moderate ToF. It is true that in severe RVOT obstruction and in pulmonary atresia, there may be reversal of the flow in the duct to left to right.[1,12–14] This emphasizes the importance of determining the direction of ductal flow in fetal echocardiography.

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Effect of Angiotensin-Converting Enzyme Insertion/Deletion Polymorphism DD Genotype on High-Frequency Heart Rate Variability in African Americans

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Seventy-nine African-American participants in the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) pilot study were genotyped for the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism and had spectral power of their high-frequency (HF) heart rate variability (HRV) determined by fast-Fourier transformation. HF HRV was highest in II, intermediate in ID, and lowest in DD (II vs DD, $p < 0.043$) genotypes, thus making an association of the ACE I/D DD genotype with decreased HF HRV that is consistent with the hypothesis that the DD genotype confers susceptibility to increased cardiovascular risk. The urban African-American population we studied had a particularly high cardiovascular risk, and these findings suggest that ACE I/D genotypes may modify that risk.

(Am J Cardiol 2003;92:1487–1490)

Genetic studies in 2 separate populations have suggested that 13% to 23%[1] or 28% to 34%[2] of variance in heart rate variability (HRV) may be attributed to 1 or a few genes. One candidate gene is angiotensin-converting enzyme (ACE), in which an insertion/deletion (I/D) polymorphism in intron 16 of the ACE gene predicts as much as 50% of the variability in measured serum ACE concentrations.[3] The clinical phenotype of this polymorphism has been defined as: the DD variant is associated with higher circulating ACE levels and enzyme activity, whereas the heterozygous I/D variant is intermediate, and the II variant has the lowest circulating ACE levels and enzyme activity. The DD variant, present in 17% to 46% of the various populations studied, has been associated with myocardial infarction,[4] left ventricular hypertrophy,[5] and impaired endothelial function as measured by vasodilator response to intra-arterial acetylcholine infusion.[6] There is also a pharmacologic phenotype with the DD variant that has an enhanced angiotensin I pressor response[7] and less regression of left ventricular hypertrophy in patients treated with ACE inhibitors.[8] We hypothesized that the ACE I/D polymorphism contributes significantly to variance in the parasympathetic component of high-frequency (HF) HRV in African-American subjects. We further hypothesized that the DD variant of ACE I/D is associated with decreased HF HRV.

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Seventy-nine African-Americans who were partic-

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Manuscript received May 22, 2003; revised manuscript received and accepted August 22, 2003.

0002-9149/03/$–see front matter
doi:10.1016/j.amjcard.2003.08.069

TABLE 1 Subject Characteristics

Genotype	ACE II (n = 11)	ACE I/D (n = 55)	ACE DD (n = 13)
Age (yrs)	56 ± 15 (46–66)	49 ± 13 (45–52)	50 ± 15 (41–59)
Men/women	6/5	24/31	7/6
Cigarette smoker	73%	72% (2 unk)	77%
Systemic hypertension	36%	38%	23%
Diabetes mellitus	27%	11%	8%
β-blocker treatment	18%	8% (3 unk)	15%
ACE inhibitor treatment	27%	6% (3 unk)	0%
Calcium antagonist treatment	0%	21% (3 unk)	15%
Body mass index (kg/m^2)	24.1 ± 5.4 (15.7–31.3)	28.3 ± 7.9 (17.3–52.1)	26.4 ± 5.5 (16.7–33.4)
Heart rate (beats/min)	72 ± 11 (56–91)	78 ± 12 (51–109)	79 ± 16 (46–111)
Systolic blood pressure (mm Hg)	153 ± 49 (97–259)	138 ± 23 (104–196)	133 ± 33 (102–231)
Diastolic blood pressure (mm Hg)	81 ± 14 (62–105)	80 ± 11 (54–97)	80 ± 13 (67–113)

Values are expressed as mean ± SD (range).
unk = unknown.

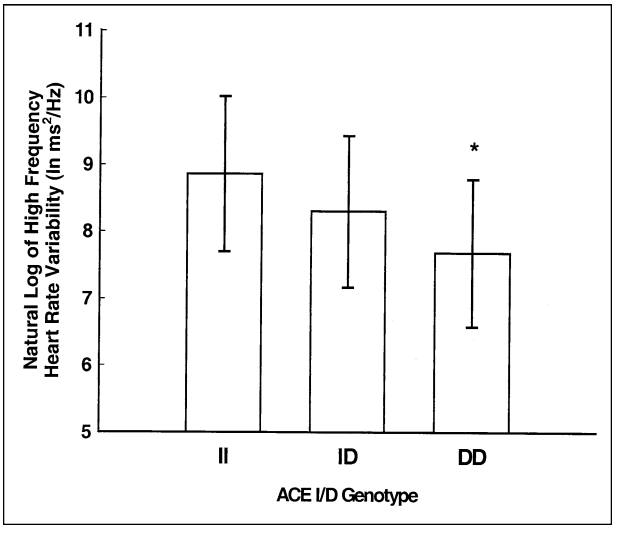

FIGURE 1. Natural log transform of HF HRV *(y-axis)* versus the ACE I/D polymorphism groups (II, I/D, DD). DD has significantly lower HF HRV than II. I/D is intermediate, but not significantly different from either group. *Error bars* represent mean ± SD. *p = 0.043, analysis of variance with between-group comparisons by least-significant difference test.

ipants in the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) pilot study were studied. There were 11 patients with the ACE II genotype, 55 with ACE I/D, and 13 with ACE DD. This distribution (14% II, 70% I/D, 16% DD) did not differ from that described in other groups (n = 7: 8% to 39% II, 34% to 55% I/D, 18% to 46% DD). Demographics of the 3 groups are listed in Table 1. The groups were reasonably matched; however, hypertension, diabetes mellitus, and ACE inhibitor exposure were somewhat over-represented in the ACE II group, and women were over-represented in the ACE I/D group. Cigarette smoking, overweight (25 to 30 kg/m^2), and obesity (>30 kg/m^2) were prevalent in all groups.

After extraction of genomic deoxyribonucleic acid from 9 ml of ethylenediaminetetraacetic acid–anticoagulated blood by standard methods,[9] the ACE I/D genotype was assigned by the triple primer method as described by Evans et al.[10]

Heart rate (interbeat interval) and systolic and diastolic blood pressures were recorded during a 5-minute resting baseline study on a beat-to-beat basis using Portapres (Biomedical Instrumentation, Amsterdam, The Netherlands). A fast-Fourier transform was then applied to the interbeat interval time series and spectral power derived in the HF range (0.15 to 0.40 Hz).[11] HRV data were natural log-transformed to normalize the distribution.

One-way analysis of variance was used to examine the relation between genotype (II, I/D, DD) and other potential contributors to HF HRV. Significant omnibus tests were performed, followed by pairwise comparisons to isolate significant genotype differences.

The natural log transform of HF HRV across the sample (expressed as mean ± SD) was 8.28 ± 1.16 ms^2/Hz (95% confidence interval [CI] 7.97 to 8.60). When groups were segregated by ACE I/D genotype, the II genotype was 8.86 ± 1.16 ms^2/Hz HF HRV (95% CI 8.18 to 9.54) , the I/D genotype was 8.30 ± 1.13 ms^2/Hz HF HRV (95% CI 8.00 to 8.60), and the DD genotype 7.68 ± 1.10 ms^2/Hz HF HRV (95% CI 7.06 to 8.31) (II vs DD; p <0.043) (Figure 1). The groups did not differ in heart rate or systolic or diastolic blood pressures (Table 1).

Other potential sources of the variance of HF HRV evaluated were age, gender, body mass index, presence or absence of hypertension, presence or absence of diabetes mellitus, treatment with β-adrenoceptor antagonists, treatment with ACE inhibitors, and treatment with calcium antagonists.

Median age for the population was 48 years, and HF HRV for patients aged ≤48 years (n = 41) compared with that of patients aged >48 years (n = 38) was 7.92 ± 1.14 ms^2/Hz (95% CI 7.40 to 8.28) versus 8.66 ± 1.08 ms^2/Hz (95% CI 8.28 to 9.16) (p = 0.006). Decreased HF HRV was noted in the younger patients across ACE I/D genotypes (II: 8.24 ± 1.23 vs 9.38 ± 0.88 ms^2/Hz; I/D: 8.03 ± 1.13 vs 8.59 ± 1.07 ms^2/Hz ; and DD: 7.25 ± 0.96 vs 8.18 ± 1.10 ms^2/

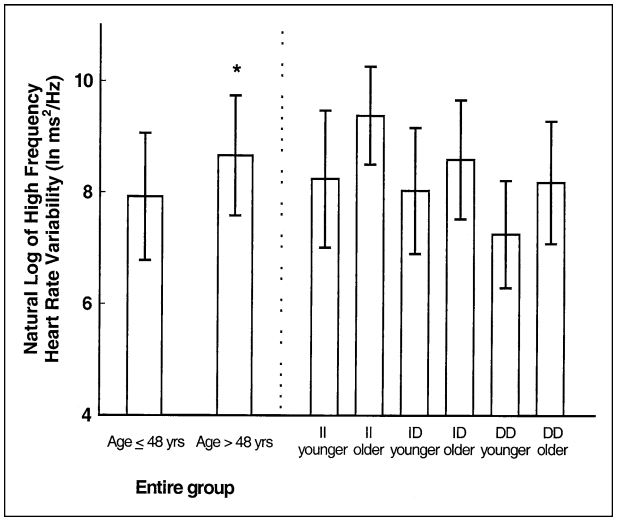

FIGURE 2. Natural log transform of HF HRV *(y-axis)* versus age *(x-axis)*. Comparisons are for all subjects below and above median age *(left side)* and subjects stratified for ACE I/D genotype *(right side)*. *Error bars* represent mean ± SD. *p = 0.006, analysis of variance with between-group comparisons by least-significant difference test.

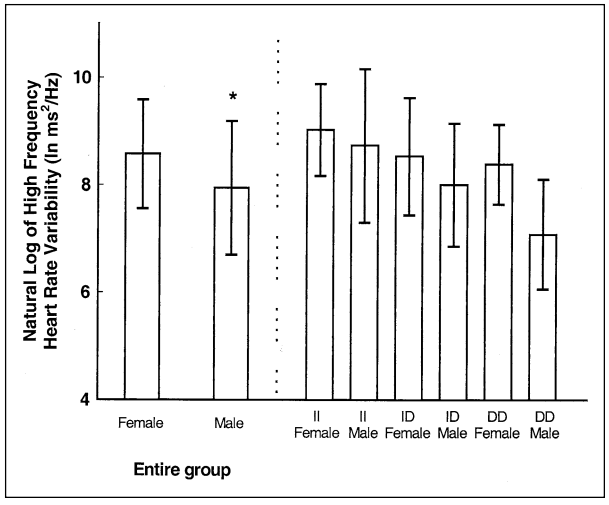

FIGURE 3. Natural log transform of HF HRV *(y-axis)* versus gender *(x-axis)*. Comparisons are for all subjects *(left side)* and subjects stratified for ACE I/D genotype *(right side)*. *Error bars* represent mean ± SD. *p = 0.028, analysis of variance with between-group comparisons by least-significant difference test.

Hz); however, these trends did not reach statistical significance (Figure 2).

Comparison of women (n = 42) with men (n = 37) showed that women had higher HF HRV than men (8.57 ± 1.01 ms^2/Hz [955 CI 8.18 to 9.10] vs 7.94 ± 1.24 ms^2/Hz [95% CI 7.51 to 8.37] (p = 0.028). Increased HF HRV was noted in women across the ACE I/D genotypes (II, 9.02 ± 0.86 vs 8.73 ± 1.43 ms^2/Hz; I/D, 8.53 ± 1.09 vs 8.00 ± 1.14 ms^2/Hz; DD, 8.38 ± 0.74 vs 7.08 ± 1.02 ms^2/Hz); however, these trends were not significantly different. Diagnoses of hypertension, diabetes, and overweight/obesity were not significantly associated with changes in HF HRV (Figure 3).

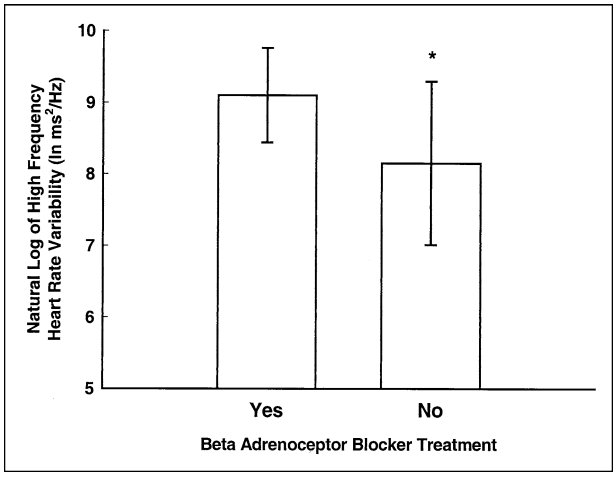

FIGURE 4. Natural log transform of HR HRV *(y-axis)* versus β-adrenoceptor blocker therapy *(x-axis)*. *Error bars* represent mean ± SD. *p = 0.015, analysis of variance.

Eight of 76 patients were taking β-adrenoceptor blockers, 6 of 76 were on ACE inhibitors, and 13 of 74 were receiving calcium antagonists. Administration of β-adrenoceptor blocker was associated with increased HF HRV (9.10 ± 0.66 vs 8.15 ± 1.14 ms^2/Hz; p = 0.015) (Figure 4). No differences in HF HRV were noted in patients who were receiving ACE inhibitors or calcium antagonists.

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In this cohort of 79 African-American patients, ACE I/D genotype, age, female gender, and β-adrenoceptor blocker therapy contributed significantly to variance in HF HRV in the resting state. The new finding shows the association of the ACE DD genotype with decreased HF HRV. The allelic dose response relation shown in Figure 1 suggests an additive effect of the I and/or D allele on HF HRV. Previous studies have shown that female gender[12] and β-adrenoceptor blocker therapy[13] are associated with increased HF HRV, which is consistent with the present report. In contrast, previous studies have also indicated an decreased HF HRV with increased age.[12,14,15] Previous studies have also indicated that ACE inhibitor[16] treatment and a decrease in body mass index[17] are associated with increased HF HRV. Possible explanations for the unexpected findings that older patients had increased HF HRV are the nature of the study population and the cross-sectional study design. The urban African-American cohort studied had prevalent concurrent disease and tobacco use. It is possible that the older group studied here was biased toward a "healthier" population; however, such a conjecture cannot be convincingly supported with these data. The absence of effects of body mass index and ACE exposure on HF HRV, unlike other reports, may be related to the relatively small sample size.

Two previous studies have examined the relation between the ACE I/D gene and HRV. One study found, in contrast to the extensively characterized clinical and pharmacologic phenotype of this polymorphism, that the DD variant was associated with

greater HF HRV.[18] Another study in patients after acute myocardial infarction found no relation between the ACE I/D polymorphism and HRV.[19] There are several important differences between these previous studies and the present study. First, in both of the previous studies, the populations were composed exclusively of Caucasian participants. Second, 1 study examined patients after a major cardiac event, in which HRV levels tend to be depressed and during which time other factors, such as renin-angiotensin system activation, may be dominant.[19] Third, we examined a number of possible variables, including the presence of disease that could explain and moderate the relation between ACE I/D and HF HRV. This was not done in the previous studies and may help to account for the observed discrepancy with the present results.

The urban African-American population studied in the present report is at particularly high cardiovascular risk.[20] The ACE I/D DD genotype may contribute to the already increased cardiovascular risk in this population.

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Coronary Tracheal Collaterals After Heart–Lung Transplant

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Coronary tracheal collaterals are often seen on annual surveillance coronary angiograms in patients with heart–lung transplants and represent a normal postoperative finding.

(Am J Cardiol 2003;92:1490–1492)

Annual surveillance coronary angiography is standard practice in patients with heart and heart–lung transplantation (HLT) to detect coronary arterial disease reflecting graft rejection. Several other abnormalities, such as congenital anomalies and fistulous communications due to endomyocardial biopsy procedures, are also incidentally detected from these angiograms. Over the years we have noticed abnormal vascular supply from the coronary arteries to the subcarinal region of the mediastinum in patients who have undergone HLT, which could be confused with coronary arteriovenous malformation. These abnormal-appearing vessels represent collateral supply to the transplanted proximal tracheobronchial tree. The purpose of this communication was to evaluate this phenomenon in patients with HLT.

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Sixteen patients who underwent HLT during a 13-year period (from 1989 to 2002) were included in

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Manuscript received May 22, 2003; revised manuscript received and accepted August 22, 2003.

0002-9149/03/$–see front matter
doi:10.1016/j.amjcard.2003.08.071