Elevated Pulmonary Artery Pressure by Doppler Echocardiography Predicts Hospitalization for Heart Failure and Mortality in Ambulatory Stable Coronary Artery Disease

The Heart and Soul Study

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Objectives
We compared the predictive ability of tricuspid regurgitation (TR) and end-diastolic pulmonary regurgitation (EDPR) gradients in outpatients with coronary artery disease.

Background
The TR and EDPR gradients, in conjunction with right atrial pressure, provide Doppler estimates of pulmonary artery systolic and diastolic pressures. We hypothesized that increases in TR or EDPR gradients in stable coronary artery disease would predict heart failure (HF) hospitalization or cardiovascular (CV) death.

Methods
We measured TR and EDPR gradients in 717 adults with completed outcome adjudications who were recruited for the Heart and Soul Study. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for HF hospitalization, CV death, all-cause death, and the combined end point. Multivariate adjustments were made for age, gender, race, history of CV or pulmonary disease, functional class, and left ventricular ejection fraction.

Results
There were 63 HF hospitalizations, 19 CV deaths, and 86 all-cause deaths at the 3-year follow-up. There were 466 measurable EDPR gradients and 573 measurable TR gradients. Age-adjusted ORs for EDPR ≥5 mm Hg predicted HF hospitalization (2.7, 95% CI 1.3 to 5.5, p = 0.006), all-cause death (2.5, 95% CI 1.4 to 4.4, p = 0.002), and HF hospitalization or CV death (2.7, 95% CI 1.4 to 5.2, p = 0.004). Age-adjusted OR for TR ≥30 mm Hg predicted HF hospitalization (3.4, 95% CI 1.9 to 6.2, p < 0.0001) and HF hospitalization or CV death (3.0, 95% CI 1.7 to 5.3, p = 0.0001). Multivariate adjusted OR per 5-mm Hg incremental increases in EDPR predicted HF hospitalization or CV death (1.9, 95% CI 1.01 to 3.6, p = 0.046) and all-cause death (1.7, 95% CI 1.05 to 2.8, p = 0.03). Multivariate adjusted OR per 10-mm Hg incremental increases in TR predicted HF hospitalization or CV death (1.6, 95% CI 1.1 to 2.4, p = 0.008).

Conclusions
Increases in EDPR or TR gradients predict HF hospitalization or CV death among ambulatory adults with coronary artery disease. (J Am Coll Cardiol 2007;49:43–9) © 2007 by the American College of Cardiology Foundation

Raised pulmonary artery (PA) pressure estimated by Doppler echocardiography has been shown to predict mortality in patients with acute myocardial infarction (1), aortic stenosis (2), acute pulmonary embolism (3), and primary pulmonary hypertension (4). Increased PA pressures also have been shown to predict mortality in patients with end-stage liver disease (5), human immunodeficiency virus infection (6), scleroderma (7), and sickle cell disease (8).

The tricuspid regurgitation (TR) gradient, added to echocardiographically estimated right atrial (RA) pressure, has been found to correlate well with catheterization-derived PA systolic pressure (9). End-diastolic pulmonary regurgitation (EDPR) gradients added to RA pressure have been found to correlate well with catheter-derived PA diastolic pressures (10,11). We have previously shown that an EDPR gradient ≥5 mm Hg is an independent marker of...
cardiac dysfunction (12). The prognostic significance of an increased EDPR gradient among individuals with coronary artery disease has not been evaluated. We hypothesized that Doppler-derived elevations in TR gradients and EDPR gradients predict heart failure (HF) hospitalization, cardiovascular (CV) death, and all-cause mortality in ambulatory adults with coronary artery disease.

Methods

The Heart and Soul Study is a prospective cohort study investigating the influence of psychosocial factors on CV events. The enrollment process for the Heart and Soul Study has been previously described (13). Criteria for enrollment were: 1) history of myocardial infarction, 2) angiographic evidence of at least 50% stenosis by area in at least 1 coronary vessel, 3) evidence of exercise-induced ischemia by treadmill electrocardiogram or stress nuclear perfusion imaging, 4) history of coronary revascularization, or 5) clinical diagnosis of coronary artery disease as documented by an internist or cardiologist. Individuals were excluded if they deemed themselves unable to walk 1 block or if they were planning to move out of the local area within 3 years. All study participants provided informed consent for baseline echocardiographic testing, laboratory testing, and review of medical records. The institutional review board at each of the enrolling centers approved the study protocol.

Tricuspid and pulmonic regurgitation measurements. Echocardiographic studies were performed in the standard left lateral recumbent and supine positions with a commercially available ultrasound system with harmonic imaging (Acuson Sequoia, Siemens Corp., Mountain View, California). The TR jet was visualized with color flow mapping, and the TR gradient was measured with continuous wave Doppler (Fig. 1). We used the modified Bernoulli equation (\( \Delta P = 4 \frac{V^2}{R} \)) to calculate gradients from velocities. Because our initial investigations of the EDPR gradient generated more intense interest in echocardiographic estimates of PA pressures (12), we changed our analysis protocol to include multiple views for detection of TR instead of the parasternal long axis alone. The peak TR gradient for the current study was the highest measurement obtainable by Doppler imaging among parasternal, apical, and subcostal views. We did not seek to add an estimate of RA pressure into the analyses because we hypothesized that measured gradients alone would have statistically significant power in predicting adverse outcomes. A single technician made all sonographic measurements, and a single cardiologist reader (N.B.S.), who was blinded to clinical and laboratory information, evaluated each echocardiogram.

The PR wave form was sought from the standard basal parasternal short-axis view by color flow interrogation across the pulmonic valve. The velocity was measured at end-diastole at termination of reverse flow after the “a”-wave (Fig. 2). This point of measurement also corresponded with the first peak deflection of the QRS complex (usually the R-wave). To minimize the significance of respiratory variation, the sonographer screened at least 10 cardiac cycles with the patient breathing quietly at rest and chose the

Figure 1

**Tricuspid Regurgitation Gradient**

On color flow Doppler signal, the highest tricuspid regurgitation gradient from parasternal, apical, or subcostal views is recorded. The apical view is shown.
highest value for measurement. Formal evaluation of the EDPR gradient occurred in the 741 participants enrolled between July 2001 and December 2002.

Although studies suggest that TR gradients normally increase with age (14), we sought to investigate the predictive power of 5- and 10-mm Hg increases in EDPR and TR, respectively. We also sought to determine the prognostic significance of a single cutoff point in predicting outcome. Studies in young healthy individuals with normal cardiac output suggest that the upper limit of normal for the TR gradient, when evaluated independently of RA pressure, should be 30 mm Hg (15,16). We previously have validated 5 mm Hg as the upper limit of normal for the EDPR gradient (12).

**Cardiovascular outcomes.** We conducted telephone follow-up interviews and questioned participants or their proxies regarding recent emergency room visits, hospitalizations, or death. Medical records, death certificates, and coroner’s reports were retrieved. Two blinded adjudicators reviewed each event and, if there was agreement, the outcome classification was binding. If there was disagreement, a third blinded adjudicator reviewed the event and determined the outcome classification.

Hospitalization for HF was defined for a clinical syndrome with a minimum 1-night hospital stay and involving at least 2 of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, a third heart sound, cardiomegaly on chest radiography, or pulmonary edema on chest radiography. These clinical signs and symptoms must have represented a clear change from the normal clinical state of the patient and must have been accompanied by either failing cardiac output as determined by peripheral hypoperfusion (in the absence of other causes such as sepsis or dehydration) or peripheral or pulmonary edema treated with intravenous diuretics, inotropes, or vasodilators.

Mortality adjudications were based on hospital records, death certificates, and autopsy results. Death was considered due to CV causes if the death certificate listed acute myocardial infarction, congestive HF, or arrhythmia as the primary cause of death. Sudden death also was considered CV if it was unexpected, otherwise unexplained, and occurred within 1 h of the onset of terminal symptoms.

**Statistical analysis.** We included only those participants with completed outcome adjudications (717 patients) in the analyses. Baseline characteristics are reported as the mean plus or minus standard deviation for continuous variables and as percentages for categorical variables. Differences in baseline characteristics between groups of study participants were determined using the Student t test for continuous variables and the chi-square test for dichotomous variables. We used logistic regression to calculate odds ratios (ORs) for predictor variables and outcome. We report ORs with 95% confidence intervals. C-statistics were recorded for PR and TR as predictors of HF hospitalization and CV death. Analyses were calculated using software (Statistical Analysis, Version 8, SAS Institute Inc., Cary, North Carolina). Predefined end points were HF hospitalization, CV death, all-cause death, and the combined end point of HF hospitalization or CV death.
Results

Of the 717 participants with completed outcome adjudications who were enrolled between July 2001 and December 2002, 466 (65%) had measurable EDPR gradients, 573 (80%) had measurable TR gradients, and 392 (55%) had both measurable EDPR and TR gradients. Among those individuals without measurable TR gradients, 74 (10% of the total) had measurable EDPR gradients. Considering either EDPR or TR as a measuring tool increased the yield of estimates of PA pressure to 90% of the study population.

Of those with measurable EDPR, there were 96 individuals (21%) with an EDPR gradient >5 mm Hg. Of those with measurable TR, there were 126 individuals (22%) with a TR gradient >30 mm Hg. The proportion of individuals with an increased EDPR gradient was similar whether TR was measurable (20%) or not (23%). The proportion of individuals with an elevated TR gradient also was similar whether EDPR was measurable (23%) or not (19%).

Baseline characteristics of study participants are shown in Table 1. Statistically significant differences were present between normal and elevated gradients with regard to age, physical activity, New York Heart Association functional class, and left ventricular ejection fraction. Statistically significant differences also were present with regard to diabetes mellitus, prior stroke, and history of HF.

During a mean follow up of 3 years, there were 63 hospitalizations for HF, 19 CV deaths, and 86 all-cause deaths. The number of participants with outcome events separated by PR and TR gradients is listed in Table 2. The age-adjusted ORs for EDPR >5 mm Hg and TR >30 mm Hg for predicting outcome are shown in Table 3.

Multivariate adjusted analyses for age, gender, body mass index, body surface area, body mass index, ethnicity, history of hypertension, myocardial infarction, stroke, chronic ob-
destructive pulmonary disease, diabetes mellitus, prior coronary revascularization, prior HF, smoking, alcohol consumption, physical activity, New York Heart Association functional class, and left ventricular ejection fraction are listed in Table 4. Each 5-mm Hg increase in EDPR was associated with a 2.5-fold increased OR for HF hospitalization. Each 10-mm Hg increase in TR was associated with a 50% increased OR for HF hospitalization. Each 5-mm Hg increase in EDPR also was associated with a 70% increased OR for all-cause death.

For the 55 individuals who had only increased rates of TR (>30 mm Hg with normal EDPR), 11% had HF hospitalization or CV death. For the 43 individuals with only elevated EDPR (>5 mm Hg with normal TR), 9% had HF hospitalization or CV death. For the 36 individuals with both elevated TR and EDPR, 36% had HF hospitalization or CV death. The number of individuals with HF hospitalization or CV death for groups of participants divided by EDPR or TR gradients is shown in Figure 3. C-statistics were similar for EDPR and TR in predicting HF hospitalization (EDPR 0.71, TR 0.66) and CV death (EDPR 0.57, TR 0.60), indicating that the tests have similar predictive power. C-statistics for predicting all-cause mortality showed slightly better predictive power for EDPR (0.66) than for TR (0.57).

**Discussion**

Doppler measurements of TR and EDPR gradients predict HF hospitalization and mortality among ambulatory adults with coronary artery disease. Previous studies have shown that Doppler estimated elevations in PA systolic pressure predict mortality in a variety of disease states, and the current study extends the adverse prognostic significance of elevated TR to adults with stable coronary artery disease. The current study also illustrates the prognostic impact of the EDPR gradient.

The EDPR gradient is a clinically useful measurement for multiple reasons. The measurement is simple to make from the parasternal short axis, and it involves a single caliper placement along a Doppler signal. In such cases where the TR signal does not provide a measurable waveform, the EDPR gradient can provide a measurable estimate of PA diastolic pressure. Although our initial investigations into Doppler estimates of PA pressures reported measurable TR gradients from the parasternal view in 61% of patients (12), we achieved a greater percentage of measurable TR gradients by incorporating the apical and subcostal views for measuring TR. The addition of EDPR measurements to TR measurements increased the yield of information about PA pressure from 80% to 90% in our study population.

The EDPR gradient correlates with catheter-derived PA diastolic pressure and may be a wedge pressure analog and a measure of LV end diastolic pressure. An increased EDPR gradient was significantly associated with history of HF at baseline (Table 1), whereas the TR gradient was not. Both EDPR and TR predict future HF hospitalizations, but a possible difference in prognostic information from each gradient merits further study.

Although TR is measured from the apical, parasternal, or subcostal views, the EDPR gradient is measured in the parasternal axis. Important technical considerations in measuring the EDPR gradient are: 1) inclusion of the highest EDPR gradient among several cycles of quiet respiration, and 2) measurement along the first-peak deflection of the QRS complex. In those cases in which the pulmonary regurgitation waveform ended before the onset of the QRS complex, we did not include a measurable EDPR gradient.

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**Table 3** Age-Adjusted Odds Ratios (With 95% Confidence Intervals) for Elevated EDPR and TR gradients

<table>
<thead>
<tr>
<th>Gradient</th>
<th>p Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDPR &gt; 5 mm Hg</td>
<td>0.006</td>
<td>0.0001</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>2.7 (1.3–5.5)</td>
<td>3.4 (1.9–6.2)</td>
</tr>
<tr>
<td>CV death</td>
<td>1.9 (0.64–5.8)</td>
<td>1.5 (0.51–4.5)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2.5 (1.4–4.4)</td>
<td>1.5 (0.87–2.7)</td>
</tr>
<tr>
<td>HF hospitalization or CV death</td>
<td>2.7 (1.4–5.2)</td>
<td>3 (1.7–5.3)</td>
</tr>
</tbody>
</table>

**Table 4** Multivariate-Adjusted* Odds Ratios (With 95% Confidence Intervals) per 5-mm Hg Increase in EDPR or 10-mm Hg Increase in TR

<table>
<thead>
<tr>
<th>Increment</th>
<th>p Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDPR 5-mm Hg</td>
<td>2.5 (1.2–4.9)</td>
<td>1.5 (1.03–2.2)</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>2.5 (1.2–4.9)</td>
<td>1.5 (1.03–2.2)</td>
</tr>
<tr>
<td>CV death</td>
<td>1.2 (0.45–3.0)</td>
<td>1.3 (0.83–2.2)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.7 (1.05–2.8)</td>
<td>1.2 (0.85–1.6)</td>
</tr>
<tr>
<td>HF hospitalization or CV death</td>
<td>1.9 (1.01–3.6)</td>
<td>1.6 (1.1–2.4)</td>
</tr>
</tbody>
</table>

*Multivariate adjustments are made for all variables in Table 1. Abbreviations as in Tables 1 and 2.
in the analyses. We have shown previously that the correlation coefficient for interobserver variability for EDPR measurements was 0.98, indicating that the measurement is reproducible (12).

**Study limitations.** Several limitations of our study must be considered. First, the study population was predominantly male, and the results may not apply to women. Second, for simplification, we did not add RA pressure to our measurements of EDPR or TR. As is typical of an ambulatory population, most (92%) of the individuals in the current study had a normal RA pressure of 5 mm Hg or less. Third, we did not correct pressure gradients for cardiac output, which could provide an analog for pulmonary vascular resistance (17). Other methods of estimating PA pressure by echocardiography also were not evaluated in the present study (10,18,19).

Although multivariate-adjusted incremental increases in EDPR and TR were significant for predicting HF hospitalization and the combined end point of HF hospitalization or CV death, the OR of EDPR or TR gradients for predicting CV death were not statistically significant. The small number of adjudicated CV deaths in the study (19 patients) could explain the lack of statistical significance.

**Conclusions.** Doppler measured EDPR and TR gradients predict HF hospitalization and the combined end point of HF hospitalization and CV mortality among ambulatory adults with stable coronary artery disease. The EDPR gradient also predicted all-cause mortality. We propose that EDPR and TR should be measured routinely in transthoracic echocardiograms to estimate PA pressure. Each level of progressive elevation in PA pressure has adverse prognostic significance, whereas the greatest levels of EDPR and TR increases in stable coronary artery disease are markedly predictive of HF hospitalization or CV death. The use of EDPR and TR may have applicability to patients with diseases of other organ systems, and future studies will be helpful to determine the predictive value of elevated TR or EDPR gradients among other populations.

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**REFERENCES**


