Evolution of P-Wave Morphology in Healthy Individuals: A 3-Year Follow-Up Study

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Background: Orthogonal P-wave morphology in healthy men and women has been described using unfiltered signal-averaged technique and holds information on interatrial conduction. The stability of P-wave morphology in healthy subjects over time is not fully known.

Methods: Sixty-seven healthy volunteers were investigated (29 males, aged 63 ± 14 years, 48 females, 60 ± 13 years). Orthogonal lead data (X, Y, and Z) were derived from standard 12-lead ECGs (recording length 6 minutes, sampling rate 1kHz, resolution $0.625 \mu\text{V}$) recorded at baseline (BL), and 3 years later at follow-up (FU). P waves were then signal-averaged and analyzed regarding P-wave morphology, locations of maxima, minima, zero-crossings, and P-wave duration (PWD).

Results: No differences of P-wave variables were observed at FU compared to BL, including PWD (127 ± 12 vs 125 ± 14 ms at BL and FU, respectively, n.s.). In 59 of the 67 subjects (88%), the P-wave morphology was unaltered at FU. However, in the remaining eight cases a distinctively different morphology was observed. The most common change ($P = 0.030$) was from negative polarity to biphasic (–/+) in Lead Z ($n = 5$). In one case the opposite change was observed and in two cases transition into advanced interatrial block morphology was evident at FU.

Conclusions: In the majority of healthy subjects, P-wave morphology is stable at 3-year FU. Subtle morphological changes, observed principally in Lead Z, suggest variation of interatrial conduction. These changes could not be detected by measuring conventional PWD that remained unchanged in the total population.

Ann Noninvasive Electrocardiol 2009;14(3):226–233

ECG; signal-averaged; interatrial conduction; healthy; P wave

Prolonged P-wave duration (PWD) is commonly regarded as a marker of deteriorated interatrial conduction and is associated with atrial fibrillation (AF).^{1,2} Additional atrial electrophysiological information is available from analysis of P-wave morphology as indicated by several studies.^{3,4} Using unfiltered signal-averaged P-wave analysis (PSAECG) our group has previously observed subtle variations of orthogonal P-wave morphology in arrhythmia-prone patients.^{5,6} Later, these different P-wave morphologies were also reported in a study of healthy men and women providing a first reference material of the normal, orthogonal P-wave

morphology.⁷ These variations were not detectable by analysis of PWD and were recently shown to hold strong correlation to different activation patterns of the left atrium (LA) in a paroxysmal AF (PAF) study population.⁸

There are only a few studies that have investigated the stability of the biological signals mirrored in the signal-averaged P wave. These studies have mainly focused on patients with PAF or coronary artery disease (CAD) and were somewhat limited by either short follow-up time (up to 1 week) or small control groups (10 subjects).^{9–13} To our knowledge no data have been published on

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The study was supported by a grant from the Torsten Westerström foundation and governmental funding of clinical research within the Swedish national health system.

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long-term follow-up of the P-wave morphology in healthy individuals. Consequently, this study was planned as a 3-year follow-up of orthogonal P-wave morphology in healthy men and women in order to explore the signal-averaged P wave over time and its stability over time.

METHODS

One hundred twenty healthy subjects (60 men and 60 women) were included at baseline (BL) and scheduled for a follow-up (FU) visit after 3 years. The inclusion process has previously been described.⁷ In brief, the subjects were interviewed and examined by a physician to ensure their good health and a 12-lead ECG was recorded. The BL and FU examinations were performed with a 3-year interval under similar circumstances and at the same time of day and year. The study was approved by the Ethics Committee of Lund University, Sweden (approval number LU 325-00). Written informed consent was obtained and the study complied with the Declaration of Helsinki (<http://www.wma.net/e/policy/b3.htm>).

Data Acquisition and Signal Processing

A standard 12-lead ECG was recorded for 6 minutes with the subjects at rest in a quiet room. Data were acquired at a rate of 1 kHz and with a resolution of $0.625 \mu\text{V}$. The data acquisition hardware used for the recordings was supplied by Siemens-Elema AB, Solna, Sweden.

Specially designed software, developed in MATLAB R14 (<http://www.matlab.com>), was used for signal processing and analysis. The method for extracting P-wave data has previously been described in detail.^{7,14} In summary, orthogonal lead data (X, Y, and Z) was derived mathematically from standard 12-lead ECG using the inverse Dower transform^{14,15} and then high-pass (0.5 Hz) and bandstop (50 Hz) filtered. Following automatic QRS-detection,¹⁶ artifacts and abnormal beats were excluded using a cross-correlation coefficient >0.90 . Signal segments, supposedly containing the P wave, preceding the QRS-complex were time-shifted in order to obtain maximum correlation in each lead. Signal segments with a cross-correlation coefficient >0.90 in each individual lead were added, merged, and averaged. The onset and end of the resulting P waves were set manually. In addition, PSAECG analysis was per-

Figure 1. Examples of the three P-wave morphology types observed. Depicted are the three P-wave morphology types observed in this study (from left to right: Type 1, 2, and 3). Type 1 is characterized by a positive Lead X, positive Lead Y and negative Z. Type 2 has a positive Lead X, positive Lead Y, and biphasic Lead Z (-/+). Type 3 also has a positive Lead X. Leads Y and Z, however, are biphasic (+/- and -/+, respectively).

formed twice in a subset of 10 individuals, 24 hours apart in order to ensure the reproducibility of the method.

Classification and Definitions of P-Wave Morphology and P-Wave Variables

From here on "P-wave morphology" is referring to the morphology in regards to all three orthogonal Leads X, Y, and Z. In our previous reports on orthogonal P waves, three distinctively different P-wave morphologies have been observed (Fig. 1).⁵⁻⁷ Classification of P-wave morphology was performed using an automated classification algorithm that has been previously described in detail and tested.¹⁷ In Leads X and Y, the distances from the onset of the P wave to the maxima were determined (X max, Y max [ms]) and similarly in Lead Z for the locations of the maxima and minima (Z max, Z min). In addition to this, the location of the zero crossing in Lead Z was measured when present (Z zero). The different variables are illustrated in Figure 2 as is a schematic illustration of the method.

Recordings from individuals with different P-wave morphologies at BL and FU according to the automated classification algorithm¹⁷ were in addition analyzed to avoid false classification of minor signal changes. BL and FU recordings were merged and analyzed as one to explore whether two distinct

Figure 2. Schematic representation of the method and the P-wave variables studied. A schematic illustration of the method is shown in the left panel. The right panel shows the different P-wave variables investigated in this study: location of maximum in Lead X (X max [A]), maximum in Lead Y (Y max [B]), location of zero crossing in Lead Z (Z zero [D]), and location of minimum and maximum in Lead Z (Z min, Z max [C, E]). P wave onset and end are marked by vertical bars.

P-wave clusters were found, in which case the morphology change was considered genuine.

Statistics

All data are presented as mean $\pm$ SD. Statistical evaluation was performed using the software StatView 4.5 (Abacus Concepts, Berkeley, CA, USA). All statistical comparisons were made using the Wilcoxon's signed rank sum-test or Fisher's exact test, and $P < 0.05$ was considered statistically significant.

RESULTS

Data Availability

Of the 120 individuals that were included at BL, 70 subjects consented for FU and reexamination 3 years later. At FU, three subjects were excluded as their ECGs were considered to represent non-sinus rhythm. Thus, a total of 67 subjects pro-

vided data available for analyses both at BL and FU (29 males, aged 63 ± 14 years). The younger, more mobile individuals in general and males in particular did not consent to FU to a greater extent making the FU population slightly dominated by female subjects.

P-Wave Morphology and Its Evolution

All three previously described orthogonal P-wave morphology types were observed in the presented material (Fig. 1). The distribution of P-wave morphology types at BL and FU was: Type 1; 19 cases vs 15, Type 2; 48 vs 50, Type 3; 0 vs 2.

In 59 of the 67 subjects (88%), the P-wave morphology type was unaltered at FU 3 years later. When morphology type transition did occur (eight cases), the predominant change was from Type 1 to 2 (5 of 19 Type 1 cases at BL [26%]). A change from Type 2 to 1 occurred in 1 of 48 Type 2 cases at BL [2%]. Two cases of transition from Type 2 to 3 were

Figure 3. Example of transition from P-wave Type 1 to 2. An example is shown of orthogonal P-wave registrations from a subject with a P wave of Type 1 morphology at baseline (left panel) and P-wave Type 2 at follow-up 3 years later (right). A difference is noted in the late part of Lead Z where the positive late phase at follow-up is not present at baseline. Lead Z represents an anterior-posterior direction of the vector and changes in the terminal portion would suggest a different activation pattern of the left atrium, possibly due to changed interatrial conduction properties.

also observed. The change from Type 1 to Type 2 or 3 was significantly more common than the reverse (Fisher's exact test, $P = 0.030$). An example of morphology transition is shown in Figure 3. Figure 4 schematically shows the overall number of transitions occurring between BL and FU.

In a subset of individuals ($n = 10$), data were also collected with an interval of 24 hours. The P-wave morphology was unchanged in all 10 cases over the 24-hour period.

P-Wave Variables and Their Evolution

There was no significant difference between PWD at BL and FU (127 ± 12 vs 125 ± 14 ms,

n.s.). Neither were there any significant differences between other P-wave variables (X max, Y max, Z min, Z zero, Z max) when comparing data at BL and FU. All P-wave variable data of the study population are presented in Table 1. No significant gender differences were observed.

The P-wave variables of the subset of 10 subjects included in the method reproducibility part of the study were not statistically different on the two different occasions.

Data were also dichotomized allowing P-wave variable comparison between those aged 60 or younger ($n = 29$) and those aged 61 or above ($n = 38$) as well as between those aged 75 or older ($n = 12$) and those 45 or younger ($n = 9$). No

Figure 4. Diagram of P-wave morphology evolution. From this schematic representation of how changes of P-wave morphology occur from BL to FU, it is clear that Type 1 morphology is less stable than Type 2. Nearly a quarter (26%) of the subjects with Type 1 at BL had Type 2 P waves at FU while 74% remained unchanged. The opposite transition only occurred in 2% of the cases with Type 2 morphology at BL. The two cases that developed Type 3 morphology (advanced interatrial block) represented 4% of the cases with Type 2 P waves at BL.

significant differences were found between the two groups in either case when comparing BL and FU data.

DISCUSSION

This study is a first long-term evaluation of P-wave morphology and shows that P-wave morphology remains unaltered at 3-year FU in a majority of healthy individuals. However, in 12% of the cases changes are seen over time indicative of deteriorated interatrial conduction. This finding is best explained by age-related deterioration of interatrial conduction that is not detectable by conventional analysis of PWD.

The Normal P Wave and Its Evolution—Temporal Variables

The depolarization of the atria is represented on the ECG as a P wave. Its first part corresponds

Table 1. P-Wave Variable Data of the Study Population at Baseline and 3-Year Follow-Up and P Values for the Respective Statistical Comparisons

	Baseline (n = 67)	Follow-up (n = 67)	P Value
PWD	127 ± 12	125 ± 14	0.50
X max	67 ± 9	67 ± 10	0.99
Y max	61 ± 10	61 ± 11	0.77
Z max	87 ± 14	87 ± 14	0.80
Z min	41 ± 6	41 ± 7	0.57
Z zero	64 ± 13	63 ± 13	0.38

to the activation of the right atrium (RA) normally originating from the sinus node and the latter part is equivalent to the activation of the LA.¹⁸ Signal averaging of the P wave provides more accurate information of atrial activation¹⁹ and has been used in different clinical settings.^{4,20,21} However, signal-averaged P waves in healthy individuals are less well described. In 2001, Ehrlich and coworkers published normal PSAECG values of 123 healthy subjects with a reported PWD of 114 ± 13 ms¹⁰ and a slight prolongation of the P wave with increasing age. Ishimoto and coworkers reported a PWD of 121 ± 9 ms in a normal control group.²² The group was, however, small (n = 34) and comprised hospitalized patients although without history of cardiovascular disease or arrhythmia. A similar but larger group was studied by Babaev who reported a PWD of 139 ± 12 ms and a positive correlation between PWD and age (r = 0.39).²³ These data were suggested to confirm the presence of age-related conduction disturbances but the lack of age-related P-wave prolongation has also been reported.²⁴ In this study, we do not observe any significant changes in P-wave variables between BL and FU. Possibly a 3-year follow-up period is too short for statistically significant age-related changes such as PWD prolongation to occur. In a previous report on the 120 subjects included at BL, we did indeed observe a prolonged PWD in subjects older than 50 years.⁷ We report a PWD for the entire study group of this study of 127 ± 12 ms (BL), which is in consistency with the above-mentioned reports on healthy subjects. It should be noted that the method used in this study and the previous report⁷ is “unfiltered” PSAECG (only 50 Hz band-stop filtering) in comparison to the more frequently used band-pass filtered signals (usually 40–300 Hz). It can be argued that as such the acquired signal is more representative of the true biological signal.¹⁹

Reproducibility (i.e., stability) of spatiotemporal variables of signal-averaged ECG has mostly been reported as good, in particular regarding PWD^{9,11–13,25} but the longest follow-up period has been no more than 1 month. In addition to this, the methods and study designs have differed making it difficult to come to a general conclusion regarding this. We report data of a 3-year follow-up in healthy, the longest follow-up yet to the best of our knowledge. No significant intraindividual change of numerical P-wave variables was seen over time suggesting that the signal-averaged P wave shows stability over time.

P-Wave Morphology and Interatrial Conduction

In this study, consistent with previous studies,⁵⁻⁷ two dominating orthogonal P-wave morphologies were observed, Type 1 and 2 (Fig. 1) with the latter previously found to be common in PAF-patients.⁵ Type 1 morphology is thought to represent an activation sequence directed from right to left, superior to inferior, and posterior to anterior. The most logical genesis of such morphology would be LA activation via posteriorly located interatrial conduction routes. Type 2 morphology differs from the prior in the terminal portion of Lead Z (biphasic -/+), which is compatible with interatrial propagation disturbances.¹⁸ The biphasic signal indicates an anterior-posterior-anterior activation, best explained by interatrial conduction via the anteriorly located Bachmann's bundle (Bb) only and suggestive of a lack of conduction in the inferoposterior region. A third Type has also been reported in a population with hypertrophic cardiomyopathy (HCM), a P-wave morphology consistent with advanced interatrial block (IAB).^{6,26,27} The correlation between morphology and interatrial conduction was recently confirmed in a study of PAF-patients where P-wave morphology was compared to electroanatomical mapping data of the site of LA breakthrough.⁸ A good correspondence was seen between Type 1 morphology and fossa ovalis breakthrough, Type 2 morphology and Bb breakthrough, and Type 3 and coronary sinus breakthrough, respectively.

This study reports a variety of P-wave morphology types in a healthy cohort in support of the theory that the interatrial conduction is more complex than merely via Bb. Type 1 and 2 are commonly found while Type 3 logically is a rare finding in a presumed healthy population, well in keeping with previously published data.⁷ Indeed, recent mapping studies by Roithinger et al. and Markides et al. have demonstrated different modes of RA-LA activation.^{28,29} In addition to the anteriorly located Bb, functional transeptal pathways were demonstrated in the coronary sinus region, near the fossa ovalis but also posteriorly located. Variable substrates for interatrial propagation at these locations have also been reported in pathoanatomical studies.^{30,31} and confirmed recently in a larger material.³² Hitherto, no long-term follow-up on P-wave morphology has been available. In the vast majority of subjects (59 of 67 cases), the P-wave mor-

phology remains stable after 3 years. In eight cases, however, the P-wave morphology type is different at FU and seen in individuals with Type 1 and Type 2 morphology at BL (Figs. 3 and 4). Two cases of transition into Type 3 morphology, that is, progression to advanced IAB was also observed. The change in morphology implies a different vector direction, not solely based on deteriorated conduction velocity, as PWD remained statistically unchanged over the 3-year period. It has previously been suggested that subtle age-related changes such as fibrosis would be the reason for changes of interatrial conduction as mirrored by P-wave morphology.³³ The least vulnerable interatrial conductive pathway would possibly be the cruder Bb that fits well with the previous observation that Type 2 morphology is more common with advancing age in healthy. Supportive of this, we observe in this study that Type 1 morphology is less stable than Type 2 suggesting that a logical transition of P-wave morphology in an individual over time would be from Type 1 to 2. One could speculate that over a longer time period, these changes might evolve into prolonged PWD, also known as partial IAB. The latter is linked to supraventricular arrhythmias and impaired LA function and highly prevalent in patients^{27,34} but also in healthy.³⁵ Indeed, we report two cases of advanced IAB morphology in this study population.

Some awareness is needed when interpreting P-wave morphology since many factors might influence it such as atrial size, location of and exit from the sinus node.³⁶ In order to rule out the possibility of the changes representing a low reproducibility of the method in itself, signal acquisition and analysis was performed with a 24-hour interval in a small subset of subjects. The P-wave morphologies were unaltered at both registrations for all ten individuals and this high reproducibility between two different recordings indicate that the observed changes of this study are genuine and not introduced by an inaccurate method. Thus, our findings show that subtle changes of interatrial conduction, represented as differing orthogonal P-wave morphologies occur in healthy subjects over time.

Limitations of the Study

The study population was unbalanced with a female majority and slightly older than the BL-population, due to a certain amount of more mobile younger subjects lost to follow-up. Although this

is not unusual for studies of healthy volunteers it might limit the interpretation of our results. Data are, however, in well keeping with previous studies. Although LA enlargement was not ruled out using echocardiography we find it unlikely that individuals with structural heart disease were included in a number that would compromise the interpretation of data.

CONCLUSIONS

In a majority of healthy men and women, the unfiltered signal-averaged P-wave morphology remains unaltered at follow-up 3 years later. Long-term change of P-wave morphology not accompanied by the prolongation of the P-wave duration is observed in a small number of individuals thus suggesting age-related changes in interatrial conduction.

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