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COMMENT

P-wave changes as an index of hypertensive organ damage and a predictor of cardiovascular events: can the P wave be used to assess atrial reverse remodeling?

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Atrial electrical excitation propagates from the upper right atrium, where the sinoatrial node resides during sinus rhythm, to the left atrium. Therefore, atrial electrical excitation of the left atrium constitutes the latter part of the P wave. It is well known that the left atrial overload associated with mitral stenosis appears as an increase in the negative component of the P wave in V1 on the electrocardiogram. This negative component of the P wave in V1 is defined as the terminal force, and it has been shown that increased terminal force not only is associated with left atrial afterload but also is a predictor of cardiovascular events [1–4]. In previous reports, a deep terminal force increased the risk of atrial fibrillation and cardiovascular death by approximately 1.5-fold [2–4].

The P wave in lead II also undergoes a change in morphology with left atrial afterload (Fig. 1). It has been speculated that conduction delay in the left atrium increases the interval between the two bimodal waves of the P wave in lead II [5]. A biphasic P wave in lead II with an interval of 40 ms or more between two peaks is considered a notched P wave, which reflects left atrial afterload with an increase in the negative component of V1 and is described as the P mitrale. De Baquer et al. classified biphasic P waves in lead II into notched P waves with a peak interval of 40 ms or longer and deflected P waves with a peak interval of less than 40 ms, and they examined the association of both types of biphasic P waves with the development of atrial fibrillation. They found that deflected P waves were associated with the development of atrial fibrillation [5]. On the other hand, in the Jichi Medical School (JMS) cohort study of a general population, we showed that notched P waves of ≥40 ms between peaks in lead II increased the risk of cardiovascular events by 1.59-fold [6]. We also measured P-wave notches with automated analysis in the Japan Morning Surge-Home Blood Pressure (J-HOP) study in patients at risk of cardiovascular risk events. When notched P waves were defined at two thresholds of 20 ms and 40 ms between peaks, notched P waves of 20 ms or longer were associated with cardiovascular events, while notched P waves of 40 ms or longer were not significantly associated with cardiovascular events [7]. The smallest unit in a visual electrocardiogram is 40 ms, but automated mechanical analysis would allow fine measurements between bimodal waves, and measurement of the P wave in lead II may allow the evaluation of mild left atrial overload.

The axis of the P wave also changes with left atrial overload. Because normal sinus rhythm propagates from the upper right atrium to the left atrium, the normal P-wave vector is positive for both lead I and aVF, with an average of approximately +60 degrees. If the left atrial component of atrial excitation is greater with left atrial enlargement, the vector of P-wave propagation deviates to the left, and individuals outside the normal range have been shown to have more atrial fibrillation and cardiovascular events [8–10]. Changes in the axis of the P wave might be ectopic rhythm and should be noted.

The prolongation of the P-wave width, unlike the P-wave morphology and axis, quantitatively reflects atrial remodeling; a broad (prolonged) P wave is also associated with atrial fibrillation and cardiovascular events [1–4, 8, 11–14]. An association between the prolongation of the P-wave width and the development of atrial fibrillation was reported by Perez et al., as well as in the Framingham heart study and the Atherosclerosis Risk in Communities Study (ARIC) study; in all these studies, a prolongation of 120 ms or

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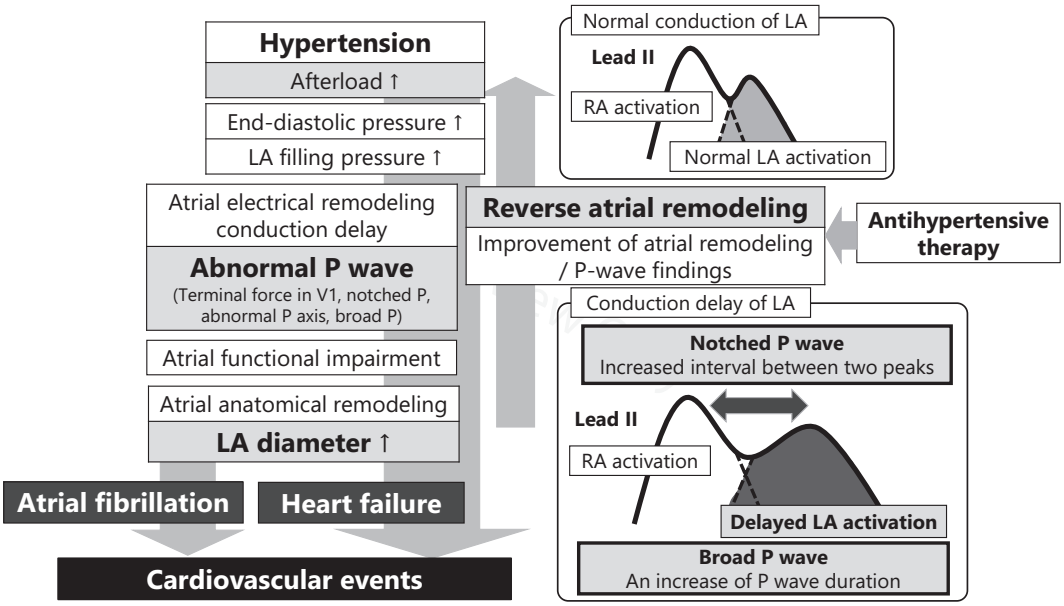

Fig. 1 The progression of atrial remodeling/reverse remodeling is demonstrated by changes in the P wave in hypertensive individuals. LA left atrium, RA right atrium.

longer was associated with an approximately 1.6-fold increase in the risk of developing atrial fibrillation [3, 8]. Moreover, an increased threshold of the P-wave width has been associated with an increased risk of cardiovascular events. Ha et al. investigated the association between the P-wave width and cardiovascular mortality in veterans <56 years of age and found that a P-wave width of ≥120 was associated with a 1.36-fold increase in cardiovascular mortality risk, while a P-wave width of ≥140 ms conferred a 2.16-fold increase in cardiovascular mortality risk [13]. We examined the P-wave width and cardiovascular events in individuals with one or more cardiovascular risk factors in the J-HOP study: a P wave ≥140 ms was associated with a 4.23-fold increased risk of cardiac events, and a P wave ≥150 ms was associated with a 5.01-fold increased risk [14]. A P wave of 137 ms was optimal for cardiac event prediction in the receiver operating characteristic curve. Collectively, these results suggest that the threshold for the P-wave width to predict cardiovascular events may be greater than that to predict the onset of atrial fibrillation.

To date, the sensitivity of P waves in electrocardiograms for left atrial enlargement on echocardiography has been low in many papers. This low sensitivity may be because changes in the P wave of electrocardiograms reflect electrical remodeling of the atrium, whereas left atrial enlargement is an anatomical change of the atrium, and anatomical changes may occur later than electrical remodeling [15]. In addition, P-wave changes do not reflect changes in the left atrium alone since P-wave changes are affected not only by the left atrium but also by the conduction delay of the right atrium and the interatrial conduction delay. Finally, although there are various methods of evaluating the left atrium other than diameter and volume [16], there is still much potential growth in the research area of left atrium evaluation by the P wave of electrocardiograms.

In summary, although various parameters of the P wave are associated with left atrial enlargement, their diagnostic ability for left atrial enlargement is still under development. However, there have been numerous studies on the P wave as a predictor of the development of atrial fibrillation and cardiovascular events (Table 1). It is assumed that P-wave changes are due in part to increased afterload caused by high blood pressure [15]. Therefore, as with the diagnosis of left ventricular hypertrophy on electrocardiogram, P-wave changes are expected to be a surrogate marker for the assessment of afterload in patients with hypertension. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, there were fewer primary endpoints in the losartan group than in the atenolol group, and both the Cornell product and Sokolow-Lyon indices of left ventricular hypertrophy showed greater reductions in the losartan group than in the atenolol group [17]. The P-wave indices in electrocardiograms could be used as a therapeutic index for patients with hypertension and as an electrocardiogram-based index of left ventricular hypertrophy. Several reports have documented a reduction in the P-wave width following antihypertensive therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. If antihypertensive therapy results in an improvement in the P-wave index, this may constitute collateral evidence that earlier intervention is successful and prevents the development of hypertensive organ damage (Fig. 1). Conversely, the Systolic Blood Pressure Intervention (SPRINT) trial showed no significant

Table 1 The association among P wave, AF and cardiovascular events.

Parameters	Author	Population	Definition	Summary
P wave terminal force	Soliman [1]	15,429 ARIC study	Upper 5th percentile	1.90-fold for incidence of AF
	Kaykha [2]	40,020 Male veterans	>40 (mm x ms)	1.47-fold for CV death
	Magnani [3]	3,110 FHS 8,254 ARIC study	>4000 μV·ms	FHS: 1.00-fold (not significant) for onset of AF ARIC: 1.56-fold for onset of AF
	Maheshwari [4]	13,580 ARIC study without prevalent CV disease	≤−4000 μV·ms	1.58-fold for sudden cardiac death 1.44-fold for CV death
P wave morphology	De Baquer [5]	160 healthy subjects aged 55 to 74 years	Deflected P	6.89-fold for odds ratio of AF
	Kabutoya [6]	2,104 JMS-cohort study Community-dwelling population	Notched P	1.59-fold for CV events
	Kabutoya [7]	810 J-HOP study with ≥1 CV risk	Notched P (20 ms)	20 ms: 1.83-fold for CV events 40 ms: 1.52-fold (not significant) for CV events
P axis	Perez [8]	42,751 Patients not necessarily known to be at high risk of AF	Abnormal P axis	1.9-fold for development of AF
	Maheshwari [9]	15,102 ARIC study	Outside of 0–75°	1.50-fold for ischemic stroke
	Dhaliwal [10]	8,965 ACCORD trial	Outside of 0–75°	2.65-fold for incidence of AF
P duration	Perez [8]	42,751 Patients not necessarily known to be at high risk of AF	>120 ms in 12-lead	1.6-fold for development of AF
	Soliman [1]	15,429 ARIC study	Maximum upper 5%tile in 12-lead	4.07-fold for incidence of AF
	Kaykha [2]	40,020 Male veterans	>120 ms in 12-lead	1.21-fold for CV death
	Magnani [11]	1,550 FHS, ≥ 60 years	95%tile in 12-lead	2.51-fold for onset of AF 1.11-fold (not significant) for all-cause mortality
	Magnani [3]	3,110 FHS 8,254 ARIC study	>120 ms in 12-lead	FHS: 1.54-fold for onset of AF ARIC: 1.55-fold for onset of AF
	Nielsen [12]	285,933 Primary care population	95th percentile (≥130 ms) in 12-lead	2.06-fold for AF, 1.30-fold for CV death vs. 100–105 ms group
	Ha [13]	20,827 veterans <56 years	≥120 ms, ≥140 ms in lead II, aVF, V1 and V2.	120 ms: 1.36-fold for CV death 140 ms: 2.16-fold for CV death
	Maheshwari [4]	13,580 ARIC study without prevalent CV disease	>120 ms	1.32-fold for sudden cardiac death 1.38-fold for CV death
	Yokota [14]	810 J-HOP study with ≥1 CV risk	≥120–150 ms in 12-lead	140 ms: 4.23-fold for cardiac events 150 ms: 5.01-fold for cardiac events

ACCORD the Action to Control Cardiovascular Risk in Diabetes, *AF* atrial fibrillation, *ARIC* the Atherosclerosis Risk in Communities, *CV* cardiovascular, *FHS* the Framingham heart study, *J-HOP study* the Japan Morning Surge Home Blood Pressure Study, *JMS-cohort study* the Jichi Medical School Cohort study.

difference in terminal force between treatment groups [18], and future studies will be needed to determine which P-wave index is appropriate for assessing hypertensive organ damage.

Standard 12-lead electrocardiography is inexpensive and noninvasive, and the evaluation of the P wave in 12-lead electrocardiography has promise as an assessment of hypertensive organ damage from a different viewpoint than atrial anatomical changes. In the future, it may be possible to visualize and evaluate atrial reverse remodeling due to antihypertension therapy by analyzing the P wave in electrocardiograms.

Compliance with ethical standards

Conflict of interest TK has no conflicts of interest to disclose. KK has received research grants from Omron Healthcare and A&D Co.

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