Right Ventricular Stress-Induced Perfusion Defects and Late Gadolinium Enhancement in Coronary Artery Disease

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Objective: The assessment of right ventricular (RV) perfusion defects has remained challenging during vasodilator stress perfusion with cardiovascular magnetic resonance (CMR). The significance of RV signal abnormalities during vasodilator stress perfusion and late gadolinium-enhanced CMR is yet uncertain.

Methods: Among 61 individuals who underwent adenosine CMR stress testing before cardiac catheterization, we assessed the severity of coronary artery stenoses, mortality, the presence of stress and rest perfusion defects, as well as the presence of late gadolinium enhancement (LGE).

Results: Right ventricular stress-induced perfusion defects were positively associated with left anterior descending artery and proximal right coronary artery stenoses but were negatively associated with left circumflex artery stenoses. The presence of RV LGE was associated with mortality, but 77% of those with RV LGE also had left ventricular LGE.

Conclusions: Proximal right coronary artery and left anterior descending artery stenoses are positively associated, whereas left circumflex artery stenoses are negatively associated with RV stress-induced perfusion defects. Right ventricular LGE was associated with mortality, but further study is needed to determine whether this is independent of left ventricular LGE.

Key Words: right ventricle, stress perfusion defect, late gadolinium enhancement

Heart disease has remained the leading cause of death in the United States for more than 75 years, and detection and treatment of coronary artery disease (CAD) can substantially improve function and mortality. Noninvasive cardiac stress testing focuses almost exclusively on the left ventricle (LV). The apex and anterior wall of the right ventricle (RV) are supplied by the left circumflex artery via the right coronary artery. Although detection of perfusion defects of the RV is difficult in the absence of RV hypertrophy, efforts to do so may augment the accuracy of stress testing to identify clinically significant left anterior descending artery (LAD) or right coronary artery (RCA) coronary lesions.

The first description of abnormal RV perfusion due to RCA stenosis was by Brachman et al in 1981. They presented 2 patients in whom stress thallium scintigraphy identified reversible perfusion abnormalities with detection at 40 minutes after injection of radiotracer, rather than the contemporary standard 4 hours used for evaluation of LV perfusion defects. Subsequent studies suggested that detection of RV ischemia with exercise is useful only in patients with severely compromised ventricular function or in corrected congenital heart disease that results in right ventricular hypertrophy. Perhaps because of this reasoning, interest in routine detection of RV perfusion defects remained sporadic.

In 1994, Travin et al described a series of 33 patients who underwent low-level exercise technetium 99m sestamibi (single-photon emission computed tomography) imaging 6 to 14 days after inferior myocardial infarction. They showed that 30% of these patients had an identifiable RV perfusion defect, which, in 50% of the subgroup, was shown to be reversible. Whereas this “proof of principle” was certified, namely, that RV ischemia could be effectively detected using standard technologies, the implications for clinical care remained uncertain.

Much of the recent focus on imaging the RV has been on the assessment of RV function or the development of RV scarring after RV myocardial infarction for further prognostication or risk stratification. Indeed, depressed RV ejection fraction (≤ 40%) predicts poor prognosis, independent of LV ejection fraction and LV infarct size, late after myocardial infarction. To date, there has been a limited description of the prospective detection of coronary lesions producing reversible RV ischemia.

Cardiovascular magnetic resonance (CMR) imaging is now considered the reference standard for functional studies of the RV. With CMR representing improved technology to detect RV ischemia during rest and stress, the challenges that thus far have limited the usefulness of RV imaging in the identification of ischemic coronary artery lesions may be surmounted. The present study sought to determine whether a significant association exists between RV perfusion defects identified by CMR stress testing and coronary artery stenoses as well as between RV late gadolinium enhancement (RV LGE) and mortality.

MATERIALS AND METHODS

This study protocol was approved by the institutional review board of Wake Forest Baptist Health (Medical Center Blvd, Winston-Salem, NC). Investigators queried the CMR report database and cardiac catheterization records for patients who had undergone, for clinical indications, an adenosine stress CMR interpreted as “positive” for CAD and patients who also underwent subsequent diagnostic coronary angiography between January 2007 and February 2013. On the basis of catheterization results, the patients were placed into 4 similarly sized groups according to the presence of (1) no significant CAD, (2) single-vessel CAD, (3) double-vessel CAD, or (4) multivessel CAD. Mortality was assessed by medical chart review and by the Social Security Death Index.

Magnetic resonance imaging (MRI) studies were reviewed for RV stress-induced perfusion defects and the presence of LGE by 2 blinded, experienced CMR interpreters. Perfusion images were obtained at the basal, mid, and apical levels. At each level, the defect was described as either anterior or inferior (Fig. 1). To be identified as having a perfusion defect, both interpreters had to identify it independently. Late gadolinium enhancement (LGE) images were obtained by performing an inversion time scout (TI Scout; Siemens Medical Solutions) sequence, and an inversion time was selected, which provided a uniform dark background in noninfarcted myocardium. Using this inversion time, multislice...
short-axis magnitude gradient-echo recovery LGE images were obtained starting from the heart base to the LV apex (8-mm-thick slices with 2-mm gap). Scan parameters included an 800-millisecond repetition time, a 4.18-millisecond echo time, a flip angle of 25 degrees, a 308-mm field of view, a 130-Hz bandwidth, a 256/C2 matrix, and no flow compensation. These images were reviewed by 2 blinded, experienced CMR interpreters for RV involvement (Fig. 2).

All CMR baseline data are presented as mean ± standard deviation. Nominal data were tested using the \( \chi^2 \) test. Continuous data were tested using the Student \( t \) test. A \( P \) value of less than 0.05 was considered statistically significant. Correlations were also used to describe unadjusted linear relationships. All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Inc, Cary, NC).

Adjusting for age, race, and sex, a logistic regression model was used to describe the potential association between significant coronary stenoses (which was defined as 70% stenosis or greater as recognized on cardiac catheterization) and RV perfusion defects. Adjusting for the same covariates, a generalized linear model was used to describe the potential association between mortality and the presence of RVLGE.

To assess interobserver and intraobserver variability, a table analysis was performed. Total agreement was measured as a percentage, and a \( \kappa \) statistic was used to assess the agreement statistically.

### RESULTS

The patients included in this analysis had a high burden of obstructive coronary disease and prior revascularization; 14 of 61 patients (23%) had a history of prior coronary artery bypass grafting. Of the 61 patients studied, 22 (36%) had proximal LAD disease, 24 (39%) had proximal circumflex disease, and 26 (43%) had

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**TABLE 1. Average Age, Proportion of Patients Having Each Risk Factor Studied (Race, Sex, Hypertension, Hyperlipidemia, Diabetes Mellitus), and Presence of RV and LV Late Gadolinium Enhancement Are Shown for Groups With No Significant CAD, 1-Vessel CAD, 2-Vessel CAD, and Multivessel CAD**

| Baseline Characteristics | No Significant CAD (n = 16) | 1-Vessel CAD (n = 18) | 2-Vessel CAD (n = 13) | Multivessel CAD (n = 13) |
|--------------------------|-----------------------------|-----------------------|-----------------------|--------------------------|
| Age, y                   | 56.8 ± 13.7                 | 59.8 ± 9.5            | 60.7 ± 12.7           | 62.0 ± 13.2              |
| Race (African American)  | 21%                         | 0%                    | 20%                   | 0%                       |
| Sex (Female)             | 63%                         | 54%                   | 30%                   | 10%*                     |
| Hypertension             | 68%                         | 86%                   | 80%                   | 90%                      |
| Hyperlipidemia           | 68%                         | 63%                   | 100%                  | 100%*                    |
| Diabetes mellitus        | 30%                         | 40%                   | 40%                   | 50%                      |
| RV late gadolinium       | 10%                         | 24%                   | 0%                    | 60%*                     |
| LV late gadolinium       | 10%                         | 14%                   | 10%                   | 70%*                     |

*A value with trend test satisfying \( P < 0.05 \).

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**FIGURE 1.** Contrast perfusion image with white line to indicate the demarcation point between an anterior defect and an inferior defect in the RV free wall.

**FIGURE 2.** Example of right ventricular late gadolinium enhancement. Late gadolinium enhancement is present in the inferior segments from an RCA infarct.

**FIGURE 3.** Bar graph demonstrating the presence of right ventricular perfusion defects by the number of stenotic coronary vessels.
proximal RCA disease demonstrated by cardiac catheterization. The average age, proportion of the patients having each risk factor studied (race, sex, hypertension, hyperlipidemia, diabetes mellitus), as well as the presence of RV and LV LGE are shown for groups with no significant CAD, 1-vessel CAD, 2-vessel CAD, and multivessel CAD (Table 1). Of these patients, 24 (39%) had an RV perfusion defect (Fig. 3). Of those with an RV perfusion defect, 10 (42%) had an inferior RV defect (Fig. 4), 9 (38%) had an anterior RV defect (Fig. 5), and 5 (20%) had both anterior and inferior defects. Overall, there were 362 segments interpreted, but 28 segments (7.7%) were unable to be interpreted owing to the presence of artifact, most commonly from sternal wires.

Right ventricular stress-induced perfusion defects were positively associated with proximal RCA and LAD stenoses ($P < 0.01$; Fig. 6). There was a trend toward a significant positive association ($P = 0.10$) between RV stress-induced perfusion defects and distal RCA disease (Fig. 6). However, left circumflex artery stenosis was negatively associated ($P = 0.024$) with stress-induced perfusion defects within the RV myocardium (Fig. 6).

The presence of RVLGE was associated with mortality (Table 2), but 77% of the patients with RVLGE also had LV LGE (Table 3). There was no relationship between RV perfusion defects and mortality.

There was decent interobserver and intraobserver variability for RV perfusion defects. For the interobserver variability, there was 86% overall agreement with a $\kappa$ statistic of 0.75, which is

| TABLE 2. Unadjusted $\chi^2$ Table Analysis of RV Late Gadolinium Enhancement by Mortality |
|-----------------------------------------------|----------------|
| Alive | Deceased |
| RV LGE absent | 46 | 2 |
| RV LGE present | 10 | 3 |

$\chi^2$ of 9.8; $P = 0.0275$. 
in which the RV is more susceptible to artifacts owing to its position relative to the LV. This limitation may be compounded because the inversion defect or RV LGE may signal a specific finding, with only 57% of these patients having a defect. Second, even in individuals with more than 1 obstructive lesion, RV perfusion defects remained a specific finding, with 57% of these patients having a defect. Third, the presence of RV LGE in the presence of CAD may have the potential to help provide prognostic information.

There are several interesting pathways that may explain how RV perfusion defects are not seen in all individuals with significant obstructive CAD. The LV systolic pressure and aortic pressure are similar, and as such, coronary blood flow predominantly occurs during diastole. By contrast, the RV may be less sensitive to ischemia owing to the RV systolic pressure being lower than the aortic systolic blood pressure, allowing meaningful coronary blood flow to the RV to occur during both systole and diastole. These findings have been described before, particularly with phase contrast flow analysis of the coronary arteries by MRI.

The observed negative association between obstructive lesions in the left circumflex artery and RV perfusion defects may further support the proposed mechanism that RV perfusion defects result from stenoses in the right coronary and left anterior descending arteries, which subclend the LV myocardium. It follows that, if a patient has more predominant coronary disease in the circumflex distribution, there is a lower likelihood of decreased perfusion in the RV; this association is thus described by the negative coefficient observed in our model, which adjusts for the presence of LAD and RCA stenoses.

Interestingly, the presence of LGE in the RV was associated with all-cause mortality. It would make intuitive sense that a scar in the RV may serve as a nidus for malignant ventricular arrhythmias, just as a scar in the LV can. Unfortunately, the majority of individuals with RVLGE also had LGE present on the LV. As such, it is difficult to tease out the specific effect of isolated RV LGE as opposed to isolated LV LGE. Further studies will need to be undertaken to help clarify any potential risk for isolated RVLGE defects in the presence of CAD.

There are several limitations to our approach. First, a significant number of our patients had multivessel disease. As a result, it is challenging to isolate the specific role that each particular lesion may have had in the formation of a given stress-induced RV perfusion defect or RVLGE signal. Second, considering the thinness of the RV wall, it can be challenging to identify perfusion defects with confidence; this limitation may be compounded because the inversion recovery time in our image acquisition was based on nulling the LV and not the RV. In addition, there are many circumstances in which the RV is more susceptible to artifacts owing to its position near the chest wall as well as to pericardial liquid or epicardial fat. These challenges, in concert with the lack of firmly established clinical significance, may help explain why the identification and reporting of perfusion defects and LGE in the RV are not yet routine practice in clinical cardiovascular imaging.

Third, patients were included in this study on the basis of identification of perfusion defects in the LV, the presence of which led to cardiac catheterization. At our institution, patients who undergo adenosine stress MRI may be more likely to have established and advanced coronary disease than those patients who undergo various other noninvasive ischemic assessment modalities as an initial diagnostic measure. The performance of adenosine stress MRI to identify RV or LV perfusion defects or LGE in the general population thus cannot be inferred from this series of patients with prevalent and severe coronary disease. However, there may also be many unrecognized patients not studied who have RV but not LV perfusion defects, the coronary stenosis patterns and prognoses of whom are not yet known. Finally, the majority of patients with RVLGE also had LV LGE, which means that our ability to speak directly to the effect of RVLGE is limited.

### DISCUSSION

There are several key observations to be noted from this particular analysis. First, as expected, there are some RV perfusion defects that correlate with certain anatomic distributions of CAD, such as LAD or RCA obstructive disease. Although not all patients with LAD or RCA stenoses had RV perfusion defects, this suggests that an RV perfusion defect may be a more specific finding rather than a sensitive finding. Second, even in individuals with more than 1 obstructive lesion, RV perfusion defects remained a specific finding, with only 57% of these patients having a defect. Third, the presence of RVLGE in the presence of CAD may have the potential to help provide prognostic information.

There are several interesting pathways that may explain how RV perfusion defects are not seen in all individuals with significant obstructive CAD. The LV systolic pressure and aortic pressure are similar, and as such, coronary blood flow predominantly occurs during diastole. By contrast, the RV may be less sensitive to ischemia owing to the RV systolic pressure being lower than the aortic systolic blood pressure, allowing meaningful coronary blood flow to the RV to occur during both systole and diastole. These findings have been described before, particularly with phase contrast flow analysis of the coronary arteries by MRI.

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### CONCLUSIONS

Proximal RCA and LAD stenoses are positively associated, whereas left circumflex artery stenoses are negatively associated with RV perfusion defects identified by adenosine stress perfusion MRI. Right ventricular LGE is associated with increased mortality, but further studies will be needed to determine whether this is independent of LV LGE.

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