Seven-Year Follow-up of Cardiovascular Study and Maximal Exercise of Chinese Men


SUMMARY

A seven-year follow-up in 1973 of a prospective cardiovascular study of 1820 initially healthy, middle-aged Chinese men of 40–59 years of age identified 1745 (95.9%) known survivors, 49 (2.7%) interim deaths, and 26 (1.4%) who could not be traced. Of the survivors, 1462 (83.8%) were re-examined, 292 (16.7%) had another treadmill test of maximal exercise, and 283 (16.2%) failed to return for re-examination. On the basis of interim surveillance of hospital admissions, questionnaires and re-examination, a greater incidence of noncardiovascular events (338 or 18.6%) than evidence of cardiovascular disease (220 or 12.1%) was found, while the majority (1021 or 56.1%) remained healthy. Total mortality was 0.29% for men under 50, and 0.76 per 100 person-years for men of 50 or more years of age. Only nine, or 18.4% of the deaths were due to cardiovascular causes, and unexpectedly for this population sample, only three were attributed to stroke. When cardiovascular morbidity was related to presence of ST depression after maximal exercise, to hypertension at rest by WHO criteria, to both findings, or to absence of either on initial intake examination, incidence increased from 2.3% for NEITHER group, to 5.7% for ST group, to 11.9% for HT group, and to 25.0% for BOTH groups. Re-examination revealed more evidence of cardiovascular disease than did surveillance of hospital admissions. Additional to effects of aging and mild adiposity, longitudinal changes in blood pressure and ST depression, increasing in the NEITHER group, but less frequent in the other groups, showed some evidence of regression toward the mean, as well as emerging disease and the confounding effects of uncontrolled treatment of hypertension in many. The potential for prediction of subsequent cardiovascular morbidity or mortality appeared stronger for hypertension than for postexertional ST depression, although the two were additive in this population, which is more prone to hypertension and stroke but now is developing clinical manifestations of coronary heart disease more frequently.

Additional Indexing Words:
Epidemiology
Mortality
Coronary heart disease

A PROSPECTIVE CARDIOVASCULAR STUDY of Chinese men was initiated in 1965 by the National Defense Medical Center in Taipei in collaboration with the University of Washington in Seattle. The primary purpose was to ascertain whether ST depression after maximal exercise testing would be predictive of future clinical manifestations of cardiovascular disease in that population. Whereas the Chinese exhibit coronary heart disease less frequently and less severely than men in the United States, they experience hypertension as the major cause of cardiovascular morbidity and stroke as the primary cause of death. A preliminary pilot study has already established lower serum concentrations of cholesterol and lower prevalence of postexertional ST depression, as well as the feasibility of maximal exercise testing with a modified multistage treadmill protocol. During 1965-1966, 1820 Chinese men of 40–59 years of age and from the upper socio-economic levels in military and civilian occupations volunteered for examination and testing. ST depression of at least 1 mm for one minute or longer was found in 18 of 476 men who were observed for only three minutes after exercise, and in 94 of 1346 men who were observed for six minutes. In the latter group, hypertension at rest (WHO criteria of systolic pressure of 160 or more, or diastolic pressure of 95 or more) was found in 161 (12%). ST depression, however, was four times as frequent in hypertensive as in age-matched normotensive men. Multivariate analysis identified age, systolic pressure at maximal exercise, and abnor-
mality in the resting ECG as major factors associated with the postexertional ST response to maximal exercise.

In the intervening years, incidence of subsequent events was appraised by questionnaire and surveillance techniques, and in 1973 all available men were re-examined. The seven-year follow-up of cardiovascular events and of maximal exercise testing of a 20% sample are reported here.

**Material and Methods**

Nearly continuous surveillance of hospital admissions for evidence and classification of causes of morbidity or mortality among the 1820 men enrolled in the study was conducted by a trained public health nurse reporting to cardiologists and epidemiologists. Periodically, questionnaires were submitted by mail to ascertain interim health status. In 1972-1973 letters and telephone calls to 1771 surviving men elicited 1745 responses, leaving only 26 (1.4% of 1820) lost to follow-up. Of these respondents, 1462 (83.2% of 1745) returned for re-examination in 1973.

For preliminary analysis of events, all men were retrospectively classified into mutually exclusive categories in rank order, beginning with subsequent cardiovascular mortality, morbidity by interim surveillance, signs of cardiovascular disease on re-examination, noncardiovascular mortality or morbidity by surveillance, persistence of initial signs without interim changes, persistent good health or status unknown (fig. 1). Also for more detailed analysis, all men have been prospectively classified into one of four mutually exclusive subgroups, i.e., those initially exhibiting neither ST depression after exercise nor hypertension at rest ("NEITHER"), those exhibiting ST depression of at least 1 mm for 1 minute or longer after maximal exercise ("ST"), those exhibiting hypertension at rest by WHO criteria ("HT"), and those exhibiting both hypertension at rest and ST depression after maximal exercise ("BOTH").

The protocol for the second examination was nearly identical to that for the first examination, except that blood samples were tested by a different laboratory with minor and negligible differences in standards. In addition to conventional 12-lead electrocardiograms at rest, Frank x,y,z leads were recorded on magnetic tapes which were sent to Seattle for analysis of polarenderiograms and vectorcardiograms (to be reported separately). Only the available men in ST, HT, and BOTH groups and in their previously age-matched control groups repeated the multistage treadmill test of maximal exercise. Another modification was the collection of expired air at 60-second intervals for determination of maximal oxygen uptakes \( (V_{O_{2\max}}) \) during exercise, and subsequent calculation of functional aerobic impairment (FAI) in relation to Chinese standards, by methods reported elsewhere.  

Data punched on Hollerith cards were verified in Taipei and sent to Seattle for computer analysis by the Conversational Computer Statistical System. Differences in fre-

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**Figure 1**

Mutually exclusive classifications, in rank order of clinical importance, after interim surveillance and second examination. (The persistence of previously recognized items, e.g., Prior LVH, HT and CM, constitutes an initial prevalence rather than incidence of new items.) Each person was entered (only once) into the highest classification appropriate.

Abbreviations: AP = angina pectoris; CM = cardiomegaly; CVA = cerebrovascular accident; CVD = cardiovascular disease; HT = hypertension; LVH = left ventricular hypertrophy; MI = myocardial infarction; SCD = sudden cardiac death. Scale is logarithmic.

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frequency of discrete variables were appraised by Chi square, whereas differences in measurements of continuous variables were appraised by t-testing. Morbidity (which was defined as admission to hospital) and mortality rates were computed per 100 person-years of observation from the observed differences in months from time of initial testing to either the event or the follow-up examination.

Results

The data are tabulated in relation to a retrospective analysis of subsequent classifications (table 1), changes over seven years in prevalences of discrete variables (table 2), changes in continuous variables at rest (table 3) and with maximal exercise (table 4), and morbidity-mortality rates (table 5).

Current Distribution of Subjects

Distribution of 820 men examined in 1965-1966 according to the retrospective analysis of subsequent mutually exclusive categories of cardiovascular and other events detected by interim surveillance or by re-examination in 1973 is shown in figure 1. The incidence of cardiovascular events was 43 (2.4%) on the basis of interim surveillance, and 177 (9.7%) on the basis of the re-examination. Thus, the total incidence was 220 (12.1%). The incidence of noncardiovascular events was 338 (18.6%). Altogether, 166 (9.1%) showed a persistence of the initial prevalence of left ventricular hypertrophy, hypertension, or cardiomegaly without any other intervening changes, additional morbidity, or mortality. The largest fraction, 1021 (56.1%) remained healthy, and the status of 75 (4.1%) was unknown.

Changes in distribution in relation to the initial four-way classification, subsequent losses to follow-up, mortality, morbidity, and known survival but lost to re-examination are shown in table 1. Since separate analysis of morbidity and mortality incidences showed

<table>
<thead>
<tr>
<th>Initial classification</th>
<th>NEITHER ST‡ nor HT</th>
<th>Only ST‡</th>
<th>Only HT</th>
<th>BOTH ST ‡ and HT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initially tested in 1965-1966</td>
<td>1571 (86.3%)</td>
<td>88 (4.8%)</td>
<td>137 (7.5%)</td>
<td>24 (1.3%)</td>
<td>1820 (100.0%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>22 (1.4)</td>
<td>1 (0.1)</td>
<td>3 (0.2)</td>
<td>0 (0.0)</td>
<td>26 (1.4)</td>
</tr>
<tr>
<td>Survival status known in 1973*</td>
<td>1549 (98.6)</td>
<td>87 (98.9)</td>
<td>134 (97.8)</td>
<td>24 (100.0)</td>
<td>1794 (98.6)</td>
</tr>
<tr>
<td>Civilian</td>
<td>797 (51.5)</td>
<td>39 (44.8)</td>
<td>58 (43.3)</td>
<td>9 (37.5)</td>
<td>903 (50.3)</td>
</tr>
<tr>
<td>Military</td>
<td>752 (48.5)</td>
<td>48 (55.2)</td>
<td>76 (56.7)</td>
<td>15 (62.5)</td>
<td>891 (49.7)</td>
</tr>
</tbody>
</table>

Mortality

Noncardiovascular

Cardiovascular

Subtotals

(Per 100 man-years observation)

40-49 years of age

50-59 years of age

Survived to September 3, 1974, without clinical events by surveillance

<table>
<thead>
<tr>
<th>Initial classification</th>
<th>NEITHER ST‡ nor HT</th>
<th>Only ST‡</th>
<th>Only HT</th>
<th>BOTH ST ‡ and HT</th>
<th>Total</th>
</tr>
</thead>
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<td>76 (56.7)</td>
<td>15 (62.5)</td>
<td>891 (49.7)</td>
</tr>
</tbody>
</table>

Morbidity by surveillance‡

Noncardiovascular

Cardiovascular

Subtotals

Lost to re-examination, but known to be alive

Reasons

Not available for examination

Currently ill

Failed appointment

Refused

Subtotals

Re-examined, 1973

Re-exercised, 1973

*Denominators for frequencies by columns.
†Omitting three men with unknown dates of death.
‡Subjects hospitalized one or more times during seven-year follow-up period.
Abbreviation: HT = hypertension.
Prevalences of Discrete Variables (Percentages)

<table>
<thead>
<tr>
<th>Initial classification</th>
<th>NEITHER ST+ nor HT</th>
<th>Only ST+</th>
<th>Only HT</th>
<th>BOTH ST+ and HT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number examined, 1965-6/1973</td>
<td>1549/1265</td>
<td>87/74</td>
<td>134/103</td>
<td>24/20</td>
<td>1794/1462</td>
</tr>
</tbody>
</table>

Clinical history

Angina | 0.0 | 0.4 | 0.0 | 5.4 | 0.0 | 1.9 | 0.0 | 15.0 | 0.0 | 1.0 |
Myocardial infarction | 0.0 | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 |
Stroke (CVA) | 0.0 | 0.1 | 0.0 | 0.0 | 0.0 | 4.9 | 0.0 | 0.0 | 0.0 | 0.4 |
Renal diseases | 1.1 | 1.4 | 0.0 | 0.0 | 0.7 | 2.9 | 0.0 | 0.0 | 1.0 | 1.4 |
Thyroid diseases | 0.3 | 0.9 | 0.0 | 0.0 | 0.0 | 3.9 | 0.0 | 0.0 | 0.2 | 1.0 |
Diabetes | 0.6 | 1.8 | 0.0 | 1.4 | 0.0 | 1.9 | 0.0 | 0.0 | 0.6 | 1.8 |

Chest X-ray

Emphysema, moderate to severe | 2.7 | 2.6 | 1.2 | 2.7 | 0.0 | 1.0 | 0.0 | 0.0 | 2.4 | 2.5 |
Bronchovascular markings, light to heavy | 3.7 | 6.1 | 1.2 | 6.8 | 1.5 | 7.8 | 4.2 | 0.0 | 3.4 | 6.2 |
Pulmonary infiltration or cavitation | 4.0 | 1.0 | 3.4 | 1.4 | 2.2 | 1.9 | 8.3 | 0.0 | 3.9 | 1.1 |
Cardiothoracic ratio > mean + 2 sd | 2.1 | 1.3 | 3.4 | 0.0 | 4.5 | 3.9 | 0.0 | 5.0 | 2.3 | 1.5 |

Resting 12-lead ECG

Q Abnormalities | 0.0 | 0.7 | 0.0 | 2.7 | 0.0 | 8.1 | 0.0 | 0.0 | 0.0 | 1.2 |
LAD (< -30°) | 3.4 | 7.8 | 3.4 | 6.8 | 3.0 | 13.5 | 16.7 | 25.0 | 3.5 | 8.1 |
LAD (> +90°) | 2.5 | 2.3 | 1.2 | 1.4 | 0.0 | 2.7 | 0.0 | 0.0 | 0.0 | 2.2 |
LVH | 2.4 | 3.2 | 0.5 | 6.8 | 4.5 | 13.5 | 8.3 | 0.0 | 2.8 | 3.8 |
RVH | 0.6 | 0.6 | 0.0 | 0.0 | 0.0 | 1.4 | 0.0 | 0.0 | 0.5 | 0.6 |
ST Depression ≥ 1.0 mm | 0.1 | 1.6 | 1.2 | 6.8 | 0.0 | 6.8 | 0.0 | 0.0 | 15.0 | 0.2 | 2.3 |
ST Depression ≥ 0.5 mm | 0.5 | 9.2 | 8.0 | 36.5 | 3.0 | 40.5 | 12.5 | 35.0 | 1.1 | 12.4 |
T Abnormalities | 2.6 | 5.5 | 12.6 | 27.0 | 6.0 | 23.0 | 25.0 | 20.0 | 3.7 | 7.5 |
Arrhythmias | 7.6 | 7.8 | 6.9 | 14.9 | 13.4 | 16.2 | 4.2 | 10.0 | 7.9 | 8.5 |
FBS ≥ mean + 2 sd, mg/100 ml | 2.1 | 2.5 | 3.4 | 1.4 | 5.2 | 2.9 | 0.0 | 10.0 | 2.4 | 2.6 |
2 hr BS ≥ mean + 2 sd | — | 2.1 | — | 0.0 | — | 1.8 | — | 0.0 | — | 2.9 |
Hypertension (WHO criteria) | 0.0 | 7.7 | 0.0 | 24.1 | 100.0 | 38.1 | 100.0 | 41.7 | 8.8 | 11.3 |

Abbreviations: LAD, RAD = left and right axis deviation; sd = standard deviation; LVH, RVH = left and right ventricular hypertrophy; FBS = fasting blood sugar.

no significant differences in relation to initial occupational classification of civilian or military personnel (Chi square = 6.03, 3 df, P = 0.11, not significant), data from these two population samples have been combined.

Analysis of Mortality

Mortality rates from all causes increased from 0.29 per 100 person-years for men initially under 50 years of age to 0.76 per 100 person-years for men of 50 or more years of age (table 1). The case fatality rates over the intervening seven years were only nine of 1820 (0.5%) for cardiovascular causes, and 40 of 1820 (2.2%) from other causes. Unlike most samples from populations of this age and sex, only 18.4% of the deaths could be ascribed to cardiovascular causes. This proportion was lower than that reported for all of Taiwan,6 Japan,7 Greece,8 and especially the United States.9 Again, unlike the usual experience for Taiwan, there were twice as many deaths from cardiovascular causes as from stroke (fig. 1).

Of nine deaths from cardiovascular causes or stroke, seven of which occurred in men from the NEITHER group, three were caused by stroke, two by myocardial infarction, one by sudden death, and one by another cardiac cause. The only death in the ST group was sudden cardiac, and the single death in the HT group was attributed to rupture of the aorta. Up to this time, there have been no deaths in the BOTH group (ST + HT). Of these four subgroups, the highest case fatality rate of one in 88 (1.1%) was in the ST group of men.

Analysis of Morbidity

The major cause of morbidity was not found to be cardiovascular. Morbidity from noncardiovascular causes occurred in 299 of 1820 men (16.4%). Only 34 men (1.9%) had hospital admissions for cardiovascular illnesses (fig. 1). The case attack rate for these increased from 2.3% in the NEITHER group to 5.7% in the ST group, and 11.9% in the HT group, and to 25% in the BOTH group of men (table 1). Whereas the in-
Table 3
Changes in Continuous Variables at Rest (Cross-Sectional Group Comparisons)

<table>
<thead>
<tr>
<th>Initial classification</th>
<th>NEITHER ST ↓ nor HT</th>
<th>Only ST ↓</th>
<th>Only HT</th>
<th>BOTH ST ↓ and HT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number enrolled with status known, 1965/1973</td>
<td>1549/1265</td>
<td>87/74</td>
<td>134/103</td>
<td>24/20</td>
<td>1794/1462</td>
</tr>
<tr>
<td>Age, years</td>
<td>47.2</td>
<td>54.2†</td>
<td>49.9</td>
<td>57.0†</td>
<td>48.3</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.3</td>
<td>168.1</td>
<td>167.2</td>
<td>167.0</td>
<td>168.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.7</td>
<td>64.4†</td>
<td>64.4</td>
<td>66.1</td>
<td>67.7</td>
</tr>
<tr>
<td>Arm circumference, cm</td>
<td>27.3</td>
<td>26.6†</td>
<td>27.9</td>
<td>26.0†</td>
<td>28.9</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>77.4</td>
<td>83.0†</td>
<td>80.7</td>
<td>80.0†</td>
<td>82.9</td>
</tr>
<tr>
<td>Relative weight, %</td>
<td>97.2</td>
<td>106.2†</td>
<td>103.0</td>
<td>110.6†</td>
<td>106.0</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>197</td>
<td>195</td>
<td>203</td>
<td>192*</td>
<td>209</td>
</tr>
<tr>
<td>Uric acid, mg/dl</td>
<td>3.8</td>
<td>5.0†</td>
<td>3.8</td>
<td>3.8</td>
<td>4.1</td>
</tr>
<tr>
<td>Fasting blood sugar, mg/100 ml</td>
<td>90.5</td>
<td>84.1†</td>
<td>93.7</td>
<td>83.8†</td>
<td>94.3</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>42.6</td>
<td>39.8†</td>
<td>42.1</td>
<td>39.1†</td>
<td>43.2</td>
</tr>
<tr>
<td>Vital capacity, liters</td>
<td>3.3</td>
<td>3.3</td>
<td>3.2</td>
<td>3.0*</td>
<td>3.3</td>
</tr>
<tr>
<td>Expiratory flow rate, liters/min</td>
<td>2.4</td>
<td>2.5†</td>
<td>2.3</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.42</td>
<td>0.45†</td>
<td>0.43</td>
<td>0.47†</td>
<td>0.44</td>
</tr>
<tr>
<td>Resting systolic blood pressure, mm Hg (physical examination)</td>
<td>116</td>
<td>122†</td>
<td>126</td>
<td>141†</td>
<td>157</td>
</tr>
<tr>
<td>Resting diastolic blood pressure, mm Hg</td>
<td>74</td>
<td>80†</td>
<td>79</td>
<td>86‡</td>
<td>100</td>
</tr>
</tbody>
</table>

The figures for each index are mean and ± standard deviation, respectively.
*P < 0.05.
†P < 0.01.
‡P < 0.001 (unpaired).
Unmarked items are not significant.
Relative Weight = \(\frac{\text{Observed Weight}}{\text{Predicted Weight}}\) × 100, where Predicted Weight in kg = −61.8 + 0.74 (height in cm) on the first examination, for all men.
### Table 1

**Changes with Maximal Exercise (Cross-Sectional Group Comparisons)**

<table>
<thead>
<tr>
<th>Response to exercise</th>
<th>NEITHER ST ↓ nor HT</th>
<th>Only ST ↓</th>
<th>Only HT</th>
<th>BOTH ST ↓ and HT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>0.6%</td>
<td>4.6%</td>
<td>5.8%</td>
<td>0.0%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13.8</td>
<td>7.7</td>
<td>12.6</td>
<td>4.3</td>
<td>20.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>40.5</td>
<td>24.5</td>
<td>41.6</td>
<td>31.9</td>
<td>29.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>86.5</td>
<td>70.6</td>
<td>78.2</td>
<td>66.7</td>
<td>80.3</td>
</tr>
<tr>
<td>Claudication</td>
<td>0.4</td>
<td>0.0</td>
<td>1.1</td>
<td>2.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4.2</td>
<td>9.1</td>
<td>4.6</td>
<td>27.5</td>
<td>6.0</td>
</tr>
<tr>
<td>ST depression ≥ 1 mm</td>
<td>0.0</td>
<td>4.2</td>
<td>100.0</td>
<td>42.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Mean duration of exercise, sec

- 492 ± 92
- 439± 92
- 467 ± 107
- 463 ± 85
- 404± 98
- 427 ± 97
- 356* ± 97
- 488 ± 92
- 421† ± 98

Mean duration of exercise, sec (unpaired)

- 492
- 439
- 467
- 463
- 404
c
- 427
- 356
- 488
- 421

FAD, %

- 7 ± 9
- 11 ± 0
- 7 ± 10
- 3 ± 85
- 4 ± 98
- 2 ± 97
- 9* ± 83
- 7 ± 92
- 3† ± 98

Before exercise

| SBP | 124 ± 122 | 134 | 141* | 157 | 143‡ | 156 | 147 | 127 | 133‡ |
| DBP | 78 ± 76* | 82 | 88‡ | 100 | 88‡ | 96 | 91 | 89 | 83‡ |

Maximal exercise

| SBP | 166 ± 173 | 182 | 194‖ | 203 | 184‡ | 208 | 204 | 170 | 182‡ |
| DBP | 74 ± 87‖ | 77 | 100 | 95 | 89 | 91 | 90 | 91 | 90 |

3' Recovery

| SBP | 143 ± 153 | 153 | 167‖ | 175 | 164‡ | 180 | 184 | 147 | 157‡ |
| DBP | 73 ± 79‖ | 77 | 90‡ | 81 | 89 | 92 | 91 | 92 | 91 |

6' Recovery

| SBP | 125 ± 135 | 135 | 140 | 154 | 144‡ | 163 | 150* | 128 | 135‡ |
| DBP | 77 ± 75‖ | 80 | 85‖ | 94 | 85‖ | 91 | 92 | 81‡ |

Resting heart rate

| SBP | 79 ± 78* | 77 | 79 | 84 | 78‖ | 75 | 77 | 79 | 78 |
| DBP | 11 ± 11 | 11 | 14 | 12 | 10 | 12 | 11 | 11 | 11 |

Maximal heart rate

| SBP | 174 ± 161‡ | 172 | 164‡ | 172 | 156‡ | 173 | 156‡ | 174 | 161‡ |
| DBP | 15 ± 17 | 15 | 15 | 15 | 16 | 16 | 16 | 16 |

3' Recovery heart rate

| SBP | 120 ± 109‖ | 118 | 112* | 121 | 105‡ | 121 | 107* | 120 | 108‡ |
| DBP | 16 ± 16 | 16 | 16 | 16 | 17 | 17 | 17 | 17 |

6' Recovery heart rate

| SBP | 108 ± 101‖ | 106 | 103 | 109 | 99‖ | 108 | 97* | 108 | 101‡ |
| DBP | 14 ± 14 | 12 | 13 | 15 | 12 | 17 | 15 | 14 |

SBPmax × HRmax/100

| 288 ± 281 | 312 | 320 | 350 | 287‖ | 358 | 324 | 294 | 294 |
| 51.3 ± 55.4 | 53.1 | 52.3 | 53.1 | 61.9 | 53.1 | 68.6 | 54.7 | 59.4 |

*P < 0.05.
†P < 0.01.
‡P < 0.001 (unpaired).
Unmarked items are not significant.
Table 5
Morbidity-Mortality Rates per 100 Person-Years of Observation (including manifestations of heart disease on second examination)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Cardiovascular and stroke events*</th>
<th>New asymptomatic hypertension†</th>
<th>Noncardiovascular events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rates (C.I.)†</td>
<td>N</td>
</tr>
<tr>
<td>Age 40–49 years</td>
<td>35</td>
<td>0.5 (0.4, 0.7)</td>
<td>95</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>46</td>
<td>1.3 (1.0, 1.7)</td>
<td>39</td>
</tr>
<tr>
<td>NEITHER</td>
<td>45</td>
<td>0.5 (0.4, 0.7)</td>
<td>117</td>
</tr>
<tr>
<td>ST</td>
<td>8</td>
<td>1.6 (0.7, 3.2)</td>
<td>17</td>
</tr>
<tr>
<td>HT</td>
<td>22</td>
<td>2.9 (1.8, 4.4)</td>
<td>0</td>
</tr>
<tr>
<td>BOTH</td>
<td>6</td>
<td>4.3 (1.6, 9.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Excluding new hypertension.
†Not apparent on first examination (1965–6).
‡C.I. = 95% confidence intervals.
P-values for one-sided tests of a difference in rates are less than 0.05 when comparing the "NEITHER" group with any of the other three groups, when comparing the two age groups for the cardiovascular and stroke rates, or when comparing the incidence of new asymptomatic hypertension between the "NEITHER" and "ST" groups.

The importance of re-examination of all available men is revealed by the greater incidence of angina pectoris by history (nine men), of diagnostic Q waves of prior myocardial infarction (not present on the first examination) (14 men), of new left ventricular hypertrophy by ECG (five men), or cardiomegaly by chest X-ray (12 men), and the appearance of new hypertension (134 men) (fig. 1). In relation to the initial four-way classifications, angina pectoris developed in 0.4% of the NEITHER group, 5.4% of the ST group, 1.9% of the HT group and 15% of the BOTH group (table 2). Q waves of old myocardial infarction were found in...
0.7%, 2.7%, 8.1% of the NEITHER, ST, and HT groups, respectively. New hypertension was observed in 7.7% of the NEITHER group and 24.1% of the ST group of men (table 2). Conversely, hypertension persisted in only 38.1% of the HT and 41.7% of the BOTH groups of men. Whereas the frequency of ST depression in the resting ECG increased in all four groups (table 2), the reproducibility of post-exertional ST depression fell to 42% of the ST group and 50% of the BOTH group (table 4). These variations in frequency of either hypertension at rest or ST depression after maximal exertion seven years after the initial observations illustrate in part the biostatistical phenomenon of regression toward the mean. Other possible factors include effects of apprehension on examination and testing, and the fact that 59 of the men were currently being treated with antihypertensive agents when re-examined. (Since the initial design of the study did not permit random allocation of patients for therapy, nor provide a protocol for treatment, the possible role of such therapy is difficult to assess.) None of the 74 men in the ST and the 20 men in the BOTH groups who were re-examined had strokes, but incidence of this event ranged from 0.1% in the NEITHER group to 4.9% of the HT group (table 2).

Relationship of Initial Findings to Subsequent Events

Comparison of 32 men who subsequently manifested coronary heart disease (CHD)* morbidity or mortality with 1549 men originally in the NEITHER group who did not experience CHD or stroke (CVA) events revealed a significantly older age (P < 0.05), increased weight and abdominal girth (P < 0.01), elevated resting and maximal systolic pressure (P < 0.05) and lower maximal heart rate (P < 0.001) on the initial examination. Ten (31%) of these men also exhibited post-exertional ST depression.

Of 12 men who developed strokes, initial examination showed even greater differences in systolic and diastolic blood pressures (P < 0.001) (fig. 3) and pressure-rate products (P < 0.01), but lacked significant differences with respect to age, weight, girth or ST responses.

Long-term Changes

Significant differences over seven years suggest three long-term changes (tables 2, 3, and 4): 1) the inexorable effect of aging with small reductions in vital capacity, arm circumference, heart rate at rest and at maximal exercise, and shorter duration of maximal exercise; 2) greater adiposity, increased body weight and abdominal girth, but no associated increase in serum cholesterol concentration; 3) an increase in blood pressure and in uric acid concentration in the NEITHER group and a fall in pressure, but not in uric acid, in the HT group of men. Cumulative distribution curves for the same 212 normotensive men and the same 80 hypertensive men who were observed at rest and during maximal exercise clearly illustrate some regression toward the mean with higher pressures in normotensive men, but with lower pressures in the hypertensive men on the second examination (fig. 4). This is less evident for diastolic pressures, especially in hypertensive men, despite the fact that some were currently receiving antihypertensive therapy at the second examination.

Variations in Resting Blood Pressure Changes with Age

The regressions of longitudinal changes in the same men over seven years, in relation to age on second examination and to classification of currently untreated hypertension (HT — no Rx), to currently treated

*Including four with angina by surveillance, nine more by re-examination, 14 with Q waves of "silent" myocardial infarction (M1) on follow-up examination in 1973, and three M1 by surveillance (with deaths of two) and two sudden cardiac deaths.
hypertension (HT-Rx) and to normotensive age-matched controls (NT) are shown in figure 5. The increments in systolic and in diastolic pressures at rest on the second examination were nearly the same in the normotensive controls over all ages observed. Likewise, the decrements in systolic and diastolic pressures were nearly the same over all ages, but only in the treated group of hypertensive men. Intermediate trends, and in opposite directions for systolic and diastolic pressures with respect to age, were found in the untreated hypertensive men. Thus, systolic pressure tended to increase in younger and to fall in older untreated patients, whereas diastolic pressure tended to fall in younger untreated hypertensive men.

Predictability of Subsequent Morbidity and Mortality

The potential predictive power of age, post-
exertional ST depression, and hypertension at rest in relation to subsequent morbidity and mortality from cardiovascular versus noncardiovascular causes is presented in table 5.

Age of 50 or more years is predictive at the 5% level (with one-sided test of difference) for cardiovascular or stroke events, but not for either new hypertension or noncardiovascular causes of morbidity or mortality. Postexertional ST depression has similar predictability for either cardiovascular events or new hypertension. Hypertension at rest, however, is a stronger predictor in these middle-aged Chinese of cardiovascular events, especially when ST depression is also observed. The higher incidence of morbidity or mortality from noncardiovascular causes is not related to the presence or absence of either hypertension at rest or postexertional ST depression.

Discussion

This seven-year study of evolving cardiovascular disease in middle-aged Chinese men in Taiwan is unique with respect to purpose, sampling, methods of testing, and follow-up appraisals. The primary purpose was to test the predictive power of postexertional ST depression for future events, particularly clinical manifestations of coronary heart disease, in a population sample known to exhibit an unusually low incidence of such events, both clinically and pathologically at autopsy.

The Chinese, like other Oriental populations, commonly experience hypertension, and the primary cause of death is stroke as a complication of hypertension. Taiwan represents a previously underdeveloped country which has rapidly evolved into a progressively more “Westernized” culture, with its associated life stresses and economic self-sufficiency. Whereas cardiovascular disease was not among the first ten causes of death ten years ago, it ranked third in 1973. The men recruited for this study were selected from the upper socio-economic ranks of military and civilian personnel, for two reasons: 1) they might be expected with time to be more prone to coronary heart disease,

![Figure 5](http://circ.ahajournals.org/)

**Figure 5**

*Longitudinal changes over seven years in resting blood pressure of the same 133 age-matched normotensive (NT), of 63 untreated hypertensive men (HT — no Rx), and of 59 hypertensive men who were currently being treated with antihypertensive medication (HT — Rx), in relation to most recent age. Note that systolic and diastolic pressures were higher, over all ages, in the normotensive controls, (P < 0.001) but lower over all ages, in the hypertensive men who were being treated. When the latter were compared with the intermediate, but different changes in the untreated hypertensive patients, the differences were not significant.*

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thus enough events were anticipated within a few years to appraise the hypothesis for the numbers of men examined; 2) all were eligible, as governmental employees, for high-quality medical care from the same group of physicians, and the opportunity for long-term continuity of medical supervision was distinctly better than average.

The method of stress testing used was a new departure for population studies, because maximal rather than only moderate exercise was required. The justification for this method was established by a prior pilot study which demonstrated its feasibility, acceptability and also lower age-specific prevalences of postexertional ST depression than had been observed on similar testing of American men in Seattle. 39

In a comparative study of 233 Chinese men who performed both a double-Master two-step test and the multistage treadmill test of maximal exercise, the prevalence of 1 mm or more ST depression was only one-third as great by the step test as by the treadmill test. 33 Furthermore, the depth of ST depression and frequency of arrhythmias were generally less with the step-test. When 31 other Chinese men in the initial pilot study were retested one year later, 29 (93%) showed identical responses to treadmill testing; of one borderline response and one positive response which became negative on retesting, the possibility of less than maximal effort could not be excluded. Inasmuch as the treadmill testing protocol used in Seattle was modified by the addition of a very low level "cool down" exertion of walking at 1 mph and 0% grade for 2 minutes, which was used to prevent postexertional hypotension originally observed in the pilot study of Chinese men, the maximal frequency of appearance of postexercise ST depression was usually delayed until four-to-six minutes after exercise. Accordingly, the observation period in recovery of 1346 men was lengthened to six minutes. A later study of 241 highly selected American men in Taiwan and Hong Kong, who were tested by the identical protocol used for the Chinese, also manifested a delay in appearance of ST depression. 44 This was attributed to the circulatory effects of walking slowly, which prevented venous pooling and a rapid decrease in cardiac output and coronary perfusion. The occurrence of ST depression was more frequently associated with higher systolic pressure during exercise than that observed for American men tested in Seattle and with minor ST-T abnormalities in the resting electrocardiogram.

The seven-year results now available are also unique with respect to causes of death, changes in blood pressure and ST responses, and the possibility of developing predictors of future cardiovascular disease. Unexpectedly, in contrast to the recent mortality experience for persons in Taiwan where the first cause of death is attributed to stroke, 41 only 3 (6%) of the 49 deaths in these selected Chinese men were due to this cause. and 25 (51%) were due to malignancy of liver, lungs, stomach, nasopharynx, and other organs. Also unexpectedly, where death due to cardiac diseases is now ranked fourth among causes of death, the six (12%) deaths from myocardial infarction (2), sudden cardiac death (2) and other cardiac diseases (2) in this study exceeded the number of fatalities from strokes.

The rising blood pressure of normotensive men, largely independent of age, and the falling pressures of hypertensive men, in part confounded by uncontrolled antihypertensive therapy in several patients, provide interesting documentation of the biostatistical phenomenon of regression toward the mean. 10 Similarly, the new manifestations of postexertional ST depression, together with loss of reproducibility of this response seven years later in the majority of subjects, may be another manifestation of this phenomenon. Yet it must be noted that parallel trends in longitudinal changes in blood pressure in relation to age are not apparent in untreated hypertensive Chinese men, and that evidence of a possible risk gradient in relation to hypertension may be emerging. There is a tendency for postexertional ST depression to be predictive of future cardiovascular events, and certainly its presence in combination with hypertension seems to be additive. Neither of these two variables, nor age over 49 years for that matter, is predictive of the more frequent occurrence of cardiovascular causes of morbidity or mortality. Thus, despite limitations in reproducibility, and regression toward the mean, both hypertension at rest and postexertional ST depression exhibit some predictability, and of the two, hypertension is, as might well be expected, more important in this population sample. The possibly confounding role of antihypertensive therapy is recognized, but a critical appraisal of its value cannot be made with this study design.

It should be noted that the relative predictive value of ST-segment depression after maximal exercise in these Chinese men, who tend to have significantly lower cholesterol levels, is different from the experience of Keys and associates who appraised ST response to low levels of exercise in relation to subsequent incidence of coronary heart disease in the United States. 15 These investigators, who had data from seven countries, found that ST depression was "highly predictive of CHD risk in U.S. men free of clinical CHD at entry to the study," but not in the non-U.S. cohorts.

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Variations in prevalence of postexertional ST depression should also be considered in pathophysiological terms. This response is merely a functional sign and not morphologic evidence of coronary vascular disease. It represents an abnormal metabolic demand-supply relationship at the myocardial cell membrane, and numerous functional causes, as cited elsewhere, contribute to this response. Thus, it is reasonable to observe a predictive relationship in population samples with a high incidence of coronary atherosclerotic heart disease which restricts oxygen supply to the myocardium, as in men in the United States, as well as to observe a relationship to minor repolarization abnormalities in the resting electrocardiogram and to greater than usual levels of systolic blood pressure as found in these Chinese men who are prone to develop hypertensive disease, and even to highly selected American men in the Orient, or to healthy asymptomatic American men in Seattle who achieve postmaximal performance.

Finally, with continued surveillance for another three years, the additional yield of morbidity and fatal events may well be enough to establish tentative predictive rates for cardiovascular disease, whether primarily due to hypertension or to coronary heart disease, which may then be applied prospectively to another population sample with similar characteristics to validate these findings.

Acknowledgments


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Seven-year follow-up of cardiovascular study and maximal exercise of Chinese men.
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