



Review

Prevalence, significance and reversal of abnormal P-wave indices in hypertension: A review and meta-analysis

Yoshifusa Aizawa, MD, PhD^{a,*}, Takao Sato, MD, PhD^b, Kohei Akazawa, PhD^c^a Research and Development, Tachikawa Medical Center and Niigata University, Nagaoka, Niigata, Japan^b Department of Cardiology, Tachikawa General Hospital, Nagaoka, Japan^c Department of Medical Informatics, Niigata University Medical and Dental Hospital, Niigata, Japan

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wave indices: P-wave duration or dispersion. However, the impact of hypertension on the P-wave indices has not been fully elucidated [20]. We reviewed the correlation between hypertension and the P-wave indices.

Review

Methods

Introduction

Atrial fibrillation (AF) is a common arrhythmia and is associated with increased morbidity and mortality; thus, preventing new-onset of AF is very important. Population-based studies have identified clinical and electrocardiogram (ECG) variables as risk factors for new-onset AF.

Among clinical risk variables, hypertension is a well-established clinical predictor for new-onset AF with a hazard ratio (HR) ranging 1.09–1.15 for each 20 mm Hg increase of systolic blood pressure [1–5].

Among ECG variables, the atrium-related ECG parameter can express the arrhythmogenic substrate for AF (Table 1). Of these, the maximum P-wave duration (defined as the longest P-wave duration among 12-leads of the surface ECG) of >120 ms was shown to be a predictor of new-onset AF with a hazard ratio (HR) of 1.6 (95% confidence interval (CI), 1.3–1.8, $P < 0.0001$) [6]. Prolonged P-wave dispersion (defined as the difference between the longest and the shortest P-wave durations among 12-leads of the surface ECG) or the standard deviation (SD) of the P-wave duration among 12-leads of the surface ECG, have been shown to be a risk for new-onset AF with HRs 2.0 or higher in a general population [6–10].

In hypertension, activation of the sympathetic nervous system [11] or the renin–angiotensin–aldosterone system [12] was shown to lead to a remodeling of the atrium and results in myocardial hypertrophy, interstitial fibrosis and electrical remodeling. In animal models of hypertension, proinflammatory cytokines were shown to be upregulated in the atrium before a rise of blood pressure [13]. The atrial remodeling leads to slowing of the conduction velocity and/or dilatation of the atrium, constituting an arrhythmogenic basis [14,15].

It would be natural to postulate that prolonged interatrial conduction time or electromechanical delay [14,16–19] is reflected on the P-

We searched the PubMed, Embase and Cochrane Library databases for studies addressing the P-wave indices and hypertension: the prevalence and significance of abnormal P-wave indices in hypertension, and the reversibility of abnormal P-wave indices in response to the treatment of hypertension. The search period was from the beginning of the database to August 2018.

After reviewing the abstracts, 15 papers were deemed eligible and subjected to full review. Of these, 5 papers examined a relationship between P-wave and hypertension, 5 papers examined significance of abnormal P-wave indices in hypertensive patients, and another 5 papers examined the reversibility of altered P-waves in response to the treatment of hypertension.

To obtain a consensus, we attempted a meta-analysis of prior literature examining the correlation between P-wave indices and hypertension and the reversibility of abnormal P-wave indices in response to the treatment of hypertension.

The maximum P wave duration, the minimum P-wave duration and P-wave dispersion indices and 95% confidence intervals (CI) were used as endpoints for this meta-analysis. Heterogeneity was assessed using

Table 1

Atrium-related ECG risks for new-onset atrial fibrillation.

P-wave indices
Maximum P-wave duration
Minimum P-wave duration
P-wave dispersion
SD of P-wave duration
P-wave morphology
P-terminal force in V1 (PTFV1)
Interatrial block (Bayes syndrome)
P-wave axis
PR interval
Premature atrial contraction/runs

* Corresponding author at: Research and Development, Tachikawa Medical Center, 1-24 Asahioka, Nagaoka 940-8621, Japan.

E-mail address: aizaways@med.niigata-u.ac.jp (Y. Aizawa).

Table 2
Correlation between hypertension on P wave indices.

Author/ (reference number)	Pts number (Pts/C)	Age (Pts/C, years)	ECG parameters	Values (Pts/C, ms or Hazard ratio)	P-value
Dagli [21]	60/60	46.9 ± 10.6	P max	91.6 ± 10.2/64 ± 10.2	<0.01
Gur [22]	149/29	50.9 ± 7.2/51.1 ± 5.2	PWD	56.1 ± 5.8/30.3 ± 6.6	<0.01
			P max	131.7 ± 17.1/116.5 ± 12.7	<0.001
Cagirci [23]	78/78	44.6 ± 11.2/43.3 ± 7.0	P min	86.9 ± 17.4/85.2 ± 12.6	0.636
			PWD	44.7 ± 14.7/30.6 ± 8.2	<0.001
Emiroglu [16]	80/80	53 ± 12.5/50 ± 12	P max	103.59 ± 19.8/93.59 ± 13.4	<0.001
			PWD	50.51 ± 18.6/39.85 ± 10.6	<0.001
Yildirim [18]	24/24	43.2 ± 9.8/45.5 ± 9.6	P max	95.6 ± 8.0/90.1 ± 9.5	0.01
			P min	54.3 ± 5.2/57.6 ± 6.2	0.08
			PWD	41.3 ± 7.1/33.5 ± 6.1	<0.001
			P max	107.0 ± 2.7/98.5 ± 10	<0.001
			P min	63.0 ± 1.0/63.0 ± 1.0	0.137
			PWD	43.5 ± 2.5/35.5 ± 10.25	<0.001

BMI: body mass index. CI: confidence interval. Pts/C: patients/control. ns: non-significant. P max/P min: the longest and shortest P wave duration across 12 leads of surface ECG. PWD: P wave dispersion defined as P maximum-P minimum. SD: standard deviation.

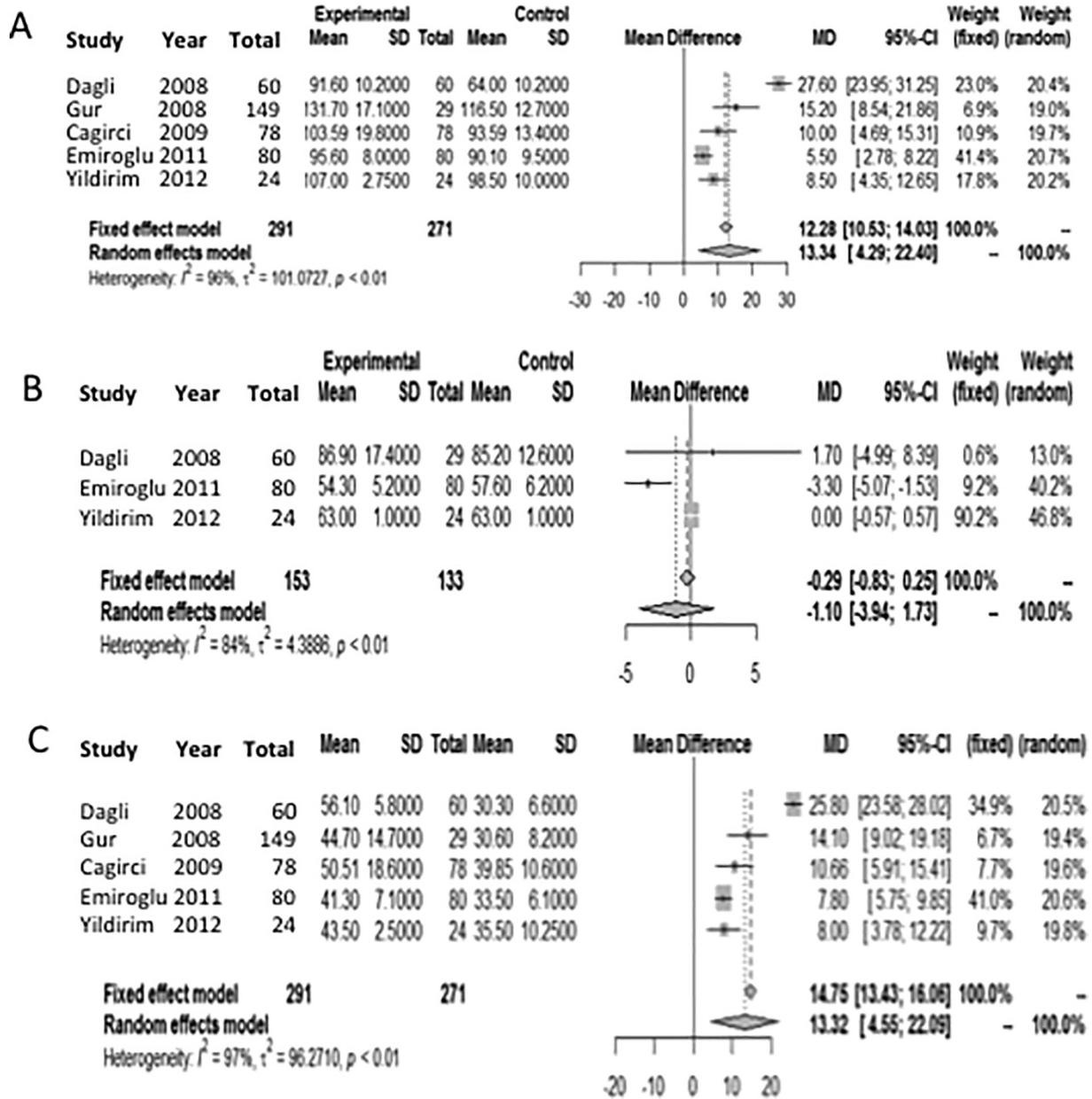


Fig. 1. Meta-analysis of correlation between P-wave indices and hypertension. A: the maximum P-wave duration defined as the longest P-wave durations among 12-leads of the surface ECG was prolonged in hypertensive patients compared with the non-hypertensive healthy control. B: The P-wave dispersion defined as the difference between the longest and the shortest P-wave durations among 12-leads of the surface ECG, was prolonged in hypertensive patients. C: the minimum P-wave duration was prolonged in hypertensive patients. MD: mean difference. SD: standard deviation.

Cochran Q statistics, and the inconsistency test was performed using I^2 statistics. Pooled differences of the maximum P-wave duration, the minimum P-wave duration and P-wave dispersion were calculated using fixed and random effect models. The R language and StatsDirect statistical software (StatsDirect Ltd., Cambridge, UK) were used for statistical computations. P values <0.05 were considered significant and are reported as two-sided values.

P wave indices in hypertension

Correlations between hypertension and P-wave duration/dispersion have been reported in 5 articles as shown [16,18,21–23]. In these studies, the mean maximum P-wave duration ranged from 91.6 ms to 131.7 ms in 391 hypertensive patients and from 64 ms to 116 ms in 271 nonhypertensive controls (Table 2). The differences were significant in all works ($P < 0.05$), and the pooled mean difference and the 95% CI (random effects model) were estimated at 13.34 and [4.29, 22.40], and there was a significant difference in the mean maximum P-wave duration between patient and non-hypertensive controls ($P < 0.05$) (Fig. 1A).

The minimum P-wave duration was examined in 3 studies (Table 2) and was found to be prolonged in 153 hypertensive patients when compared to 133 controls: 54.3–86.9 ms vs. 57.7–85.2 ms, but the differences were not significant [16,18,21]. The pooled mean difference and the 95% CI were estimated at -1.10 and $[-3.94, 1.73]$ (Fig. 1B).

The P-wave dispersion was significantly prolonged in 291 hypertensive patients when compared to 271 controls, 41.3–50.5 ms vs. 30.3–39.8 ms, respectively and the differences between hypertensive and non-hypertensive patient groups were significant in all works (Table 2, $P = 0.001 - P < 0.0001$) [16,18,21–23]. The pooled mean difference and 95% CI were estimated at 13.32 and [4.55, 22.09], respectively ($P < 0.05$) (Fig. 1C). However, heterogeneity was large as estimated from I^2 value.

In the ARIC study with 14,433 participants [24], the maximum P-wave duration was shown to prolong by 2.8 ms in hypertensive patients when compared to nonhypertensive subjects (CI, 2.41–3.21), and in population-based studies [9,25,26], the P-wave duration was shown to increase as systolic blood pressure rises. From all of these findings, it seems certain that P-wave indices are abnormal more often in hypertensive patients than in non-hypertensive controls.

Significance of prolonged P wave indices in hypertension

Five studies addressed the significance of abnormal P-wave indices in hypertension. Prolonged P-wave duration in lead aVR was observed in 44 hypertensive patients with a history of AF when compared to 44 age-matched hypertensive subjects without a history of AF: 115 ± 18 ms vs. 101 ± 14 ms ($P < 0.0001$) [27], and P-wave duration ≥ 100 ms was found to be an independent predictor of a presence of AF using multivariable logistic regression (relative risk = 3.7; 95% CI: 1.3–10.3; $P = 0.02$). In other studies, P-wave dispersion was able to discriminate between hypertensive patients with and without paroxysmal AF: 50 ± 12 vs. 38 ± 8 ms [28] and 52 ± 19 vs. 41 ± 15 ms (both $P < 0.001$), respectively [29].

Furthermore, prolonged P-wave duration was shown to be a predictor of AF recurrence [30] or new-onset AF [31]. In 97 consecutive hypertensive patients with no known history of AF or cardiovascular events, the maximum P wave duration was a predictor of new-onset AF, in addition to age, blood pressure, echocardiographic left ventricular mass, left atrial dimension and A wave velocity [30]. After correction for age, the maximum P-wave duration and P-wave dispersion remained independent predictors for new-onset AF in hypertensive patients. Thus, abnormal P-wave indices in hypertensive patients are significantly associated with a history AF, recurrence and new-onset AF.

Reversal of P wave indices in hypertension

Experimentally, treatment of hypertension is known to result in regression of atrial remodeling [13,32]. The reversibility of P-wave indices in response to the treatment of hypertension was investigated in 222 hypertensive patients in 5 studies (Table 3). Hypertension was treated with angiotensin 2 receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs) or beta-blocker. After the treatment of hypertension, blood pressure (systolic/diastolic) decreased from 146.8–167.9 mmHg/87.7–103.2 mmHg to 120.7–141.5 mmHg/76.3–93.3 mmHg ($P < 0.001$), and the maximum P-wave duration was decreased from 105.7–109.0 ms to 93.9–109.2 ms; these decreases were significant after therapy with telmisartan [33,34], ramipril [33], and perindopril [35] but not after treatment with cilazapril [36] or atenolol [36].

The minimum P-wave duration decreased significantly after treatment with cilazapril [36] and atenolol [36] but decreased nonsignificantly after treatment with telmisartan and ramipril [33]. P wave

Table 3
Reversal of P wave duration/dispersion with hypertension treatment.

Author/(reference number)	Pts #	Age (mean \pm SD, years)	Rx duration	Drug (dose)	P-wave indices (Before/after, mean \pm SD, ms)	P-value
Celik [33]	50	51.8 \pm 6.1	6 months	Telmisartan (80 mg)	P max, 106.30 \pm 9.78/97.60 \pm 7.43 P min, 65.70 \pm 12.97/66.00 \pm 13.09 PWD, 40.60 \pm 8.72/31.00 \pm 10.69	$P < 0.001$ $P = 0.32$ $P < 0.001$
	50		6 months	Ramipril (10 mg)	P max, 105.70 \pm 10.54/101.80 \pm 8.00 P min, 64.80 \pm 13.77/65.30 \pm 13.18 PWD, 40.90 \pm 9.01/36.50 \pm 10.31	$P < 0.001$ 0.37 $P < 0.001$
Tuncer [36]	19	50.9 \pm 8.4	1 month	Cirazapril (5 mg)	P max, 107.3 \pm 11.4/109.2 \pm 11.1 P min, 46.5 \pm 11.7/57.5 \pm 9.6 PWD, 61.6 \pm 13.8/53.1 \pm 12.5	ns $P < 0.05$ $P < 0.001$
	19		1 month	Atenolol (50 mg)	P max, 106.9 \pm 13.9/106.5 \pm 11.1 P min, 45.5 \pm 10.5/58.4 \pm 14.7 PWD, 61.6 \pm 14.6/48.5 \pm 13.1	ns $P < 0.05$ $P < 0.001$
Ozben [35]	48	57.4 \pm 11.8	6 months	Perindopril	P max, 109 \pm 12/104 \pm 11 P min, 55 \pm 10/66 \pm 12 PWD, 54.3 \pm 9.2/38.3 \pm 7.1	$P < 0.001$ $P = 0.001$ $P < 0.001$
Sengul [34]	36	64.8 \pm 9.4	6 months	Telmisartan (80 mg)	P max, 108.4 \pm 5.1/93.9 \pm 6.2 PWD, 33.4 \pm 8.6/19.5 \pm 7.0	$P < 0.001$ $P < 0.001$
Nomura [36]	20	68.5 \pm 8.5	24 weeks	Losartan	f-P max, 148 \pm 10/116 \pm 13 ^a	$P < 0.01$
	20		24 weeks	CCBs	f-P max, 141 \pm 12/139 \pm 15 ^a	ns

CCB: calcium channel blocker. Δ PWD: difference of P-wave dispersion. f-Pmax: filtered maximum P-wave duration measured by signal averaged ECG. ns: non-significant. Rx: treatment. Celik (53): Manual measurement of P-wave duration was performed with digital calipers on a high-resolution computer screen and Nomura (55) included patients with paroxysmal AF.
^a Values read from figures.

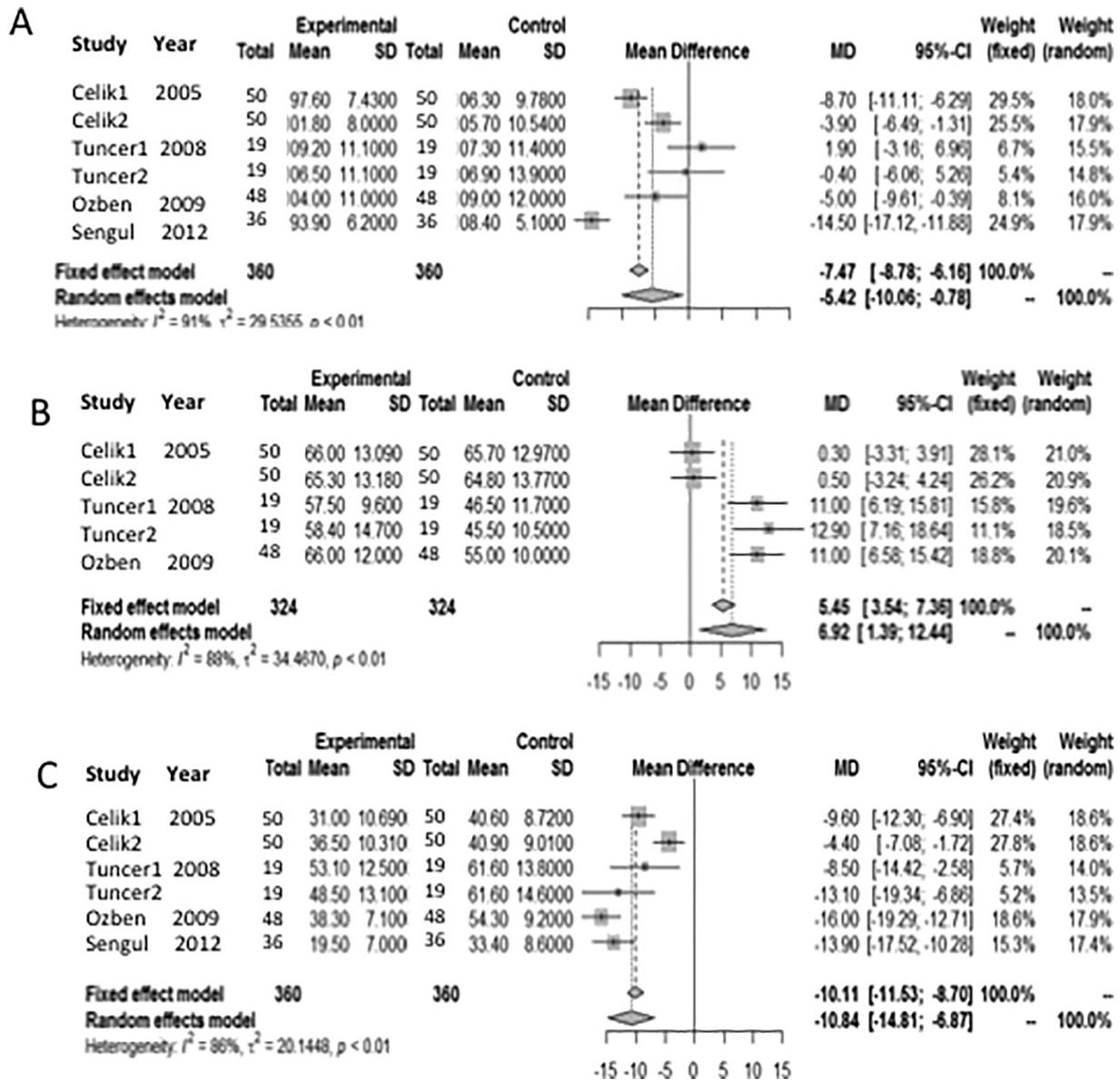


Fig. 2. Meta-analysis of reversal of P-wave indices by treatment of hypertension. A: In 222 hypertensive patients, the maximum P-wave duration decreased in duration. B: The minimum P-wave durations decreased in duration. C: The P-wave dispersion was also reverted by hypertensive therapy. MD: mean difference. SD: standard deviation.

dispersion was decreased significantly after treatment with telmisartan [33,34], ramipril [33], perindopril [35], cilazapril and atenolol [36].

In one study using surface signal-averaged ECG, the filtered maximum QRS was shown to revert in response to losartan but not to calcium channel blockers [37]. The inhibition of cardiac fibrosis was suggested by a reduction of procollagen C propeptide type I after treatment with losartan [37].

The mean differences calculated from a random-effects model based on a meta-analysis of the reversibility of P-wave indices are shown in Fig. 2, and changes in the maximum P-wave duration and P-wave dispersion were significantly different based on the means of all endpoints after treatment of hypertension (Fig. 2A and C). Again, the analysis in the pooled data showed heterogeneity, partly due to various drugs tested.

The results in these studies with a small sampling size are compatible with findings in large clinical trials. In a subanalysis of LIFE study [38], the treatment of hypertension was found to reduce the volume of the left atrium and the incidence of abnormal P-wave with an HR of 0.21 for every 1-cm decrease in LA diameter (95% CI, 0.14–0.32, $P < 0.001$). In the ACCORD trial [39], the intensive treatment of hypertension was shown to decrease the incidence of abnormal P-waves.

The Danish HealthCare Data Base study [40] is suggesting that the risk of recurrent AF or new-onset AF can be reduced by the treatment of hypertension. It needs to be shown that a reversal of the atrial remodeling and a reversal of P-wave indices leads to the reduction of incident AF.

Conclusion

Hypertension induces atrial remodeling and leads to abnormal conduction characteristics, and the remodeling will result in the arrhythmogenic substrate for AF development. Such changes will be manifested as prolongation of P-wave duration or dispersion. Correlations between hypertension and P-wave indices can be summarized as follows.

- 1) Abnormal P-wave indices are more frequently observed in hypertensive patients compared to the nonhypertensive controls.
- 2) Presence of abnormal P-wave indices is a predictor for AF recurrence or new-onset AF in hypertensive patients.
- 3) Abnormal P-wave indices can be corrected by treating hypertension.

- 4) In future, it is to be proved that a reversal of P-wave indices by treating hypertension is really associated with a reduced incidence of new-onset AF.

For confirmation of these items, ECG plays a key role, and accurate and automated measurement of P-wave duration is essential.

Conflict of interest

None.

Supporting information

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Clinical significance

Hypertension is one of major risks for new-onset AF, and prolonged P-wave indices are another risk for incident AF.

P-wave indices can represent the atrial remodeling induced by hypertension and, abnormal P-wave indices are more prevalent in hypertensive patients compared to the nonhypertensive controls.

A presence of abnormal P-wave indices is a risk for AF recurrence or new-onset AF.

Abnormal P-wave indices can be reversed by treating hypertension, but whether a reversal of P-wave indices is associated with a reduced incidence of new-onset AF or not needs confirmation.

Accurate and automated measurements of P wave duration on ECG are essential.

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