart* 2016;**102**:672–80.
6. Kutyifa V, Stockburger M, Daubert JP, Holmqvist F, Olshansky B, Schuger C *et al.* PR interval identifies clinical response in patients with non-left bundle branch block: a multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy substudy. *Circ Arrhythmia Electrophysiol* 2014;**7**:645–51.
7. Lin J, Buhr KA, Kipp R. Effect of PR interval on outcomes following cardiac resynchronization therapy: a secondary analysis of the COMPANION Trial. *J Cardiovasc Electrophysiol* 2016;**34**:1–6.
8. Olshansky B, Day JD, Sullivan RM, Yong P, Galle E, Steinberg JS. Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION Trial. *Heart Rhythm* 2012;**9**:34–9.
9. Stockburger M, Moss AJ, Klein HU, Zareba W, Goldenberg I, Biton Y *et al.* Sustained clinical benefit of cardiac resynchronization therapy in non-LBBB patients with prolonged PR-interval: MADIT-CRT long-term follow-up. *Clin Res Cardiol* 2016;**105**:944–52.
10. Friedman DJ, Bao H, Spatz ES, Curtis JP, Daubert JP, Al-Khatib SM. Association between a prolonged pr interval and outcomes of cardiac resynchronization therapyclinical perspective. *Circulation* 2016;**134**:1617–28.
11. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D *et al.* Long-term outcomes in individuals with a prolonged PR interval or first-degree atrioventricular block. *JAMA* 2009;**301**:2571–7.
12. Barold SS, Ilercil A, Herweg B. Echocardiographic optimization of the atrioventricular and interventricular intervals during cardiac resynchronization. *Europace* 2008;**10(Suppl 3)**:iii88–95.
13. Barold SS, Ilercil A, Leonelli F, Herweg B. First-degree atrioventricular block. *J Interv Card Electrophysiol* 2007;**17**:139–52.
14. Kyriacou A, Pabari PA, Francis DP. Cardiac resynchronization therapy is certainly cardiac therapy, but how much resynchronization and how much atrioventricular delay optimization? *Heart Fail Rev* 2012;**17**:727–36.
15. Panidis IP, Ross J, Munley B, Nestico P, Mintz GS. Diastolic mitral regurgitation in patients with atrioventricular conduction abnormalities: a common finding by Doppler echocardiography. *J Am Coll Cardiol* 1986;**7**:768–74.
16. Ishikawa T, Kimura K, Miyazaki N, Tochikubo O, Usui T, Kashiwagi M *et al.* Diastolic mitral regurgitation in patients with first-degree atrioventricular block. *Pacing Clin Electrophysiol* 1992;**15**:1927–31.
17. Barold SS. Indications for permanent cardiac pacing in first-degree AV block: class I, II, or III? *Pacing Clin Electrophysiol* 1996;**19**:747–51.
18. Eicher J-C, Laurent G, Mathé A, Barthez O, Bertaux G, Philip J-L *et al.* Atrial dyssynchrony syndrome: an overlooked phenomenon and a potential cause of "diastolic" heart failure. *Eur J Heart Fail* 2012;**14**:248–58.
19. Sweeney MO, Prinzen FW. Ventricular pump function and pacing: physiological and clinical integration. *Circ Arrhythmia Electrophysiol* 2008;**1**:127–39.
20. Carroz P, Delay D, Girod G. Pseudo-pacemaker syndrome in a young woman with first-degree atrio-ventricular block. *Europace* 2010;**12**:594–6.
21. Brignole M, Auricchio A, Baron-Esquivias G, Brodachar P, Boriani G, Breithardt O *et al.* 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–118.
22. Aro AL. First-degree atrioventricular block: risk marker or innocent finding? *Heart* 2016;**102**:655–6.
23. Magnani JW, Wang N, Nelson KP, Connelly S, Deo R, Rodondi N *et al.* Electrocardiographic PR interval and adverse outcomes in older adults: the health, aging, and body composition study. *Circ Arrhythmia Electrophysiol* 2013;**6**:84–90.
24. Smith JW, O'neal WT, Shoemaker MB, Chen LY, Alonso A, Whalen SP *et al.* PR-interval components and atrial fibrillation risk (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol* 2016;**119**:466–72.
25. Cheng M, Lu X, Huang J, Zhang S, Gu D. Electrocardiographic PR prolongation and atrial fibrillation risk: a meta-analysis of prospective cohort studies. *J Cardiovasc Electrophysiol* 2015;**26**:36–41.
26. Uhm J-S, Shim J, Wi J, Mun H-S, Park J, Park S-H *et al.* First-degree atrioventricular block is associated with advanced atrioventricular block, atrial fibrillation and left ventricular dysfunction in patients with hypertension. *J Hypertens* 2014;**32**:1115–20.
27. Crisel RK, Farzaneh-Far R, Na B, Whooley MA. First-degree atrioventricular block is associated with heart failure and death in persons with stable coronary artery disease: data from the Heart and Soul Study. *Eur Heart J* 2011;**32**:1875–80.
28. Schoeller R, Andresen D, Büttner P, Oezcelik K, Vey G, Schröder R. First- or second-degree atrioventricular block as a risk factor in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993;**71**:720–6.
29. Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjær H, Johannessen A *et al.* Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *Eur J Heart Fail* 2009;**11**:699–705.
30. Nishimura RA, Hayes DL, Holmes DR, Tajik J. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterization hemodynamic study. *J Am Coll Cardiol* 1995;**25**:281–8.
31. Hochleitner M, Hörtnagl H, Ng CK, Hörtnagl H, Gschnitzer F, Zechmann W. Usefulness of physiologic dual-chamber pacing in drug-resistant idiopathic dilated cardiomyopathy. *Am J Cardiol* 1990;**66**:198–202.
32. Brecker SJD, Xiao HB, Sparrow J, Gibson DG. Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. *Lancet* 1992;**340**:1308–12.
33. Gold MR, Feliciano Z, Gottlieb SS, Fisher ML. Dual-chamber pacing with a short atrioventricular delay in congestive heart failure: a randomized study. *J Am Coll Cardiol* 1995;**26**:967–73.
34. Sweeney MO, Ellenbogen KA, Tang ASL, Whellan D, Mortensen PT, Giraldi F *et al.* Atrial pacing or ventricular backuponly pacing in implantable cardioverter-defibrillator patients. *Heart Rhythm* 2010;**7**:1552–60.
35. Sweeney MO, Ellenbogen KA, Tang ASL, Johnson J, Belk P, Sheldon T. Severe atrioventricular decoupling, uncoupling, and ventriculoatrial coupling during enhanced atrial pacing: incidence, mechanisms, and implications for minimizing right ventricular pacing in ICD patients. *J Cardiovasc Electrophysiol* 2008;**19**:1175–80.

36. Vernooy K, van Deursen CJM, Strik M, Prinzen FW. Strategies to improve cardiac resynchronization therapy. *Nat Rev Cardiol* 2014;**11**:481–93.
37. Prinzen FW, Vernooy K, Auricchio A. Cardiac resynchronization therapy: state-of-the-art of current applications, guidelines, ongoing trials, and areas of controversy. *Circulation* 2013;**128**:2407–18.
38. Whinnett ZI, Briscoe C, Davies JER, Willson K, Manisty CH, Davies DW *et al*. The atrioventricular delay of cardiac resynchronization can be optimized hemodynamically during exercise and predicted from resting measurements. *Heart Rhythm* 2008;**5**:378–86.
39. Linde C, Ellenbogen K, Mcalister FA. Cardiac resynchronization therapy (CRT): clinical trials, guidelines, and target populations. *Heart Rhythm* 2012;**9**:S3–13.
40. Jones S, Lumens J, Sohaib SMA, Finegold JA, Kanagaratnam P, Tanner M *et al*. Cardiac resynchronization therapy: mechanisms of action and scope for further improvement in cardiac function. *Europace* 2016;euw136.
41. Auricchio A, Ding J, Spinelli JC, Kramer AP, Salo RW, Hoersch W *et al*. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. *J Am Coll Cardiol* 2002;**39**:1163–9.
42. Joshi NP, Stopper MM, Li J, Beshai JF, Pavri BB. Impact of baseline PR interval on cardiac resynchronization therapy outcomes in patients with narrow QRS complexes: an analysis of the ReThinQ Trial. *J Interv Card Electrophysiol* 2015;**43**:145–9.
43. Lee Y-H, Wu J-H, Asirvatham SJ, Del Carpio Munoz F, Webster T, Brooke KL *et al*. Effects of atrioventricular conduction delay on the outcome of cardiac resynchronization therapy. *J Electrocardiol* 2014;**47**:930–5.
44. Januszkiewicz Ł, Vegh E, Borgquist R, Bose A, Sharma A, Orencole M *et al*. Prognostic implication of baseline PR interval in cardiac resynchronization therapy recipients. *Heart Rhythm* 2015;**12**:2256–62.
45. Pires LA, Abraham WT, Young JB, Johnson KM. Clinical predictors and timing of New York Heart Association class improvement with cardiac resynchronization therapy in patients with advanced chronic heart failure: results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multice. *Am Heart J* 2006;**151**:837–43.
46. Loewe A, Krueger MW, Holmqvist F, Dossel O, Seemann G, Platonov PG. Influence of the earliest right atrial activation site and its proximity to interatrial connections on P-wavemorphology. *Europace* 2016;**18**:iv35–43.
47. Soliman EZ, Cammarata M, Li Y. Explaining the inconsistent associations of PR interval with mortality: the role of P-duration contribution to the length of PR interval. *Heart Rhythm* 2014;**11**:93–8.
48. Bernheim A, Ammann P, Sticherling C, Burger P, Schaer B, Brunner-La Rocca HP *et al*. Right atrial pacing impairs cardiac function during resynchronization therapy. *J Am Coll Cardiol* 2005;**45**:1482–7.
49. Cha YM, Nishimura RA, Hayes DL. Difference in mechanical atrioventricular delay between atrial sensing and atrial pacing modes in patients with hypertrophic and dilated cardiomyopathy: an electrical hemodynamic catheterization study. *J Interv Card Electrophysiol* 2002;**6**:133–40.
50. Burri H, Bennani I, Domenichini G, Ganière V, Sunthorn H, Stettler C *et al*. Biatrial pacing improves atrial haemodynamics and atrioventricular timing compared with pacing from the right atrial appendage. *Europace* 2011;**13**:1262–7.
51. Matsumoto K, Ishikawa T, Sumita S, Matsushita K, Kawasaki N, Kobayashi T *et al*. Beneficial effects of biatrial pacing on cardiac function in patients with bradycardia – tachycardia syndrome. *Circ J* 2005;**69**:831–6.
52. Doi A, Takagi M, Toda I, Yoshiyama M, Takeuchi K, Yoshikawa J. Acute haemodynamic benefits of biatrial atrioventricular sequential pacing: comparison with single atrial atrioventricular sequential pacing. *Heart* 2004;**90**:411–8.
53. Stockburger M, Gerhardt L, Helms S, Schlegl M, Butter C. Bifocal versus unifocal right atrial pacing under plasma level controlled sotalol to prevent atrial fibrillation in patients with symptomatic sinus bradycardia and paroxysmal atrial fibrillation. *Herzschrittmacherther Elektrophysiol* 2007;**18**:250–8.
54. Schnittger I, Appleton CP, Hatle LK, Popp RL. Diastolic mitral and tricuspid regurgitation by Doppler echocardiography in patients with atrioventricular block: new insight into the mechanism of atrioventricular valve closure. *J Am Coll Cardiol* 1988;**11**:83–8.