Blood Pressure and the Cystic Fibrosis Gene
Evidence for Lower Pressure Rises With Age in Female Carriers

Maurice Super, Ayesha Irtiza-Ali, Stephen A. Roberts, Martin Schwarz, Michele Young, Alison Smith, Theresa Roberts, Joanna Hinks, Anthony Heagerty

Abstract—Individuals homozygous for the autosomal recessive disorder CF are known to have low blood pressure, thought to be caused by greatly increased sweat salt loss. We examined whether carriers of the CF gene also have low blood pressure. Our pilot studies had suggested an effect limited to females, leading to 2 further studies in white females. In the first, blood pressure was measured in 232 known CF mutation carriers and compared with 246 mutation-negative control subjects. The carriers showed a significantly lower rate of increase in systolic blood pressure with age than the controls, especially after age 50 (3.5% per decade compared with 5.4% per decade, \( P=0.010 \)). In a small substudy, sweat sodium and chloride levels were highest in those CF carriers with the lowest blood pressures. In the second study, CF carrier status was investigated in 563 normotensive females and in 607 women with essential hypertension diagnosed to test whether a lower incidence of carriers in the hypertensives suggested a protective effect. Twenty-five of the normotensives (4.4%) were carriers compared with 21 (3.5%) of the hypertensive group (\( P=0.45 \)). Older CF carrier females had lower systolic and diastolic pressures than matched control subjects, with a tendency for blood pressure to increase less with age. This could result in significant reduction in stroke and heart disease. The effect on blood pressure is insufficient to prevent hypertension, though it remains conceivable that the severity might be ameliorated in carriers.

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Key Words: blood pressure ■ women ■ DNA ■ mutation

Individuals homozygous for the autosomal recessive disorder CF (CF) are known to have low blood pressure, explained by greatly increased sweat salt losses.\(^1\) It was suggested that healthy carriers of the CF gene might also have low blood pressure,\(^2\) but this was not formally investigated. Individuals with CF have sweat sodium and chloride levels between 2 and 5 times normal. In the days before CF carrier detection was possible, it was shown that obligate carriers, the parents of affected children, had, on average, levels of sweat sodium and chloride intermediate between those with the disease and presumed normal controls;\(^2\) similarly, it was shown more recently that newborn carriers of major mutations of the CF gene have slightly increased sweat electrolytes when compared with negative newborn controls.\(^3\) Thus, one might postulate that such life-long increases in sweat sodium and chloride could reduce blood pressure.

We conducted a pilot study of 21 male CF carriers versus 26 negative male controls and found no differences between systolic and diastolic pressures in the 2 groups. However, 25 female carriers and 38 negative controls studied at the same time showed markedly lower systolic and diastolic pressures in the carriers.\(^4\) Our pilot studies also suggested reduced numbers of carriers in hypertensive females, whereas there were no differences in hypertensive males. This prompted us to limit our present studies to females. We investigated white British adult women in 2 concurrent cross-sectional studies to establish whether there was a true relationship between carrier status of CF and blood pressure. In study 1, blood pressures in women known to carry a major CF mutation were compared with matched female controls known to be negative on mutation testing. At the end of this study, sweat tests were performed in a sample of those carriers and negative controls with the lowest and highest blood pressures. In study 2, the frequency of major CF mutations was compared between white British normotensive and hypertensive women.

Methods

Both studies were confined to nonpregnant white British adult females from North West England. The CF mutation status of this population has been tested extensively and a high proportion of the mutations present are known,\(^3\) whereas the mutation status of other ethnic groups, excluded from the study, is less well-established. Field workers (M.Y. and A.S., 2 experienced nurses) were trained to measure seated blood pressure according to the guidelines of the

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The average of 2 readings was recorded after 5 minutes of rest, using a standard mercury sphygmomanometer. In no case were the 2 readings >3 mm Hg different in either systolic or diastolic pressure. In both studies the existence of any medical disorders and the taking of drugs that might affect blood pressure in the study subjects were recorded; also, a family history of CF in any known relative and one of hypertension, angina, or ischemic heart disease in any first-degree relative. All subjects gave full, informed, signed consent.

Study 1 was designed as a cross-sectional study to investigate levels of blood pressure and CF gene mutation carrier status. Hypertension was suspected if the average pressure was >140/90 mm Hg, and if such readings were obtained subjects were informed and, in accordance with the patient information leaflet, were advised to visit their family practitioner for monitoring. Systolic and diastolic blood pressures were measured in known CF carriers and in a group of females matched for age and known to be negative on carrier testing for the 12 commonest mutations in the North West of England. Both field workers were blind to the CF carrier status of the women. The major cohort of subjects came from the CF Cascade program of the Royal Manchester Children’s Hospital,7 thus a proportion of the women were members of the same nuclear or extended families. Subjects were examined in their own homes. The stage of the menstrual cycle and use of oral or injected contraceptives were recorded. Height, weight, and skin-fold thickness were measured.

At the end of the study, we performed sweat tests on a subset of the subjects taking a sample of those with the lowest blood pressures and highest blood pressures. Sweat sodium and chloride levels were measured by the standard Gibson and Cooke method by staff experienced in sweat testing and blind to the carrier status of the subjects.

Study 2 was designed as a cross-sectional study of CF gene mutation carrier status in women with essential hypertension and in normotensive controls. Patients were recruited from local hospital hypertension clinics and a primary care clinic and a group of normotensive control women with a similar age range was recruited from other hospital environments. Again, readings in excess of 140/90 mm Hg were communicated to prospective controls with the advice to visit the family practitioner for follow-up measurements. Such women were excluded from further study. Mouth wash specimens for DNA extraction were collected from both cohorts.

The DNA specimens were tested for 12 of the most common mutations in the UK by means of Elucigene kits (Orchid Biosciences), which cover >87% of UK CF mutations, F508, G551D, G542X, 621+1 g>t, R560T, W1282X, 1717–1 g>a, 3849+10Kb c>t, R553X, R117H, R1162X, and R334W. Given the benign nature of the 1717–1 g>a and 621+1 g>t polymorphisms, a finding of R117H was followed by a reflex test of the intron 8 exon acceptor site and, for the purposes of this study, only those with the 5t polymorphism were regarded as having a mutation.8

The results of carrier testing were divulged to women who wished to know them and, with their permission, to their medical care givers. The letter giving the result offered genetic counseling. All studies received ethical approval from the Central Manchester, Salford, and South Manchester Local Research Ethics Committees.

### Data Analysis

The primary analysis for study 1 was prespecified as an analysis of covariance allowing for age. Because the blood pressure data showed a skewed distribution, log-transformed blood pressures were used in the analysis. Inspection of the data showed some curvature in the age effect and therefore a quadratic term was included in the analysis. Likelihood ratio tests were used to compare models including group and group by age interactions with models excluding the group effects. To give more interpretable parameters, models excluding the quadratic term were used, giving an overall age-averaged slope for comparison between groups. For presentation, this log-scale slope is expressed as a percentage change in blood pressure per decade. Because there was evidence of influential outliers, a robust regression was used to confirm the significance of the main findings.9

Additionally, the data were divided arbitrarily into 3 age groups, based on the tertiles of the age distribution, and blood pressure compared between groups using Mann–Whitney U tests and their associated 95% confidence intervals. The choice of 3 equal-sized groups was prespecified, but the actual tertiles were derived from the data.

The proportions of mutation carriers in the 2 groups of study 2 were compared using Fisher exact tests and by computing odds ratios and their exact confidence intervals. Logistic regression was used to produce age-adjusted odds ratios.

### Results

#### Study 1

The 232 CF mutation carriers and 246 mutation-negative controls were well-matched for age and anthropometric and menstrual cycle stage characteristics (Tables 1 and 2). Both systolic and diastolic pressures showed the expected increase with age in both groups of women (Figure). However, the CF mutation carriers showed a smaller rise with a more gradual slope, especially after 50 years. A quadratic regression model of log-transformed blood pressure shows that the 2 groups are significantly different for systolic pressure (P=0.017) but not diastolic (P=0.22).

A simpler linear model gives age-averaged rates of change in blood pressure (Table 3). The data show a decreased slope for carriers compared with controls (3.5%/decade compared

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Characteristics of the 2 Groups</th>
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<tbody>
<tr>
<td>Demography*</td>
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<tr>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
</tr>
<tr>
<td>Age (median, IQR) cm</td>
</tr>
<tr>
<td>Height (median, IQR) cm</td>
</tr>
<tr>
<td>Weight (median, IQR) kg</td>
</tr>
<tr>
<td>BMI (median, IQR) kg/m²</td>
</tr>
<tr>
<td>Skinfold thickness (median, IQR) mm</td>
</tr>
<tr>
<td>Hormonal contraceptive use, %</td>
</tr>
<tr>
<td>Menstrual cycle (early, mid, late, NA†)</td>
</tr>
</tbody>
</table>

*Height, weight, body mass index, and hormonal contraceptive use and cycle data were obtained for 229 carriers (and all controls); skinfold measurements were obtained for 204 carriers.†Not available because of irregular cycle, postmenopausal, or not recorded.

IQR indicates interquartile range.
with 5.4%/decade), again statistically significant for systolic (P=0.010) but not diastolic pressure (P=0.28) (Table 3).

The data show a few potential outliers (Figure), particularly one of the older carriers, which shows the lowest blood pressure in the study and has symptomatic hypotension. A sweat test in this subject showed sodium 69 mmol/L and chloride 50 mmol/L, which are high levels and a possible cause of her low blood pressure. This subject was included in the sweat test study. There is no objective reason to exclude any participants. Therefore, we undertook a robust regression analysis that downweights the outliers in a systematic way, and in this analysis the difference in systolic blood pressure–age relationship remained significant (P=0.037).

The increasing effect of CF carrier status with age is readily seen if the data are divided into 3 age bands using the tertiles of the age distribution (Table 4). Here both systolic and diastolic blood pressure are significantly lower in CF carriers than controls in the older age group, although the diastolic difference would not be considered significant if an adjustment for multiple testing were used.

Within the ANCOVA framework, there is no evidence of a differential effect on blood pressure between the most common CF mutation ΔF508 and the other mutations, although by far the biggest number carried ΔF508.

We have recomputed the effect sizes adjusting for each of the potential confounders in addition to age: body mass index, menstrual cycle stage, hormonal contraceptive usage, and use of medication, all of which can affect blood pressure (data not shown). These adjustments make no substantive difference to the estimated effect sizes nor do their confidence intervals, and the difference in the slope with age remains statistically significant.

The median sweat sodium in 9 carriers with especially low blood pressure was 49 mmol/L (range, 19 to 107) compared with a median of 30 mmol/L (range, 22 to 90) in 7 hypertensive carriers with the highest blood pressures and compared with a median 28 mmol/L (range, 16 to 33) in 7 negative controls, of whom 4 had especially low blood pressure, 1 had normotension, and 2 had high blood pressure. Sweat chloride levels showed very similar trends. Three carriers with especially low blood pressures had very high sweat sodium and chloride levels, as did 1 hypertensive carrier (see discussion).

None of the subjects had any symptoms of CF, and in all cases sweat sodium exceeded sweat chloride, whereas in the disease the converse occurs. Given the small number of recruits, these results are not significant in themselves.

Study 2
We recruited 563 normotensive females and 607 women with essential hypertension. The median age range was 60, with a range of 17 to 89 (interquartile range, 50 to 69). Twenty-five (4.4%) of the normotensive group were found to be carriers of a CF mutation, compared with 21 (3.5%) of the hypertensive carriers with the highest blood pressures and compared with a median 28 mmol/L (range, 16 to 33) in 7 negative controls, of whom 4 had especially low blood pressure, 1 had normotension, and 2 had high blood pressure. Sweat chloride levels showed very similar trends. Three carriers with especially low blood pressures had very high sweat sodium and chloride levels, as did 1 hypertensive carrier (see discussion). None of the subjects had any symptoms of CF, and in all cases sweat sodium exceed sweat chloride, whereas in the disease the converse occurs. Given the small number of recruits, these results are not significant in themselves.

Discussion
This is the first full study to our knowledge to test the hypothesis of a link between the CF carrier state and reduced

![Systolic and diastolic blood pressure as a function of age for CF mutation carriers (closed symbols and solid lines) and controls (open symbols and dashed lines). The lines represent the fit from a quadratic regression model of log-transformed blood pressure.](http://hyper.ahajournals.org/)
blood pressure. Blood pressures in our study group agree closely with those of the 1946 British birth cohort\(^{10}\) for female blood pressure. Blood pressures in those women negative on CF mutation testing also compared well with the results from the 1996 Health Survey for England.\(^{11}\)

Our findings of lower systolic blood pressures and a slower rise in pressure with age in white female CF mutation carriers are of potential public health significance. Diastolic pressure showed a similar trend, but the association with carrier status was statistically weaker. Much has been written on the causes of the rise in blood pressure in postmenopausal females. Our data suggest a role for the CF gene in modulating this age-associated rise.

The mechanism for the blood pressure differences is likely to reside in changes in sodium loss, with the sweat gland more likely than the kidney to account for this. Increased sweat salt losses in carriers would contribute to lower blood pressure. This effect could be confined to females if it is more than offset by factors such as the increased blood volume and red cell count,\(^{12}\) androgens causing stimulation of renal sodium reabsorption,\(^{13}\) and increased muscle bulk,\(^{13}\) all of which result in higher blood pressure of males. Differences in aldosterone responsiveness in postmenopausal females may explain the gender difference and why our findings are confined to older women. However, we do intend to study a male cohort.

The kidney is the main organ implicated in genetic abnormalities of sodium associated with low blood pressure.\(^{14}\) Thus, in Gitelman syndrome, mutations in the Na\(^+\)Cl\(^-\) transporter result in reduced blood pressure by diminishing renal sodium reabsorption. Different mutations in the \(\alpha\), \(\beta\), and \(\gamma\) subunits of ENaC cause pseudohypoaldosteronism with reduced renal and sweat gland sodium reabsorption and lower blood pressures. It is interesting to note that Lifton\(^{14}\) postulates that heterozygotes for these rare disorders might also have low blood pressure. Although the CF transmembrane conductance regulator (CFTR) is expressed in the kidney, and proximal convoluted tubule urine is sodium-rich, with the adrenal–renal axis intact, reabsorption of this sodium occurs and no net sodium and chloride renal losses occur in CF patients.\(^{15}\)

The same does not apply to the sweat gland in which chloride loss is the basic defect caused by mutations of the CF gene CFTR\(^{16}\). Further, there is a close interaction between CFTR and ENaC in the sweat gland. Quinton and Reddy\(^{17}\) have shown clearly that ENaC function in the sweat gland depends critically on intact CFTR in reabsorbing sodium and that failure to absorb NaCl in CF is not only a result of loss of intact CFTR but also a result of secondary inability to activate ENaC. Under resting conditions, serum sodium and chloride levels in CF patients are the same as in healthy controls, although they decrease on salt depletion.\(^{18}\) There have been no such studies on CF carriers. Legris et al\(^{18}\) found reduced mean blood pressure in CF patients, which decreased significantly during a salt depletion phase of their experiments, despite markedly increased plasma renin, aldosterone, and angiotensin. They ascribe their findings to sweat salt loss with vigorous renin, aldosterone, and angiotensin responses helping to maintain blood pressure. The lower blood pressures and further drop on salt depletion show that the kidney is not able to compensate fully for the excessive sweat sodium and chloride losses. Clearly, effects would be less marked in healthy carriers than in those affected by CF, but there is likely to be slight chronic hyperstimulation of the renin-angiotensin-aldosterone axis in them, too. It is interesting that differences in blood pressure between our carriers and negative controls only manifested in middle age. Although ours was a cross-sectional and not a longitudinal study, it is tempting to speculate whether, with chronic hyperstimulation of the renin-angiotensin-aldosterone axis, relative failure of these mechanisms in older CF carriers occurs, leading to lowering of blood pressure with continuing sweat hyperelectrolytemia. Postmenopausal females have been shown to have low basal aldosterone levels and a reduced increment in aldosterone in response to angiotensin II on a low-salt diet.\(^{19}\) This is in contrast to males of any age and premenopausal women. Thus, men and younger women, including CF carriers, may maintain blood pressure despite sweat salt losses. Further studies in elderly male and female carriers are indicated.

An inverse relationship between sweat sodium and blood pressure was found by Quintero-Acenzio\(^{20}\) both in normotensives and hypertensives, although Levi in a separate study\(^{21}\) could not confirm this. It is interesting to note that 47 of the 53 who Quintero-Acenzio studied were female, whereas only 12 of 31 were female in Levi’s study. Our small sweat test study is consistent with the suggestion that the sweat sodium and chloride losses account for lower blood pressure in CF carriers. Although we studied rather few subjects, there were remarkably high sweat sodium and chloride levels in 3 women with especially low blood pressures (all <100 mm Hg systolic and 50 mm Hg diastolic) and sodium (107, 85, and 69 mmol/L) and chloride (93, 63 and 50 mmol/L) levels, respectively. One hypertensive carrier had sweat sodium of 90 and sweat chloride of 74 mmol/L. None of the subjects had any symptoms to suggest CF. None of the controls with low or high blood pressure had raised sweat electrolytes.

### TABLE 4. Blood Pressure for Age Using 3 Equal-Size Groups Based on the Tertiles of the Age Distribution (33.7 and 48.5 Years)

<table>
<thead>
<tr>
<th>Age Tertile</th>
<th>Controls Median (IQR)</th>
<th>CF Carriers Median (IQR)</th>
<th>Difference (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;33.7</td>
<td>114 (105–120)</td>
<td>113 (105–121)</td>
<td>0 (−3 to 4)</td>
<td>0.87</td>
</tr>
<tr>
<td>33.7–48.5</td>
<td>118 (106–128)</td>
<td>116 (108–131)</td>
<td>−1 (−5 to 4)</td>
<td>0.62</td>
</tr>
<tr>
<td>&gt;48.5</td>
<td>133 (123–147)</td>
<td>129 (114–138)</td>
<td>7 (2 to 13)</td>
<td>0.009</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;33.7</td>
<td>65 (58–74)</td>
<td>63 (57–72)</td>
<td>2 (−1 to 4)</td>
<td>0.32</td>
</tr>
<tr>
<td>33.7–48.5</td>
<td>69 (62–80)</td>
<td>68 (62–78)</td>
<td>0 (−3 to 3)</td>
<td>0.91</td>
</tr>
<tr>
<td>&gt;48.5</td>
<td>79 (69–85)</td>
<td>73 (67–80)</td>
<td>4 (0 to 8)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Median and IQRs are shown along with the CI and significance level of the difference using a Mann–Whitney U test.
It should be noted that CFTR forms part of a macromolecular complex\(^\text{22}\) and interacts with a number of other pathways that regulate blood pressure.\(^{23,24}\)

Lower systolic and diastolic pressure in older women carrying a CF gene is likely to have significant protective effect against the development of stroke and of heart disease. Lowering blood pressure is associated with reduced incidence of both conditions.\(^{25}\) In this context, our finding of a reduction of 7 mm Hg in systolic and 4 mm Hg in diastolic pressure may be viewed as highly significant and could be associated with a 30% reduction in stroke and 20% reduction in myocardial infarction. Because in many Western populations as many as 1 in 25 carry a CF gene, this is an observation of considerable significance. Indirectly, our study supports the findings of the Inersen Trial in which rise in blood pressure with age was correlated with sodium intake.\(^{26}\)

Macek\(^{27}\) found a significant excess of the B haplotype, the background on which most important CF mutations occur in 191 elderly (older than age 75 years; mean age, 83 years) Czechoslovakian women, when compared with younger women and elderly or young men. There was a steady rise in this haplotype from female infancy to old age. Macek suggests that the selection process for this haplotype might have been subtle and extending from prereproductive to postreproductive years in these women but gives no explanation as to a possible cause of his finding. A lower incidence of stroke and heart disease might be the explanation. The B haplotype has been more closely associated with actual levels of sweat sodium and chloride than specific CFTR mutations, including ΔF508 in CF patients,\(^{28}\) and it is possible that there are genes just outside the CFTR gene but in strong linkage equilibrium with it, which are as important in regulating sweat electrolytes as is CFTR.

Our findings suggest that the cardiovascular benefit gained from lower blood pressure in female CF carriers would confer a survival advantage. This could increase public interest in being carrier-tested. Although study 2 did not show a statistically significant reduction in the number of CF carriers in the hypertensive versus normotensive groups, the estimate of the odds ratio of 0.71 is in the expected direction and the 95% CIs are wide (0.35 to 1.41) and consistent with a strong protective effect against hypertension. With relatively low carrier rates of 1 in 25, a much larger study (\(\approx 10,000\) participants) would be needed to confirm the modest effect found. Although other factors resulting in clinical hypertension are likely to be more powerful than any protection afforded by the CFTR gene, it remains conceivable that the level of blood pressure observed in carriers is not as severe as in noncarriers, perhaps with hypertension easier to control. To demonstrate this would require a longitudinal study of blood pressure levels and drug dosages. If it were shown to be true, then new avenues of hypertension treatment based on modulation of CFTR effects could emerge.\(^{29}\)

**Perspectives**

We have demonstrated that older CF carriers have lower blood pressures than noncarrier women and a substantially attenuated rise in pressure with age. This could confer considerable protection against circulatory diseases and be of considerable public health significance. It could explain the increased life expectancy reported in other European cohorts. A cohort of males needs to be studied to ensure whether the phenomenon is truly confined to females.

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