# Limited Myocardial Perfusion Reserve in Patients with Left Ventricular Hypertrophy

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Experimental studies in animals have suggested that coronary flow reserve may be limited in patients with left ventricular hypertrophy (LVH). Accordingly, to noninvasively determine the effect of LVH on myocardial perfusion reserve, 25 patients, 9 with LVH and 16 controls, underwent positron imaging with rubidinum-82 ($^{82}$Rb) (30–55 mCi) or nitrogen-13 ($^{13}$N) ammonia (12–19 mCi) at rest and following intravenous dipyridamole and handgrip stress. LVH was documented by echocardiographic and/or electrocardiographic measurements. LVH patients had either no chest pain (n = 8) and/or a normal coronary angiogram (n = 6). Nine simultaneous transaxial images were acquired, and the mean ratio of stress to rest activity (S:R), based on all regions for each heart, was calculated as an estimate of myocardial perfusion reserve. There were no regional differences in activity (i.e., perfusion defects) in any of the studies. S:R averaged 1.41 ± 0.10 (s.d.) for controls and 1.06 ± 0.09 for patients with LVH ($p < 0.0001$). These data provide support for an abnormality in perfusion reserve in patients with LVH.

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Left ventricular hypertrophy (LVH) has been associated with angina and focal myocardial necrosis in the absence of occlusive coronary disease (*1*). Several experimental studies have shown that coronary flow reserve is impaired after hypertrophy is induced by hypertension, volume overload, or left ventricular outflow obstruction (*2–4*). Marcus reported that intraoperative coronary reactive hyperemia, derived from Doppler flow velocity measurements of the left anterior descending (LAD) coronary artery, was decreased in patients with normal coronary arteries and LVH secondary to aortic stenosis (*5*). The purpose of the present study is to determine whether global and regional myocardial perfusion reserve are impaired in patients with LVH. Myocardial perfusion reserve was measured in unanesthetized patients with positron tomography in conjunction with dipyridamole-handgrip stress.

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## METHODS

### Patient Population

Twenty-five patients (22 men and 3 women), who underwent positron imaging for the screening of coronary artery disease, were retrospectively evaluated. The control group consisted of 16 patients without chest pain or hypertrophy who had a normal resting electrocardiogram and a negative electrocardiographic stress test. The second group of patients included nine patients with LVH secondary to hypertension. Coronary arteriograms were available in 6/9 patients and were normal in those patients. Eight patients had no chest pain. The remaining patient had typical angina but a normal coronary angiogram. Five of nine LVH patients had echocardiographic evidence of LVH (LV posterior wall and septal diastolic thickness >1.2 cm). The other four patients had electrocardiographic evidence of LVH by Estes criteria (*6*).

### Positron Imaging Protocol

Patients were fasted for at least 4 hr prior to the study, and drinks or drugs containing theophylline or caffeine were withheld for at least 8 hr to avoid antagonizing the hyperemic response to dipyridamole. Chest fluoroscopy was performed to mark the inferior border of the heart, and patients were then positioned in the University of Texas positron camera (TOFPET I). A transmission scan (200 million counts) was performed using a Plexiglass ring containing 3 mCi of $^{68}$Ga. The ring was then removed, the patient's position was rechecked, and a resting emission scan was obtained by intravenous (i.v.) infusion of rubidium-82 ($^{82}$Rb) (n = 11, mean dose = 45.3 ± 5.6 mCi/infusion) or an i.v. injection of nitrogen-13- ($^{13}$N) ammonia (n = 14, mean dose = 17.4 ± 0.9 mCi/injection) in an ungated mode without time-of-flight correction as previously described (*7*). Nine controls and 5 LVH patients received [$^{13}$N]ammonia. Rubidium-82 infusions were complete within 12–20 sec. Rubidium-82 emission images acquisition was started 1 min after the end of elution to minimize blood-pool activity. The acquisition was then stopped after 5–7 min. Nitrogen-13-ammonia image acquisitions were started 3 min after injection and continued for 15 min. After an appropriate delay to allow counts to decay from the resting study, the same tracer was injected during stress-induced imaging by dipyridamole plus handgrip. Particular attention was paid to positioning of the patient in the same location as in the rest scan. In brief, patients were given a 0.142-mg/kg/min i.v. infusion of dipyridamole for 4 min

(total dose 0.568 mg/kg). The i.v. line was then flushed with normal saline and ECGs were recorded; handgrip was performed by the patient using a mechanical spring device at 25% of maximal strength and maintained for 4 min. Two minutes into handgrip, the tracer was injected and emission images were acquired in the manner identical to the resting study. Heart rate and systemic arterial pressures (systolic, diastolic, and mean) were obtained from a vital signs monitor (Critikon Dynamap 845XT) at baseline, immediately after infusion of dipyridamole was complete, and at the time of administration of tracer during stress images.

### Analysis of Positron Images

Nine transaxial slices of the rest and dipyridamole studies were displayed in color on a CRT monitor. Regions of interest in the lateral, anterior, septal and posterior left ventricular walls were defined using an interactive software program that recorded the mean activity, number of pixels and standard deviation of the activity. In addition, a region of interest was defined for the entire left ventricle on each slice for global measurements. A histogram of the activity in each region of interest was also obtained to allow recognition of admixtures of normal and abnormal tissue. Mean activity in each region had a standard deviation under 10% of mean activity.

Average activity for each region was calculated for resting and stress images. Myocardial perfusion reserve (MPR) by positron tomography was calculated by dividing mean stress activity by mean rest activity of the corresponding area. Final values were corrected for differences in tracer dose between stress and rest injections. Since each region contained a differ-

**TABLE 1**
Hemodynamic Changes During Dipyridamole-Handgrip Stress

| | Heart Rate | | | Systolic Pressure | | | Diastolic Pressure | | | Mean Pressure | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient No. | Rest | Dipy | Hdgp | Rest | Dipy | Hdgp | Rest | Dipy | Hdgp | Rest | Dipy | Hdgp |
| Controls | | | | | | | | | | | | |
| 1 | 67 | 94 | 104 | 131 | 138 | 178 | 86 | 92 | 115 | 101 | 107 | 136 |
| 2 | 61 | 82 | 86 | 120 | 115 | 111 | 63 | 71 | 51 | 82 | 80 | 71 |
| 3 | 78 | 92 | 97 | 123 | 131 | 134 | 85 | 83 | 86 | 98 | 99 | 102 |
| 4 | 66 | 78 | 77 | 159 | 165 | 166 | 102 | 98 | 97 | 121 | 120 | 120 |
| 5 | 54 | 66 | 88 | 118 | 113 | 122 | 65 | 61 | 76 | 83 | 78 | 91 |
| 6 | 50 | 58 | 85 | 123 | 122 | 143 | 77 | 71 | 91 | 92 | 88 | 108 |
| 7 | 48 | 65 | 77 | 121 | 101 | 128 | 68 | 66 | 70 | 85 | 77 | 89 |
| 8 | 60 | 65 | 88 | 152 | 142 | 141 | 83 | 70 | 73 | 106 | 94 | 96 |
| 9 | 61 | 76 | 87 | 138 | 133 | 125 | 86 | 76 | 77 | 103 | 95 | 93 |
| 10 | 84 | 85 | 96 | 151 | 145 | 166 | 90 | 79 | 84 | 110 | 101 | 111 |
| 11 | 57 | 63 | 76 | 168 | 171 | 184 | 111 | 90 | 114 | 130 | 117 | 137 |
| 12 | 64 | 85 | 104 | 122 | 126 | 176 | 65 | 69 | 97 | 84 | 88 | 123 |
| 13 | 72 | 92 | 102 | 133 | 112 | 125 | 84 | 68 | 74 | 100 | 83 | 91 |
| 14 | 65 | 90 | 101 | 109 | 119 | 142 | 65 | 77 | 87 | 80 | 91 | 105 |
| 15 | 58 | 63 | 70 | 118 | 120 | 122 | 70 | 72 | 74 | 86 | 88 | 90 |
| 16 | 58 | 75 | 94 | 120 | 118 | 108 | 86 | 78 | 84 | 97 | 91 | 92 |
| Mean | 62.7 | 76.8 | 89.5 | 131.6 | 129.4 | 141.9 | 80.4 | 76.3 | 84.4 | 97.5 | 94.0 | 103.0 |
| S.D. | 9.5 | 12.2 | 10.8 | 17.2 | 19.1 | 24.7 | 14.0 | 10.1 | 16.3 | 14.5 | 12.0 | 18.0 |
| P value R vs. Dipy | <0.001 | | | ns | | | ns | | | ns | | |
| R vs. Hdgp | | <0.001 | | | ns | | | ns | | | ns | |
| LVH | | | | | | | | | | | | |
| 1 | 82 | 85 | 88 | 191 | 172 | 162 | 80 | 65 | 65 | 117 | 101 | 97 |
| 2 | 60 | 84 | 92 | 129 | 140 | 133 | 84 | 70 | 65 | 99 | 93 | 88 |
| 3 | 61 | 92 | 97 | 161 | 151 | 174 | 94 | 96 | 106 | 116 | 114 | 129 |
| 4 | 82 | 85 | 88 | 166 | 147 | 144 | 82 | 67 | 76 | 110 | 94 | 99 |
| 5 | 72 | 78 | 85 | 182 | 143 | 151 | 97 | 92 | 88 | 125 | 109 | 109 |
| 6 | 82 | 89 | 93 | 140 | 127 | 140 | 79 | 78 | 79 | 99 | 94 | 99 |
| 7 | 84 | 88 | 92 | 155 | 142 | 153 | 84 | 78 | 77 | 108 | 99 | 102 |
| 8 | 80 | 81 | 78 | 172 | 157 | 140 | 97 | 89 | 90 | 122 | 112 | 107 |
| 9 | 90 | 93 | 96 | 158 | 156 | 164 | 86 | 87 | 97 | 110 | 110 | 119 |
| Mean | 77.0 | 86.1 | 88.8 | 161.6 | 148.3 | 151.2 | 87.0 | 80.2 | 82.6 | 111.9 | 102.9 | 105.4 |
| s.d. | 10.4 | 4.9 | 6.4 | 19.3 | 12.7 | 13.4 | 7.1 | 11.4 | 13.9 | 9.2 | 8.4 | 12.4 |
| P value R vs. Dipy | <0.04 | | | <0.02 | | | <0.02 | | | <0.003 | | |
| R vs. Hdgp | | <0.02 | | | ns | | | ns | | | ns | |
| P value Control vs. LVH | <0.004 | <0.02 | ns | <0.002 | <0.007 | ns | ns | ns | ns | <0.006 | <0.05 | ns |

Values are mean ± s.d. Measurements occurred at rest, after dipyridamole (Dipy) and during handgrip at the time of imaging (Hdgp).

ent number of pixels, the global activity does not represent a simple mean of regional MPR.

### Statistical Analysis

The differences in MPR between the two groups was determined using a Student's t-test for unpaired data. Differences in arterial pressures and heart rate were determined using paired or unpaired Student's t-tests for intra- and inter-group comparisons respectively. Regional homogeneity of MPR was tested using analysis of variance. Results are reported as mean ± s.d.

## RESULTS

### Hemodynamic Responses to Dipyridamole-Handgrip Stress

*Intra-group Changes.* Heart rate rose in the control group from 63 ± 10 to 77 ± 12 after the dipyridamole infusion and to 90 ± 11 with handgrip ($p < 0.001$ for each vs. resting) (Table 1). Arterial pressure did not significantly change during the study in controls. In patients with LVH, heart rate also rose after dipyridamole and handgrip but by a lesser amount (77 ± 10 to 86 ± 4 to 89 ± 6, $p < 0.04$ and $p < 0.01$, respectively, vs. baseline). In contrast to controls, systolic, diastolic, and mean arterial pressure in patients with LVH fell with dipyridamole but returned to baseline values during handgrip.

*Inter-group Comparison.* Resting heart rate was greater in patients with LVH than in controls. This difference was also present after dipyridamole. At the time of stress imaging, mean heart rates of the two groups were similar. Systolic and mean arterial pressure was higher in the hypertrophy group than in controls at rest and after dipyridamole. At the time of imaging, there were no significant differences in arterial pressure between the groups.

### Myocardial Perfusion Reserve

Myocardial perfusion reserve was significantly lower in patients with LVH than in controls (1.06 ± 0.09 vs. 1.41 ± 0.10, $p < 0.0001$, Fig. 1). The reduction in MPR in these patients was not due to regional differences in stress perfusion ratios (Table 2). There was no significant differences between $^{82}$Rb and [$^{13}$N]ammonia measures of MPR within each group. In controls, MPR with [$^{13}$N]ammonia averaged 1.44 ± 0.10 and 1.36 ± 0.10 for $^{82}$Rb. In LVH patients, the values were 1.08 ± 0.10 and 1.05 ± 0.06, respectively.

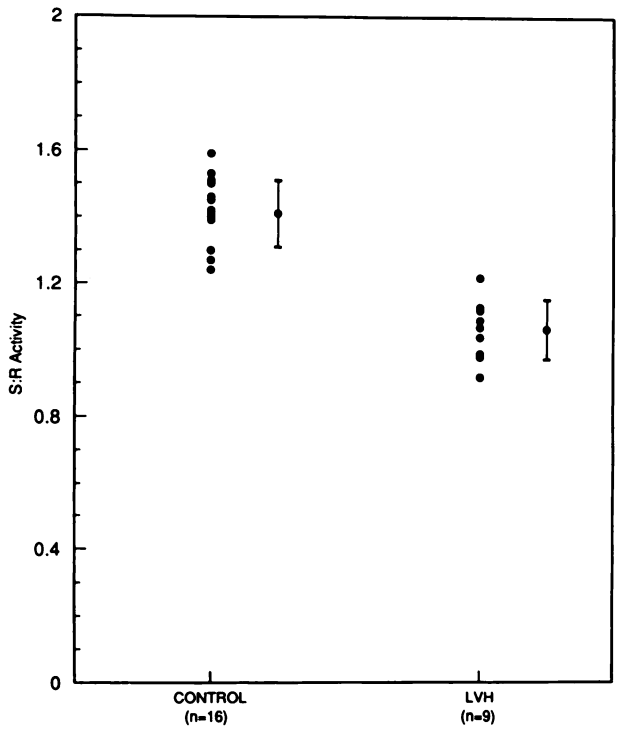


**FIGURE 1**
Ratio of stress:rest (S:R) activity in controls and patients with LVH. The differences were significant at $p < 0.0001$.

**TABLE 2**
Changes in Regional Perfusion Reserve

| Patient no. | Tracer | Dose | | LAT | ANT | SEP | POS |
|---|---|---|---|---|---|---|---|
| | | Rest | Stress | | | | |
| Controls | | | | | | | |
| 1 | R | 56.0 | 57.0 | 1.25 | 1.32 | 1.30 | 1.28 |
| 2 | R | 40.0 | 40.0 | 1.31 | 1.34 | 1.30 | 1.27 |
| 3 | N | 17.3 | 17.1 | 1.19 | 1.16 | 1.20 | 1.13 |
| 4 | N | 17.0 | 17.8 | 1.52 | 1.62 | 1.70 | 1.54 |
| 5 | N | 17.5 | 17.8 | 1.38 | 1.38 | 1.45 | 1.36 |
| 6 | N | 17.5 | 17.6 | 1.41 | 1.53 | 1.52 | 1.53 |
| 7 | N | 17.3 | 17.6 | 1.62 | 1.55 | 1.58 | 1.71 |
| 8 | R | 49.2 | 48.6 | 1.47 | 1.49 | 1.47 | 1.53 |
| 9 | N | 17.3 | 17.7 | 1.46 | 1.46 | 1.47 | 1.63 |
| 10 | N | 19.0 | 18.6 | 1.23 | 1.28 | 1.25 | 1.24 |
| 11 | N | 17.8 | 17.9 | 1.53 | 1.55 | 1.57 | 1.53 |
| 12 | R | 40.0 | 40.0 | 1.42 | 1.43 | 1.41 | 1.60 |
| 13 | R | 50.0 | 50.0 | 1.35 | 1.39 | 1.38 | 1.47 |
| 14 | R | 47.6 | 47.4 | 1.43 | 1.39 | 1.38 | 1.43 |
| 15 | R | 50.0 | 50.0 | 1.28 | 1.22 | 1.22 | 1.28 |
| 16 | N | 18.0 | 18.5 | 1.68 | 1.67 | 1.69 | 1.72 |
| Mean | | | | 1.41 | 1.42 | 1.43 | 1.45 |
| s.d. | | | | 0.13 | 0.14 | 0.15 | 0.17 |
| LVH | | | | | | | |
| 1 | N | 16.5 | 16.5 | 1.09 | 0.91 | 0.91 | 0.97 |
| 2 | R | 40.0 | 40.0 | 0.98 | 1.01 | 1.00 | 1.02 |
| 3 | N | 14.5 | 17.3 | 1.08 | 1.13 | 1.14 | 1.04 |
| 4 | N | 15.8 | 18.6 | 1.23 | 1.24 | 1.21 | 1.12 |
| 5 | R | 40.0 | 40.0 | 1.11 | 1.12 | 1.12 | 1.10 |
| 6 | R | 45.0 | 45.0 | 1.08 | 1.06 | 1.09 | 1.14 |
| 7 | N | 16.3 | 16.8 | 1.13 | 1.16 | 1.14 | 1.11 |
| 8 | N | 17.5 | 17.0 | 1.03 | 1.04 | 1.06 | 1.00 |
| 9 | R | 40.0 | 40.0 | 0.98 | 0.98 | 0.99 | 0.95 |
| Mean | | | | 1.08 | 1.07 | 1.08 | 1.05 |
| s.d. | | | | 0.07 | 0.10 | 0.08 | 0.07 |

Values are averages from multiple slices of each region and are corrected for differences in dose between rest and stress injection. R = $^{82}$Rb; N = [$^{13}$N]ammonia; LAT = lateral; ANT = anterior; SEP = septal; and POS = posterior. There were no significant differences in regional perfusion reserve in either group.

## DISCUSSION

Myocardial perfusion imaging for the diagnosis of coronary artery disease is based on disparities in regional activity of tracers during exercise or pharmacologic vasodilation. In general, the differences between activity in normal areas and territories supplied by coronary stenoses is related to the severity of the lesion (*7*). This approach assumes that regions with the highest activity during stress have normal coronary flow reserve (the ratio of maximal perfusion to resting perfusion). However, a number of other variables may reduce coronary flow reserve in the absence of coronary disease (*8*). Anything that preferentially increases resting flow or decreases the response to high flow stimulation will lower coronary flow reserve. In an animal model of LVH, O'Keefe found that coronary flow reserve was reduced by 21% and suggested that it may be due in part to thickening of the arterial media (*3*). The proportion of capillaries was similar in control and LVH hearts, indicating that there was an absolute increase in capillaries to match the increase in myocardial mass.

The results of the present study indicate that there is less increase in activity during pharmacologic vasodilation in patients with LVH than in controls without hypertrophy. Stress:rest myocardial activity was 25% less in patients with LVH than in controls (1.06 vs. 1.41). These findings are consistent with those previously reported by Strauer who found that coronary flow reserve was decreased by ~33% in patients with LVH due to hypertension using argon washout (*9*). Part of this reduction in reserve was due to an 18% increase in resting flow. In the current study, there was a statistically higher resting heart rate and systolic and mean arterial pressure in patients with hypertrophy, which may have caused a similar effect on resting flow although no independent measure was obtained in this study.

### Limitations of the Study

This study has several limitations that must be considered. First, data was retrospectively acquired so that echocardiograms were not available in all patients. Therefore, the diagnosis of hypertrophy was based on electrocardiography in some patients. Estes criteria has only a 50% sensitivity but a 95% specificity for this diagnosis, making it highly likely that the patients included in the LVH group had the correct diagnosis but possibly resulting in the inadvertent inclusion of a patient in the control group that was not identified by the electrocardiogram (*6*).

The value of perfusion reserve of ~1.4 reported in normals using MPR by PET in this study is considerably lower than the usual reported value of 5 when flow is measured directly. This discrepancy is due in part to the lack of inclusion of an arterial input curve and direct measure of extraction fraction so that, in effect, myocardial uptake ratios are measured as an indirect index of perfusion reserve. It is also possible that background scatter from adjacent noncardiac structures decrease this estimate of perfusion reserve.

### Implications

This study provides evidence that the increase in myocardial activity following dipyridamole-handgrip stress is reduced in patients with LVH. This reduction of coronary flow reserve could lead to an underestimation of the severity of coronary stenoses in patients with hypertrophy since defects are referenced to normal appearing segments which in fact have submaximal flow reserve. The study also suggests that assessment of images could be improved by quantitatively evaluating the changes in activity after stress to verify normal reserve in regions that do not contain visible defects.


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