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Original Research
Journal of Atrial Fibrillation

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Abnormal Atrial Activation at Surface Electrocardiogram Examination in Born Underweight Young Adults

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Abstract

Introduction: Recent published data demonstrated how subjects born preterm are at higher risk of developing early atrial fibrillation (AF).

Materials and Methods: The surface ECG of twenty-four adults, former preterm infants born with an extremely low birth weight (ex-ELBW; mean age at study: 23.2±3.3 years; mean gestational age: 27.8±2.3 weeks; mean birth weight: 840±120.1 grams), were compared with those of 24 healthy counterparts born at term (C). A few parameters known to be capable of predicting a predisposition to develop AF were examined: P wave duration and dispersion, P terminal force, isoelectric interval length, PR interval length, and advanced interatrial blocks.

Results: A shorter PR interval length was found in ex-ELBW compared to C ($p<0.0003$) as well as longer P wave duration and dispersion, p terminal force, and isoelectric interval ($p<0.0001$, $p<0.0001$, $p<0.01$, and $p<0.0004$, respectively). Four cases of advanced interatrial block were detected in ex-ELBW, and none in C ($p<0.0001$). P wave duration, PR interval length, and P wave dispersion were significantly correlated with birth weight ($r=0.51$ $p<0.01$, $r=0.46$ $p<0.02$, and $r=0.42$ $p<0.04$, respectively).

When excluding the possible influence of gestational age on birth weight, P wave duration and dispersion were found to be the only statistically significant determinants of abnormal atrial electrical activation ($p<0.03$ and $p<0.04$, respectively). On the contrary, when excluding the possible influence of birth weight on gestational age, only P wave duration remained statistically significant ($p<0.05$).

Conclusions: Surface ECG findings of abnormal atrial activity in ex-ELBW may explain their previously reported predisposition to developing AF.

Introduction

It has been highlighted how birth weight is associated with an increased risk of early onset of atrial fibrillation (AF), in patients of both genders and with no traditional cardiovascular risk factors, thus suggesting that early life determinants may play a pivotal role in the pathogenesis of AF[1,2]. This relationship was not attenuated even following adjustment for cardiovascular risk factors and ethnicity at multivariate analysis[3].

Abnormal atrial activation, defined as atrial structural change, conduction abnormalities, and sinus node dysfunction, is likely to predispose to the development and progression of AF[4].

The aim of this study was to evaluate a series of signs of atrial activation at surface electrocardiogram (ECG) in a group of young adults born preterm with an extremely low birth weight (ex-ELBW; birth weight <1,000 grams), and to compare the findings with results obtained in a group of healthy counterparts born at term[5,6], in order to identify a potential correlation between these electrocardiographic signs and perinatal factors including birth weight and gestational age[7].

Key Words

Surface Electrocardiogram, Atrial, Atrial Fibrillation, Gestational Age, Birth Weight, Intrauterine Growth Restriction.

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Materials and Methods

A comparison was carried out between 24 ex-ELBW (4 males and 20 females) ranging between about 20 and 30 years (mean age±SD, 23.2±3.3 years; mean gestational age±SD, 27.8+2.3 weeks ; mean birth weight±SD, 840+120.1 grams) and a control group (C) comprising 24 healthy subjects born at term, matched for sex, age and BMI. All subjects were contacted in alphabetical order from the Records of the Neonatal Intensive Care Unit (NICU) of the University of Cagliari, Italy. Subjects represent the first surviving ex-ELBW assisted in the sole NICU present in Cagliari (Italy).

Exclusion criteria were as follows: patients suffering from conditions and/or assuming compounds known to predispose to the onset of AF (for example, hypertension, mitral valve disease, caffeine and alcohol addiction)[8]. In this respect, nine patients were excluded.

Arterial blood pressure was measured by auscultatory method. A standard 12-lead surface ECG was performed (Cardioline ar2100 view 12-channel electrocardiograph, Italy) in order to evaluate several parameters of atrial activation (P wave duration, dispersion, P terminal force (in precordial lead V1), isoelectric interval length, and

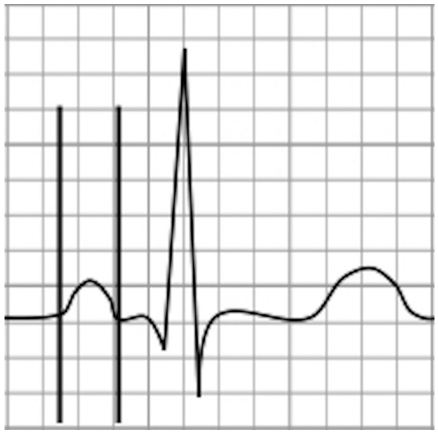

Figure 1: P wave duration, defined as the first onset and the last offset of the P wave

PR interval length). They were measured manually by the same trained cardiologist with expertise in electrophysiology (98.5%intraobserver reproducibility rate)[5]. For the sake of precision in measuring, a magnifying glass was used.

Specifically, P wave duration [Figure 1] is defined as the first onset and the last offset of the P wave (at three standard leads), while P wave dispersion is the difference between the maximum and the minimum P wave duration detected in a 12-lead standard ECG. P terminal force [Figure 2] is defined as the duration (in seconds) of the terminal part (negative) of the P wave in lead V1 multiplied for its depth (in millimeters). If the P wave terminal part is positive, then the interval extending from the first notch to the wave end must be considered. Precordial V1 (and V2) leads were corrected displaced in the fourth intercostal space. Isoelectric interval length [Figure 3] is defined as the difference between total P wave duration and maximum P wave duration. PR interval length [Figure 4] is the period that extends from the beginning of the P wave until the beginning of the QRS complex. It was measured in lead V1. Lastly, advanced or third degree interatrial blocks are characterized by a p wave duration >120 msec as well as a p wave bifid morphology in leads D1 and aVL and biphasic in D2, D3, aVF, V1, and V2[5,9].

Three measures were taken for each of the examined parameters and their average used. The data were blinded, so that the examiner did not know if the ECGs belonged to the population in the study or controls.

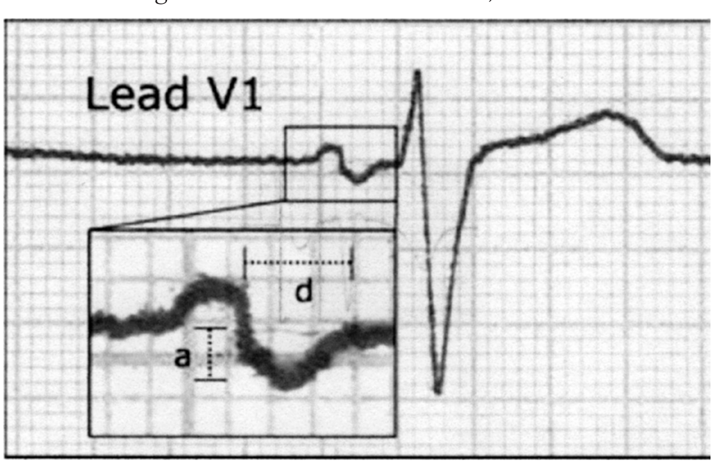

Figure 2: P terminal force, defined as the duration (in seconds) of the terminal part (negative) of the P wave in lead V1 multiplied for its depth (in millimeters)

The assessed ECG parameters were subsequently compared to birth weight and gestational age, as reported on clinical records.

A 24-hour Holter ECG registration was performed in both ex-ELBW and controls as well.

Informed written consent for participation in the study was obtained from all ex-ELBW. The research was formally approved by the internal Ethics Committee (PG/2015/1859) and conducted in accordance with the Helsinki declaration.

Statistical Analysis

The results of the entire study population (n=24), which was normally distributed, were first analyzed, and ex-ELBW subjects subsequently compared to C (n=24) using the parametric Student t-test. Relationships between the various parameters studied were assessed by means of univariate analysis. Multivariate analysis was not been applied due to the inadequacy of sample size for this statistic test. However, partial correlation analysis was applied, in order to hive off the possible influence of a variable on another one, when these two are deeply correlated, such as birth weight and gestational age.

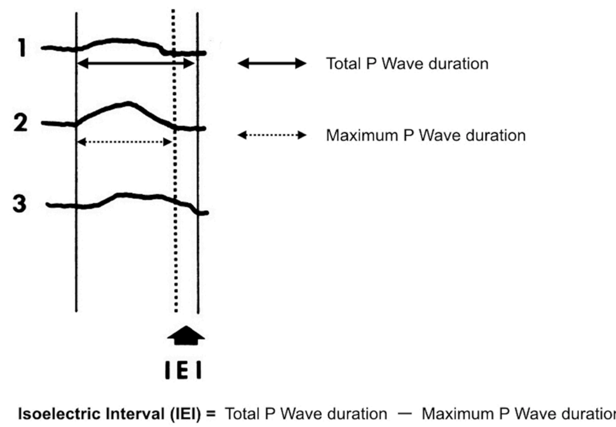

Figure 3: Isoelectric interval length, defined as the difference between total P wave duration and maximum P wave duration

Figure 4: PR interval length is the period that extends from the beginning of the P wave until the beginning of the QRS complex

The presence of a potential correlation between the above stated parameters of atrial activation and both gestational age and birth weight was investigated in accordance with Pearson's correlation coefficients. Values of p<0.05 were set as the minimum level of statistical significance throughout the study. For all analyses, commercially available computer software (SPSS version 22.0, SPSS Inc., Chicago, Illinois, USA) was used.

Results

The clinical characteristics of the population investigated (ex-ELBW vs C) are summarized in [Table 1]. The assessed ECG parameters are reported in [Table 2].

A statistically significant difference was detected for PR interval length, which was found to be shorter in ex-ELBW compared to the same values in C (p<0.0003). Furthermore, longer P wave prolongation and dispersion, P terminal force, and isoelectric interval were detected in ex-ELBW compared to C (p<0.0001; p<0.0001; p<0.01; and p<0.0004, respectively).

P wave duration, PR interval length, and P wave dispersion were significantly correlated with birth weight (r=0.51 p<0.01, r=0.46 p<0.02, r=0.42 p<0.04, respectively). When excluding the possible influence of gestational age on birth weight, P wave duration and dispersion were found to be the only statistically significant determinants of abnormal atrial electrical activation (p<0.03 and r= p<0.03). On the contrary, when excluding the possible influence of birth weight on gestational age, only P wave duration remained statistically significant (p<0.05).

Table 1: Clinical characteristics (patients and control group)

	Ex-ELBW	C	P
Gestational age (weeks)	27.8 ± 2.3	39.4 ± 0.7	0.0001
Birth weight (grams)	840 ± 120.1	3.257 ± 0.391	0.0001

Furthermore, four cases of advanced interatrial block (16.6%) - a strong marker of paroxysmal supraventricular tachyarrhythmias - were detected in ex-ELBW, and none in the control group (p<0.0001)[9].

At 24-hour Holter ECG registration the incidence of supraventricular ectopic beats and supraventricular tachycardia runs in ex-ELBW was higher compared with controls (31 premature atrial complexes/hour vs 4/hour, p<0.0001; longest supraventricular run /24 hours =12 vs 0, p<0.0001).

Table 2 : Examined electrocardiographic parameters of atrial activation that predispose to the onset of atrial fibrillation (patients and control group)

	Ex-ELBW	C	P
HR (beats/min)	78 ± 3	82 ± 3	ns
P dur (msec)	122.4 ± 3.5	79.6 ± 4.1	0.0001
PWD (msec)	44.4 ± 3.5	37.1 ± 1.1	0.0001
PTFV1 (mm x sec)	0,06 ± 0.1	0.04 ± 0.1	0.01
IEI (msec)	39.0 ± 9.9	84.6 ± 19.9	0.0004
PR (msec)	141.4 ± 13.4	164.2 ± 24.0	0.0003
Advanced interatrial Blocks (%)	4/24 (16.6%)	0/24 (0%)	0.0001

Acronyms: HR: heart rate; P dur: P wave duration; PWD: P wave dispersion; PTF: P terminal force in the lead V1; IEI: isoelectric interval; PR: PR tract length

Discussion

Although old age continues to be the strongest predictor for the development of AF, in recent years other factors capable of increasing the risk of incident AF have been identified, including low birth weight[1,3]. Also higher birth weight was associated with an increased risk of AF during adulthood. The two highest categories were associated with a 70% and 71% increased risk after multivariable adjustment[2].

Analysis of atrial activation at surface 12-lead ECG may help to identify subjects with a predisposition to developing this form of arrhythmia[10]. All examined parameters of atrial activation were previously shown to be able to give information about the anatomical substrate predisposing to the onset of AF[5]. In fact, they represent an electromechanical interaction, being the electrocardiographic expression of atrial stretching/enlargement, impaired atrial conduction, and various changes in the atrial activation vector. Accordingly, in our study all these parameters presented significant differences compared to those of the control group, although only P wave duration and dispersion continued to be significantly correlated with birth weight following the exclusion of possible influence of gestational age, and only P wave duration when excluding the influence of birth weight on gestational age. It means that low birth weight (i.e. intrauterine growth restriction) is an atrial fibrillation predisposing factor stronger than gestational age, in accordance with previous reports[1-3].

An excessive prolongation of P wave duration at surface ECG reflects the presence of intra-atrial conduction abnormalities[11]. A slow conduction velocity is crucial in the development of reentrant arrhythmia, since a shortened refractory period makes atrial tissue sensitive to premature atrial depolarization. This would indeed imply the possibility of obtaining a series of important data from analysis of P wave characteristics measured at surface ECG in our patients.

Specifically, the use of different definitions for P wave duration may influence results[11]. In this study, P wave duration was detected manually at three standard leads and the averaged measure used. The cut-off points used were the first (onset) and last (offset) deflections from baseline. Previous reports have shown that an increased P wave duration at 12-lead surface ECG and signal averaged ECG recordings is a reliable predictor of the future onset of AF, featuring a high sensitivity and specificity[12].

On the other hand, P wave dispersion is defined as the difference between the longest and shortest P wave durations recorded from multiple different ECG leads. It represents the inhomogeneity and discontinuation in atrial conduction and has proven to be a marker capable of predicting the development of AF in a number of clinical scenarios[13].

Advanced or third degree interatrial blocks are considered strong markers of paroxysmal supraventricular tachyarrhythmias[9]. They are not uncommon in the general population and associated with ischemic stroke at multivariate analysis, thus strengthening the hypothesis that left atrial disease should be considered an indipendent risk factor for stroke[14,15]. An underlying atrial pathology in term of remodelling was clearly demonstrated at advanced echocardiography as well as cardiac MRI in those presenting with interatrial blocks[16,17].

A pathophysiological explanation of our findings is likely linked to the fact that prematurity at birth and low birth weight may result just in atrial remodeling, as a consequence of the modifications induced on atrial structure, function, electrophysiological and metabolic activities[18]. Our research group had previously demonstrated an approximately 30% prevalence in ex-ELBW of atrial septal aneurysms at echocardiography, while prevalence of this defect in the general population ranges from 0.2 to 3.2% and was 2.7% in controls[19]. This finding is in agreement with the traditional hypothesis of Hanley et al., according to which extremely mobile atrial septal aneurysms are correlated with the onset of AF in adults[20]. The high prevalence of an aneurismal aspect of the interatrial septum may be induced by the presence of a marked difference in pressure between the two atria (atrial stretching), such as in born preterm subjects with a long time patency of ductus arteriosus and/or the presence of severe respiratory distress at birth[21].

An abnormal electrical remodelling has also been recently described in cardiac ventricles of adolescents born preterm and/or with intrauterine growth restriction[22]. This is likely the underlying cause of reported repolarization abnormalities (QTc and QT dispersion prolongations) at standard ECG in adult individuals meeting either of these criteria[23-25].

This study is undoubtedly hampered by a series of limitations: a) small sample size, which we would enlarge in future studies. It probably explains even the lack of a possible relationship between interatrial advanced blocks and gestational age and/or birth weight. This objective limitation is due to the restricted number of patients available with suitable characteristics at our University; b) definition of P wave duration, owing to the lack of universally accepted cut-off points - although the highest accuracy in detecting P wave points is achieved manually, intra and inter-observer measurement errors continue to confound this method[26,27] ; c) parameters of atrial activation were only investigated at surface ECG, whilst a comparison with results obtained at transoesophageal ECG may have facilitated a more precise evaluation of atrial electrophysiological activity[28]; d) inducibility of AF in ex-ELBW has not been confirmed in electrophysiological studies of the heart. However, the examined patients in the study were decidedly younger compared to those enrolled in the previous studies showing an increased risk of developing atrial fibrillation[1-3]. The follow up was shorter as well. Even though none of the ex_ELBW developed atrial fibrillation, at 24-h Holter ECG the incidence of supraventricular ectopic beats and supraventricular tachycardia runs –which are known to be predictors of AF- was higher compared with controls[29]; e) it may prove beneficial to take other factors that might potentially contribute towards increasing susceptibility of developing AF into consideration, such as the augmented thickness of epicardial fat previously demonstrated in ex-ELBW, which has been hypothesized to exert a local pathogenetic effect on the arrhythmogenic substrate supporting AF[30,31].

Conclusions

Although considerable progress has recently been made in predicting the onset of AF, to date no reliable methods of detection have been proposed. In line with a series of previously established markers, which may be capable of predicting the onset of AF, ex-ELBW seem to display an abnormal atrial activity at surface ECG, possibly explaining the previously reported predisposition of these subjects to develop AF. The findings of this study also provide further confirmation of the arrhythmic vulnerability of this population[1,20,21,32].

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