Noninvasive study of effect of isometric exercise on left ventricular performance in normal man

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The effect of isometric skeletal muscle contraction on the performance of the normal left ventricle was studied noninvasively in 20 subjects. Studies were conducted at rest and at 3 minutes of isometric handgrip exercise at 50 per cent of maximum voluntary contraction, and consisted of simultaneous recording of left ventricular echocardiogram, external carotid pulse, phonocardiogram, and electrocardiogram, while blood pressure was measured by sphygmomanometer. These data permitted evaluation of left ventricular performance in terms of left ventricular ejection fraction, mean circumferential fibre shortening velocity, and the ratio pre-ejection period/ejection time.

In relation to values at rest, isometric exercise resulted in insignificant change in all three variables. The considerable increase in blood pressure, however, indicated significant increase in left ventricular wall tension, since echocardiographic left ventricular internal dimension remained practically unchanged during exercise. Diastolic volume reserves were not utilized, and the fact that ejection fraction, mean circumferential fibre shortening velocity, and the pre-ejection period/ejection time period remained unaltered during exercise, despite considerable increase in afterload, supports the hypothesis that isometric exercise leads to enchantment of the inotropic state of the heart.

The haemodynamic alterations induced by isometric skeletal muscle contraction in patients with impaired heart function (Houston, Atkins, and Blomqvist, 1970; Mullins et al., 1970; Helfant, DeVilla, and Meister, 1971; Kivowitz et al., 1971; Grossman et al., 1973; Payne, Horwitz, and Mullins, 1973) differ from those observed in subjects with intact cardiac reserves (Lind et al., 1964; McDonald et al., 1966; Houston et al., 1970; Mullins et al., 1970; Helfant et al., 1971; Grossman et al., 1973) to an extent that permits evaluation of the heart function by use of this intervention. Such evaluation has traditionally been based on studying the effect of isometric muscle contraction on the relation between left ventricular end-diastolic pressure and stroke work, and therefore it necessitates cardiac catheterization, an inconvenient, expensive, and potentially hazardous procedure.

During the past few years, several methods have been described that permit assessment of left ventricular function in a noninvasive manner by use of such variables as the systolic time intervals (Weissler, Harris, and Shoenfeld, 1968, 1969) or the echocardiographically determined left ventricular ejection fraction (Pombo, Troy, and Russell, 1971; Fortuin et al., 1971; Fortuin, Hood, and Craigie, 1972) and the mean velocity of shortening of the circumferential fibres (Paraskos et al., 1971; Cooper et al., 1972; Fortuin et al., 1972).

It is the purpose of this study to assess the effect of sustained isometric muscle contraction on the performance of the normal left ventricle, as determined by noninvasive means.

Subjects and Methods

Twenty healthy volunteers, whose age and sex are listed in the Table, formed the study population. All were considered as normal on the basis of history, physical examination, and electrocardiogram. Maximal voluntary isometric contraction was determined at least 10 minutes before the study as the average of three consecutive maximal handgrip attempts, using a dynamometer.

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### TABLE Echocardiographic and other data from 20 normal subjects

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/sex</th>
<th>Re</th>
<th>Dd</th>
<th>Ds</th>
<th>EF</th>
<th>Mean VCF (circ/sec)</th>
<th>ET (msec)</th>
<th>PEP/ET</th>
<th>Blood pressure (mmHg)</th>
<th>HR (beats/min)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>51 F</td>
<td>R</td>
<td>42</td>
<td>25</td>
<td>0.79</td>
<td>1:04</td>
<td>338</td>
<td>0.21</td>
<td>120/80 (95)</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>25 M</td>
<td>R</td>
<td>46</td>
<td>24</td>
<td>0.86</td>
<td>1:46</td>
<td>327</td>
<td>0.20</td>
<td>140/80 (106)</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>18 F</td>
<td>R</td>
<td>45</td>
<td>30</td>
<td>0.70</td>
<td>1:09</td>
<td>322</td>
<td>—</td>
<td>110/60 (77)</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>27 M</td>
<td>R</td>
<td>47</td>
<td>26</td>
<td>0.68</td>
<td>1:28</td>
<td>318</td>
<td>0.25</td>
<td>100/60 (73)</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>42 F</td>
<td>R</td>
<td>45</td>
<td>27</td>
<td>0.80</td>
<td>1:38</td>
<td>299</td>
<td>0.22</td>
<td>120/80 (97)</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>45 F</td>
<td>R</td>
<td>46</td>
<td>26</td>
<td>0.81</td>
<td>1:63</td>
<td>260</td>
<td>—</td>
<td>150/90 (117)</td>
<td>115</td>
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<td>7</td>
<td>26 M</td>
<td>R</td>
<td>48</td>
<td>30</td>
<td>0.72</td>
<td>1:19</td>
<td>292</td>
<td>0.30</td>
<td>110/70 (85)</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>27 M</td>
<td>R</td>
<td>50</td>
<td>30</td>
<td>0.79</td>
<td>1:28</td>
<td>318</td>
<td>0.25</td>
<td>100/60 (73)</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>24 M</td>
<td>R</td>
<td>47</td>
<td>28</td>
<td>0.77</td>
<td>1:19</td>
<td>324</td>
<td>0.31</td>
<td>120/75 (95)</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>24 M</td>
<td>R</td>
<td>53</td>
<td>36</td>
<td>0.69</td>
<td>1:07</td>
<td>327</td>
<td>0.29</td>
<td>170/100 (125)</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>23 M</td>
<td>R</td>
<td>54</td>
<td>36</td>
<td>0.70</td>
<td>1:15</td>
<td>329</td>
<td>0.31</td>
<td>165/95 (129)</td>
<td>79</td>
</tr>
<tr>
<td>12</td>
<td>15 M</td>
<td>R</td>
<td>47</td>
<td>26</td>
<td>0.75</td>
<td>1:35</td>
<td>277</td>
<td>—</td>
<td>150/110 (125)</td>
<td>83</td>
</tr>
<tr>
<td>13</td>
<td>30 M</td>
<td>R</td>
<td>48</td>
<td>33</td>
<td>0.68</td>
<td>1:25</td>
<td>284</td>
<td>0.26</td>
<td>160/110 (133)</td>
<td>110</td>
</tr>
<tr>
<td>14</td>
<td>26 M</td>
<td>R</td>
<td>48</td>
<td>33</td>
<td>0.68</td>
<td>1:08</td>
<td>299</td>
<td>0.32</td>
<td>110/75 (86)</td>
<td>66</td>
</tr>
<tr>
<td>15</td>
<td>24 M</td>
<td>R</td>
<td>48</td>
<td>36</td>
<td>0.69</td>
<td>1:26</td>
<td>281</td>
<td>0.29</td>
<td>105/60 (76)</td>
<td>74</td>
</tr>
<tr>
<td>16</td>
<td>25 M</td>
<td>R</td>
<td>44</td>
<td>29</td>
<td>0.74</td>
<td>1:21</td>
<td>327</td>
<td>0.31</td>
<td>140/90 (107)</td>
<td>56</td>
</tr>
<tr>
<td>17</td>
<td>17 F</td>
<td>R</td>
<td>47</td>
<td>33</td>
<td>0.65</td>
<td>1:14</td>
<td>262</td>
<td>0.36</td>
<td>185/130 (155)</td>
<td>88</td>
</tr>
<tr>
<td>18</td>
<td>26 M</td>
<td>R</td>
<td>45</td>
<td>27</td>
<td>0.70</td>
<td>1:29</td>
<td>295</td>
<td>0.27</td>
<td>135/80 (97)</td>
<td>91</td>
</tr>
<tr>
<td>19</td>
<td>29 M</td>
<td>R</td>
<td>45</td>
<td>30</td>
<td>0.75</td>
<td>1:07</td>
<td>247</td>
<td>0.39</td>
<td>130/75 (97)</td>
<td>89</td>
</tr>
<tr>
<td>20</td>
<td>25 M</td>
<td>R</td>
<td>44</td>
<td>31</td>
<td>0.66</td>
<td>1:06</td>
<td>287</td>
<td>0.35</td>
<td>125/70 (88)</td>
<td>80</td>
</tr>
</tbody>
</table>

Mean 

<table>
<thead>
<tr>
<th>Re</th>
<th>46.5</th>
<th>29.5</th>
<th>0.73</th>
<th>1:21</th>
<th>297</th>
<th>0.30</th>
<th>119/73 (90)</th>
<th>79</th>
</tr>
</thead>
<tbody>
<tr>
<td>±SEM</td>
<td>0.7</td>
<td>0.8</td>
<td>0.01</td>
<td>0.04</td>
<td>5</td>
<td>0.01</td>
<td>2/2 (2)</td>
<td>3</td>
</tr>
</tbody>
</table>

Mean 

| Re       | 47.5 | 30   | 0.74 | 1:31 | 285 | 0.29 | 157*103* (126)* 101* |
|---------|------|------|------|------|-----|------|--------------|---|
| ±SEM    | 0.7  | 0.9  | 0.01 | 0.06 | 6   | 0.01 | 4/3 (4)     | 4 |

Abbreviations: D = diastolic, Dd and Ds = end-diastolic and end-systolic internal dimension of the left ventricle, E = isometric exercise, EF = ejection fraction, ET = ejection time, HR = heart rate, PEP = pre-ejection period, R = at rest, S = systolic, SEM = standard error of the mean.

*P value less than 0.01 in comparison to value at rest.

The subjects were suitably instructed in order to avoid performing the Valsalva manoeuvre, and carefully observed for this during handgrip test. All studies were conducted in the postabsorptive state and consisted of simultaneous measurement of blood pressure by sphygmomonometry (Kirkendall et al., 1967) and recording of left ventricular echocardiogram and systolic time intervals just before and at the end of a three-minute period of isometric handgrip exercise at 50 per cent of maximum voluntary contraction.

The indirect carotid pulse tracing, phonocardiogram, and electrocardiogram were simultaneously recorded from the apex area, using a Cambridge (No. 53643) microphone.
recorded on an Electronics for Medicine DR-6 photographic recorder at a paper speed of 100 mm/sec. Sphygmomanometric blood pressure measurements from the arm not involved in the isometric handgrip exercise were used in conjunction with indirect carotid pulse analysis for the determination of mean blood pressure, as previously reported from this laboratory (Stefadouros et al., 1973). The distance from the onset of the QRS complex of the electrocardiogram to the onset of the aortic component of the second heart sound of the phonocardiogram (Q-A2), as well as the distance from the onset of upstroke to the dicrotic notch of the carotid pulse (ejection time, ET), were measured and averaged over five heart cycles. The difference (Q-A2) – (ET) was the pre-ejection period that was used to calculate the ratio pre-ejection period/ejection time (PEP/ET), an index of the left ventricular performance that is reportedly independent of heart rate (Weissler et al., 1969).

Using a Smith Kline Ekoline 20 echograph1 equipped with a 2-25 megahertz focused transducer (model C-12), left ventricular echocardiograms were recorded on Polaroid films during M-motion presentation at a medium sweep velocity that permits completion of a full sweep cycle within 2 seconds. While most of the studies were conducted in the supine position, in some instances having the trunk slightly raised and rotated to the left side provided more stable monitoring of the left ventricular echocardiogram throughout the cardiac cycle. The objective of the echocardiographic study was the recording of echoes originating from the endocardium of the left side of the interventricular septum and that of the posterior left ventricular wall, at a plane immediately below the mitral valve, as previously described (Popp et al., 1969; Popp and Harrison, 1970; Feigenbaum et al., 1972); the distance between these two echoes, approximating the left ventricular internal minor axis, was measured at the end of diastole (Dd) and end of systole (Ds) in all (2 to 3) available cycles on each picture, and the average values, rounded to the nearest 0.5 mm, were used to calculate left ventricular ejection fraction (see below). End-systole was defined as the moment when the vertical distance from the endocardium of the left ventricular posterior wall and from the left side of the septum became minimal; end-diastole was defined at the peak of the R wave of the electrocardiogram. The effect of skeletal muscle contraction during isometric handgrip exercise on the electrocardiogram, however, was so profound that identification of the QRS complexes on the Polaroid pictures was impossible in some cases, even on leads not involving the exercising arm (Fig. 1). In these cases, the time relation of the peak of the R wave to the movement of the left ventricular posterior wall echo was noted on the resting echocardiogram (Kraunz and Kennedy, 1970) and used for the identification of the corresponding moment of end-diastole on the picture taken during exercise. Similar but less severe problems were also encountered with the electrocardiogram on the strip chart recordings used for calculation of the PEP/ET ratio; whereas in 15 cases QRS complexes were easily identified, calculation of PEP/ET was impossible in 4 cases (No. 2, 4, 6, and 10 in the Table) because of severe distortion of the electrocardiogram, and in 1 instance (Case 11, Table) because of poor inscription of the dicrotic notch of the carotid pulse curve.

Angiographic left ventricular end-diastolic and endsystolic volumes have been shown to correlate well with the cube of the echocardiographic left ventricular internal dimension at end-diastole (Dd3) and end-systole (Ds3), respectively (Feigenbaum et al., 1972). Therefore, the difference (Dd3-Ds3), representing the left ventricular stroke volume, was divided by the end-diastolic volume (Dd3) to provide left ventricular ejection fraction (EF):

\[ EF = \frac{(Dd - Ds)}{(Dd \times ET)} \]

where ET was the left ventricular ejection time measured from the indirect carotid pulse, except for Case 11 (Table) in whom the ejection time was measured on the echocardiogram as the time from the onset to the peak of the anterior movement of the echo from the endocardium of the left ventricular posterior wall.

During the isometric handgrip exercise test, specific care was taken by the examiner to avoid false changes in left ventricular dimensions produced by involuntary alterations in either the exact point of application of the ultrasonic transducer on the chest wall or the direction of the ultrasonic beam in relation to the heart. To minimize this possibility, the following rules were adopted:

1) Isometric contraction started immediately (seconds) after a satisfactory left ventricular echocardiogram was obtained at rest.
2) Once the resting left ventricular echocardiogram was recorded, and throughout the 3-minute period of the exercise test, neither change in the position and tilt of the transducer nor modification in the setting of the several control switches of the echograph was permitted.

Strict application of this policy resulted in abandonment of the study in several subjects in whom, for unexplained reasons, unacceptable deterioration in the resolution of the left ventricular echocardiogram was observed during isometric exercise. Additional subjects were excluded from this study because of their inability to maintain the required level of contraction for 3 minutes or because of performing the Valsalva manoeuvre during exercise. Therefore, the data presented were derived from 20 subjects with high quality echocardiograms, selected out of 31 subjects in whom the study was attempted.

Statistical analysis of the results was done on an Olivetti (Programma 101) calculator using the t-test for paired data. The level of statistical significance was set at \( P < 0.01 \).
The results are summarized in the Table and Fig. 2. As can be seen, isometric exercise was vigorous enough to raise heart rate from 79 ± 3 to 101 ± 4 beats/min (mean ± standard error) and mean arterial pressure from 90 ± 2 to 126 ± 4 mmHg. Despite this, small and statistically insignificant changes were noted in left ventricular dimensions, ejection fraction (from 0.73 ± 0.01 to 0.74 ± 0.01), mean circumferential fibre shortening velocity (from 1.21 ± 0.04 to 1.31 ± 0.06 cm/sec), and the pre-ejection period/ejection time ratio (from 0.30 ± 0.01 to 0.29 ± 0.01).

There was significant correlation between ejection fraction and pre-ejection period/ejection time both at rest (r = -0.897) and on exercise (r = -0.775), during which changes in ejection fraction correlated less well, but still significantly, with changes in the pre-ejection period/ejection time ratio (r = -0.693).

Similar correlations between the dependent variables, mean circumferential fibre shortening velocity and ejection fraction (both sharing Dd and Ds), or between mean circumferential fibre shortening fraction and pre-ejection period/ejection time ratio (both sharing ejection time), though statistically significant, are scientifically unimportant.

**Discussion**

Angiographically determined ejection fraction (Miller and Swan, 1964; Miller, Kirklin, and Swan, 1965; Dodge and Baxley, 1968) and mean circumferential fibre shortening velocity (Gault, Ross, and Braunwald, 1968; Karliner et al., 1971; Cooper et al., 1972) have been shown to represent satisfactory indices of left ventricular performance, and the use of ultrasound for their determination has been validated by reference to standard angiocardiographic techniques (Pombo et al., 1970; Fortuin et al., 1971; Cooper et al., 1972). The mean value for ejection fraction in our group at rest compares favourably with the echocardiographic (Cooper et al., 1972) or angiocardiographic (Arvidsson, 1961; Dodge, Hay, and Sandler, 1962; Kennedy et al., 1966; Karliner et al., 1971; Cooper et al., 1972) values previously reported, but it is somewhat higher than the echocardiographic value reported by Fortuin et al. (1972).

In calculating mean circumferential fibre shortening...
ing velocity, division by either end-diastolic circumference or average circumference \((\text{end-diastolic} + \text{end-systolic} \text{c}

Preload, afterload, and contractile state are the three factors that determine the performance of the ventricle (Sonnenblick, Parmley, and Urschel, 1969). Catheterization studies in subjects with normal heart function have shown that isometric exercise is not associated with significant changes in left ventricular end-diastolic pressure (Kivowitz et al., 1970; Mullins et al., 1970; Helfant et al., 1971; Grossman et al., 1973), and our data indicate that left ventricular end-diastolic volume also remains unaffected by this intervention. Therefore, during isometric exercise, changes in either pressure or volume preload do not constitute a significant factor affecting the performance of the normal left ventricle which seems to depend primarily on the interplay between the remaining two factors, the afterload and the contractile state of the myocardium.

Experiments on isolated heart muscle preparations have shown that when the muscle contracts from a constant preload (initial length), the extent
and the velocity of shortening are inversely proportional to the afterload (force) (Abbott and Mommaerts, 1959; Sonnenblick, 1962; Sonnenblick and Downing, 1963). Similar observations have also been made on the isolated canine heart, where changes in afterload (arterial pressure) were induced while the preload was held constant (Ross et al., 1966); an increase in afterload was accompanied by a decrease in stroke volume and the instantaneous circumferential fibre shortening velocity. Since left ventricular end-diastolic volume was held constant, these changes in stroke volume corresponded to similar changes in ejection fraction. A decrease in ejection fraction has also been observed in the intact heart of the dog 2 to 3 minutes after acute rise in the aortic pressure by angiotensin infusion (Tsakiris et al., 1968). Based on these experimental findings, a decrease in ejection fraction would, therefore, be expected in our group during isometric exercise when from a practically constant preload (left ventricular end-diastolic volume), the left ventricle contracted against an increased afterload,1 assuming that no change in myocardial contractility had occurred during this intervention. The fact that such a decrease in ejection fraction was not actually observed suggests that the increase in afterload was met by a compensatory increase in the inotropic state of the myocardium.

In this study, instantaneous circumferential fibre shortening velocity and wall tension could not be measured, so that accurate analysis of the possible changes in the left ventricular contractile state induced by isometric exercise was not feasible. However, it was felt that changes in mean circumferential fibre shortening velocity elicited by isometric exercise would reflect directionally similar changes in instantaneous circumferential fibre shortening velocity. Support for this contention is found in a recent study where a good correlation was shown between mean circumferential fibre shortening velocity and peak instantaneous circumferential fibre shortening velocity as determined by angiocardiography (Karliner et al., 1971). Thus in 7 subjects of our group mean circumferential fibre shortening velocity decreased during isometric exercise, as would be expected from the inverse relation between velocity of shortening and wall tension. In the remaining 13 subjects mean fibre shortening velocity increased slightly, indicating that a positive inotropic response was elicited by isometric exercise, enabling the left ventricle to increase its fibre shortening rate in the presence of an augmented afterload.

The performance of the left ventricle can also be evaluated by use of the systolic time intervals (Weissler et al., 1968, 1969). Previous reports on the effect of isometric exercise on the systolic time intervals are scanty and their results inconsistent. Thus, in four separate studies involving a total of 15 normal subjects, the pre-ejection period/ejection time ratio was found to increase (Houston et al., 1970; Martin et al., 1971), decrease (Grossman et al., 1973) or remain unchanged (Siegel et al., 1972) during isometric exercise. The magnitude of these changes was of the order observed on some subjects of our series. The fact that the ratio did not significantly change in our group is not incompatible with the hypothesis that isometric exercise enhances myocardial contractility, for the latter represents only one of several factors that are known to affect the systolic time intervals. Among these factors preload, heart rate (Wallace et al., 1963; Weissler et al., 1968, 1969), cardiac and stroke index (Wallace et al., 1963; Weissler et al., 1968, 1969), arterial pressure (Wallace et al., 1963; Shaver et al., 1968), and myocardial contractility (Weissler, Peeler, and Roehl, 1961; Wallace et al., 1963; Harris, Schoenfeld, and Weissler, 1967) are the ones most likely to have influenced the systolic time intervals in this study. Preload and heart rate can be safely excluded from consideration; the former because it remained practically unaffected by isometric exercise; the latter because it is known to have no significant effect on the selected index pre-ejection period/ejection time (Wallace et al., 1963). The effect of cardiac index on this ratio, being directionally similar (Weissler et al., 1968, 1969) to that of its other determinant, the stroke index, need not be discussed separately. Other factors being constant, an increase in stroke index or myocardial contractility (Weissler et al., 1969)
results in a diminution of the pre-ejection period/ejection time ratio, whereas a rise in arterial pressure has the opposite effect (Wallace et al., 1963; Weissler et al., 1968, 1969), though the latter was not the experience of Shaver et al. (1968). Since the observed increase in stroke index (+6.6%) during isometric exercise in this study was insignificant, it is unlikely that it may have fully counterbalanced the increase in the pre-ejection period/ejection time ratio expected from the considerable rise (+40%) in mean arterial pressure. An enhancement of myocardial contractility, however, could adequately explain the observed failure of the ratio to increase during isometric exercise.

In conclusion, this study has shown that in normal subjects such variables of left ventricular performance as ejection fraction, mean circumferential fibre shortening velocity, and the pre-ejection period/ejection time ratio remain unaffected by isometric exercise, despite considerable increase in afterload. In view of the insignificant use of pre-load (volume) reserves, this finding supports the hypothesis that isometric exercise augments the inotropic state of the heart.

The authors wish to extend appreciation to the medical students and other persons who volunteered in this study. They also acknowledge the technical assistance of Mrs. Beryl Wilson.

References


fusion as a stress test for evaluation of left ventricular function. American Journal of Cardiology, 31, 428.


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