Original Paper

# Mortality in Patients With Microvascular Disease

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*Patients with chest pain/ischemic cardiac disease and normal coronary arteriography are thought to have a benign prognosis despite diminished quality of life. Many patients with hypertension fall into this group, at least in the early stage of their disease. Whether abnormalities in coronary flow reserve in these patients are associated with increased morbidity and mortality is unknown. One hundred sixty-eight patients with chest pain/ischemic cardiac disease and normal coronary angiograms who underwent invasive measures of coronary flow reserve were followed longitudinally. Mortality and quality of life were ascertained by query of the national death index and telephone administration of standardized questionnaires. Patient follow-up occurred at a mean of 8.5 years. In the abnormal coronary flow reserve group, 12 deaths (20%) were documented in 60 patients compared with eight out of 108 patients (7%; p=0.016) with normal coronary flow reserve. Coronary flow reserve did not predict impairment in functional health status in long-term follow-up. Thus, invasive measures of coronary flow reserve in patients with chest pain/ischemic cardiac disease and normal coronary angiograms predicted increased mortality.*

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*Surviving patients with chest pain/ischemic cardiac disease and normal coronary angiograms have significant morbidity. (J Clin Hypertens. 2004;6:304–309)*


Hypertension is associated with many end organ effects. A commonly described but poorly understood sequelae of hypertension is microvascular coronary disease. This problem may present in patients with chest pain and no evidence of obstruction on coronary arteriography. These patients represent a diverse group with multiple biologic and somatic disorders. Studies evaluating the long-term prognosis of patients with this disorder tend to suggest a favorable prognosis. However, these reports frequently include a small number of patients and a short duration of follow-up. The functional capacity and symptoms[1] of these patients tend to be of clinical significance, requiring ongoing health care utilization despite the absence of discrete clinical events.

Recent reports suggest that invasive testing allows for a specific diagnostic strategy by which to tailor medical therapy. Whereas noninvasive measures of flow reserve, like pharmacologic radionuclide perfusion studies (dipyridamole or adenosine), may provide relative measures of coronary flow reserve (CFR), invasive techniques provide a measure of absolute flow reserve.[2–3] This study is accomplished during cardiac catheterization by placing a Doppler probe in the coronary artery and measuring blood flow velocity at rest and maximal vasodilation. Because oxygen extraction in the coronary bed is near maximal, changes in coronary flow are thought to be the normal homeostatic mechanisms by which increases in myocardial oxygen demand are met.

**Table I.** Baseline Characteristics of All Patients Undergoing Invasive Measures of Coronary Flow Reserve (CFR)

| | Abnormal CFR (n=60) | | Normal CFR (n=108) | | |
|---|---|---|---|---|---|
| Variable | n | % | n | % | *P* Value |
| Race | | | | | 0.534 |
| White | 27 | 45 | 54 | 50 | |
| African American | 33 | 55 | 54 | 50 | |
| Sex | | | | | 0.087 |
| Man | 16 | 26.7 | 43 | 39.8 | |
| Woman | 44 | 73.3 | 65 | 60.2 | |
| Hypertension | | | | | 0.309 |
| Yes | 53 | 88.3 | 89 | 82.4 | |
| No | 7 | 11.7 | 19 | 17.6 | |
| Diabetes mellitus | | | | | 0.005 |
| Yes | 20 | 33.3 | 16 | 14.8 | |
| No | 40 | 66.7 | 92 | 85.2 | |
| Age (mean ± SD) | 51.0±10.2 | | 52.6±8.8 | | 0.3147 |

**Table II.** Clinical Characteristics of Patients Who Died During Follow-Up by Coronary Flow Reserve (CFR) Status

| | Abnormal CFR (n=12) | | Normal CFR (n=8) | | |
|---|---|---|---|---|---|
| Characteristic | n | % | n | % | *P* Value |
| Male | 4 | 33.33 | 5 | 62.5 | 0.360 |
| African American | 7 | 58.33 | 3 | 37.5 | 0.650 |
| Diabetes mellitus | 6 | 50 | 1 | 12.5 | 0.158 |
| Hypertension | 12 | 100 | 4 | 50 | 0.014 |
| Left ventricular mass index ($g/m^2$ ± SD) | 162.7±52.7 | | 94.8±14.4 | | 0.002 |
| Age at study start (y ± SD) | 49.4±11.3 | | 54.2±10.2 | | 0.342 |
| Age of death (y ± SD) | 49.0±11.8 | | 58.7±10.1 | | 0.232 |

CRF measures have provided additional clinical insight by which to tailor therapy to improve coronary blood flow. Such therapies may include angiotensin converting enzyme inhibition or the administration of L-arginine, the substrate of nitric oxide synthase, the enzyme for the powerful vasodilator nitric oxide.[2–4] Yet, the long-term outcome of patients stratified by these specific tests, such as CFR assessment, is unclear. Therefore, we undertook a retrospective study evaluating the functional status and mortality of patients with chest pain and normal coronary arteriography.

## METHODS

### Patients

The patients recruited for this study were part of a larger investigation to examine the influence of hypertension, left ventricular hypertrophy, hemodynamically insignificant atherosclerosis, gender, and ethnicity on coronary vasoreactivity. Multiple reports from these investigations have been published previously.[5–9] This patient subset represents all patients who underwent invasive CFR evaluation.

Left ventricular mass (LVM), when reported, was calculated using the method of Troy et al.[10] and indexed using the gender-specific normal limits from the Framingham Heart Study.[11] Intravenous dipyridamole-limited stress thallium-201 scintigraphy was performed using standard technique and interpreted in a blinded fashion.[12,13] Coronary vasodilator reserve testing was undertaken after diagnostic angiography. CFR was calculated as the ratio of peak to baseline flow velocity and normal CFR defined as ≥3.0. Impaired CFR was defined as CFR <3.0.[14,15]

Utilizing medical records and publicly available resources, the patients of the cohort were contacted by telephone and detailed questionnaires (the Medical Outcomes Study 36-Item Short-Form [SF-36][16] and the Duke Activity Scale Index[17]) were administered. Summary measures for the SF-36 were prepared.[18–20] The National Death Index was queried for all patients in the cohort not contacted by phone. Death certificates were obtained for each deceased person, including state and cause of death.

### Statistical Analysis

Summary data are expressed as mean ± standard deviation. Statistical tests, including the $\chi^2$, Fisher exact, Wilcoxon Rank Sum, and *t* test were used where appropriate to determine if differences in age, race, gender, hypertension and diabetes status, and death existed between those with abnormal and normal CFR. Survival analysis was used to determine if differences occurred in survival curves for death after catheterization by CFR status. A backward, stepwise elimination procedure was used to arrive at the final model. For the survival analysis, if not contacted in person, patients were assumed to be alive if a death certificate was not obtained. The Human Assurance Committee of the Institutional Review Board at the Medical College of Georgia approved all studies, including this follow-up evaluation.

## RESULTS

Follow-up was performed at a mean of 8.5±1.6 years in the abnormal CFR groups and 8.4±2.1 years in the normal CFR group. Differences between patients studied with abnormal or normal CFR are reported in Table I. There were no significant differences in age, race, gender, hypertension, or cardiac cause of death. More patients with an abnormal CFR had diabetes mellitus compared with those with a normal CFR (33.3% vs. 14.8%; $p$=0.005).

The invasive measure of CFR in this population strongly predicted death. In the abnormal coronary flow reserve group, 12 deaths (20%) were documented in 60 patients compared with eight out of 108 patients (7%; $p$=0.016) in the normal CFR group. Characteristics of the patients who died are presented in Table II. Patients who died with an abnormal CFR were more likely to have hypertension (12 [100%] vs. four [50%]; $p$=0.014) and a greater LVM index compared with those with a normal CFR (162.66±52.71 g/m$^2$ vs. 94.76±14.43 g/m$^2$; $p$=0.002). Although more patients who died with abnormal CFR examinations were diabetic, no statistical difference was found in this small number of patients (six [50%] vs. one [12.5%]; $p$=NS). The Figure demonstrates the event-free survival plot of patients by CFR status.

A multivariable proportional hazards model was created to further investigate the mechanism and confounding variables that might affect the effect of CFR on survival. The results of the model are presented in Table III. The final model reduced the univariable model containing only CFR. Those with CFR <3 were 6.08 times as likely to die.

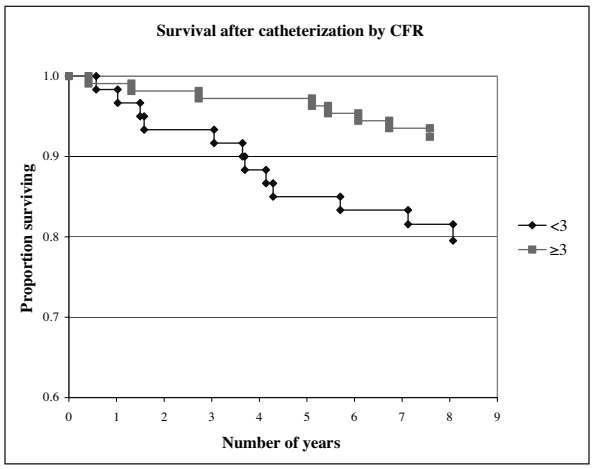


*Figure. Kaplan-Meier survival curves from invasive testing to death by coronary flow reserve (CFR) status*

Functional and quality-of-life outcomes were analyzed. Table IV reveals the baseline characteristics and outcomes of the 57 patients contacted for follow-up. No significant differences between baseline characteristics and functional studies were seen when grouped by CFR. Both groups demonstrated significant impairment in all measures of health outcomes when compared with national normative values.[20] Marked impairment (lower scores) of both mental and physical health (SF-36 physical and mental health summary scales) was noted between patients in the current study when compared with established cohorts of patients with angina, hypertension, and angina with hypertension.

## DISCUSSION

This study demonstrates an adverse prognosis in patients with chest pain/ischemic heart disease

**Table III.** Multivariable Proportional Hazards Models for All-Cause and Cardiac Mortality

| Variable | Hazard Ratio | 95% CI | *p* Value |
|---|---|---|---|
| Full model—all cause | | | |
| African-American race | 0.85 | 0.33–2.17 | 0.734 |
| Male gender | 2.81 | 0.92–8.58 | 0.069 |
| Age | 1.02 | 0.97–1.08 | 0.353 |
| CFR | 7.01 | 2.74–17.90 | 0.0001 |
| Diabetes | 2.31 | 0.75–7.11 | 0.146 |
| Hypertension | 0.58 | 0.17–1.99 | 0.385 |
| Final model—all cause | | | |
| CFR | 6.08 | 2.48–14.90 | 0.0001 |

CI=confidence interval; CFR=coronary flow reserve

**Table IV.** Differences in Demographic, Clinical, and Outcome Variables by CFR Status in Patients Contacted for Follow-Up Based on $\chi^2$ and *t* Tests

| | Abnormal CFR (n=17) | | Normal CFR (n=40) | | |
|---|---|---|---|---|---|
| Variable | n | % | n | % | *p* Value |
| Race | | | | | |
| White | 9 | 52.94 | 17 | 42.50 | 0.566 |
| African American | 8 | 47.06 | 23 | 57.50 | 0.190 |
| Gender | | | | | |
| Male | 2 | 11.76 | 12 | 30.00 | 0.190 |
| Female | 15 | 88.24 | 12 | 70.00 | |
| Hypertension | | | | | |
| Yes | 15 | 88.24 | 38 | 95.00 | 0.575 |
| No | 2 | 11.76 | 2 | 5.00 | |
| Diabetes | | | | | |
| Yes | 6 | 35.29 | 8 | 20.00 | 0.314 |
| No | 11 | 64.71 | 32 | 80.00 | |
| Age | 53.7±6.6 | | 53.5±9.2 | | 0.6465 |
| DASI | 20.29±13.27 | | 19.23±13.81 | | 0.4922 |
| SF-36 mental subscale | 41.18±15.29 | | 44.3±11.59 | | 0.4961 |
| SF-36 physical subscale | 31.12±9.17 | | 31.95±11.14 | | 0.9165 |

CFR=coronary flow reserve; DASI=Duke Activity Scale Index; SF-36=Medical Outcomes Study Short-Form Survey

without angiographic coronary artery disease and abnormal CFR. Although CFR was a significant predictor of mortality, it did not predict functional health status of these patients when compared with a group of patients with essential hypertension who had not been studied for microvascular disease.

Hypertension was prevalent in this group of patients. Left ventricular hypertrophy and microvascular dysfunction[21] are described sequelae of longstanding hypertension. Increased LVM has been associated with increased mortality,[22] both in the presence and absence of coronary artery disease.[23] Similarly, increased LVM has been associated with coronary vascular remodeling, endothelial dysfunction, and nonendothelial vascular abnormalities.[24] Although hypertension was present in this series of patients, it occurred with equal frequency among the normal and abnormal CFR groups. It might have been expected that hypertensive subjects would show a decreased CFR. The multivariate analysis did not demonstrate significance to any clinical variable except CFR. The association between hypertension, abnormal CFR, and mortality requires further investigation.

The clinical evaluation of patients with chest pain/ischemic heart disease and normal coronary angiograms can be perplexing. Exercise testing[25]—even with the addition of perfusion imaging[26]—may be abnormal in this group of patients. Invasive testing evaluating both endothelial dependent and independent microvascular function has been proposed[2] with therapy tailored toward microvascular disease, regardless of endothelium dependence.[3,4] Ockene et al.[1] and others[27,28] promote the use of invasive diagnostic measures of CFR as a cost-effective measure with clinical utility in patients with a normal coronary arteriogram.[1] The utility of measuring CFR in response to pharmacologic stress has been shown to have clinical utility.[27,28] The prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of coronary baloon angioplasty demonstrated the use of examining CFR after a coronary intervention in predicting 6-month cardiac events.[29] Diminished CFR was associated with the recurrence of angina or ischemia. Several groups have demonstrated the utility of CFR in lesion analysis and follow-up.[30,31] Previous studies have demonstrated the prognosis for patients with chest pain/ischemic heart disease and normal/near normal coronary arteriograms to be quite favorable.[32,33] Recently, investigators described an adverse prognosis in patients with hypertrophic cardiomyopathy and abnormal myocardial blood flow as measured by positron-emission tomography.[34]

The important interactions of diabetes, hypertension, and cardiovascular disease have recently been highlighted.[35] Persons with diabetes, even in

the absence of a prior myocardial infarction, are at high risk for a cardiovascular event.[36] More patients in the abnormal CFR group had diabetes, although there was not a statistically significant increase in the number of patients with diabetes among those who died. Due to the small number of patients in this study, we cannot exclude an interaction of diabetes with abnormal CFR, although the multivariate analysis did not find an association between diabetes and mortality in this cohort during the period of follow-up.

Previous assessments of quality of life in patients with chest pain/ischemic heart disease and normal coronary arteriograms have demonstrated marked impairment despite few cardiac events. Atienza[37] demonstrated marked impairment in quality of life and created a specific questionnaire to evaluate the impairment in patients with chest pain and normal coronary arteriograms. Our study demonstrates a marked impairment of both mental and physical health in patients with chest pain/ischemic heart disease and normal coronary angiograms. The utilization of the SF-36 physical and mental health summary scales allows for comparison to established normative values. Although our data re-establishes the long-term morbidity associated with this syndrome; invasive evaluation of CFR does not assist in the prediction of functional impairment.

### Limitations

Our study has several limitations. First, the cohort, although representative of patients with chest pain/ischemic heart disease and normal coronary arteriograms, has a high prevalence of hypertension. Second, the functional health outcomes assessments of these patients were performed via telephone interview. Although consistent, many of the functional questionnaires were designed for patients to complete the forms in a tabular format. Similarly, only 46% of the original group consented to participate in the telephone interview, limiting the generalizability of the functional status analysis of the patients in the follow-up. Third, the historical analysis of the procedure limits our data analysis. Some variation in procedure was present with patients receiving a variety of agents to achieve a maximal vasodilator state. Because CFR is a computed value, we do not anticipate this variation to significantly affect our data analysis. The data are not available to control for various vasodilators, maximal hyperemia, or the hemodynamic state at the time of the study. Intravascular ultrasound was not performed; occult coronary atherosclerosis may have been present in some patients. The inability to obtain these procedural variables limits the generalizability of our results. Fourth, we assumed patients who were not available for follow-up, but not listed in the death registry, to be living. This assumption could possibly confound and limit our analysis. Finally, this study did not allow for the independent assessment of clinical outcomes including myocardial infarction, the development of congestive heart failure, or revascularization. These data are important but difficult to obtain in a valid fashion in a retrospective analysis. Despite the lack of clinical outcomes other than mortality, the striking difference in this hard end point suggests significant pathology to be further elucidated in prospective studies.

## SUMMARY

The invasive measure of CFR in this population of patients with chest pain/ischemic heart disease and normal coronary arteriograms predicts mortality. CFR did not predict health outcomes, although patients with chest pain/ischemic heart disease and normal coronary arteriograms had markedly diminished health status components. This study may suggest a means by which to classify the risk of patients with chest pain and a normal coronary arteriogram. Further study is needed to validate these findings and evaluate the mechanism by which microvascular disease is associated with increased mortality. Similarly, further study is needed to understand if hypertension therapy mitigates the increased risk associated with this condition.

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