Heritability of cardiac size: an echocardiographic and electrocardiographic study of monozygotic and dizygotic twins

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ABSTRACT Because of the uncertainty as to the extent to which cardiac size is determined by exercise training vs genetic endowment, this study investigated familial (genetic plus common family environment) vs nonfamilial influences on cardiac size. College-age monozygotic twins (group 1, 31 sets), dizygotic twins (group 2, 10 sets), siblings of like sex (group 3, six sets), and nonrelated subjects (group 4, 15 sets) underwent echocardiographic and electrocardiographic tests, measurement of maximum oxygen uptake (VO₂max), and evaluation of pulmonary and body composition; mean intrapair differences of the four groups were compared. Mean intrapair differences in cardiac size varied as much for subjects in group 1 as for those in groups 2 and 3. However, subjects in groups 1, 2, and 3 had less variation (p < .05) than those in group 4. After the initial testing, 14 pairs of monozygotic twins, five sets of dizygotic twins, and six sets of siblings underwent 14 weeks of exercise training (both members participated) and all tests were repeated. After exercise training, subjects in group 1 still had as much intrapair variability in cardiac size as those in groups 2 and 3. The data suggest cultural familial influences are more important in determining cardiac size than nonfamilial influences or even genetic influences alone.


SEVERAL echocardiographic studies have been done on various groups of well-trained athletes to assess differences in cardiac size and function and how they may or may not relate to the specific mode of training. Additional studies have used echocardiography to evaluate cardiac changes that occur among nonathletic individuals who undergo a physical fitness program. However, very little information has been reported on the influence of heredity on the size, structure, and function of the heart. The question still remains, therefore, as to what extent the variations in cardiac function among individuals engaged in physical performance can be attributed to environmental conditions (primarily exercise training) or genetic endowment.

The purpose of this study was to determine the influence of familial (genetic plus family environment) vs nonfamilial factors on cardiac size with data from college-age subjects. Participants included monozygotic or identical twins, dizygotic or nonidentical twins, siblings of like sex (similar in age), and randomly paired unrelated subjects. With twins as subjects, the degree of genetic vs environmental contributions can be assessed, since monozygotic twins have the same genetic makeup (having descended from the same fertilized egg) and dizygotic twins are the same as brothers and sisters in their heredity (having descended from two separate fertilized eggs). Echocardiographic and electrocardiographic examination as well as measurements of maximal oxygen uptake (VO₂max) were used to assess intrapair differences between groups before and after exercise training.

Methods

Testing. Forty-one pairs of twins (n = 82; 31 sets of monozygotic twins [group 1] and 10 sets of dizygotic twins [group 2]) of both sexes, six pairs of siblings of like sex (group 3, n = 12; five pairs of sisters and one pair of brothers), and nonrelated male subjects (group 4, n = 30; 15 sets) participated in the study. A computer program randomly paired the nonrelated subjects. All subjects were of college age, and the age differ-

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Supported by funds from the Deseret Foundation and the Research Division of Brigham Young University.

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Received May 14, 1984; revision accepted Sept. 27, 1984.
ence of the group 3 pairs was less than 12 months. The members of each set of twins and sibling pair were raised together, and in most cases both individuals were living together at the time this study was conducted. All subjects were in good health and without history of heart disease. Twins were classified as monozygotic or dizygotic on the basis of serologic analysis. A 10 ml sample of venous blood was drawn from each twin. Seven blood group systems were tested (ABO, Rh, Kell, Duffy, MNS, Lewis, and P), identifying 18 blood group markers. Blood typing was performed according to the techniques of the American Association of Blood Banks and the manufacturer’s directions. Discordance in one or more of the blood typings was used as criteria for dizygosity. The twin pairs with identical genotypes were termed syngeneic. Because syngeneicism does not prove monozygosity, the probability of the twins being monozygotic was calculated. The probability for monozygosity was greater than 90% in all cases.

Informed consent was obtained from each patient before testing. All subjects underwent the following tests: appraisal of health and lifestyle history, a resting 12-lead electrocardiogram (ECG), a maximal graded stress test with the measurement of VO₂max, an M mode echocardiogram, and hydrostatic weighing.

The treadmill test protocol called for constant speed of 6 mph with increasing grades of 2.5% every 2 min until the subject reached exhaustion. Subjects were not allowed to use handrails. Expired air was continuously analyzed for percent oxygen and carbon dioxide with an OM-11 02 analyzer and an LB-2 CO2 analyzer (Beckman Instruments). Expired volume was measured with a Parkinson-Cowan high-speed gasometer (Dynascience) and was corrected to standard temperature, pressure, and dry conditions. An on-line computer (IMSAI 8080) was used to continuously compute oxygen uptake, CO₂ production, and respiratory exchange ratio. A five-breath summation was used for analysis. Subjects were hydrostatically weighed according to a method described by Luft et al.

A standard 12-lead resting ECG was recorded on a Siemens 3170 four-channel instrument. Chest electrodes were carefully placed to ensure consistency of the location of precordial leads. ECGs were recorded at end-tidal volume at paper speeds of 25 and 100 mm/sec for each lead. Measurements of intervals, durations, QRS voltages, and axes were carefully made with calipers. Heart rate and R wave voltages were statistically analyzed for this study.

M mode echocardiographic examination was performed with subjects in a supine and slight right anterior oblique position by means of a commercially available ultrasonic unit (Primus, Rohé Scientific) equipped with a 3.5 MHz transducer, long interval focus. All measurements were recorded on an LS-6 fiberoptic recorder (Honeywell) at end-tidal volume according to standards developed by the American Society for Echocardiography. A lead II ECG was also recorded simultaneously. The protocol followed during the echocardiographic examination has been previously described by Popp et al. A computerized system, previously described, was used to interpret the echocardiographic data. This system continuously measured and calculated left ventricular parameters and dimensional changes over several cardiac cycles. The following echocardiographic measurements were obtained by this computerized system: (1) left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) dimensions, measured at the onset of the QRS complex (F1) and at the point of maximum excursion of the left ventricular posterior wall (F2), respectively; (2) the point of greatest and least dimension between the endocardial surfaces of the interventricular septum and the left ventricular posterobasal wall, measured for left ventricular maximum and minimum dimensions; (3) left ventricular postero basal wall thickness measured as the distance between left ventricular endocardium and epicardium at F1 and F2. Based on the above measurements, the percent shortening of the left ventricular internal diameter was calculated as \((\text{LVEDD} - \text{LVESD}) / (\text{LVEDD} \times 100)\).

A method previously described by Teichholz et al. was used for left ventricular volume calculations, including (1) stroke volume as the difference between end-diastolic and end-systolic left ventricular volumes, (2) left ventricular wall volume calculated at F1 and F2, and (3) ejection fraction measured as stroke volume divided by left ventricular volume at end-diastole.

All ECGs were analyzed by one cardiologist and echocardiographic tracings were made by two echocardiologists. Random numbers were assigned to all subjects’ charts to ensure the cardiologist and echocardiologists would have no knowledge of the status and test sequence of subjects. Seventeen of the echocardiographic tracings that did not have an adequate number of cycles for computer measurement were measured by hand by an echocardiologist.

**Training.** After the initial testing, 28 monozygotic twins (14 pairs from group 1), 10 dizygotic twins (five pairs from group 2), and six pairs of siblings (from group 3) volunteered to participate in 14 weeks of supervised exercise. Both members of the pairs exercised. The training program consisted of 45 min jogging sessions 4 days per week at 85% maximal measured heart rate. A log was kept of each subject’s exercise progress in terms of exercise heart rate, duration, and distance covered during the exercise training sessions. Subjects repeated all tests after successful completion of the 14 weeks of training.

**Statistical analysis.** A one-way analysis of variance (ANOVA) was used to test the mean intrapair differences among the four groups before exercise training. Mean intrapair differences in group 1 were compared with the combined mean intrapair differences in groups 2 and 3. This can be justified by the fact that the pairs in group 3 were as genetically similar as those in group 2 and their ages were less than 12 months apart. One-way ANOVA was also used to determine postexercise mean intrapair differences for group 1 vs combined group 2 and group 3 pairs. Changes produced by training among groups 1 to 3 were also tested. In all cases, unequal variances between groups were assumed. Careful review of statistical methodology for genetic research as suggested by Bouchard and Malina was made in conjunction with the analysis of the data.

**Results**

**Pretraining results.** The mean anthropometric, electrocardiographic, and VO₂max data and the mean intrapair differences for all groups are listed in table 1. The mean intrapair differences in group 1 were significantly less than those in groups 2 and 3 with respect to height and percent body fat (p < .05), indicating a strong genetic component for these two variables. Although the mean intrapair weight difference of the twins in group 1 (2.2 kg) was less than that of the twins in group 2 (7.3 kg) and the siblings in group 3 (6.4 kg), as indicated in table 1, this was not a significant difference. Groups 1, 2, and 3 had significantly less mean intrapair difference in weight than group 4.

As indicated in table 1 and illustrated in figure 1, there was no significant mean intrapair difference in VO₂max among the four groups. The ECG data (intrapair difference) showed no significant difference...
among groups 1, 2, and 3 with regard to heart rate and R wave voltages. However, the resting heart rates for group 1 (mean intrapair difference 6.4 beats/min) and group 2 (mean intrapair difference 6.8 beats/min) were significantly more similar than that for group 4 (mean intrapair difference 11.1 beats/min). This is graphically illustrated in figure 1. The ECG voltage, R wave amplitude in lead V5 (also displayed in figure 1), was significantly more similar among the pairs in groups 1, 2, and 3 compared with group 4, whereas for

**TABLE 1**

Anthropometric, cardiac performance, and electrocardiographic variables (mean ± SD) and mean intrapair differences with sample size (number of sets)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Monozygotic (group 1)</th>
<th>Dizygotic (group 2)</th>
<th>Siblings (group 3)</th>
<th>Random pairs (group 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>MID</td>
<td>Mean ± SD</td>
<td>MID</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.8 ± 2.2 (29)</td>
<td>62.6 ± 7.3 (7)</td>
<td>62.8 ± 6.4 (6)</td>
<td>79.0 ± 15.4 (15)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.8 ± 1.3 (29)</td>
<td>168.6 ± 8.2 (7)</td>
<td>168.8 ± 5.7 (6)</td>
<td>—</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>9.6 ± 1.0</td>
<td>9.3 ± 4.9</td>
<td>8.6 ± 6.2</td>
<td>—</td>
</tr>
<tr>
<td>VO2 max (ml/kg)</td>
<td>51.7 ± 4.3 (29)</td>
<td>49.3 ± 4.8 (7)</td>
<td>44.5 ± 4.0 (6)</td>
<td>16.1 ± 9.0 (14)</td>
</tr>
<tr>
<td>Rest HR (bpm)</td>
<td>10.7 ± 2.5</td>
<td>7.0 ± 4.7</td>
<td>4.7 ± 3.3</td>
<td>6.4 ± 5.6</td>
</tr>
<tr>
<td>R wave V5 (mV)</td>
<td>15.5 ± 2.6 (30)</td>
<td>10.5 ± 4.1 (10)</td>
<td>12.8 ± 2.8 (6)</td>
<td>18.3 ± 7.0 (14)</td>
</tr>
<tr>
<td>R wave V6 (mV)</td>
<td>13.3 ± 2.4 (30)</td>
<td>9.7 ± 3.1 (10)</td>
<td>11.7 ± 3.0 (6)</td>
<td>14.0 ± 4.7 (14)</td>
</tr>
<tr>
<td>R wave max (mV)</td>
<td>16.0 ± 3.0 (30)</td>
<td>11.7 ± 4.8 (10)</td>
<td>13.0 ± 3.8 (5)</td>
<td>18.9 ± 7.0 (14)</td>
</tr>
</tbody>
</table>

MID = mean intrapair difference; HR = heart rate.

*Significant intrapair difference when compared with nonrelated subject (group 4) intrapair difference, p < .05.

**FIGURE 1.** Graphic display of the mean intrapair differences of echocardiographic, electrocardiographic, and VO2 max data of four groups of college-age subjects (monozygotic, group 1; dizygotic, group 2; siblings, group 3; random subjects, group 4). Mean intrapair differences are represented by bar graphs (see key at base of figure). R max = maximal ECG R wave voltage; LV = left ventricular; ED = end-diastole; ES = end-systole; PW = posterobasal wall thickness.
maximum R wave amplitude, the pairs in groups 1 and 3 were more similar when compared with subjects in group 4.

Table 2 lists the mean echocardiographic data and the mean intrapair difference of the four groups. Only the left ventricular posterobasal wall at end-systole showed significantly less difference in group 1 twins when compared with the group 2 twins and group 3 pairs combined. As indicated in the table, the mean intrapair difference of the left ventricular dimension at end-diastole was significantly less (p < .05) among the pairs in group 1 (2.3 mm), group 2 (2.6 mm), and group 3 (2.0 mm) when compared with the pairs in group 4 (5.5 mm). Intrapair differences of left ventricular dimension at end-systole were also less among the pairs in group 1 (2.0 mm) and group 2 (2.0 mm) (p < .05) when compared with the pairs in group 4 (5.0 mm). The mean intrapair difference in group 3 (2.6 mm) approached being significantly less than that in group 4 (p < .1). There was a trend in the pairs in groups 1, 2, and 3 toward less difference in stroke volume and ejection fraction than the group 4 sets, but only the stroke volume mean intrapair difference in group 3 (7.9 ml) was significantly less than that in group 4 (15.7 ml) (p < .05). See figure 1 for a graphic comparison of stroke volume and ejection fraction.

Training. After the 14 weeks of exercise training, the pooled data from all subjects indicated a significant training effect. The left ventricular end-diastolic dimension tended to increase, although the change did not reach significance (mean increase 1.9 mm; p < .07 after training). There was a significant decrease in resting heart rate (mean decrease 2.6 beats/min; p < .01) and percent body fat (mean decrease 2.7%; p < .01) and a significant increase in \( \overline{V_{O_2}} \text{max} \) (mean increase 9.2 ml/kg/min; p < .0001) and R wave amplitude in leads V5 and V6 (mean increases 2.3 and 2.6 mV, respectively; p < .05) after the 14 weeks of exercise.

There were no significant changes, however, in mean intrapair differences among pairs in group 1 vs groups 2 and 3 sets after training, suggesting that the

### TABLE 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Monozygotic (group 1)</th>
<th>Dizygotic (group 2)</th>
<th>Siblings (group 3)</th>
<th>Random pairs (group 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>MID</td>
<td>Mean ± SD</td>
<td>MID</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>44.8 ± 5.1</td>
<td>2.6 (26)</td>
<td>44.3 ± 5.1</td>
<td>2.6 (26)</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>30.4 ± 5.1</td>
<td>2.6 (26)</td>
<td>30.9 ± 5.1</td>
<td>2.6 (26)</td>
</tr>
<tr>
<td>Septal wall thickness at ED (mm)</td>
<td>8.8 ± 5.1</td>
<td>2.6 (26)</td>
<td>9.0 ± 5.1</td>
<td>2.6 (26)</td>
</tr>
<tr>
<td>LV wall vol. at ED (ml)</td>
<td>103.7 ± 5.1</td>
<td>2.6 (26)</td>
<td>100.7 ± 5.1</td>
<td>2.6 (26)</td>
</tr>
<tr>
<td>LV vol. at ED (ml)</td>
<td>93.2 ± 5.1</td>
<td>2.6 (26)</td>
<td>89.4 ± 5.1</td>
<td>2.6 (26)</td>
</tr>
<tr>
<td>LV wall vol. at ES (ml)</td>
<td>113.8 ± 5.1</td>
<td>2.6 (26)</td>
<td>112.6 ± 5.1</td>
<td>2.6 (26)</td>
</tr>
<tr>
<td>LV vol. at ES (ml)</td>
<td>39.2 ± 5.1</td>
<td>2.6 (26)</td>
<td>33.8 ± 5.1</td>
<td>2.6 (26)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>53.3 ± 5.1</td>
<td>2.6 (26)</td>
<td>55.6 ± 5.1</td>
<td>2.6 (26)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>58.6 ± 5.1</td>
<td>2.6 (26)</td>
<td>61.8 ± 5.1</td>
<td>2.6 (26)</td>
</tr>
</tbody>
</table>

MID = mean intrapair difference; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; ED = end-diastole; ES = end-systole; LVPW = left ventricular posterobasal wall thickness.

*Significant intrapair difference when compared with group 4, p < .05.
*S{Significant intrapair difference when compared with groups 2 and 3 combined, p < .05.}
group 1 pairs did not become more similar with exercise training.

Discussion

The assessment of functional capacity has wide application in both the clinical testing of patients as well as the evaluation of human performance. Normal values, expressed as VO2 max, have been established and correlated with both the healthy and the diseased populations. Occasionally, however, an individual’s VO2 max will be well above the upper normal range, as is the case with champion endurance runners. The question has been raised as to whether or not these unusually high values are a result of genetic endowment or environmental conditions (i.e., years of regular exercise training). In identical (monozygotic) and nonidentical (dizygotic) twins, exercise performance studies have been done in which VO2 max and other related parameters were measured.18-23 Two of the investigations, conducted by Klissouras et al.,20,21 have found the mean intrapair difference of the monozygotic twins to be significantly less than that of the dizygotic twins, indicating a strong and predominant genetic contribution. Komi and Karlsson,22 Howald,19 and Bouchard et al.,18 on the other hand, found as much intrapair variation in VO2 max among the monozygotic twins as among the dizygotic twins, suggesting a greater environmental influence. The lack of a significant similarity in the VO2 max of the monozygotic twins reported by Komi and Karlsson22 was somewhat surprising in that a strong genetic component for slow-twitch muscle fibers was found (mean intrapair difference of slow-twitch fibers was almost identical in the monozygotic pairs as compared with a large intrapair difference among the dizygotic pairs).

Engstrom and Fischbein,23 using a large sample size (39 monozygotic pairs, 55 dizygotic pairs) of boys found approximately two times as much intrapair difference in VO2 max in the dizygotic twins as compared with that in the monozygotic twins. When the amount of physical exercise performed during leisure activity was controlled for, however, the monozygotic pairs were as dissimilar as the dizygotic pairs. The authors suggested that the phenotype, physical work capacity, may be strongly influenced by the environment, which would include physical training. Our findings of no significant mean intrapair difference in VO2 max among the four groups support those of Komi and Karlsson, Howald, and Bouchard et al., suggesting that genetic factors alone do not play a role as significant as has been previously thought in establishing VO2 max.

Since VO2 max is the product of the cardiovascular delivery system and the peripheral oxygen extraction, this study attempted to ascertain what contribution the blood transport system made in the degree of intrapair variation. Both Klissouras20 and Howald,19 before the refinement of echocardiographic techniques, approximated heart volumes from chest x-rays and found that the monozygotic twins demonstrated as much mean intrapair variability as the dizygotic twins. In a more recent echocardiographic study, Diano et al.24 reported a significant familial similarity in left ventricular dimensions in members of nuclear families. The results of a study investigating the genetic influence on heart rate and the ECG have recently been reported by Havlik et al.,25 who reported a modest genetic influence (35%) on the PR duration and a 54% variance in heart rate caused by genetic variation. There was no genetic influence reported on the variability of QRS duration and QT interval. No data were reported regarding R wave voltages. Our study showed the greatest influence on cardiac size to be familial.

As indicated in Methods, both members of the twin sets and sibling pairs were asked to train for a 14 week period. If, with exercise training, the monozygotic twins obtained identical gains in cardiac size and VO2 max and/or reached an identical potential while the nonidentical twins and sibling pairs had unequal cardiac and VO2 max training gains, then the role of genetic influence could be considered stronger than the environmental factors. After exercise training, however, the monozygotic twins still showed as much intrapair difference as the dizygotic twins and sibling pairs with regard to cardiac size and VO2 max. Bouchard and Malina26 in a recent review article indicated that there is evidence to support the presence of a genotype-environment interaction with regard to the training of maximal aerobic power. The question still remains as to whether or not 14 weeks is long enough for the possible genotype-environment interaction to fully express itself. Landry et al.27 recently reported on a small population of monozygotic twins (nine sets) who underwent 20 weeks of endurance training. Echocardiographic data were obtained before and after exercise training. The postraining intrapair difference was more similar when compared with the pretesting data, suggesting a possible “homogenizing effect” of the exercise training on cardiac size and structure. Further twin exercise training studies with larger populations are needed to verify these findings and those of our study.

In conclusion, the greater similarity in cardiac size between monozygotic twins, dizygotic twins, and sibling pairs as compared with that of pairs of unrelated
subjects suggests that familial influences, which include common environmental plus genetic factors, are more important determinants of cardiac size than non-familial or purely genetic influences. Further studies are needed to fully characterize the specific contributions made by environmental and/or genetic factors and how each of these factors interact to produce a training effect on cardiovascular parameters.

We thank Bill Varley, Monica Noble, Janet Jones, Abbe Talbert, Craig Fotheringham, Dr. Minken Pat Yeh, and Judy Beesley (LDS Hospital Blood Laboratory) for their technical assistance in this study.

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Circulation. 1985;71:39-44
doi: 10.1161/01.CIR.71.1.39

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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