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REVIEW

Characteristics of PR interval as predictor for atrial fibrillation: association with biomarkers and outcomes

Katja Schumacher[1] · Nikolaos Dagres[1] · Gerhard Hindricks[1] · Daniela Husser[1] · Andreas Bollmann[1] · Jelena Kornej[1]

Abstract The PR interval may be considered as a simple and easily obtainable predictor for adverse events, including atrial fibrillation (AF), pacemaker implantation, and mortality. Interestingly, both high and low extremes of the PR duration are associated with AF risk. However, the results regarding PR prolongation as a risk factor for AF are inconsistent. Some studies have analyzed the impact of P duration (as a part of the PR interval) and demonstrated that the P-duration contributes to the length of PR interval and adverse outcomes. The PR prolongation could be considered as a marker for cardiovascular degenerative aging caused by myocardial fibrosis and vascular inflammation. Furthermore, due to PR prolongation chronically raised intra-atrial pressure and consequential neuro-hormonal activation predispose systemic vascular endothelial dysfunction and explain the associations with adverse vascular events. In this review, we discuss the association between biomarkers with PR interval in AF.

Keywords Atrial fibrillation · PR prolongation · P wave morphology · AF incidence · Biomarkers

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. It is associated with an increased risk of dementia, heart failure, and most importantly thromboembolism, leading to an increased mortality [1]. Pathophysiological, AF leads to electrical and later to structural remodelling of the atrial myocardium (inflammation, fibrosis, and atrial dilatation) [2].

The PQ or PR interval on the electrocardiogram is defined as the time needed for an electrical impulse to be transmitted from the sinus node through the atrioventricular node to the Purkinje fibers, and therefore, it represents the atrioventricular conduction and possible interferences [3]. The first-degree atrioventricular block or prolonged PR interval is defined as a duration longer than 200 ms. This prolongation may result from conduction retardation in the atrial myocardium, the AV node and the His bundle or at multiple sites. So far, PR prolongation without structural heart disease or additional conduction disturbances has been considered as a benign occurrence [4]. However, recent studies have demonstrated an association between PR prolongation and the incidence of AF [4, 5]. The electrocardiographic PR interval reproduces the atrial and atrioventricular conduction, and thus, the connection between a pathological PR interval and AF seems reasonable. Furthermore, it has also been demonstrated that PR interval prolongation is related to other adverse events such as pacemaker implantation, thromboembolism, and an increased mortality [5, 6]. Paradoxically, it had been shown that the short PR interval (<120 ms) is also a predictor for AF [6]. This could be explained by a different P wave duration (as a part of PR interval). The P wave duration is a relevant part of PR interval and may, therefore, contribute to the effect of the PR interval on outcomes [7]. While most of the studies have used the length of the entire PR interval as the measure of interest, others have investigated P wave indices [8]. Recent study by Smith et al. [9] examined the associations of the PR interval and its components hypothesizing that

✉ Jelena Kornej
jelena.kornej@gmx.de

1 Department of Electrophysiology, Heart Center, HELIOS Kliniken GmbH, University of Leipzig, Struempellstrasse 39, 04289 Leipzig, Germany

inconsistencies may be due to the fact that the PR interval represents a composite of several distinct components.

Several studies have analysed the association between different biomarkers (e.g., genetic variants, peripheral plasma markers, etc) and PR interval. Recently, the link between genetic variations (e.g., SCN5A SNPs) and prolonged PR interval was demonstrated [10, 11]. Similarly, peripheral biomarkers—especially natriuretic peptides, pro-inflammatory, pro-thrombotic, and markers of endothelial damage—and their association with PR interval as a risk factor for adverse cardiovascular outcomes have been investigated [12–15]. Still, the question whether a normalization of a pathological PR interval and/or a reduction of AF-associated biomarkers leads to a reduction of the AF risk is understudied. Furthermore, there is a huge interest whether biomarkers and the PR interval could improve the prediction value of common risk stratification scores [16].

In this review, we discuss the role of PR interval as a risk factor for AF incidence as well as the impact of blood biomarkers and their association with PR interval in AF patients.

Search strategy

Electronic searches of English literature were performed in the PubMed database for relevant publications from 2005 to 2017 evaluating the connection between PR interval, biomarkers, and atrial fibrillation. The following search terms were used in this review: "atrial fibrillation" AND/OR "AF" AND/OR "biomarkers" AND/OR "PR interval" AND/OR "short" AND/OR "prolongation". Articles were used when studies investigated different blood biomarkers, genetic markers, clinical markers, and/or PR interval/P wave indices in relation to AF. Two authors (K.S. and J.K.) screened all the studies for qualification by abstract screening and full-text reviewing.

Pathophysiology

Fibrosis and PR prolongation

Atrial fibrosis may be considered as the main component of disturbed atrial conduction. It could be categorized into distinct patterns, e.g., compact, patchy, interstitial, and diffuse [17]. While atrial fibrosis is associated with reduced treatment success in patients with AF [4, 18], left-ventricular fibrosis is associated with increased mortality [8]. Tiffany et al. [19] demonstrated that diffuse interstitial LV fibrosis directly impairs interatrial conduction leading to changes in the P terminal force in lead V1 (PTFV1) and other P wave indices such as (averaged P wave duration, P prime in V1 amplitude and duration, PR interval). Furthermore, this study demonstrated that LV interstitial fibrosis affected P wave to a greater degree than QRS duration. This indicates that P prime in V1 reflects the extent of interstitial fibrosis better than QRS duration.

The LA size is another clinical marker related to AF pathophysiology which has been shown to predict adverse outcomes in numerous investigations. Tiffany et al. demonstrated that PTFV1 can be used as a tool to predict LA size and function [19]. The larger the LA size, the deeper the terminal negativity of P wave in lead V1 and larger the PTFv1. Thus, the relation between LV fibrosis and P-wave patterns can be explained as a consequence of diastolic LV dysfunction, impaired LA filling leading to LA pressure increases and, therefore, increase of LA wall tension. The LA overloading modulates the P-wave vector causing a prominent negative component of the P wave in V1. Furthermore, it had been shown that total atrial conduction time could be visualized in echocardiography [20]. In addition, it may be useful to predict AF in patients with cryptogenic stroke.

Gender specific ECG differences

The impact of gender on ECG parameters had been investigated in several studies [3, 21–23]. ECG intervals are age- and gender specific [24]. Thus, previous studies have reported that men have longer PR interval and QRS duration which is likely due to men having larger hearts that take longer to depolarize [25]. Age-specific ECG interval prolongation may be partly explained by fibrotic replacement in the atrial tissue. Similar differences have been found in the QTc intervals with several studies reporting significantly shorter QTc in men caused by shorter early repolarization. This difference diminishes with age [23]. Simulations of testosterone's effects on I_{CaL} and I_{Ks} in animal models confirmed this finding demonstrating the significant role of testosterone, higher levels of which lead to shorter action potential duration in men [26]. Furthermore, assessing age-related changes in men, falling testosterone levels were associated with early repolarization prolongation.

As already mentioned, some previous studies have indicated gender specific differences in PR interval [21, 23]. Another new and controversial finding is a significant association between short PR interval in women and increased AF risk [6]. This might be explained as follows. On the one hand, congenital hypoplastic AV node may lead to the short PR syndrome with normal QRS complexes and high incidence of paroxysmal supraventricular tachyarrhythmia's described by Lown et al. [27] which is mainly observed in women. On the other hand, the presence of different accessory pathways is associated with short PR intervals and AF as in Wolff–Parkinson–White syndrome, which

is characterized by both a short PR interval and a higher incidence of AF. Interestingly, among WPW patients, AF develops more often in men than in women, so that the association between short PR interval and AF could not be explained only by the presence of accessory pathways. Finally, AV asynchrony might partly explain that both short and long PR intervals are associated with AF. According to this new finding, some researchers recommend to improve the Framingham risk score for AF by also assigning points for a very short PR interval in women [6].

Biomarkers associated with PR prolongation

Although there are many studies investigating the association between PR interval and AF on the one hand and between biomarkers and AF on the other hand, only a few studies have investigated the triad of atrial conduction, biomarkers and AF. Considering PR prolongation as an intermediate phenotype related to AF, it would be meaningful to discover different blood biomarkers related to both PR prolongation and AF, which might be especially useful in AF beginning stages (e.g., lone, paroxysmal AF) (Fig. 1).

Genetics

Smith et al. reported an estimated heritability of prolonged PR interval up to 34% [11]. Further studies analyzed the role of genetic variants associated with PR prolongation and AF (Table 1). Kolek et al. demonstrated that the rs2200733 polymorphism at the 4q25 locus is connected with PR interval duration in patients with and without AF [28]. Furthermore, it was shown that the minor allele—that

is associated with AF—was more common in patients with lone AF. This finding is in accordance with a previous report that carriers of the minor allele (rs2200733T) were diagnosed at a younger age [29]. In addition, the authors hypothesized that PITX2—which encodes the transcription factor Pitx2c and represents a link to the pathophysiology of AF—deficiency is connected with the rs2200733 polymorphism. Of note, Pitx2c insufficiency leads to cellular and molecular changes causing atrial electrical and structural remodeling [30].

Smith et al. observed a significant association between SCN5A single nucleotide polymorphism (SNP) located at chromosome 3p22.2 with increased P wave duration and PR prolongation [11]. SCN5A is a cardiac sodium channel and for this reason strongly related to cardiac conduction and PR variations in ECG and consequently different rhythm outcomes like AF [31].

In another study, Pfeufer et al. described nine gene loci associated with the PR interval: at chromosome 3p.22.2 the voltage gated sodium channel genes SCN10A and SCN5A, and additionally CAV1/CAV2, NKX2-5 (CSX1), SOX5, WNT11, MEIS1, and TBX5/TBX3 which are located near cardiac developmental genes [10]. Five of these loci were also associated with AF (as SCN5A, SCN10A, NKX2-5, CAV1/CAV2, and SOX5). The strongest genome-wide association signal for PR interval was in chromosomal region 3p22.2 where two different sodium channels are encoded, the Nav1.8 from SCN10A and Nav1.5 from SCN5A. Whereas Nav1.5 is the major cardiac sodium channel, mutations of which result in different arrhythmias, Nav1.8 is expressed in the peripheral sensory nervous system. Especially, the identification of SCN10A was

Fig. 1 Association between biomarkers (blood markers, PR interval, and/or P wave morphology with AF). Composite analysis of different markers might be useful to predict adverse events associated with AF
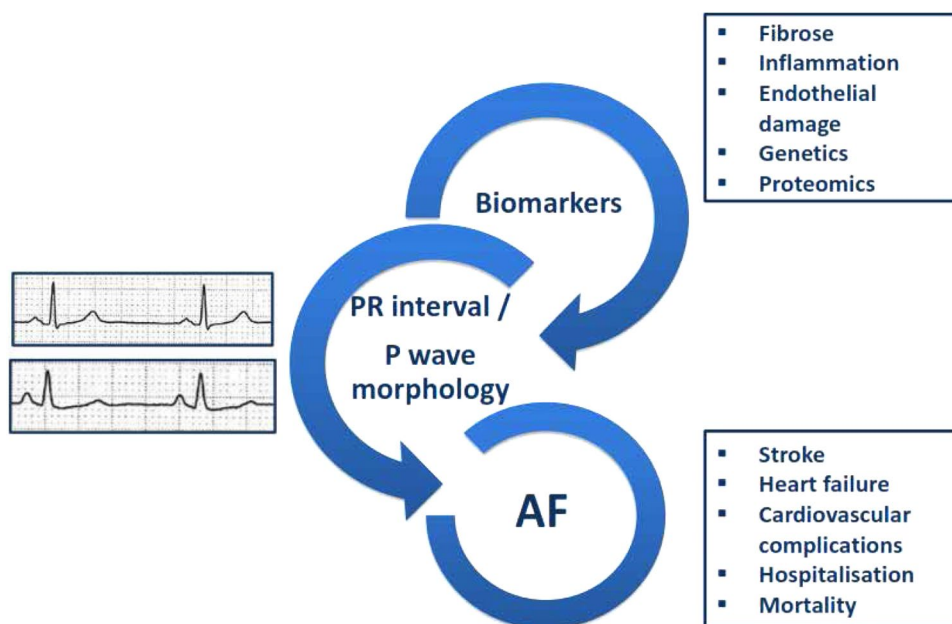
Table 1 Genetic factors: associations with PR interval and AF

Study	Year	Participants	Markers	Results
Smith et al. [11]	2009	1604	SCN5A	Genetic factors explain 34% of variability in PR interval. There is a significant association between SCN5A SNPs and prolonged PR interval
Pfeufer et al. [10]	2010	Overall: 28,517 AF: 5741	SCN10A, SCN5A CAV1/CAV2, NKX2-5 (CSX1), SOX5,WNT11; MEIS1; TBX5/TBX3	Several genetic loci are associated with PR interval (SCN5A, SCN10A, NKX2-5, CAV1/CAV2 and SOX5)
Kolek et al. [28]	2014	Control: 1403 Lone AF: 169 typical AF 269	Variant on chromosome 4q25	The rs2200733 polymorphism at the 4q25 locus is associated with PR-interval duration in patients with AF
Sigurdsson et al. [32]	2015	Overall: 1227 participants who underwent coronary artery bypass grafting No post-operative AF: 847 post-operative AF: 377	677 SNPs from 40 loci	There are no genetic variations that cause both AF and PR prolongation. Genetic variants in the 1q21 and 4q25 regions were proved to be significantly correlated with AF in particular

unexpected, because Nav1.8 was not previously connected to cardiac electrophysiology. Moreover, CAV1/CAV2, encoding caveolins necessary for the development of caveolae in signal transduction, SOX5, encoding a cardial transcription factor, and NKX2-5, encoding the cardiac specific homebox transcription factor Nkx2.5, whose deprivation is associated with different structural and arrhythmogenic heart diseases were identified to be associated with the PR interval [10].

An association between genetic variants and PR prolongation in patients with postoperative AF has been demonstrated by Sigurdsson et al. [32]. Although a significant correlation between prolonged PR interval and postoperative AF was shown (especially genetic variants in the 1q21 and 4q25 regions), the authors were unable to identify genetic variations responsible for both AF and PR prolongation [32].

Blood biomarkers

Since PR prolongation might be considered the result of structural changes in the atrioventricular conduction system of the myocardium, there is an enormous interest to investigate peripheral biomarkers (especially pro-fibrotic and pro-inflammatory) showing an association between atrial remodeling and ECG pattern/deviations. However, the correlation of biomarkers and PR interval prolongation is still understudied.

There have been investigations for the association of several peripheral biomarkers with PR interval as a risk factor for adverse cardiovascular outcomes (inflammatory markers as CRP, osteoprotegerin; markers of cardiac stress and damage as natriuretic peptides, Troponin T and I, soluble ST2, galectin-3, urinary biomarkers as albumin, and biomarkers representing thrombosis and endothelial damage as D-Dimer, or von Willebrand factor) [2, 14, 33, 34]. In most of these studies, the inflammatory biomarkers and markers of cardiac stress, especially CRP and BNP, seem to play the major role and are considered to be associated with the incidence of AF. As an example, the natriuretic peptide axis (BNP, ANP, and their precursors) is stimulated by increased intracardiac pressure and is an important marker for cardiac dysfunction [12]. While there is a discrepancy regarding the association of CRP with incidence of AF, the predictive power of BNP and also of its precursor NT-proBNP has been proven in several studies [14, 15, 21, 22]. In particular, it has been shown that the plasma levels of NT-pro-BNP are significantly elevated in patients with persistent AF [12]. In addition, high NT-pro-BNP levels in patients without AF are associated with increased risk of new onset AF [35]. CRP levels are also associated with incident AF, but its contribution to AF risk stratification is limited, partially because of its lack of organ specificity [15].

Another study examined the relationship between PR prolongation, endothelial dysfunction, and activation of vascular repair in patients with cardiovascular risk compared to healthy subjects [36]. Brachial flow-mediated dilatation (FMD) was used to assess vascular function and circulating CD133+/KDR+ endothelial progenitor cells (EPCs) for the rate of vascular repair. As a result, PR prolongation was more common in patients with high cardiovascular risk. Furthermore, the PR interval was inversely associated with FMD in both high-risk patients and healthy

participants. However, in contrast to healthy objects, a positive correlation between PR prolongation >200 ms and circulating CD133+/KDR+ EPCs was found in cardiovascular risk patients [36].

Other biomarkers

Clinical biomarkers may also be associated with PR prolongation. Recently, it has been shown that the association between pericardial fat and atrioventricular conduction might be considered another link to AF incidence [37]. Thus, a significant association has been described between pericardial fat and P wave indices such as PR interval, P wave duration, P wave amplitude, P wave area, and P wave terminal force [8, 19]. Although the direct link(s) between adiposity measured by waist circumference, BMI, and different fat deposits (e.g., intraabdominal, intrathoracic, and especially pericardial) with atrial conduction modification is unclear, these data confirm previous results where cardiometabolic co-morbidities were associated with AF incidence and therapeutic failures after different AF treatment strategies [38].

PR interval and the risk factor for AF

Disturbed atrioventricular conduction might be associated with AF and its adverse outcomes as stroke, heart failure, and dementia. This had been recently demonstrated in recent meta-analysis by Kwok et al. [39]. Some researchers have proposed to consider the PR as a prognostic marker for AF incidence/risk as well as other adverse cardiovascular outcomes as pacemaker implantation and increased mortality [3]. Although several studies have established a strong and significant association between prolonged PR interval and increased risk for AF, others have provided different results (Table 2). Nevertheless, recent meta-analysis demonstrated association between PR prolongation with adverse cardiovascular events and mortality [39].

Thus, several studies found a close connection between prolonged PR interval >200 ms (e.g., first-degree atrioventricular block) and incidence of AF [4–6]. AF is related to structural remodeling of atrial myocardium which is often due to pro-fibrotic changes [2]. These remodeling processes could also modify the atrioventricular conduction resulting in PR prolongation. Moreover, there are also indications for an association of PR prolongation with other more severe adverse endpoints: Cheng et al. [3] have reported an association between prolonged PR interval and pacemaker implantation and, importantly, all-cause mortality compared to patients with a normal PR interval. These data have led to the assumption that PR prolongation can degenerate in more severe degrees of conduction blocks and other cardiac arrhythmias.

Nevertheless, as recently demonstrated by Smith et al. [9] in a large epidemiologic cohort, PR interval represents a composite of distinct components that are not uniformly associated with AF. While prolonged PR >200 ms had the strongest association with AF incidence, its distinct components (P-wave onset to P-wave peak duration, P-wave peak to P-wave end duration) showed varying levels of association with AF. Some examples of PR-interval prolongation and P-wave duration/dispersion are presented in Fig. 2.

Interestingly, the incorporation of PR prolongation to the $CHADS_2$ and CHA_2DS_2-VASc scores has been demonstrated to result in a significant improvement of the predictive power of both scores regarding new-onset cardiovascular events (e.g., stroke, myocardial infarction, and cardiovascular death) in high-risk cardiovascular patients without clinical AF [36].

Nevertheless, the results are conflicting. Aro et al. [40] could not demonstrate an association between prolonged PR interval and adverse outcomes such as increased mortality or hospitalization because of AF, stroke, or heart failure. Furthermore, a normalization of the prolonged PR interval was observed in a substantial proportion during the follow-up. This underlines a main restriction of all studies using PR interval as a parameter, namely, its circadian variation and change over time [4].

These inconsistent results have led to the initiation of a study, which analyzed the P duration as the main factor contributing to the length of the PR interval [7]. In this study, an association between prolonged (>200 ms) and normal (<200 and >120 ms) PR intervals and mortality was reported but only in patients with high P-duration contribution. Interestingly, the low P-duration contribution did not correlate with mortality neither in patients with long nor with short PR duration. This novel finding had led to the hypothesis that the prolongation of the P duration—and not of the PR interval—is associated with mortality [7]. However, because only one endpoint was analyzed, namely, mortality, the association of other adverse events with the P duration is unknown.

Interestingly, AV-nodal blocking medication as beta-blockers or calcium antagonists reduces the effect of PR prolongation and decrease the AF risk. Therefore, these drugs may be considered as protective for patients with altered PR interval [6].

P-wave dispersion is another important ECG parameter analyzing the risk for AF development. It is defined by subtracting minimum P-wave duration from the maximum in any of the 12 ECG leads [41] and is considered as increased by a value close to 40 ms. P-wave dispersion represents a marker for atrial remodeling, and, therefore, can be used as a predictor for AF [42]. Both increased P-wave duration and P-wave dispersion reflect prolongation of intraatrial and interatrial conduction resulting in

Table 2 PR interval and clinical markers: association with AF and adverse outcomes

Study	Year	Participants	Marker	Results
Cheng et al. [3]	2009	Overall: 7575 Baseline PR interval >200 ms: 124 Baseline PR interval <200 ms: 7451	PR interval	PR is associated with AF, pacemaker implantation and mortality
Nielsen et al. [6]	2013	Overall: 288,181 Incident AF: 11,087	PR interval	Both long and short PR interval increase the risk of AF. The relation between PR interval duration and AF risk is stronger in patients without AV nodal blocking medication
Magnani et al. [5]	2013	Overall: 2722 PR <200 ms: 2383 PR >200 ms: 339	PR interval	There is an association between prolonged PR interval and heart failure and AF in older adults. Thereby, every SC increase (29 ms) in PR interval corresponds to a 13% greater 10-year risk of heart failure and AF
Chan et al. [36]	2013	Overall: 498 Control: 150 CVD patients: 348	PR interval, FMD, circulating CD133+/KDR+EPCs	PR prolongation is more common in patients with cardiovascular diseases and is also associated with flow-mediated dilatation. In patients with increased cardiovascular risk PR prolongation is positively related to the level of circulating CD133+/KDR+EPCs
Aro et al. [40]	2014	Overall: 10,785 PR <200 ms: 10,563 PR >200 ms: 222	PR interval	Prolonged PR interval is not associated with an increased mortality. There is also no relation between PR prolongation and hospitalization due to AF, heart failure or stroke
Chan et al. [16]	2014	Overall: 579 Combined cardiovascular endpoints: 82 No events: 497	PR interval CHADS2 CHA2DS2-VASC	Both CHADS2 and CHA2DS2-VASC scores were significant predictors for new on-set ischemic stroke, myocardial infarction and cardiovascular death in patients without AF. Incorporating PR prolongation, the CHA2DS2-VASC score achieved the highest C-statistics for these diseases
Soliman et al. [7]	2014	Overall: 7501 High P-duration contribution to PR interval: 3524 Low P-duration contribution to PR interval: 3977	P-duration contribution to the length of PR interval	Short but not long PR interval was associated with mortality. Improving the P-duration contribution to the length of PR interval, both long and short PR interval were associated with mortality in patients with high P-duration contribution but not in patients with a low one
Friedman et al. [37]	2014	Overall: 1946	Pericardial fat P-wave indices	Pericardial fat is associated with atrial conduction as measured by P wave indices. Abnormal atrial conduction is related to the development of AF
Tiffany Win et al. [19]	2015	91 participants without AF	P terminal force in lead V1, P wave indices	There is a coherence between the P terminal force in lead V1 (PTFV1) and other P wave indices (averaged P wave duration, P prime in V1 amplitude and duration, PR interval) and left-ventricular fibrosis

AF atrial fibrillation, *FMD* flow-mediated dilatation, *PTFV1* P terminal force in lead V1, *PWI* P-wave indices, *SNP* single nucleotide polymorphism
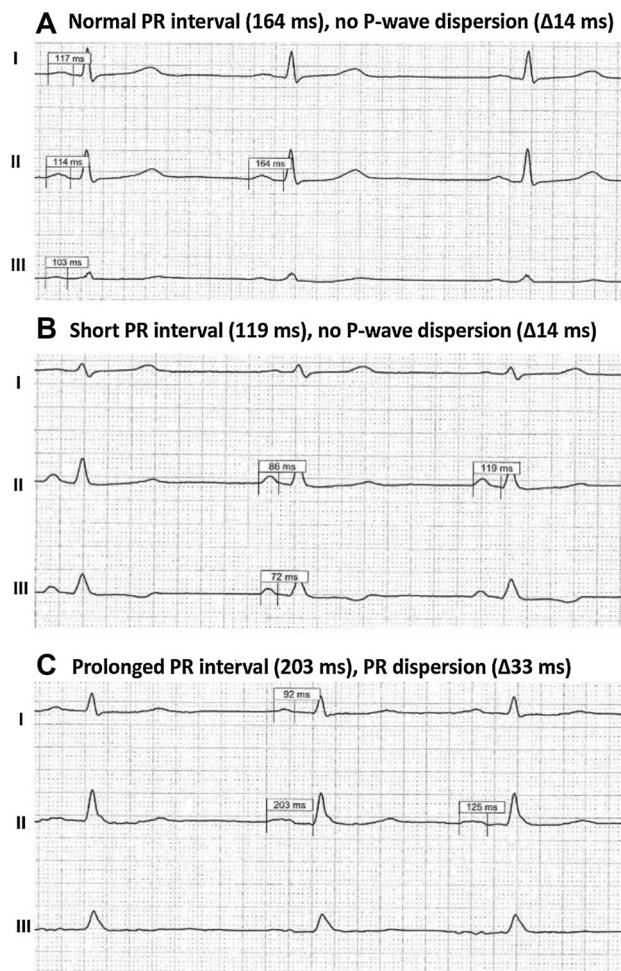
Fig. 2 Examples of PR-interval prolongation and P-wave duration/dispersion

Future directions and conclusions

Based on current evidence, a PR interval prolongation could be used as a surrogate parameter for changes in the cardiovascular system such as autonomic or structural abnormalities, or alterations in the conduction system. Interestingly, some changes in ECG intervals had been observed during vasovagal maneuver, which might be explained by alterations in heart or lung volume [48]. An increase in sympathetic stimulation and a decrease in vagus tone will produce PR interval shortening, while the increase in P wave amplitude is more related to changes in autonomic balance as well as to the effect of lung volume on electrical resistance of the heart [48]. Nevertheless, further studies are needed to investigate the role of prolonged PR interval in other cardiovascular diseases, such as heart failure and arrhythmias.

Based on the observations that a modulation of PR interval is associated with modulating occurrence of AF and with AF associated adverse outcomes, the association between PR interval prolongation and AF incidence should be analyzed during check-up visits. Further studies should evaluate whether PR prolongation could improve the predictive and prognostic value of widely used clinical scores (e.g., CHA_2DS_2-VASc or the Framingham risk scores). Finally, more studies are needed to clarify the relationship between AF, biomarkers, and prolonged PR interval as a triad and to improve the current diagnostic and therapeutic strategies.

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Compliance with ethical standards

arrhythmias. Several studies used P-wave dispersion as possible predictor for AF recurrences after cardioversion [43], catheter ablation [44] or in post-operative AF [45].

There are only few data analyzing association between P-wave indices and biomarkers in AF patients. While P-wave dispersion and inter-atrial desynchrony seem to be independent A-promoters in patients with hypertrophic cardiomyopathy, the plasma NT-proBNP levels were correlated neither with P-wave dispersion nor with inter-atrial desynchrony [46]. In contrast, the hs-CRP—another important and with AF-associated biomarker—was related to P-wave dispersion in patients with lone AF [47]. The interaction between hs-CRP and AF may be mediated by P-wave dispersion, supporting the role of inflammation in the atrial electrophysiological remodeling predisposing to AF [47].

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