The effects of iron deficiency anemia on p wave duration and dispersion

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OBJECTIVES: The association between P wave dispersion and iron deficiency anemia has not been documented in the literature. In this study, we evaluated P wave dispersion in patients with iron deficiency anemia and the possible relationships between P wave dispersion and other echocardiographic parameters.

INTRODUCTION: The iron status of an individual may play an important role in cardiovascular health. Anemia is an independent risk factor for adverse cardiovascular outcomes. P wave dispersion is a simple electrocardiographic marker that has a predictive value for the development of atrial fibrillation. Apart from cardiovascular diseases, several conditions, such as seasonal variation, alcohol intake and caffeine ingestion, have been demonstrated to affect P wave dispersion.

METHODS: The study included 97 patients who had iron deficiency anemia and 50 healthy subjects. The cases were evaluated with a clinical examination and diagnostic tests that included 12-lead electrocardiography and transthoracic echocardiography.

RESULTS: Compared to the control group, patients with iron deficiency anemia showed significantly longer maximum P wave duration (Pmax) (91.1±18.0 vs. 85.8±6.7 msec, p = 0.054), P wave dispersion (PWD) (48.1±7.7 vs. 40.9±5.6 msec, p < 0.001), mitral inflow deceleration time (DT) (197.5±27.9 vs. 178.8±8.9 msec, p < 0.001) and isovolumetric relaxation time (IVRT) (93.3±9.2 vs. 77.4±8.2 msec, p < 0.001); they also showed increased heart rate (85.7±16.1 vs. 69.0±4.4, p < 0.001) and frequency of diastolic dysfunction (7 (7.2%) vs. 0). Correlation analysis revealed that PWD was significantly correlated with IVRT, DT, heart rate, the presence of anemia and hemoglobin level.

CONCLUSIONS: Iron deficiency anemia may be associated with prolonged P wave duration and dispersion and impaired diastolic left ventricular filling.

KEYWORDS: Diastolic dysfunction; Electrocardiogram; Iron deficiency; Anemia; P wave; Dispersion.

INTRODUCTION

P wave dispersion (PWD) is defined as the difference between the longest and the shortest P-wave duration recorded from multiple different surface ECG leads. To date, the most extensive clinical evaluation of PWD has been performed in the assessment of the risk for atrial fibrillation (AF), which is characterized by inhomogeneous and discontinuous atrial conduction. Several studies have shown that PWD has a predictive value for the development of AF in patients without apparent heart disease and in patients who were hypertensive or had various cardiac conditions.¹⁻³ Apart from cardiovascular diseases, several conditions such as seasonal variation, alcohol intake and caffeine ingestion have been demonstrated to affect PWD.⁴⁻⁶

Anemia is an independent risk factor for adverse cardiovascular outcomes.⁷⁻⁸ The iron status of an individual may play an important role in cardiovascular health because either an excess of iron or iron deficiency can lead to significant problems.⁹ Increased risks of left ventricular (LV) dilatation, systolic dysfunction, chronic heart failure and death have been shown to be associated with a decrease in hemoglobin (Hb) concentration of as little as 1 g/dL.¹⁰⁻¹¹

To our knowledge, the association between PWD and iron deficiency anemia (IDA) has not been documented in the literature. In this study, we evaluated PWD in patients with IDA and the possible relationships between PWD and other echocardiographic parameters.

MATERIALS AND METHODS

In this study, 97 patients with IDA and 50 healthy controls were included, and the following laboratory tests were
Several factors have been shown to influence PWD. In this study, we found that P max and PWD were significantly prolonged in patients with iron deficiency anemia. In addition, the frequency of left ventricular diastolic dysfunction was increased in IDA.

DISCUSSION

In this study, we found that P max and PWD were significantly prolonged in patients with iron deficiency anemia. In addition, the frequency of left ventricular diastolic dysfunction was increased in IDA.
A seasonal variation has been demonstrated in healthy subjects; specifically, PWD is shortest in the summer and longest in the winter.\(^\text{17}\) Furthermore, the effects of obesity, acute caffeine ingestion, alcohol intake and high altitude on PWD in healthy subjects have been evaluated in several studies, and differences between trained athletes and control subjects have also been demonstrated.\(^\text{5,6,18-20}\)

Therefore, it might be inappropriate to use a single PWD measurement as a predictor of AF in healthy people because PWD is influenced by many parameters, which may be risk factors for the long-term development of AF. To our knowledge, there is no study that has investigated the effect of iron deficiency anemia on P wave measurements.

Compromised oxygen delivery capacity due to anemia may result in chronic tissue hypoxemia, which may then lead to myocyte dysfunction. Because iron moieties bind to myoglobin, a total-body iron deficit could further impair the ability of myocytes to extract oxygen from circulating hemoglobin. Several mechanisms operate to compensate for tissue hypoxia induced by anemia. When the hemoglobin concentration drops below 10 g/dl or during non-resting conditions, non-hemodynamic factors are surmounted, and hemodynamic mechanisms begin to compensate for tissue hypoxia.\(^\text{21}\)

Although increased cardiac output is the main hemodynamic factor and is mediated by lower afterload, increased preload and positive inotropic and chronotropic affects, the mechanisms of hemodynamic compensation are complex. These mechanisms include (i) a reduction in afterload due to a decrease in systemic vascular resistance, (ii) an increase in preload due to an increase in venous return and (iii) increased left ventricular (LV) function attributed to increased sympathetic activity and inotropic factors. In addition, heart rate is increased in anemic patients due to hypoxia-stimulated chemoreceptors.\(^\text{22,23}\)

In the present study, the frequency of LV diastolic dysfunction was significantly increased in patients with IDA. Several mechanisms may explain this association. Tissue hypoxia induced by anemia may impair diastolic function. Diastolic dysfunction without systolic dysfunction may present at an early stage of myocardial ischemia, and this is consistent with the finding that left ventricular diastolic function is more susceptible to ischemia than systolic function.\(^\text{24}\)

Adaptation to an anemic state involves the augmentation of heart rate, cardiac index, stroke work and increased plasma volume.\(^\text{23,25}\)

This overall increase in sympathetic and inotropic activity places additional stress on the myocardium and may lead to remodeling of myocytes and the vasculature. Anemia also has numerous hormonal and metabolic effects that can result in direct myocardial toxicity and ischemia.\(^\text{26}\)

These specific effects have been observed when the anemia is severe (HB <10 g/dl). Therefore, subendocardial ischemia, increased heart rate and altered loading conditions may contribute to the anemia-associated diastolic dysfunction. LV diastolic dysfunction has also been shown to be associated with increased PWD and may partially explain our finding of increased PWD in IDA.\(^\text{27}\)

P wave duration and PWD have also been reported to be influenced by autonomic tone, which induces changes in the velocity of impulse propagation. Increased sympathetic activity causes a significant increase in PWD.\(^\text{28}\)

Elevated levels of norepinephrine in plasma and urine in IDA patients support the role of increased sympathetic activity in this effect.\(^\text{29}\)

Low oxygen tension in the tissues may explain the autonomic dysfunction in IDA. Hypoxia has an important pathophysiological role in various diseases, including anemia.\(^\text{30}\)

Cardiac autonomic dysfunction has been documented in various anemic patient populations, such as those with vitamin B12 deficiency, sickle cell anemia, thalassemia and iron deficiency anemia.\(^\text{31,32}\)

Although it is unknown how low oxygen tension is detected by cells, the influence of the carotid body on ventilatory and cardiovascular reflexes seems to play a major role in altered autonomic balance.\(^\text{33}\)

### Table 1 - Comparison of clinical and echocardiographic variables for patients with iron deficiency anemia versus healthy subjects.

| Parameters | IDA (n = 97) | Control (n = 50) | P value |
|------------|-------------|-----------------|---------|
| Age (years) | 37.4 ± 11.9 | 37.2 ± 5.5 | 0.816 |
| Male (n,%)| 30 (30.9%) | 13 (26%) | 0.824 |
| Body mass index (kg/m²) | 23.3 ± 2.9 | 24.0 ± 1.8 | 0.194 |
| Smoking (n,%) | 20 (20.6%) | 14 (28%) | 0.483 |
| Systolic BP (mmHg) | 117.5 ± 9.3 | 118.0 ± 9.2 | 0.788 |
| Diastolic BP (mmHg) | 73.3 ± 6.3 | 73.3 ± 7.8 | 1.000 |
| HB (g/dl) | 7.9 ± 1.6 | 14.2 ± 0.4 | <0.001 |
| Htc (%) | 25.3 ± 4.9 | 40.3 ± 1.7 | <0.001 |
| LVDD (mm) | 48.1 ± 4.2 | 47.7 ± 2.2 | 0.914 |
| LVSD (mm) | 30.8 ± 2.4 | 32.6 ± 2.1 | 0.462 |
| LVEF (%) | 63.0 ± 3.2 | 63.2 ± 2.2 | 0.385 |
| IVS (mm) | 9.3 ± 1.3 | 9.5 ± 0.6 | 0.297 |
| PW (mm) | 9.1 ± 1.2 | 9.4 ± 0.9 | 0.178 |
| LA diameter (mm) | 35.6 ± 4.5 | 34.4 ± 12.8 | 0.07 |
| E/A | 1.3 ± 0.3 | 1.3 ± 0.1 | 0.553 |
| DT (msec) | 197.5 ± 27.9 | 178.8 ± 8.9 | <0.001 |
| IVRT (msec) | 93.3 ± 9.2 | 77.4 ± 8.2 | <0.001 |
| Diastolic dysfunction (n,%) | 7 (7.2%) | 0 | 0.012 |
| SI (ug/dl) | 19.5 ± 5.10 | 76.92 ± 23.60 | 0.001 |
| Ferritin (ng/ml) | 4.54 ± 3.51 | 42.55 ± 47.71 | 0.001 |
| Transferrin saturation (%) | 8.10 ± 2.18 | 34.23 ± 12.14 | 0.001 |

BP: Blood pressure, HB: Hemoglobin, Htc: Hematocrit, LVDD: Left ventricular diastolic diameter, LVSD: Left ventricular systolic diameter, LVEF: Left ventricular ejection fraction, IVS: Interventricular septum, PW: Posterior Wall, LA: Left atrium, DT: Deceleration time, IVRT: Isovolumetric relaxation time, SI: Serum Iron.

### Table 2 - Comparison of P wave variables and heart rate for iron-deficient anemic patients versus healthy subjects.

| Parameters | IDA (n = 97) | Control (n = 50) | P value |
|------------|-------------|-----------------|---------|
| Pmax (msec) | 91.1 ± 18.0 | 85.8 ± 6.7 | 0.054 |
| P min (msec) | 44.8 ± 9.3 | 44.9 ± 9.1 | 0.957 |
| PWD (msec) | 48.1 ± 7.7 | 40.9 ± 5.6 | <0.001 |
| Heart rate (bpm) | 85.7 ± 16.1 | 69.0 ± 4.4 | <0.001 |

Pmax: Maximum P wave duration, Pmin: Minimum P wave duration, PWD: P wave dispersion.
standard signal size and paper speed may have questionable accuracy and reproducibility. It is unclear whether prolonged PWD may be associated with the long-term development of AF. Pulsed wave Doppler indices used for the evaluation of LV diastolic properties have been known to be altered by numerous factors, including loading conditions and heart rate, both of which can be altered by anemia. However, to evaluate diastolic function, we also used tissue Doppler indices, which are relatively independent of loading conditions.

CONCLUSIONS

Iron deficiency anemia may be associated with prolonged P wave duration and dispersion and impaired diastolic left ventricular filling. Tissue hypoxia, altered loading conditions and impaired autonomic balance with increased sympathetnic activity may be among the possible mechanisms that explain these findings.

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