Hypertension and arrhythmia: blood pressure control and beyond

A. Yildirir1, M. K. Batur2 and A. Oto3

1 Başkent University, 2 Adana Numune Hospital and 3 Hacettepe University Cardiology Departments, Turkey

Arrhythmias are common problems in hypertensive patients. The presence and complexity of both supraventricular and ventricular arrhythmias may influence morbidity, mortality, as well as the quality of life of patients. Diastolic dysfunction of the left ventricle, left atrial size and function, and left ventricular hypertrophy have been suggested as the underlying risk factors for supraventricular and ventricular arrhythmias in hypertensives. Recently, several non-invasive electrocardiographic parameters have been defined and widely investigated to identify the hypertensive patient at risk for the development of arrhythmias. These parameters include signal averaged analysis of P wave, QT interval dispersion, heart rate variability, ventricular late potentials and T wave morphology analysis. The aim of this review was to evaluate the relationships between high blood pressure, ventricular and supraventricular arrhythmias, relevant non-invasive cardiac parameters for risk assessment in hypertensive patients and the effects of blood pressure control.

(Europace 2002; 4: 175–182)
© 2002 The European Society of Cardiology. Published by Elsevier Science Ltd. All rights reserved.

Key Words: Hypertension, left ventricular hypertrophy, arrhythmias, risk assessment.

Introduction

Hypertension is a major public health problem due to its high prevalence and complications. It is an important risk factor for sudden cardiac death and the incidence increases with rises in blood pressure1.1

Arrhythmias in hypertensive patients have received great attention. The presence and the complexity of both supraventricular and ventricular arrhythmias have been shown to influence the morbidity, mortality and the quality of life of hypertensive patients2–4. These arrhythmias have a wide spectrum ranging from supraventricular premature beats to atrial fibrillation (AF) and from ventricular premature complexes to ventricular tachycardia or sudden cardiac death. In some cases the patients may complain of palpitation or irregular heart beats, whereas others are totally asymptomatic and an ambulatory electrocardiogram is usually needed to reveal the underlying rhythm problem.

Recently, several non-invasive electrocardiographic parameters have been defined and widely investigated to identify the hypertensive patient at risk for the development of arrhythmia (Table 1). The relationships between high blood pressure, ventricular and supraventricular arrhythmias, relevant non-invasive electrocardiographic parameters for risk assessment and the effects of blood pressure control on these parameters are the subjects of this review.

High blood pressure and supraventricular arrhythmias

Atrial fibrillation is one of the most frequent supraventricular arrhythmias in hypertensive patients. For
men and women the risk of AF increases by 1.5 and 1.4 fold, respectively, in the presence of hypertension and because of its high prevalence, hypertension is responsible for more AF in the population (14%) than any other risk factor[5]. Furthermore, AF is a well-defined predictor of stroke and the risk is increased up to five fold in the presence of AF. It is also associated with 1.5- to 1.9-fold mortality risk after adjustment for the associated cardiovascular conditions[5,6]. The relationship of atrial ectopic beats to morbidity and mortality is less well-defined. However, a recent study indicated a significant association between frequent atrial ectopic beats and stroke in hypertensive men (relative risk=2.5) after adjustments for potential confounders[7].

An increased incidence of impairment of left ventricular diastolic filling and left atrial enlargement were noted in hypertensive patients[8]. In a population based study, the echocardiographic predictors of non-rheumatic AF were defined as left atrial enlargement, reduced left ventricular fractional shortening, and increased left ventricular wall thickness. These echocardiographic features offered prognostic information in addition to the traditional clinical risk factors[5]. A clinical study investigating the predictive parameters for the onset of AF in patients with essential hypertension indicated that those who developed AF had higher mean systolic diurnal and nocturnal blood pressures on ambulatory blood pressure monitoring than patients who did not develop AF despite the similarities in the clinical blood pressure readings[9]. Furthermore, in the same study increases in left atrial dimension and left ventricular mass, prolongation of the maximum duration and dispersion of the P wave and reduced A-wave velocity were also defined as predictors for the onset of AF. In another study the incidence of supraventricular premature beats was observed to be higher during the peaks of systolic blood pressure and heart rate values in hypertensive patients without left ventricular hypertrophy (LVH)[10].

Patients with no systolic blood pressure reduction during night time, i.e. non-dippers, had significantly larger left atrial dimension, left ventricular mass index, as well as, a larger number of total supraventricular and ventricular ectopic beats during daytime compared with dippers[11]. However, contradictory results, reporting similar number of premature atrial and ventricular contractions per h in dipper and non-dipper hypertensive patients also exist[12].

We investigated the relationships between echocardiographic left ventricular diastolic function parameters and the frequency of supraventricular premature beats in 89 patients with uncontrolled hypertension[13]. Our results indicated that the frequency of supraventricular premature beats were positively correlated with isovolumic relaxation time and E wave deceleration time and negatively correlated with peak E velocity/peak A wave velocity ratio (all P<0.01). Furthermore, nine out of 89 hypertensive patients (10%) had paroxysms of AF on 24-h Holter electrocardiogram.

Since the occurrence of AF is associated with increased morbidity and mortality in hypertensive patients, the identification of the patients at risk for the development of AF is crucial. Signal averaged P wave analysis has been suggested to be useful for the risk assessment of hypertensive patients. A study performed by our group evaluated the effects of echocardiographically measured diastolic function on signal averaged P wave duration and the incidence of paroxysmal AF in 24 hypertensive patients and 14 healthy subjects[14]. After 10 months of follow-up four out of 13 patients (31%) with diastolic dysfunction and one out of 11 patients (9%) with normal diastolic function developed paroxysms of AF, whereas no episodes of AF were observed in the controls. In addition, the filtered P wave duration was longer in hypertensive patients with diastolic dysfunction compared with those with normal diastolic function. Our results indicated that, diastolic dysfunction of the left ventricle was an important predictor of AF in hypertensive patients and signal averaged P wave could be a helpful tool to predict the prevalence of diastolic dysfunction.

A similar study by Dilaveris et al.[15] confirmed our findings indicating that hypertensive patients at risk for paroxysmal AF could be detected in sinus rhythm by computer-assisted electrocardiographic P-wave analysis.

P-wave dispersion has recently been suggested as a new marker for the prediction of AF[16]. A recent study comparing the P wave dispersion between 44 hypertensive patients with a history of paroxysmal AF and 50 hypertensive patients without AF showed a significantly greater dispersion of P wave from the 12-lead ECG in

Table 1: Non-invasive electrocardiographic risk assessment markers for arrhythmia prediction in hypertensive patients

<table>
<thead>
<tr>
<th>Supraventricular arrhythmia</th>
<th>P wave duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT interval dispersion</td>
<td>QT interval dynamicity</td>
</tr>
<tr>
<td>Late potentials</td>
<td>Heart rate variability</td>
</tr>
<tr>
<td>T wave morphology analysis (T wave duration/angle)</td>
<td>T wave alternans</td>
</tr>
</tbody>
</table>

Europace, Vol. 4, April 2002
those with AF\cite{17}. However, more data are needed for further evaluation of the predictive value of P-wave dispersion in the development of AF in hypertensive patients with sinus rhythm.

**High blood pressure and ventricular arrhythmias**

A variety of ventricular arrhythmias can be observed in hypertensive patients being mostly asymptomatic. In our study on 89 hypertensive patients, ventricular premature beats>10/h were observed in 24 patients (27%) on Holter monitoring. Meanwhile, the prevalence of bigeminy, trigeminy, couplets and non-sustained ventricular tachycardia were detected in nine patients (10%), seven patients (8%), 12 patients (13%) and three patients (3%), respectively (unpublished data by the authors).

The association between hypertension, ventricular arrhythmias and cardiac mortality has been well-defined. In an epidemiological survey conducted in France on 19600 men and 10800 women the presence of ventricular premature contractions increased the risk of cardiac death by a factor of 2.2 in hypertensive patients even in the absence of coronary artery disease\cite{1}.

The Framingham Study also indicated that the presence of ventricular premature contractions increased the risk of sudden death by a factor of 2.9 in men and 1.6 in women\cite{21}.

The development of left ventricular hypertrophy (LVH) in hypertensive patients appears to be the main link between hypertension and ventricular arrhythmias. A large proportion of hypertensive individuals develop LVH, which initially is an adaptive event. However, beyond a critical value it significantly increases the morbidity and mortality of the patients, particularly of sudden cardiac death\cite{19,20}.

The first report on the increased incidence of ventricular arrhythmias in hypertensive patients with LVH was published by Messerli et al.\cite{21}. They found that hypertensive patients with electrocardiographically determined LVH had a significantly higher incidence of ventricular premature beats and ventricular arrhythmias during ambulatory monitoring than hypertensive patients without LVH or normotensive subjects. In another study, McLenachan et al.\cite{22} demonstrated a strong correlation between hypotension and the incidence and complexity of ventricular arrhythmias. A similar direct relationship between ventricular arrhythmias and cardiac events in hypertensive patients with LVH was reported by Zehender et al.\cite{23} in a 3-year follow-up study. In these earlier studies, electrocardiographically established criteria were used for the diagnosis of LVH. However, in daily clinical practice, the presence of electrocardiographic criteria of LVH occurs in only a small proportion (5–10%) of the total hypertensive population and it has been shown that echocardiography has greater value in the determination of LVH\cite{24}.

In the Framingham Study, the presence of LVH, as demonstrated by electrocardiography and echocardiography, was associated with an increased risk of death in asymptomatic subjects\cite{25,26}. A graded relationship between the frequency and complexity of ventricular arrhythmias and LVH was reported by Ghali et al.\cite{27}, who also defined the presence of LVH by both electrocardiographic and echocardiographic criteria. However, there are also reports indicating that the prevalence and severity of ventricular arrhythmias were not affected by the existence of echocardiographic evidence of mild to moderate LVH\cite{3,28}. These findings suggest that the degree of hypertropy may be more important than its presence in arrhythmogenesis in hypertensive patients.

The circadian rhythm of high blood pressure, i.e. dipper and non-dipper patterns, could play a crucial role in arrhythmogenesis. A recent study by Schillaci et al.\cite{29}, identified the non-dipping pattern, persistently elevated blood pressures over 24 h, as an independent predictor of the frequency and complexity of ventricular arrhythmias in untreated hypertensive patients.

**Non-invasive risk assessment in hypertensive patients**

The traditional tools used in the risk assessment of the hypertensive patients are standard electrocardiography, Holter electrocardiogram and echocardiography. However, recently other non-invasive markers have been defined and widely investigated for the risk stratification of hypertensive patients. These parameters include QT interval dispersion (QTd), QT interval dynamicity, ventricular late potentials (LP), heart rate variability (HRV) and T wave morphology analysis.

**QT interval dispersion and dynamicity**

QT interval dispersion is the difference between maximal and minimal QT intervals on a 12-lead surface electrocardiogram\cite{30}. It is thought to represent the degree of repolarization inhomogeneity in the heart with abnormal values predicting a high rate of malignant arrhythmias and sudden cardiac death\cite{31,32}.

Galinier et al.\cite{33} evaluated the prognostic value of multiple arrhythmogenic risk markers in hypertensive patients and identified the age \( \geq 65 \) years, electrocardiographic strain pattern, non-sustained ventricular tachycardia and QTd\( >80 \) ms as indicators of cardiac mortality. However, on multivariate analysis only non-sustained ventricular tachycardia had a prognostic value. The association between QTd and left ventricular mass in hypertensive patients was investigated by Ichikhan et al.\cite{34}, who reported a significantly increased QTd in patients with LVH compared with those without LVH. Furthermore, in the same study QTd was increased in parallel with the increase in LV mass.

Kulan et al.\cite{35} investigated the arrhythmogenic effect of LVH and corrected QT interval (QTc) prolongation in 68 hypertensive patients with LVH and 30 healthy
subjects. In patients with LVH, the incidence of complex ventricular arrhythmias was between two- and five-fold higher compared with patients without LVH and with controls, respectively. The QTc duration was positively correlated with left ventricular mass index and left ventricular internal diastolic dimension with the highest QTc intervals detected in patients with LVH and complex ventricular arrhythmias. Their results suggested the QTc prolongation could be a good marker for the increased risk of arrhythmias in hypertensive patients. Similarly, Saadeh et al.\[37\] reported a strong correlation between the prevalence of complex ventricular arrhythmias and QTc dispersion in untreated newly presenting hypertensive patients. The pattern of 24-h blood pressure variation might influence the QT interval and dispersion parameters. A recent study investigating the relationships between QTd, left ventricular mass index and circadian rhythm of blood pressure control in 62 hypertensive patients indicated a significantly prolonged maximum QTc interval and QTc dispersion values, as well as a tendency to higher left ventricular mass index in non-dippers compared with dippers\[38\].

In normal subjects QT interval shows a delayed adaptation to sudden changes in heart rate\[39\]. Abnormalities in the rate-dependent adaptation of the QT interval, i.e. increased QT interval dynamicity, may facilitate the development of ventricular arrhythmias\[40\]. There is a paucity of data related to the association between hypertension and QT interval dynamicity. A study investigating the QT interval dynamics in hypertensive patients with or without LVH indicated that the QT interval response to changes in RR interval is rapid and exaggerated in the presence of LVH\[41\]. This finding may be one of the explanations for the increased vulnerability to serious ventricular arrhythmias in hypertensive patients with LVH.

In summary, based on the available data, hypertensive patients have increased QTd values compared with normotensives, and this increases further in the presence of LVH. A good correlation has been demonstrated between increased QTd values and ventricular arrhythmias in hypertensive patients. On the other hand, the limitations of the method itself with its intra- and inter-observer variability need to be considered in the evaluation of QTd data.

QT interval dynamicity is a rather new, but a promising technique in the arrhythmia area. However, the clinical significance of QT dynamicity in hypertensive patients needs to be clarified.

**Late potentials**

Late potentials are high frequency low amplitude signals following the QRS complex within the ST segment, which are considered to originate from myocardial scar areas. These fibrotic areas surrounded by normal tissue play an important role in the genesis of re-entrant circuits and consequent ventricular arrhythmias\[42\]. In hypertensive patients, even in the absence of coronary artery disease, subendocardial scar formation can occur due to coronary microangiopathy or LVH and predispose to ventricular arrhythmias\[43\]. Several studies investigated the prevalence and the clinical significance of LPs in hypertensive patients.

Brune et al.\[44\] evaluated the prevalence of LPs in 17 hypertensive and 20 normotensive patients by signal averaging. Late potentials were found to be more common in hypertensives than normotensives suggesting the idea that increased arterial pressure leads to LVH and the hypertrophy to disorganized ventricular activation. This idea has been confirmed by Vester et al.\[45\] who indicated an increased prevalence of LPs in hypertensive patients with echocardiographic LVH compared with those without LVH. In addition, a linear correlation was observed between LVH and the incidence and severity of developed ventricular arrhythmias. In another study, Vardas et al.\[46\] investigated the prevalence of LP’s and ventricular arrhythmias in hypertensive patients without electrocardiographic signs of hypertrophy. Their results indicated that the higher prevalence of ventricular arrhythmias was not related to the LVH defined by echocardiography but was correlated with the existence of ventricular LP.

The relationships between ventricular filling patterns, signal averaged electrocardiography and 24 h Holter monitoring were investigated by Palatini et al.\[47\] on 107 hypertensive subjects with echocardiographic signs of LVH and 70 normotensive controls. In this study, the LP positivity was 25% for the hypertensive subjects compared with 6% for the controls and the hypertensive patients with LP’s had a higher prevalence of ventricular tachycardia than those without LP’s (33% vs 13%).

The higher prevalence of LPs may serve as a marker of an arrhythmogenic substrate in hypertensive patients. However there are many drawbacks regarding the value of LPs in the hypertensive patients. First of all the studies on LPs in hypertensive patients have all been small scale usually with short follow-up. Much more importantly, there is no study with power to show prognostic significance of LPs in hypertensives.

**Heart rate variability**

There is considerable evidence to suggest that the autonomic nervous system plays an important role in blood pressure regulation and the development of hypertension\[48,49\]. Since changes in blood pressure may affect autonomic tone and vice versa, baroreflex sensitivity and HRV measures are expected to differ in hypertensive subjects compared with normotensives. Framingham data indicated a reduced HRV in men and women with systemic hypertension\[50\]. In addition, normotensive men with lower HRV were associated with a greater risk of developing hypertension supportive for the hypothesis that autonomic dysregulation is present in an early stage of essential hypertension. Contrary to the similar HRV parameters in hypertensive men irrespective of the presence of LVH\[51\], Martini et al.\[52\] reported reduced HRV measures in borderline hypertensive patients with LVH compared with normotensive subjects and those without LVH. Furthermore, the severity of chronic
essential hypertension seemed to be related to the severity of impairment of cardiac autonomic function[53].

Rizzo et al.[54] compared the HRV parameters of 20 elderly hypertensive patients with nocturnal blood pressure falls with 20 of those without blood pressure falls. Their results indicated a reduction in autonomic nervous system activity in non-dipper hypertensives compared with dippers. Similar results have also been reported by Nakano et al.[55], who indicated a higher daytime low frequency/high frequency ratio and a lower night-time high frequency component in non-dipper patients with essential hypertension.

The data on HRV in hypertensive patients are limited. A reduced autonomic nervous system activity has been demonstrated in hypertensive patients compared with controls, which seems to be more prominent in non-dippers. However, the positive predictive value of changes in HRV parameters has still to be proven with prospective studies.

Heart rate turbulence has recently been suggested as a new non-invasive risk marker to assess the effect of the autonomic nervous system[56]. However, data on the prognostic significance of heart rate turbulence in hypertensive patients are lacking.

**T wave morphology analysis/T wave alternans**

The T-loop morphology analysis, in other words changes in T wave amplitude and angle, is a novel method aimed at quantifying ventricular depolarization and repolarization characteristics. Dilaveris et al[57] reported the T wave amplitude as the only marker among QTd and other T-loop parameters, which differed significantly between hypertensive patients and controls. Another recent study by the same author indicated the increased QRS-T angle, the angle between the direction of ventricular depolarization and repolarization, as a sensitive marker of repolarization alterations in patients with systemic hypertension[66].

The analysis of T wave alternans (TWA) is another new diagnostic tool for identification of patients with an increased risk of ventricular tachyarrhythmia or sudden cardiac death[59]. However, there are very limited data on the significance of TWA in hypertension. A recent study by Hennersdorf et al.[60] investigated the value of TWA in hypertension and reported increased microvolt-level TWA in arterial hypertension, which was more pronounced in the presence of LVH. However, no prognostic data are yet available.

**Blood pressure control and arrhythmias**

Since the presence of LVH in hypertensive patients is a risk factor for the development of ventricular arrhythmias, achievement of regression of LVH must be a challenge to prevent sudden death. Despite the fact that regression of LVH is the long-term effect of almost all of the antihypertensive medications, the drugs may differ with respect to their potential for arrhythmia control.

Diuretics have been extensively studied due to the potential for causing electrolyte disturbances and arrhythmias. Although some studies indicated worsening of arrhythmias with diuretic therapy and concomitant hypocalaemia, others revealed no change or a trend toward improvement[61–65]. Among the group of diuretics spironolactone deserves to be mentioned separately based on it is potential for causing reduction in ventricular arrhythmias and improvement of HRV parameters especially in the presence of systolic dysfunction[66,67].

Antihypertensives may affect the haemodynamic predictors of arrhythmias other than LVH, as a part of their antiarrhythmogenic potential. Gottdiener et al.[68] indicated that, the chronic use of different classes of antihypertensive medications; atenolol, captopril, clonidine, diltiazem, hydrochlorothiazide and prazosin, were all effective in reducing the left atrial size in mild to moderate hypertension. This reduction may be a contributing factor to their antiarrhythmogenic effect.

The control of blood pressure with antihypertensive medications may improve the non-invasive electrocardiographic parameters besides the control of arrhythmias and regression of LVH. The prolongation of QTd in association with an increased left ventricular mass index and systolic blood pressure in hypertensive patients was significantly reduced by a 6-month course of antihypertensive therapy with ramipril and felodipine[69]. In a similar study, the regression of LVH by angiotensin-converting enzyme (ACE) inhibitors or calcium antagonists is associated with a significant reduction in QTd[70]. The QT shortening effect of antihypertensive medications appears to be consistent during long-term follow-up[71]. The direct effect of certain antihypertensive medications, i.e. angiotensin type 1 receptor antagonists, on autonomic nervous system and myocardium has also been speculated to be responsible for the improvement in QTd in hypertensive patients[72].

There is limited data related to the effects of blood pressure control on ventricular LPs. The normalization of LP parameters is generally expected in association with the reduction of left ventricular mass. However, long-term therapy is required to observe such a favourable effect. A single study evaluating a 4-week course of hydrochlorothiazide therapy on signal-averaged electrocardiographic variables indicated no alteration of LP parameters with therapy[64]. However, more powerful studies with longer duration of follow-up are required to reach a conclusion.

The effect of blood pressure control on HRV parameters may be related to the properties of the antihypertensive agent. A study on two different calcium channel blockers, verapamil and felodipine, indicated that, only verapamil significantly decreased the sympathetic predominance and had favourable effects on other parameters of cardiac autonomic control despite comparable anti-hypertensive effects[73]. Similar to verapamil, diltiazem retard also had favourable effects on heart rate and the autonomic nervous system[74]. A recent study or four different antihypertensive medications, the beta-blocking agent atenolol, the calcium antagonist isradipine, the diuretic hydrochlorothiazide and the
ACE inhibitor spirapril only atenolol had beneficial effects on heart rate and blood pressure variables\(^7\). Recently we conducted a prospective study to explore the effect of blood pressure control on the frequency of ventricular and supraventricular arrhythmias and related non-invasive cardiac parameters in 89 consecutive patients with essential hypertension\(^13,76\). Left ventricular diastolic function parameters, signal averaged filtered P-wave duration, frequency domain analysis of HRV and QTd values of the patients, as well as the frequency of ventricular and supraventricular arrhythmias were investigated before and after 15·8 weeks of blood pressure control with amlodipine or cilazapril. We observed significant decreases in the frequencies of ventricular and supraventricular ectopic beats after treatment (both \(P<0\cdot001\)). We also noted significant reductions in the signal averaged filtered P wave duration and low frequency/high frequency ratio in frequency domain analysis of HRV after blood pressure control has been achieved (both \(P<0\cdot001\)), whereas the reduction in QTd was not significant (\(P=0\cdot07\)). The control of blood pressure with antihypertensive therapy significantly decreased isovolumic relaxation time (\(P<0\cdot001\)) and E wave deceleration time (\(P<0\cdot01\)), whereas a significant increase was noted in the peak E velocity/peak A wave velocity ratio (\(P=0\cdot02\)). The effects of antihypertensive drugs on the studied electrocardiographic parameters and arrhythmia frequency were similar for both medications. We concluded that blood pressure control improved the 24-h frequency of ventricular/supraventricular arrhythmias and non-invasive electrocardiographic parameters without any antiarrhythmic drugs.

We also investigated the effect of blood pressure control on QT interval dynamicity in the subgroup of 53 hypertensive patients\(^7\). After 18·1 ± 4·7 weeks of anti-hypertensive therapy the QTapex/RR and QTend/RR slopes were reduced (\(P=0\cdot044\) and \(P=0\cdot066\)) in addition to the shortening of QT intervals (For QTc apex \(P=0\cdot001\), QTc end \(P=0\cdot006\)) (Fig. 1). Accordingly, the 24-hour frequency of ventricular premature beats was significantly reduced after blood pressure control (\(P<0\cdot001\)). However, QTd and left ventricular mass index were not significantly altered during the follow-up period (\(P>0\cdot05\)). Our results suggests that susceptibility to ventricular arrhythmias in patients with uncontrolled blood pressure may be related to the abnormal dynamics of ventricular repolarization rather than spatial repolarization abnormalities.

**Conclusion**

A significant association has been demonstrated between hypertension and arrhythmias. Diastolic dysfunction of the left ventricle, left atrial size and function, as well as LVH have been suggested as the underlying risk factors for supraventricular and ventricular arrhythmias in hypertensives. The presence of hypertension is a risk for sudden death and this risk is higher in those with LVH. The increased incidence of ventricular premature beats, complex ventricular arrhythmias and the presence of LVH are the major predictors of mortality in hypertensive patients. Regression of LVH is associated with reduced ventricular ectopy. Anti-arrhythmic drug therapy has been questioned in the setting of hypertension due to the accumulation of data about their side effects and pro-arrhythmic properties. These factors in fact may worsen the prognosis of patients instead of improving the life expectancy. On the other hand, the results of several studies including our own data suggest that optimal control of blood pressure by antihypertensive therapy is effective in arrhythmia control in many cases. Such an approach is associated with a reduction in both ventricular and supraventricular ectopy with less side effects compared with antiarrhythmic drugs.

**References**


Hypertension and arrhythmia 181


