Ventricular Function by Radionuclide Ventriculography in Malignant Hypertension

Helio Bernardes Silva, Luiz Aparecido Bortolotto, Dante Marcelo A. Giorgi, Clovis de C. Frimm, Maria Clementina P. Giorgi, Giovanni Bellotti, and Fulvio Pileggi

Malignant hypertension is a unique and natural model for the study of abnormalities of left ventricular function due to arterial hypertension, because the development and regression of these abnormalities can be observed in a short period. Studies of ventricular function by radionuclide ventriculography, either before or after therapy, have not been previously reported in malignant hypertensive patients. We used this methodology to study left ventricular function in 17 malignant/accelerated hypertensive patients at the time of admission to the hospital and 3, 6, and 9 months after discharge. Seventy percent of patients (12 of 17) had symptoms of congestive heart failure at admission. We compared these data with those obtained in 12 normotensive subjects and 13 mild-to-moderate untreated hypertensive patients. Blood pressure of malignant hypertensive patients was 213±26/140±17 mm Hg at admission and 165±23/101±15 after 9 months of therapy. Radionuclide ventriculography at admission showed that peak filling rates of malignant hypertensive patients (2.13±0.21 end-diastolic volume [counts] [EDV]/sec) were significantly lower than those in normotensive subjects (2.40±0.41) and in mild-to-moderate hypertensive patients (2.46±0.21). In contrast, peak ejection rates were significantly higher in malignant hypertensive patients (3.44±0.38 EDV/sec) than in the two control groups (3.01±0.32 and 3.10±0.43, respectively). Ejection fractions were similar in the three groups of patients. After 9 months of therapy, peak filling rates of malignant hypertensive patients increased to 2.38±0.35 EDV/sec, whereas peak ejection rates decreased to 2.89±0.43 EDV/sec, both not significantly different from data in controls. Ejection fraction was not modified by treatment. We conclude that left ventricular systolic function is preserved in malignant hypertension, even in the presence of pulmonary congestion. The latter may be explained by diastolic dysfunction, as suggested by the measured abnormalities of left ventricular filling, and may occur despite a significant increase in left ventricular contractility. Changes in both ventricular filling and contractility are reversible by antihypertensive therapy.

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Malignant hypertension (MH) is a severe complication of untreated arterial hypertension often leading to heart failure, which, before the advent of effective antihypertensive therapy, was a common cause of death.1,2 The abnormalities of left ventricular function leading to heart failure in MH patients are not well understood. Because these abnormalities can develop and regress rapidly, MH represents a unique and natural model for the study of cardiac alterations due to arterial hypertension. Studies based on echocardiography, including preliminary data from our group,3 have shown impairment of diastolic function in benign4 and malignant5 hypertensive patients by demonstrating disproportionate thickening of the interventricular septum, delayed mitral valve opening, and impaired relaxation.

Studies of left ventricular function by radionuclide ventriculography (RV) have not been previously reported in MH patients. The objective of the present investigation was to use RV for 1) assessment of left ventricular function abnormalities in MH patients, 2) study of the effects of therapy, and 3) comparison of the observations to those obtained in a group of normotensive subjects and a group of patients with benign hypertension.

Methods

We studied 17 patients who had a diagnosis of malignant/accelerated hypertension based on World Health Organization criteria, that is, presence of retinal exudates and hemorrhages with or without papilledema. The groups consisted of 12 men and five women (10 whites, seven blacks), aged 30–48 years.
(mean, 41±6 years), with a history of arterial hypertension of 6 months’ to 20 years’ duration. Mean blood pressure at presentation was 213±32/140±25 mm Hg, heart rate was 90±12 beats per minute, and serum creatinine was 2.02±1.4 mg/dl. The main symptoms at admission were dyspnea (70%), headache (65%), and precordial pain (45%). Two thirds of the patients with heart failure at admission were in functional classes I (three of 12) and II (five of 12), and the remaining patients (four of 12) were in functional classes III and IV of the New York Heart Association classification.

Left ventricular function was analyzed by gated RV performed after intravenous administration of 20–25 mCi technetium-99m-labeled human serum albumin with the patient in a 40° left anterior oblique position. Gated scans were performed with an Ohio Nuclear-100 apparatus using a 64x64 matrix. Data were stored in a Sopha-500 computer. The acquisition, in wordmode, was obtained from 32 individual frames of 400,000 counts preset to blanket the RR interval with a threshold of 10% of RR. One beat was dropped after the occurrence of a premature ventricular complex. Image acquisition was performed with modified C-82 software, and diastolic and systolic left ventricular peak regions of interest were drawn by hand. Systolic left ventricular function was determined on the basis of ventricular ejection fraction and peak left ventricular ejection rate (PFR). Left ventricular diastolic function was determined on the basis of left ventricular peak filling rate (PFR) and time to peak filling rate (TPFR). Data were provided by the first derivative of the volume curve. The early peak negative deflection of the first derivative curve was defined as PFR, both of them computed as end-diastolic volume (counts) per second (EDV/sec). TPFR was defined as the time from end systole on the volume curve to the time of the late peak of the first derivative curve. TPFR was normalized to the RR interval to remove effects of changes in heart rate.

Two groups of patients were studied as controls: 1) Normotensive subjects: 12 normotensive subjects (eight men, four women) aged 29–50 years (mean, 41±6 years) with a mean blood pressure of 123±25/84±10 mm Hg and a mean heart rate of 72±17 beats per minute. 2) Hypertensive patients: 13 patients with mild-to-moderate hypertension (10 men, three women) aged 32–52 years (mean, 43±12 years) with a mean blood pressure of 172±12/104±14 mm Hg and a mean heart rate of 84±5 beats per minute.

Patients with MH were first studied 6 or 7 days after the institution of antihypertensive therapy and again at 3, 6, and 9 months after discharge. The patients received three or four drugs for adequate control of blood pressure, most commonly diuretics, β-adrenergic blockers, and angiotensin converting enzyme inhibitors (Table 1).

### Results

#### Left Ventricular Systolic Function

At admission, PER values were significantly higher in MH patients than in the two control groups (Table 2), whereas after 9 months of treatment, there were no differences in PER between patients with MH and controls (Table 2). The left ventricular ejection fraction observed in MH patients at admission did not differ from either control group and was not modified by treatment (Table 2).

#### Left Ventricular Diastolic Function

At admission, PFR values were lower, and TPFR values were longer in MH patients than in the group of normal subjects. When normalized by the RR interval, the TPFR values of MH patients were still longer than those of controls. After 9 months of treatment, PFR increased and TPFR decreased to values that did not differ significantly from those observed in the control groups (Table 2). At admission, blood pressure was significantly higher (213±26/140±17 mm Hg) in MH patients than in mild-to-moderate hypertensive patients (172±21/108±13 mm Hg). Heart rates were similar in the three groups (Figure 1). After 9 months of treatment, blood pressure of MH patients was significantly reduced to 165±23/101±15 mm Hg. Heart rates were also significantly reduced by therapy (Figure 1). These changes were followed by significant clinical improvement in all 12 MH patients with heart failure at admission; that is, after 9 months of treatment, nine of 12 patients were in functional class I, and three were in functional class II.

### Discussion

MH is a complication of arterial hypertension with clinical and physiological peculiarities that permit the study of arterial hypertension–induced abnormalities in target organs within a short period of time. Heart failure was responsible for the high mortality of MH.

**Table 1. Percent of Malignant Hypertensive Patients on Drug Therapy**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>3 Mo.</th>
<th>6 Mo.</th>
<th>9 Mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>73%</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>ACEI</td>
<td>73%</td>
<td>85%</td>
<td>70%</td>
</tr>
<tr>
<td>ACB</td>
<td>34%</td>
<td>41%</td>
<td>30%</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>18%</td>
<td>41%</td>
<td>47%</td>
</tr>
</tbody>
</table>

ACEI, angiotensin converting enzyme inhibitors; ACB, adrenergic central blockers.

**Statistical Analysis**

Data are reported as mean±SD. Data from MH patients were analyzed by the paired Student’s t test and by two-way analysis of variance. Comparisons among the three groups were carried out by analysis of variance and by the Bonferroni test. Statistical significance was defined at a value of p<0.05.
TABLE 2. Variables of Radionuclide Ventriculography

<table>
<thead>
<tr>
<th>Variable</th>
<th>Admission</th>
<th>3 Mo.</th>
<th>6 Mo.</th>
<th>9 Mo.</th>
<th>HT</th>
<th>NL</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>61±7</td>
<td>58±5</td>
<td>62±7</td>
<td>65±6</td>
<td>65±8</td>
<td>62±8</td>
</tr>
<tr>
<td>PER</td>
<td>3.44±0.38</td>
<td>2.71±0.51*</td>
<td>2.61±0.53*</td>
<td>2.89±0.43*</td>
<td>3.10±0.43†</td>
<td>3.01±0.32†</td>
</tr>
<tr>
<td>PFR</td>
<td>2.13±0.21</td>
<td>2.15±0.42</td>
<td>2.25±0.31</td>
<td>2.38±0.35*</td>
<td>2.36±0.21</td>
<td>2.40±0.41†</td>
</tr>
<tr>
<td>TPFR</td>
<td>218.8±23</td>
<td>198±23</td>
<td>196±24</td>
<td>193±37*</td>
<td>190±24†</td>
<td>178±35††</td>
</tr>
<tr>
<td>TPFPR</td>
<td>25±7</td>
<td>24±8</td>
<td>23±7</td>
<td>21±4</td>
<td>21±5†</td>
<td>19±4†</td>
</tr>
</tbody>
</table>

Values are mean±SD. MH, malignant hypertension; HT, hypertensive patients; NL, normotensive subjects; EF, ejection fraction; PER, peak ejection rate; PFR, peak filling rate; TPFR, time to peak filling rate.

* p<0.05, MH posttreatment vs. pretreatment values.
† p<0.05, MH admission values vs. control groups.
‡ p<0.05, MH end-of-treatment values vs. control groups.

Recent studies on MH patients have used echocardiographic analysis of systolic and diastolic function. Using computerized analysis of the M-mode echocardiogram, Shapiro et al investigated abnormalities of diastolic function in patients with MH and detected delayed mitral valve opening, reduced PFR, and outward endocardial motion during isovolumic relaxation. Although the Shapiro study compared data obtained in MH patients with those of normal subjects and benign hypertensive patients, it did not explore the effect of antihypertensive treatment on these abnormalities. More recently, some investigators have concluded that RV is more advantageous than echocardiography for the study of abnormalities in diastolic function of hypertensive patients. RV permits the measurement of relative volume changes with time, without the geometric assumptions necessary for echocardiography. The major advantages of RV are its ease of performance, lack of dependence on patient anatomy, and generation of measurements of diastolic function by computer processing. The disadvantages of RV include dependence of acquisition on a regular cardiac rhythm and inability to time important cardiac events such as the opening and closing of cardiac valves. Nevertheless, RV provides an attractive qualitative approach to the analysis of left ventricular diastolic function, circumventing the need for invasive techniques and permitting the study of large patient populations. Studies of left ventricular function by RV in MH patients have not been published previously. Our study demonstrated preservation of left ventricular systolic function in patients with MH, even in those with pulmonary congestion at admission. The latter can be explained by reduced left ventricular filling indicative of impaired diastolic function. Symptoms of pulmonary congestion occurred despite an increase in the ejection rate. These abnormal myocardial characteristics of MH may be due to 1) increased work from pressure overload, 2) myocardial ischemia due to impaired perfusion caused by arteriolitis, 3) increased stiffness induced by the severe degree of hypertrophy, or 4) increased sympathetic drive to the heart.

The reduction of blood pressure with treatment progressively improved ventricular filling and re-
duced contractility to values comparable to those in the control groups. The significant decrease in ejection rate at 3 months, to levels below those obtained for the control groups, can be explained by the use of β-adrenergic blockers, and this is supported by the lower heart rates observed after therapy. β-Blockers reduce left ventricular contractility because of the inhibition of sympathetic stimulation of the heart. Our MH patients sustained their clinical improvement with these agents while their ejection fractions continued to be normal throughout the follow-up period. These data suggest a beneficial effect attributable to this group of drugs, which is not consistent with the recent recommendations by Calhoun and Oparil10 to avoid β-blockers in MH because of the risk of impairing cardiac function.

The improvement of diastolic filling in MH patients might simply reflect a change in heart rate induced by β-blockers rather than a resolution of the pathophysiological changes associated with MH. Using atrial pacing in patients with hypertrophic cardiomyopathy, Bonow et al11 demonstrated that a reduction in heart rate is associated with decreases in PFR and prolongation of TPFR. Our patients maintained increases in PFR and decreases in TPFR during reduction of heart rate by β-blockers. In addition, TPFR normalized by the RR interval was also reduced by therapy. Therefore, our data indicate that improvement of diastolic filling occurred independent of reduction in heart rate. Our data are in agreement with those reported by Bonow et al,11 who, using verapamil in patients with hypertrophic cardiomyopathy, obtained increased PFR and decreased TPFR despite a decrease in heart rate.

In summary, the abnormalities of left ventricular function accompanying the development of MH are characterized by impairment of diastolic function and increased contractility with preserved systolic function. These abnormalities can be reversed by adequate treatment.

**References**


**KEY WORDS** - radionuclide ventriculography • malignant hypertension • ventricular function
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