P Wave Dispersion in Hypertensive Crisis and Assessment of Effects of Sodium Nitroprusside and Nitroglycerin Treatments

Hipertansif Krizde P Dalga Disparyiyonu ve Nitroprussid ile Nitrogliserin Tedavilerinin Etkilerinin Değerlendirilmesi

**ABSTRACT**
Objective: Prolongation of P-wave duration and increase of P-wave dispersion (PWD) were demonstrated to be independent predictors of atrial fibrillation (AF). Although many clinical trials have shown the effectiveness of sodium nitroprusside (NIP) and nitroglycerin (NIT) for the treatment of hypertensive crisis, to our knowledge, there are no data available concerning PWD during hypertensive crisis and effect of treatment on PWD. The aim of this study is to evaluate the effects of intravenous sodium nitroprusside and nitroglycerin treatments on PWD in patients admitted to emergency department for hypertensive crisis. Material and Methods: Thirty-seven patients admitted to emergency department for hypertensive crisis, aged from 37 to 75 years were randomly allotted to NIP or NIT. Blood pressures were measured by a manual sphygmomanometer at 15 minute intervals. Electrocardiographic recordings of patients were obtained before treatment and after 20-25% reduction in blood pressure. Changes in P wave durations and PWD were calculated. Results: Both with NIP and NIT systolic/diastolic blood pressures (199.8±16.8/119.2±13.4 mmHg to 154.6±11.7/90.8±5.3 mmHg, p<0.001 vs. 196.4±18/114.7±9.5 mmHg to 159.8±11.1/92.3±7.1 mmHg, p<0.001), mean arterial pressure (146.1±12.3 mmHg to 112.1±5.4 mmHg, p<0.001 vs. 141.9±10.4 mmHg to 114.8±7.6 mmHg, p<0.001), Pmax (108.9±11.0 msec to 96.8±12.0 msec, p<0.001 vs. 108.3±12.5 msec to 97.8±11.1 msec, p<0.001) and PWD (68.4±16.8 msec to 54.7±11.7 msec, p<0.001 vs. 67.8±16.6 msec to 59.4±10.0 msec, p<0.039) were decreased. Conclusions: PWD decreased after treatment with either NIP or NIT in patients with hypertensive crisis. Reduction of blood pressure and consequent decrease in left atrial stretch is probably responsible for improvement in PWD.

**Key Words:** Emergency treatment, hypertension, nitroglycerin, sodium nitroprusside

**ÖZET**
P dalga süresi ve P dalga dispersiyonunun uzamasının atrial fibrilasyon için başlıca öngörüldüğü açıklandığı için araştırılmıştır. Sodyum nitroprussid (NIP) ve nitroglicerini (NIT) hipertansif kriz tedavisinde etkin olduklarını birçok çalışmadan gösterilmiş olmasına karşın bildirimdeki kadarla hipertansif krizin ve tedavisinin PWD üzerine etkisi araştırılmamıştır. **Amaç:** Acil ünitesinde hipertansif krizle gelen hastalara intravenöz verilen NIP ve NIT tedavilerinin P dalga dispersiyonü üzerine olan etkisini araştırmaktır. **Gereç ve Yöntemler:** Hipertansif kriz ile acil ünitesinde kabul edilen 37-75 yaş grubundaki 37 hasta rasgele NIP veya NIT ile tedavi edildiler. Kan basıncı manüel bir sfigmomanometre ile 15 dakika aralıklarla ölçüldü. Elektrokardiografik kayıtlar tedaviden önce ve kan basınçlarında %20-25 azalma sağlanktan sonra alındı. **Bulgarlar:** Nitroprussid tedavisi ile sistolik/diyastolik kan basıncı 199.8±16.8/119.2±13.4 mmHg dan 154.6±11.7/90.8±5.3 mmHg’ya (p<0.001), ortalamada kan basıncı 146.1±12.5 mmHg dan 112.1±5.4 mmHg’ya (p<0.001), Pmax 108.9±11.0 msec’den 96.8±12.0 msec’ye (p<0.001), PWD 68.4±16.8 msec’den 54.7±11.7 msec’ye (p<0.001), nitroglicerinin tedavisi ile sistolik/diyastolik kan basıncı 196.4±18/114.7±9.5 mmHg’den 159.8±11.1/92.3±7.1 mmHg’ye (p<0.001), ortalamada kan basıncı 141.9±10.4 mmHg dan 114.8±7.6 mmHg’ya (p<0.001), Pmax 108.3±12.5 msec’den 97.8±11.1 msec’ye (p<0.001), PWD 67.8±16.6 msec’den 59.4±10.0 msec’ye (p<0.039) düştü. **Sonuçlar:** Hipertansif kriz hastalarının NIP veya NIT ile tedavi edilmesiyle Pmax ve PWD kısalmaktadır. Kan basıncının azalması ve takip eden sol atrial gerilimin azalması PWD’deki düşelmeyi beraberinde getirebilir.

**Anahtar Kelimeler:** Acil tedavi, hipertansiyon, nitroglicerin, sodyum nitroprussid
P wave dispersion (PWD), described as the difference between maximum P wave duration (P max) and minimum P wave duration (P min), has been accepted as a predictor for atrial fibrillation (AF) in hypertension\textsuperscript{1,2} and some other cardiac diseases.\textsuperscript{1,3-7}

Hypertensive crisis is defined as a severe elevation in blood pressure, generally a systolic blood pressure greater than 180 mmHg and/or a diastolic blood pressure greater than 120 to 130 mmHg. Hypertensive crises occur less than 1% of patients with hypertension and diastolic blood pressure is generally above 120 to 130 mmHg.\textsuperscript{8} Although the hypertensive crisis is a frequently seen problem in the emergency departments, effect of treatment of hypertensive crisis on P wave dispersion is not known.\textsuperscript{9,10}

Sodium nitroprusside (NIP) and nitroglycerin (NIT) are among the frequently selected agents for acute reduction of blood pressure. Nitroprusside is very potent arteriolar vasodilator, with an almost instantaneous onset and withdrawal of action that allows minute-by-minute titration. Although nitrates are predominantly considered for venodilatation, higher doses produce arterial dilatation and therefore reduce systemic vascular resistance and ventricular impedance. However, the blood pressure response to NIT is not as predictable as with NIP.\textsuperscript{10-12} Although many clinical trials have demonstrated the effectiveness of NIP and NIT for the treatment of hypertensive crisis, to our knowledge, there are no data available concerning their effectiveness on P wave dispersion at hypertensive crises.

Therefore, the objective of this study was to evaluate PWD during hypertensive crisis and to compare the outcomes of intravenous NIP and NIT treatments on PWD.

**MATERIAL AND METHODS**

**Study group:** The study group included 37 patients admitted to our emergency department with hypertensive urgency. All the patients were judged to have essential hypertension on the basis of history, physical examination and laboratory findings. The hypertensive urgency was defined as a severe elevation in blood pressure (a systolic blood pressure greater than 180 mmHg and/or a diastolic blood pressure greater than 120 to 130 mmHg) without evidence of progressive end-organ deterioration such as coronary ischemia, stroke and acute renal failure. All patients were hemodynamically stable and in normal sinus rhythm.

The patients were randomly assigned to treatment with NIT or NIP. All patients gave written informed consent for the study, which had been approved by the hospital ethical committee.

**Blood pressure measurements:** Heart rate, systolic blood pressure and diastolic blood pressure were measured with the patient in a sitting position. Blood pressure was measured from both arms with a manual sphygmomanometer. If a difference in blood pressure was detected between two arms (>5 mmHg for diastolic blood pressure and >10 mmHg for systolic blood pressure), the arm with the highest blood pressure was used for subsequent measurements. Systolic blood pressure and diastolic blood pressure were recorded at Korotkoff phases I and V. Blood pressure was taken two times in every measurement. The average of two blood pressures was reported. Blood pressures were measured at 15 minute intervals after initiation of treatment.

**Electrocardiographic evaluation:** ECGs were obtained from all patients at 10 mm/mV amplitude and speed of 50 mm/sec with 12 lead at resting (Marquette Case Hellige Medical System, Cardiosmart, Hellige Instrument Company, Freiburg, Germany). The measurements of the P wave durations were performed manually by two investigators without knowledge of patient assignment using calipers and magnifying lens. P wave duration; the onset of P-wave was defined as the junction between the isoelectric line and the beginning of P-wave deflection and the offset of P-wave as the junction between the end of P-wave deflection and the isoelectric line. P-wave dispersion was calculated as the difference between the longest and the shortest measured P-wave durations.

**Drug administration:** Patients were randomized to receive an infusion of NIT or NIP. After the...
first electrocardiographic examination, NIT was infused at a starting dose of 10 μg/min or NIP was infused at 0.25 μg/kg/min. The infusion rate was increased with close blood pressure monitoring and adjusted to decrease mean arterial pressure by 25%. This blood pressure reduction was obtained within two hours in all patients. The maximum dose was 1 μg/kg/min for NIP and 50 μg/min for NIT. After post-treatment electrocardiography, the drug infusion was stopped and treatment was continued with proper oral antihypertensive agents.

Statistical analysis: An SPSS package (version 10.0) was used for statistical analysis. All data were expressed as mean ± standard deviation. Differences in mean values between groups were assessed using the Student t test and for variables without normal distribution with Mann-Whitney’s U-test and Chi-square test for qualitative variables. The changes of parameters after treatment were compared with paired t-tests. A two-tailed p-value of less than 0.05 was considered significant.

RESULTS

Baseline characteristics of patients were given in Table 1. There were no differences between two groups in baseline demographic and electrocardiographic parameters (Pmax, Pmin and PWD). The drugs were well tolerated and no patient experienced significant side effects.

Heart rate, systolic and diastolic blood pressure, and electrocardiographic parameters were summarized in Table 2. Both with NIP and NIT treatments systolic/diastolic blood pressures (199.8±16.8/119.2±13.4 mmHg to 154.6±11–7/90.8±5.3 mmHg, p<0.001 vs. 196.4±18/114.7±9.5 mmHg to 159.8±11.9/92.3±7.1 mmHg, p<0.001), mean arterial pressure (MAP) (146.1±12.5 mmHg to 112.1±5.4 mmHg, p<0.001 vs. 141.9±10.4

<table>
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<tr>
<th>TABLE 1: Baseline characteristics of patients.</th>
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<tr>
<td>Nitroprusside (n=19)</td>
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<td>Age (years)</td>
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<td>Gender (Male/Female)</td>
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<td>Therapy and duration of hypertension (years)</td>
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<td>Heart rate (bpm)</td>
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<td>Systolic blood pressure (mmHg)</td>
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<td>P wave maximum (msec)</td>
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<td>P wave dispersion (msec)</td>
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<th>TABLE 2: Effects of NIP and NIT treatments on P wave duration parameters.</th>
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<tr>
<td>Before</td>
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<td>Heart rate (bpm)</td>
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<td>Systolic BP (mmHg)</td>
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<td>Diastolic BP (mmHg)</td>
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<td>MAP (mmHg)</td>
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<td>P wave minimum (msec)</td>
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<td>P wave dispersion (msec)</td>
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BP: blood pressure, MAP: mean arterial pressure.
mmHg to 114.8±7.6 mmHg, p<0.001), Pmax (108.9±11.0 msec to 96.8±12.0 msec, p=0.001 vs. 108.3±12.5 msec to 97.8±11.1 msec, p<0.001) and PWD (68.4±16.8 msec to 54.7±11.7 msec, p<0.001 vs. 67.8±16.6 msec to 59.4±10.0 msec, p=0.039) were decreased. No significant changes were observed in heart rate in both groups. Pmin was not statistically affected by these agents. There were no significant differences between NIT and NIP groups in respect to after treatment values of blood pressures and P wave values (p>0.05 for all comparisons).

**DISCUSSION**

It was demonstrated that both NIT and NIP therapies significantly decreased blood pressure and improved P wave dispersion parameters in patients with hypertensive urgency in this study. However, no differences were observed between the two agents.

Hypertension is one of the most common causes of AF. Myocardial fibrosis and impairment in left ventricle compliance and relaxation caused by hypertension result in electrophysiological and structural heterogenesis of atrial myocardium via increasing intra-atrial pressure, diameter of left atrium and atrial hypertrophy. These morphological changes occurred in left atrium cause development of non-homogeneous fibrosis of left atrial wall, alteration of geometry of atrial fibrils, inhomogeneous and isotropic propagation of sinus impulses, which are considered to play a major role at onset of atrial re-entry. These changes are reflected as an increase in the length of PWD on ECG recording.1-4

P wave dispersion is frequently increased in hypertensive patients. Currently it has been reported that P-wave dispersion is a non-invasive predictor for estimation of atrial fibrillation risk with 12 lead ECG recording.13,14 Thus, any improvement in treatment of hypertension is an important goal for treatment of P wave dispersion by correcting atrial conduction and consequently AF. Stafford et al.15 and Steinberg et al.16 have demonstrated that P wave dispersion can be corrected by improving the impairment in atrial conduction using drug therapy in chronic hypertensive patients. Similarly, Song et al.17 found a significant correlation between average P wave duration and amount of diuresis. It was speculated that the reduction in P wave duration was caused by the reduction of preload in this study. However, there is no study evaluating the sudden changes that may occur after acute treatment of hypertensive crisis on PWD in literature.

Hypertensive crisis is relatively rare and defined as such only when there is an immediate threat to the integrity of cardiovascular system. Patients with hypertensive crisis require an immediate reduction in blood pressure to avoid further end-organ damage by means of intravenous therapy in an intensive care setting. Furthermore, the maintenance of sinus rhythm and atrial contractions is so important for the stability of cardiac output due to increased end-diastolic pressure in hypertensive crisis. If atrial fibrillation occurs, the loss of atrial contraction, which is responsible for up to 40% of atrial output, worsens patient’s clinic. Thus, rapid interventions are crucial to prevent diastolic heart failure and end-organ damage in hypertensive urgency settings. In the light of this information, we aimed to examine PWD, a predictor of AF development, during and after treatment of hypertensive crisis. After the achievement of blood pressure reduction PWD decreased with both NIP and NIT treatments (P<0.01).

The major hemodynamic effect of nitrates is to evoke a reduction in ventricular filling pressure and volume by increasing venous capacitance through venodilatation. Although these agents are predominantly considered for venodilatation, higher doses of nitrates produce arterial dilatation and therefore reduce systemic vascular resistance and ventricular impedance. NIP is also a powerful venous and arterial vasodilator with potent afterload reducing properties. As with NIT, NIP causes preload reduction, diminishing heightened venous tone and increasing venous capacitance.17

The reduction of P wave dispersion via drugs can be explained by improvement of intra-atrial conduction, which was under pressure of hemodynamic changes resulted from acutely decreasing tension. Supporting our data, Villani et al.18 reported that there were significant reductions in both
pulmonary capillary wedge pressure and P wave duration by administration of NIT and the signal-average P wave duration was more closely related to left atrial pressure than left atrial diameter. The results of Villani et al.\textsuperscript{18} and our findings suggest that atrial stretch and increased atrial pressure could be responsible for increased P wave duration, which suggest that atrial stretch is a factor in atrial fibrillation.

Yıldırırt et al.\textsuperscript{19} and our previous study\textsuperscript{7} with these drugs has also showed the significant improvement in diastolic dysfunction parameters with sudden decrease in pressure. The administration of these drugs to patients with hypertensive urgency may decrease the blood pressure and LA stretch and consequently improve diastolic function and prolong P wave duration and dispersion as seen in the present study.

**CONCLUSION**

This study has shown that PWD was increased during hypertensive crisis and both NIP and NIT treatments significantly improved PWD, but no differences were observed between two agents. Reduction of blood pressure and consequent decrease in LA stretch is probably responsible for improvement in P wave dispersion.

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**REFERENCES**