OBJECTIVES

This study was performed to determine the association between clinical characteristics, particularly body mass and race, and the likelihood of hypertension as the primary etiology for heart failure (HTNCM).

BACKGROUND

Although held to be important in the development of heart failure, the clinical characteristics predictive of HTNCM have not been well delineated.

METHODS

The study analysis was conducted using 680 patients from the University of North Carolina Heart Failure Database. This data set is racially diverse (44% African-American) and contains data concerning baseline clinical characteristics and cardiac function in patients with and without HTNCM. Logistic regression techniques determined independent predictors of HTNCM among the entire study population as well as the subgroup of study patients with hypertension.

RESULTS

Hypertension was present in 51% of the study patients but was the primary etiology of heart failure in only 25%. Body mass, race, gender and baseline systolic blood pressure were identified as significant independent predictors of the likelihood of HTNCM (all p < 0.001). These characteristics were predictors in the total study population and also in the subgroup of study patients with hypertension.

CONCLUSIONS

Hypertension remains a common etiologic factor for the development of heart failure but was the primary cause of heart failure in a minority of study patients. However, the presence of increased body mass, female gender, African-American ethnic origin or elevated baseline systolic blood pressure significantly increased the likelihood of HTNCM. (J Am Coll Cardiol 1999;34:1602–8) © 1999 by the American College of Cardiology

Natural history studies continue to demonstrate that systemic hypertension is a significant risk factor for the development of heart failure (1). Part of the explanation for the association between heart failure and hypertension arises from the increased risk of coronary artery disease (CAD) and myocardial infarction among hypertensives. However, clinical observation continues to suggest that hypertension may be the sole apparent cause for heart failure.

Despite this clinical impression, the characteristics associated with hypertension as the principal cause of heart failure, in the absence of other etiologic factors like CAD, have not been well delineated. Prior studies suggest that obesity might be a significant predictor for the development of hypertension-associated heart failure (2). Even in the absence of hypertension, increased body mass has been correlated with the development of left ventricular hypertrophy (3–5), and marked obesity is associated with cardiomyopathy (6,7). Studies of cardiac structure have demonstrated the adverse consequences when obesity and hypertension coexist. Cardiac remodeling, as evidenced by left ventricular dilatation and hypertrophy, is greater in patients with obesity and hypertension compared with patients with hypertension alone and could predispose patients to develop left ventricular dysfunction and clinical heart failure (8–12). Early work by Blake et al. (8) demonstrated that left ventricular dysfunction during exercise in hypertensive patients was associated with eccentric ventricular hypertrophy and increased body mass. The potential association between female gender, African-American race and hypertension as the primary etiology of heart failure (HTNCM) deserves further investigation as well. Hypertension and obesity are particularly frequent in black females and seem to be important contributors to cardiovascular disease in this demographic group (13).

The potential association between these factors and HTNCM was investigated using the University of North Carolina (UNC) Heart Failure Database. This data set has
Etiologic classification. The presence or absence of CAD before or within three months after their study entry date was determined not to have CAD based on the following: 1) current or previous administration of medication specifically as antihypertensive pharmacologic treatment or 2) blood pressure readings of ≥140 mm Hg systolic or ≥90 mm Hg diastolic on at least three separate occasions before or within three months after their study entry date (15).

Definition of hypertension. Patients were given a diagnosis of hypertension by study criteria (HTNDX) if they had a history of this disorder and evidence of at least one of the following: 1) current or previous administration of medication specifically as antihypertensive pharmacologic treatment or 2) blood pressure readings of ≥140 mm Hg systolic or ≥90 mm Hg diastolic on at least three separate occasions before or within three months after their study entry date (15).

Etiologic classification. The presence or absence of CAD was determined in the study patients as previously reported (13). The presence of CAD was established in 239 patients based on: 1) angiographic (191 patients) or autopsy (10 patients) results demonstrating ≥70% stenosis of at least one major epicardial coronary artery; 2) prior myocardial infarction documented by standard electrocardiographic and enzymatic criteria (34 patients); or 3) the presence of typical angina and a stress radionuclide examination consistent with ischemia (4 patients). Coronary artery disease was absent in 264 patients based on angiographic (248 patients) or autopsy (16 patients) results. A total of 177 study patients were determined not to have CAD based on the following clinical criteria: no evidence of previous myocardial infarction by history or electrocardiographic findings and no history of angina pectoris.

Available clinical, laboratory and autopsy data were utilized to assign a primary etiology for heart failure in each patient as previously described (13). Ischemic heart disease was the primary cause in 211 of the 239 patients with evidence of CAD. Specific criteria were utilized to establish alcohol, valvular heart disease, peripartum cardiomyopathy or other rarer but well-recognized primary causes of heart failure in 188 study patients (13,16). HTNCM was assigned in 168 patients with HTNDX and no other specific cause of cardiomyopathy. Idiopathic cardiomyopathy was the primary etiology in the remaining 113 study patients. Hypertension was assigned as a coetiology in 178 patients with HTNDX who also met study criteria for another potential etiology of heart failure.

Body habitus. Self-reported height and body weight given at the time of the qualifying radionuclide ventriculogram were used in the study analysis. Previous studies attest to the accuracy of patient estimates of height and weight (17–19). Our own validation study in 100 consecutive study patients demonstrated that height and body weight measured in the clinic were highly correlated with self-reported values (for height, r = 0.99, p < 0.0001; for weight, r = 0.97, p < 0.0001). Patients were categorized as overweight if they exceeded the following body mass criteria proposed by the National Institutes of Health Consensus Development Panel: for men >27.8 kg/m², and for women >27.3 kg/m² (20). Patients were obese if their body mass exceeded 30 kg/m². Morbid obesity was defined as a body weight greater than 136 kg (7).

Statistical analysis. Data are presented as the mean ± standard error of the mean. Differences in categorical and continuous variables between various study groups were assessed by the chi-square test or analysis of variance methods as appropriate.

The principal study analysis was made to determine independent predictors of HTNCM by stepwise, multivariate logistic regression in the subset of patients with HTNDX (21). Two indices of body habitus, body weight as overweight based on the criteria above or body mass divided into quintiles, along with the following clinical characteristics, were considered as predictors in the modeling analysis: race coded as black versus other, gender, age, presence or absence of electrocardiographic evidence of left ventricular hypertrophy (EKGLVH), history of diabetes, years of hypertension and the resting systolic blood pressure obtained at study entry (22). Each significant predictor was then confirmed in a backward selection process with all potential characteristics forced into the model. Additional modeling was undertaken in two subsets of HTNDX patients created: 1) after exclusion of 13 patients who met study criteria for morbid obesity or 2) after exclusion of 109 patients in whom the absence of CAD was determined by clinical criteria alone, as well as three additional patients with a primary etiology of hypertension but angiographic evidence of significant single-vessel CAD (>70% stenosis of either the right or circumflex coronary artery). Multicat-
egory logistic modeling was also performed to determine predictors of hypertensive status (no diagnosis of hypertension, hypertension as a coetiology and HTNCM) in the total study population (680 patients).

RESULTS

Study population. The majority of the 680 total study patients were New York Heart Association (NYHA) functional class II (29%) or III (50%); only 14 patients (2.1%) were NYHA class I at entry. The mean left ventricular ejection fraction was 26% ± 0.5%. The mean body weight for the study population was 81 ± 0.8 kg, and the mean body mass was 27 ± 0.3 kg/m². The percentage of study patients in each category of body habitus is shown in Figure 1. The mean age of the total study population was 51 ± 0.5 years, with women comprising 31% of the total patients, while 44% were African-American.

The 346 patients in the total study group with HTNDX had a mean left ventricular ejection fraction of 27 ± 0.7, with 41 patients (12%) in this subset having a value greater than 45%. The race-gender distribution in patients with HTNDX was: 70 (20.2%) black females, 42 (12.1%) nonblack females, 129 (37.3%) black males and 105 (30.3%) nonblack males.

Hypertensive etiology. A history of elevated blood pressure was present in 55% of the study population, while 51% met the study criteria for hypertension. The frequency of the diagnosis of hypertension varied significantly by racial group, with blacks more likely to have this characteristic than nonblacks (67% vs. 39%, p < 0.0001). Despite its underlying frequency, hypertension was assigned as the primary etiology of heart failure in only 25% of the study patients. Comparisons of clinical characteristics based on hypertensive status suggested potential predictors of HTNCM (Table 1). In addition to racial makeup, body mass, gender, systolic blood pressure, left ventricular ejection fraction, history of diabetes and EKGLVH demonstrated overall differences between these groups. Comparison of these characteristics between patients with HTNCM versus patients with hypertension as a coetiology demonstrated significant differences (p < 0.05) for all except those with history of diabetes (p = 0.611).

Table 1. Differences in Clinical Characteristics Based on the Relationship of Hypertension to Etiology of Heart Failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-HTNCM</th>
<th>HTN Coetiology</th>
<th>No HTN</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>168</td>
<td>178</td>
<td>334</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>53 ± 1.0</td>
<td>54 ± 1.0</td>
<td>49 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body habitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 ± 1.0</td>
<td>173 ± 1.0</td>
<td>173 ± 1.0</td>
<td>0.768</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91 ± 2.0</td>
<td>80 ± 1.5</td>
<td>77 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass (kg/m²)</td>
<td>30 ± 0.6</td>
<td>27 ± 0.6</td>
<td>26 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>134 ± 1.8</td>
<td>123 ± 1.5</td>
<td>112 ± 0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>30 ± 1.1</td>
<td>24 ± 0.9</td>
<td>24 ± 0.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>26</td>
<td>54</td>
<td>68</td>
<td>0.001</td>
</tr>
<tr>
<td>EKG LVH (%)</td>
<td>56</td>
<td>45</td>
<td>33</td>
<td>0.001</td>
</tr>
<tr>
<td>History of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>100</td>
<td>100</td>
<td>8</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>30</td>
<td>27</td>
<td>17</td>
<td>0.003</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>0</td>
<td>27</td>
<td>13</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Results are shown as mean ± SEM. p values reflect overall differences across the three types of hypertensive status.

CABG = coronary artery bypass surgery; EKG LVH = left ventricular hypertrophy by EKG criteria; HTN Coetiology = patients with study diagnosis of hypertension but another potential etiology heart failure; LVEF = left ventricular ejection fraction; No HTN = patients not meeting study criteria for hypertension; SBP = systolic blood pressure.
Associations in all patients. In the total study population, as the body mass increased, HTNCM was more likely (Fig. 2). A similar relationship was observed when body habitus was categorized according to the study criteria for overweight or obesity. Hypertension was the primary etiology of heart failure in 40% of overweight patients versus 17% of patients who were not overweight (p < 0.001), while 45% of the obese patients had HTNCM versus 18% of the nonobese patients (p = 0.001). In the total study population, blacks were significantly more likely than nonblacks (40% vs. 7.1%, p < 0.001) and females significantly more likely than males (34% vs. 21%, p < 0.001) to have HTNCM. The combined associations of racial group and gender with the likelihood of hypertension and heart failure due to hypertension are shown for the total study population in Figure 3.

Hypertensive patients. Similar relationships were seen when body mass, race and gender were considered as predictors of the likelihood of HTNCM in the subset of study patients with HTNDX (Fig. 4). A threshold relationship between body mass and the likelihood of HTNCM was most evident for nonblack males. By contrast, black patients of either gender and nonblack females tended to have increasing likelihood of HTNCM with each increment in body mass quintile. The likelihood of HTNCM appeared greatest in obese black females and lowest in lean nonblack males (p = 0.02 for the pair-wise comparison of the slope of the relationship between body mass quintile and likelihood of HTNCM in these two groups) (Fig. 4).

Multivariate modeling in the subset with HTNDX demonstrated that overweight, race and gender and baseline systolic blood pressure were significant independent predictors of the likelihood of HTNCM after taking into account a variety of clinical factors including age, the presence or absence of EKGLVH and years of hypertension (Table 2). Body mass quintile was a significant predictor when substituted for overweight in the final model (odds ratio [OR] 1.43; 95% confidence interval [CI] 1.20 to 1.71; p < 0.0001). History of diabetes was not a significant predictor for the likelihood of HTNCM (OR for a positive vs.
negative history 0.84; CI 0.49 to 1.46; p = 0.542). The characteristics in Table 2 remained significant predictors when patients with morbid obesity were excluded. Additional modeling was performed in 234 of the 346 study patients with HTNDX (68%) who had their CAD status well documented. Multivariate analysis in this subset yielded the same predictors for HTNCM as found for all 346 patients with hypertension.

**Associations by hypertensive status.** Multicategory logistic regression modeling confirmed overweight, race and baseline systolic blood pressure as significant independent predictors of HTNCM not only for the comparison of patients when hypertension was primary versus a coetiology but also for primary versus nonhypertensive patients (Table 3). There was a strong trend for gender to be a predictor in both comparisons as well. Age and EKGLVH emerged as marginally significant predictors in the primary versus coetiology comparison done as part of the multicategory regression. Only trends toward significance were present for these variables when hypertensive study patients alone were modeled.

### DISCUSSION

Our study makes an important contribution toward understanding the current role of hypertension in heart failure. The seminal investigation of the Framingham cohort established the important role played by hypertension in the promotion of symptomatic left ventricular dysfunction (1,23). By contrast, recent studies based on clinical trial data sets have emphasized the importance of ischemic heart disease as an etiologic factor for heart failure. Through the UNC Heart Failure Database, our study provides a unique opportunity to investigate the role of hypertension in heart failure in a diverse, contemporary patient population well characterized with respect to potential etiologic factors. In agreement with the Framingham results, hypertension was found to be a common, important causal factor for heart failure in our patients, a total of 51% of whom met the study criteria for the diagnosis of hypertension. By contrast, hypertension appeared to be the sole etiologic factor for heart failure in a minority of study patients (25%). By carefully defining study patients with HTNCM, our analysis delineated the specific clinical characteristics that significantly influenced the risk of hypertension as the sole apparent cause of heart failure. High body mass, female gender, African-American ethnic origin and elevated baseline systolic blood pressure significantly increased the likelihood of having HTNCM. Multivariate logistic regression confirmed the importance of these factors as independent predictors of HTNCM both among patients with the diagnosis of hypertension and in the total study population.

#### Specific predictors

Body weight has long been appreciated as a modulator of cardiac anatomy and function and more recently as a possible contributor to the development of heart failure (24). We found that excess body mass was strongly associated with greater likelihood of having HTNCM. The relationship between increasing body mass and greater likelihood of HTNCM reflected differences in body weight, not height. Although morbid obesity has been previously associated with the development of cardiomyopathy (25,26), this degree of adiposity was rare in our study population. In fact, the relationship to body mass was detected even though the median body weight of patients with HTNCM was 190 lbs and the median body mass was 29.3 m/kg², with 42% of the patients failing to meet standard criteria for overweight. Our data suggest that body

### Table 2. Predictors of HTNCM in Hypertensive Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>2.52</td>
<td>1.52–4.15</td>
<td>0.0003</td>
</tr>
<tr>
<td>African-American race</td>
<td>2.83</td>
<td>1.71–4.69</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.68</td>
<td>1.56–4.61</td>
<td>0.0004</td>
</tr>
<tr>
<td>Baseline systolic blood pressure (per 5 mm Hg)</td>
<td>1.13</td>
<td>1.07–1.20</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Overweight is defined as patients exceeding the following body mass criteria: for men > 27.8 kg/m² and for women > 27.3 kg/m². p values are based on logistic regression analysis. CI = confidence interval.

### Table 3. Multicategory Logistic Modeling of Predictive Factors for Various Types of Hypertensive Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HTNCM vs. No HTN</th>
<th></th>
<th>HTN Coetiology vs. No HTN</th>
<th></th>
<th>HTNCM vs. HTN Coetiology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>p Value</td>
<td>Odds Ratio</td>
<td>p Value</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>African-American race</td>
<td>6.99</td>
<td>&lt; 0.001</td>
<td>2.35</td>
<td>&lt; 0.001</td>
<td>2.98</td>
</tr>
<tr>
<td>Age (per 10 yrs)</td>
<td>1.81</td>
<td>&lt; 0.001</td>
<td>1.49</td>
<td>&lt; 0.001</td>
<td>1.25</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.61</td>
<td>0.057</td>
<td>1.36</td>
<td>0.193</td>
<td>0.45</td>
</tr>
<tr>
<td>Overweight</td>
<td>4.38</td>
<td>&lt; 0.001</td>
<td>1.76</td>
<td>0.012</td>
<td>2.49</td>
</tr>
<tr>
<td>Systolic blood pressure (per 5 mm Hg)</td>
<td>1.33</td>
<td>&lt; 0.001</td>
<td>1.18</td>
<td>&lt; 0.001</td>
<td>1.12</td>
</tr>
<tr>
<td>EKG LVH</td>
<td>2.47</td>
<td>&lt; 0.001</td>
<td>1.46</td>
<td>0.080</td>
<td>1.69</td>
</tr>
</tbody>
</table>

Abbreviations are the same as in Table 1.
mass may predispose to HTNCM with only modest increases in body weight above established norms.

The work of Messerli et al. (9) has demonstrated the additional hemodynamic burden that obesity places on the hypertensive heart. Their studies of cardiac performance and structure in obese hypertensive patients have demonstrated increased stroke volume and left ventricular dilation compared with normal subjects. Results from an unselected population of hypertensive patients demonstrated that the obese patients maintained a similar cardiac index compared with normal-weight subjects but did so through ventricular dilation and the use of preload reserve (10). A number of studies in hypertensive populations have found that obesity is the strongest clinical predictor of left ventricular hypertrophy and increased left ventricular mass (11), factors known to be associated with the risk of developing heart failure (12). The review by Reaven et al. (27) provides some additional insight into the mechanisms that may account for the association between increased body mass and risk of developing heart failure among patients who are hypertensive. Increased body mass appears to promote greater activation of the sympathetic nervous system. Natural history studies and the therapeutic benefit of beta-blockade in heart failure attest to the pathophysiologic importance of the sympathetic nervous system and point to a role for this factor in hypertension-associated heart failure (28,29).

**Other predictors.** Our findings demonstrated that African-American ethnicity significantly increased the likelihood of hypertension being the predominant cause of heart failure. Hypertension is known to be more common among blacks and has been associated with greater mortality and morbidity due to cardiovascular disease and renal failure in this ethnic group compared with Caucasians (30,31). Data reported by Bourassa et al. (32) from the SOLVD registry supports our finding that hypertension was more commonly the primary etiology of heart failure in African-Americans. Whether this racial difference reflects underlying differences in the biology of hypertension in blacks or differences in access to care or in treatment compliance remains to be determined. Hinderliter et al. (33) have found differences in ventricular geometry between healthy blacks and whites, suggesting fundamental racial disparities in cardiac morphology during normal aging. Gottdiener et al. (11) found that the incidence of left ventricular hypertrophy by echocardiographic criteria was similar in blacks and Caucasians enrolled in a clinical trial of antihypertensive agents, but that relative wall thickness was increased in black males compared with white males. These findings suggest the possibility that clinically important differences in left ventricular adaptation to hypertension may occur in black and white patients. We found that females were significantly more likely than males to have hypertension as their primary etiologic factor for heart failure. This disparity likely reflects the relative lack of ischemic heart disease in women, particularly in the age group we studied. Gender might not be a predictor in an elderly cohort, where the likelihood of ischemic cardiomyopathy in females would increase. In addition, the findings of de Simone et al. (3) concerning differences in hypertrophy between males and females may help explain our results. They found that coexisting obesity and hypertension were more likely to increase left ventricular mass-to-height ratios in females compared with males. We did not find that diabetes was a predictor of hypertension as the primary etiology of heart failure. This may be attributed to the etiologic classification we used. Patients with hypertension as a coetiology (typically along with CAD) were separated from those patients in which hypertension was the only apparent etiology of heart failure.

**Study limitations.** Our study utilized a cross-sectional design to test the association of specific clinical characteristics with the outcome of interest: heart failure due to hypertension. Our design has the advantage of identifying many patients with this form of heart failure, which is infrequent in clinical studies of hypertensive patients. However, our study structure does not allow us to determine cause-and-effect relationships between the predictors we have identified and the likelihood of HTNCM. Our study population was limited to a single center and was relatively youthful. Additional studies in a broader patient population will help confirm the generalizability of our findings. Our population had predominantly systolic ventricular dysfunction. Studying a larger sample size of patients with preserved systolic function might yield a model different from the one we found. Data on coronary anatomy were not available in all study patients, and this may have prevented identification of ischemic heart disease as the primary etiology of heart failure in some subjects. This could have biased the determination of the predictors of hypertension as the primary etiology of heart failure. However, the same predictors were found when modeling was conducted in the subset of study patients who had their CAD status well documented.

**Conclusions.** Hypertension remains a common, important etiologic factor but was the primary cause of heart failure in a minority of study patients. Increased body mass, African-American ethnicity and female gender all appear to be factors associated with the likelihood of developing HTNCM. Although cause and effect have not been established, our study supports another potential benefit from weight reduction in patients with hypertension, especially black females.

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REFERENCES