Silent ST Depression and Cardiovascular End-Organ Damage in Newly Found, Older Hypertensives

Willem F. Terpstra, Johan F. May, Andries J. Smit, Pieter A. de Graeff, Frits H. Schuurman, Betty Meyboom-de Jong, Harry J.G.M. Crijns

Abstract—In hypertension, both reduced vascular supply and increased cardiac demand contribute to the development of (silent) myocardial ischemia. Our aim was to determine the prevalence of ST-segment depression and to analyze contributing factors in asymptomatic, previously untreated, older hypertensives. From a population survey, in 184 patients with mild hypertension (4 times systolic blood pressure \( \geq 160 \) mm Hg and/or diastolic blood pressure \( \geq 95 \) mm Hg), 60 to 75 years of age, cardiovascular end-organ damage was measured. Episodes of ST-segment depression were measured by 48-hour ambulatory Holter monitoring and were observed in 21 hypertensives (12\%). They showed a significantly higher combined far-wall intima-media thickness of carotid and femoral arteries and more arterial plaques as measured by B-mode ultrasound compared with hypertensives without ST depression (0.00098±0.00021 versus 0.00088±0.00016 mm and 5.2±3.7 versus 3.7±2.8 plaques, \( P<0.05 \), respectively), whereas left ventricular mass index was not different (111±18 versus 104±24 g/m\(^2\); \( P=0.18 \), respectively). In hypertensives with transient ST-segment depression, a significant relation was found between left ventricular mass and ischemic burden (\( r=0.51, P=0.02 \)). Approximately 1 of 8 unselected and previously untreated older hypertensives show asymptomatic ST-segment depression, suggestive of silent myocardial ischemia. These data suggest that vascular factors mainly determine the occurrence of ischemic ST-segment depression and cardiac factors determine the ischemic burden in older hypertensives. (*Hypertension. 2001;37:1083-1088.*)

Key Words: ischemia ■ hypertrophy, left ventricular ■ ventricular function, left ■ elderly ■ hypertension, secondary

Silent myocardial ischemia is defined as transient myocardial ischemia in the absence of angina pectoris or other cardiac symptoms. It is frequent among hypertensive patients with or without atherosclerotic coronary disease, even in the absence of epicardial coronary artery disease or left ventricular hypertrophy.\(^1,2\) Zehender et al\(^3\) observed transient ST-segment depression on Holter monitoring in 33\% of 150 middle-aged, ineffectively treated, hypertensive patients without manifest coronary artery disease. The majority of these episodes of transient myocardial ischemia was not associated with symptoms. Hedblad and Janzon\(^4\) reported a high incidence of ischemic ST depression of 41\% in treated hypertensive men with inadequate blood pressure control. Whether antihypertensive treatment influences the ST-segment depression in hypertension is debatable; without these drug treatment effects, the pathophysiology of ST-segment depression can be studied. To our knowledge, no study reported prevalence of asymptomatic ST-segment depression in a large group of never-treated, hypertensive patients.

Important vascular factors contributing to the occurrence of myocardial ischemia in hypertensive patients include atherosclerotic obstruction of the large coronary arteries and a reduced vasodilatory capacity of the coronary microcirculation caused by arteriolar hypertrophy and endothelial dysfunction. Another factor contributing to the occurrence of myocardial ischemia is the increased myocardial oxygen demand to supply the hypertrophic myocardium as it is seen in hypertension. Both vascular supply and cardiac demand factors reduce the capacity of the coronary circulation to increase myocardial blood flow during stress and therefore reduce the coronary blood flow reserve.

The objective of this study was to determine the prevalence and characteristics of transient ST-segment depression and its relation with cardiovascular end-organ damage as measured by left ventricular mass and large-vessel intima-media thickness (IMT) in previously untreated, older hypertensive patients.

**Methods**

**Patients**

Patients with previously untreated mild to moderate hypertension were recruited from a population survey performed in the north of...
lesions were obvious and the IMT was not measurable, lesions were considered plaques. Plaques were scored as a dichotomous variable in the 10 predefined arterial segments in both the near and far walls, and the score of plaques was expressed as the total amount of plaques of all arterial segments. The average plaque score of all arterial segments per patient was used for analysis. The measurement error of variation in the population studied was 0.03 mm for the mean maximum far-wall IMT. The primary end point of the B-mode ultrasound study was the combined mean far-wall IMT of the 10 segments of the carotid and femoral arteries.

Echocardiography
Echocardiographic examinations were recorded by a single trained operator. An Acuson XP-10 echocardiograph (Acuson Corp) with a 2.5- to 4.0-MHz transducer was used. Left ventricular dimensions were measured in 2D mode according to the Penn Convention in the left lateral decubitus position. Three recordings were made of the end-diastolic left ventricular wall (LVPW), interventricular septum (IVS), and left ventricular end-diastolic diameter (EDD). To estimate left ventricular mass, the cube formula of Devereux and Reichek was used.8 To calculate left ventricular mass index, the left ventricular mass was divided by body surface area. For classification of the 4 groups of left ventricular geometry (normal geometry, concentric remodeling, eccentric left ventricular hypertrophy [LVH], and concentric LVH), the following cutoff values were used. LVH was defined as left ventricular mass index ≥125 g/m²; increased relative wall thickness (RWT) was defined as RWT ≥0.45, as proposed by Koren et al.6 Systolic wall stress was determined according to the formula

$$\text{Systolic wall stress (10\,\text{dyne/m}^2)} = \frac{1.33 \cdot \text{SBP} \cdot \text{LVEDD}/2}{(\text{IVS} + 1)}.$$  

Statistical Analysis
Descriptive statistics and comparisons between groups were performed with the SPSS statistical package (SPSS for Windows, version 8.0, SPSS Inc). All descriptive data are expressed as mean±SD. Equality of variances between groups with or without transient ST-segment depression were tested with Levene’s test. The independent t test for equality of means was used to detect significant differences between the two groups as appropriate. In the case of categorical variables, the χ² test was used. Changes in heart rate within patients were tested by a paired t test. Univariate analysis of the associations between end-organ damage and parameters of ST-segment depression were performed with Pearson correlation coefficients after natural log transformation of the ST-segment parameters. To identify the determinants of episodes of ST-segment depression, logistic regression analysis was used. Clinical baseline variables included age, gender, body mass index, smoking, total cholesterol, HDL, LDL, non-insulin-dependent diabetes, SBP and DBP, pulse pressure, rate-pressure product, systolic wall stress, combined mean far-wall IMT, average plaque score, and left ventricular mass index.

Results
Patients
From the population survey, 1969 subjects had their blood pressure taken. A total of 1162 subjects had normal blood pressure, 421 subjects were treated with antihypertensive drugs, 214 subjects were identified as having untreated systolic hypertension, and 172 subjects were identified as having untreated diastolic hypertension. From these 386 untreated subjects, 184 fulfilled the inclusion and exclusion criteria and entered the study. Table 1 shows a comparison between hypertensive subjects with and those without ST-segment depression. The two groups differed with respect to body mass index and pulse pressure but not with respect to age, SBP and DBP, and lipid profile.
Prevalence of ST-Segment Depression

Recordings of Holter monitoring of adequate quality could be obtained from 178 patients (53% men), with a monitoring period of at least 46 hours. Of 6 patients, the quality of the Holter monitoring was inadequate for analysis. A total of 21 patients (12%) had a total of 97 episodes of significant ST-segment depression (median, 3.0 episodes per patient; range, 1 to 19). The prevalence was 9% in women and 13% in men. The duration of the single episodes was between 1.2 and 17.2 minutes (mean ± SD: 6.3 ± 3.3). The range of total ischemic burden was between 2.5 and 453 mm/min. All patients had sinus rhythm, and no patient was taking digitalis medication. No patient recorded symptoms such as angina pectoris, so all ischemic periods were symptomatic or at least not likely to be associated with definite symptoms of angina pectoris.

Circadian Variation in Ischemic Episodes and Relation to Heart Rate

Circadian variation in the frequency of ischemic episodes is shown in Figure 1. Ischemic episodes were nearly absent during the 6 night hours from 11 PM to 5 AM and had a peak during the morning hours after awakening between 7 AM and 11 AM and another less prominent peak during the evening between 7 PM and 10 PM. This circadian variation in ischemic episodes was not statistically significant (P=0.3).

The heart rate (± SD) during ST depression was significantly higher than the mean heart rate during 48 hours (92±22 versus 70±8 bpm, P<0.001, respectively). Mean heart rate at the onset of an ischemic episode was 92±22 bpm; mean heart rate at the peak of an ischemic episode was 106±18 bpm. A total of 17% of all episodes was accompanied by a reduction of heart rate, 25% of all episodes were accompanied by a small (1% to 15%) increase in heart rate, and 42% of all episodes were accompanied by a significant increase in heart rate (>15%). Three patients, with a total of 6 events (16%), had a heart rate at the onset of an ischemic event >130 bpm. No patient showed paroxysmal atrial fibrillation.

ST-Segment Depression and Vascular End-Organ Damage

Table 2 shows a comparison of cardiovascular end-organ damage in patients with or without ST-segment depression. Hypertensive patients with ST-segment depression showed an increased IMT, expressed as total mean far-wall IMT, and an increased frequency of plaques in the arterial segments studied. Within the group of hypertensives with ST-segment depression, the ischemic burden was not correlated with total

---

**Prevalence of ST-Segment Depression**

**Circadian Variation in Ischemic Episodes and Relation to Heart Rate**

**ST-Segment Depression and Vascular End-Organ Damage**
TABLE 2. Cardiovascular End-Organ Damage in Hypertensive Patients With and Those Without ST-Segment Depression

<table>
<thead>
<tr>
<th>End-Organ Damage</th>
<th>Patients With ST Depression</th>
<th>Patients Without ST Depression</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI, g/m²</td>
<td>111±18</td>
<td>104±24</td>
<td>0.177</td>
</tr>
<tr>
<td>RWT</td>
<td>0.49±0.07</td>
<td>0.48±0.05</td>
<td>0.304</td>
</tr>
<tr>
<td>IVS, m</td>
<td>0.0113±0.001</td>
<td>0.0111±0.0011</td>
<td>0.495</td>
</tr>
<tr>
<td>LVPW, m</td>
<td>0.0108±0.0008</td>
<td>0.0106±0.0009</td>
<td>0.209</td>
</tr>
<tr>
<td>LVEDD, m</td>
<td>0.0448±0.0050</td>
<td>0.00446±0.0047</td>
<td>0.872</td>
</tr>
<tr>
<td>Wall stress, 10⁻² dyne/m²</td>
<td>245±31</td>
<td>243±31</td>
<td>0.749</td>
</tr>
<tr>
<td>IMTTOT, m</td>
<td>0.00098±0.00021</td>
<td>0.00088±0.00016</td>
<td>0.014*</td>
</tr>
<tr>
<td>IMTAC, m</td>
<td>0.00099±0.00021</td>
<td>0.00092±0.00016</td>
<td>0.067</td>
</tr>
<tr>
<td>IMTAF, m</td>
<td>0.00096±0.00032</td>
<td>0.00084±0.00021</td>
<td>0.112</td>
</tr>
<tr>
<td>Average plaque score</td>
<td>5.2±3.7</td>
<td>3.7±2.8</td>
<td>0.025*</td>
</tr>
</tbody>
</table>

LVMI indicates left ventricular mass index; IMTAC, IMT of arteria carotis; IMTAF, IMT of arteria femoralis; and IMTTOT, IMT+IMTAF.

Values are expressed as mean±SD.

*Difference significant at P<0.05.

IMT (r=0.20, P=0.38), nor with the mean far-wall IMT of carotid (r=0.16, P=0.50) or femoral (r=0.16, P=0.08) artery segments, respectively. Moreover, the ischemic burden was also not associated with the total amount of plaques (r=0.22, P=0.33).

ST-Segment Depression and Cardiac End-Organ Damage

No significant difference was found in left ventricular dimensions and left ventricular mass index between the two groups. Rate-pressure product and the systolic wall stress were not different between the two groups. However, within the group of hypertensives with ST-segment depression, left ventricular mass was significantly correlated with the ischemic burden (r=0.51, P=0.02), as seen in Figure 2, and with the duration of ST-segment depression (r=0.51, P=0.02). In left ventricular geometry, the prevalence of hypertensives with ST-segment depression was not significantly different over the four groups. In the normal geometry group (n=49), 6 patients demonstrated ST-segment depression. In the concentric remodeling group (n=105), 11 patients demonstrated ST-segment depression. Finally, in the eccentric LVH group

(n=12) and the concentric LVH group (n=12), only 2 patients demonstrated ST-segment depression in each group.

Factors Contributing to Ischemic Episodes

From a variety of baseline characteristics, logistic regression analysis identified pulse pressure (P<0.05), body mass index (P<0.05), and combined mean far-wall IMT (P<0.05) as significant independent factors relating to the occurrence of ST-segment depression in these older hypertensive patients, as seen in Table 3.

Discussion

This study documents a lower-than-expected prevalence of ST-segment depression in older hypertensive patients: 9% in women and 13% in men. Among the studies concerning hypertensive patients free from clinical signs of coronary artery disease but after antihypertensive drug treatment, the prevalence was reported to vary in the range of 23% to 37%.13–15 In the study of Zehender et al,3 hypertensive patients were selected on the basis of ineffective or untolerated antihypertensive treatment, whereas 2 other studies at variance with ours included obese patients (type I diabetes).13–12 Trenkwalder et al13 found 37% prevalence of ST-segment depression in an even older but smaller (n=41) hypertensive group with a mean age of 79 years (range, 70 to 94 years). Our findings comply with the Cardioscreening Study, which documented a prevalence of 15% of ST-segment depression during 48 hours of Holter monitoring or exercise stress testing in 414 mild to moderate hypertensives, but this was found in a younger age group (50 to 70 years of age). The majority of ST-segment depression was observed during Holter monitoring (10.9%) and a minority during exercise stress testing (6.1%), but in contrast with our results, ST-segment depression was more common for women than for men (17.5% versus 5.2%, respectively), and only 31% of their patients were previously untreated.14 It should be remarked that all our patients were in a primary care setting and were previously untreated for hypertension. In the unselected, population-based Cardiovascular Health Study, the prevalence of ST-segment depression in ambulatory ECGs in a sample of 1511 men and women >65 years of age was also similar to ours, with 9% in women and 13% in men.15 However, this study also included patients with conditions known to interfere with the ST segment, such as previous myocardial infarction, angina pectoris, atrial fibrillation, and

Figure 2. Scatterplot shows correlation between ischemic burden and left ventricular mass in older hypertensive patients with episodes of ST-segment depression.
Digitalis medication. The majority of their participants was not hypertensive, and ambulatory monitoring was done for 24 hours instead of 48 hours, which has been shown to increase episodes of patients with asymptomatic ST-segment depression by ~30%.16

**Significance of ST-Segment Depression**

The observed ST-segment depression in our study was likely to reflect myocardial ischemia. Patients with specific ECG abnormalities at rest that could have influenced the ST segment had been excluded. Because left ventricular mass was not significantly different in the groups with or without ST-segment depression, repolarization abnormalities secondary to increased left ventricular mass are not likely to be responsible for the transient asymptomatic ST-segment depressions observed in our population. Moreover, only two of these mild-to-moderate hypertensive patients with ST-segment depression had concentric LVH, and the rest of the patients with ST-segment depression were not significantly different divided over the remaining left ventricular geometry groups. The finding of a high percentage of hypertensives with concentric remodeling and a relatively low percentage of hypertensives with LVH is similar to a previous study in primary care.17 Although caution should be used in the interpretation of episodes of transient ST-segment depression for patients free from clinical signs of coronary artery disease, the absence of ST-segment depression on resting ECG, the circadian pattern, and the relation with heart rate of the majority of the events observed are compatible with being episodes of silent myocardial ischemia.

**Mechanisms of Myocardial Ischemia**

This study shows that vascular remodeling induced by hypertension is an important determinant for silent ischemia. Therefore, the threshold for ischemia to develop depends mainly on vascular supply factors in older hypertensives, whereas cardiac demand factors mainly determine the extent of the ischemia. Both structural factors such as intima-media hypertrophy and arterial plaques and functional factors such as increased vasomotor tone caused by abnormal endothelial-derivation relaxation play a crucial role in the induction of transient myocardial ischemia.18,19 Although increased IMT as assessed by B-mode ultrasound imaging is only moderately correlated to the percentage of coronary stenosis as assessed by quantitative coronary arteriography,20 there is some evidence that increased IMT in older subjects is associated with asymptomatic ischemia, as evidenced by exercise ECG or exercise thallium scintigraphy.21 The observed difference in pulse pressure, positively related with increased IMT,22 partly supports the view of the vascular supply being the major determinant for the occurrence of ischemic ST-segment depression because pulse pressure can also be expressed as a determinant of myocardial oxygen demand.

Myocardial demand appears to be less important for the occurrence of ischemic ST-segment depression because left ventricular mass and LVH do not explain the occurrence of transient ST-segment depression in these older hypertensives. These findings are in agreement with those of previous studies that did not reveal any difference between left ventricular mass of hypertensives with and without ischemia.1,12-14,23 Moreover, the lower body mass index in the group with ST-segment depression further suggests that the occurrence of ischemic ST-segment depression is not primarily determined by cardiac demand because overweight has been reported to be associated with increased left ventricular mass.24 A possible explanation might be the reduced level of physical activity among overweight subjects. Our findings are supported by findings from the Cardiovascular Health Study, in which overweight was associated with a 33% reduction of likelihood of ischemic episodes after adjustment for other risk factors.15

The severity of myocardial ischemia, expressed as ischemic burden, is mainly determined by cardiac demand factors because increased myocardial mass rather than vascular abnormalities was associated with the extent of transient ST-segment depression. This might be associated with endothelial dysfunction because recently a significant relation was found between increased left ventricular mass and endothelial dysfunction in hypertensive patients.25 In contrary, the ischemic burden was not associated with structural vascular supply factors such as IMT and arterial plaques.

**Conclusions**

Our study provides strong evidence that in older hypertensives, the occurrence of ischemic ST-segment depression is determined mainly by vascular factors rather than left ventricular mass. Thus, supply markers such as IMT and arterial plaques as markers of generalized atherosclerosis are mainly responsible for the occurrence of ischemic ST-segment depression, and demand markers such as left ventricular mass are mainly responsible for the ischemic burden. The occurrence of silent ischemia during daily life has been found to be an independent predictor of cardiovascular events in hypertensive patients.4,26 Until now, the risks of myocardial infarction and cardiovascular death associated with the occurrence of silent ischemia in hypertensive patients are unknown. However, the early detection of silent myocardial ischemia by Holter monitoring might be useful for the identification of hypertensive patients who should be investigated further and considered for a more specific treatment.

**References**

6. de Groot E, Zwierdeman AH, van der Steen AF, Ackerstaff RG, Montauban van SA, Bom N, Lie KI, Bruschke AV. Variance components


9. Korn MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1991;114:345–352.


Silent ST Depression and Cardiovascular End-Organ Damage in Newly Found, Older Hypertensives
Willem F. Terpstra, Johan F. May, Andries J. Smit, Pieter A. de Graeff, Frits H. Schuurman, Betty Meyboom-de Jong and Harry J. G. M. Crijns

Hypertension. 2001;37:1083-1088
doi: 10.1161/01.HYP.37.4.1083

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/37/4/1083

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/