Prognostic significance of renal function in patients undergoing dobutamine stress echocardiography

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Abstract

Background. Dobutamine stress echocardiography (DSE) is used for risk stratification of patients with suspected coronary artery disease (CAD). However, the prognostic value of DSE among the entire strata of renal function has yet to be determined. We assessed the prognostic value of renal function relative to DSE findings.

Methods. We studied 2292 patients, divided into 729 (32%) patients with normal renal function [creatinine clearance (CrCl) > 90 ml/min] and 1563 (68%) with renal dysfunction, classified as mild (CrCl: 60–90 ml/min) in 933, moderate (CrCl: 30–60 ml/min) in 502 and severe (CrCl < 30 ml/min) in 128 patients. All patients underwent DSE for the evaluation of known or suspected CAD and were followed for a mean of 8 years.

Results. New wall motion abnormalities during DSE and mildly, moderately and severely abnormal CrCl were powerful independent predictors for all-cause mortality, cardiac death and hard cardiac events (cardiac death and non-fatal myocardial infarction). Kaplan–Meier curves demonstrated that patients with normal DSE and renal dysfunction have greater probability for cardiac death and hard cardiac events compared to those with normal renal function. The warranty of a normal DSE in the presence of moderate renal dysfunction was 15 and 36 months for 10 and 20% risk for cardiac death and hard cardiac events, respectively.

Conclusions. The presence and severity of renal dysfunction has additional independent prognostic value over DSE findings. The low-risk warranty period after a normal DSE is determined by the severity of renal dysfunction.

Keywords: dobutamine stress echocardiography; prognosis; renal function

Introduction

Cardiovascular disease is the major cause of death in patients with renal dysfunction [1]. In particular, coronary artery disease (CAD) is an important predictor of mortality in chronic renal failure patients [2]. Dobutamine stress echocardiography (DSE) is a widely used non-invasive imaging technique for detection of CAD [3]. Several studies have demonstrated the high predictive value of DSE for long-term cardiac events in patients with normal renal function [4]. It has also been suggested as a tool for risk stratification of patients with chronic renal failure, specifically in patients undergoing evaluation for kidney transplantation [5]. However, the value of wall motion abnormalities (WMA) during DSE among the entire strata of renal function has yet to be determined. The identification of clinical variables that influence prognosis in addition to abnormalities on DSE is important to optimise risk stratification in a given patient. The aim of this observational follow-up study was to assess the prognostic value of renal function relative to DSE findings in patients with known or suspected CAD.

Subjects and methods

Study population and baseline measurements

The study population included 2292 consecutive patients with known or suspected CAD who were referred at the Erasmus MC (Rotterdam, The Netherlands) for DSE between 1993 and 2003. Diabetes mellitus was defined as fasting plasma glucose level of ≥ 126 mg/dl on at least two occasions and/or requirement for insulin or oral hypoglycaemic agents, according to the criteria by the American Diabetes Association [6]. Hypercholesterolemia was defined as total cholesterol of 200 mg/dl or use of a cholesterol-lowering agent. Hypertension was defined as systolic blood pressure of 140 mmHg, diastolic blood pressure of 90 mmHg or use
of anti-hypertensive medication. Heart failure was defined according to the New York Heart Association classification.

Renal function assessment

Serum creatinine was assessed by a non-kinetic alkaline picrate (Jaffe) method. Creatinine clearance (CrCl) was estimated with the Cockcroft-Gault [7] equation: CrCl (ml/min) = (140 - age) × weight (kg) ÷ 72 × serum creatinine (mg/dl) (×0.85 for women) and standardized for body surface area using the Dubois formula. This equation has close correlation with the measured CrCl and gives a more accurate assessment of renal function than of serum creatinine alone.

The severity of renal disease was estimated according to the widely used American National Kidney Foundation (NKF) classification of chronic kidney disease (CKD) Stages I–V [8]. These NKF criteria for renal failure are: Glomerular filtration rate (GFR) > 90 ml/min/1.73 m² (Stage I), GFR > 60–89 ml/min/1.73 m² (Stage II), GFR > 30–59 ml/min/1.73 m² (Stage III), and GFR < 30 ml/min/1.73 m² (Stages IV and V).

By this definition patients were divided into four groups: normal renal function (CrCl > 90 ml/min) and mild (CrCl = 60–90 ml/min), moderate (CrCl = 30–60 ml/min) and severe (CrCl < 30 ml/min) renal dysfunction. The local medical ethics committee approved the study protocol. Patients gave an informed consent to undergo this observational follow-up study and the results were derived from a secondary analysis.

Dobutamine stress echocardiography

The DSE protocol was approved by the local medical ethics committee and was performed in accordance with the well-established protocols [9]. Studies were performed using a Sonos 5500 imaging system (Phillips Medical Systems, Eindhoven, The Netherlands). Patients underwent a rest-stress echocardiography examination of the standard apical and parasternal views. Images were recorded on videotape and also digitized for comparison between the two assessors, a third investigator viewed the echocardiographic images without the knowledge of the previous assessments. Between the two assessors, a third investigator viewed the images without the knowledge of the previous assessments, and a majority decision was reached.

Follow-up

During follow-up, the end points of the study were all-cause mortality, cardiac death and hard cardiac events [cardiac death or non-fatal myocardial infarction (MI)]. Clinical information was obtained by outpatient visits, mailed questionnaires, telephone interviews or by reviewing hospital records and the electronic patient database. Survival status was obtained by approaching the referring physician or the municipal civil registries. Cardiac death was defined as death caused by acute MI, cardiac arrhythmias or congestive heart failure (CHF). Sudden unexpected death was included as cardiac death.

Statistics

The t-test was used for continuous variable and chi-square test was used for categorical variables. Characteristics were summarized as percentages for categorical variables and as mean ± standard deviation for continuous variables. Univariate and multivariate analysis of clinical and echocardiographic variables with the end points were assessed using the Cox proportional hazards model. Clinical variables that were tested for univariate significance were sex, prior MI, prior coronary artery bypass grafting (CABG), prior percutaneous coronary intervention (PCI), CHF, typical angina, diabetes, hypertension, high cholesterol and smoking. Only clinical variables with univariate significance and representative DSE variables were considered as selection strategy for model building. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The fitted model included age only for the purpose of adjustment; all other models were based on the variables selected in the stepwise algorithm,
which were replaced by dichotomous versions to facilitate the ease of clinical use. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). The probability of all-cause mortality, cardiac death and hard cardiac events free survival was calculated by the Kaplan–Meier method and the resulting curves were compared by the log rank test [11,12].

Results

The patients’ demographics and clinical characteristics are presented in Table 1.

According to renal function, the total study population was divided into 729 (32%) patients with normal renal function and 1563 (68%) with renal dysfunction. This was classified as mild in 933 patients, moderate in 502 patients and severe in 128 patients. The overall prevalence of hypertension was 36% (809 patients). The respective percentages for mild, moderate and severe renal dysfunction were 33% (298 patients), 45% (223 patients) and 54% (66 patients). The prevalence of diabetes in these groups was 12, 16, and 54% (223 patients), 45% (223 patients) and 54% (66 patients). The prevalence of hypercholesterolemia was 33% (809 patients), 45% (223 patients) and 54% (66 patients). The prevalence of other cardiac risk factors was similar across the strata.

Table 3 summarizes the hazard ratios after multivariate analysis for predictors of all-cause mortality, cardiac death and hard cardiac events either unadjusted or adjusted for age and clinical variables with univariate significance, i.e. prior MI, prior CABG, prior PCI, CHF, diabetes, hypertension,

Long-term follow-up

During a mean long-term follow up of 8 years, 553 patients (24%) died, which included 86 (12%) patients with normal CrCl, 192 (21%) with mild renal dysfunction, 209 (42%) with moderate and 66 (52%) with severe renal dysfunction. Cardiac death occurred in 317 patients (14%); the respective numbers among the strata of CrCl was 42 for normal CrCl (6% of normal), 109 for mild renal dysfunction (12% of mild), 133 for moderate (26% of moderate) and 33 for severe renal dysfunction patients (26% of severe). One hundred (4%) patients suffered non-fatal MI. Overall, 417 (18%) patients had at least one hard cardiac event.

Patient characteristics and hemodynamic response

During DSE the heart rate increased significantly from rest to peak stress. The target heart rate was reached in 91% of patients. Atropine was administered in 206 patients. The mean maximal dobutamine dose was 38 ± 8 mcg/kg/min. Side-effects included hemodynamically stable sustained ventricular tachycardia (>10 complexes) in 23 (1%) patients, non-sustained ventricular tachycardia (<10 complexes) in 115 patients (5%), atrial fibrillation in 23 patients (1%) and severe hypotension (decrease of systolic blood pressure >40 mmHg) in 23 patients (1%).

The WMSI was 1.47 ± 0.60 at rest and 1.55 ± 0.67 at peak stress. Rest WMA were observed in 1469 (64%) patients and new WMA at peak stress were present in 1546 (68%) patients (Table 2).

Predictors of all-cause mortality, cardiac death and hard cardiac events

Table 3 summarizes the hazard ratios after multivariate analysis for predictors of all-cause mortality, cardiac death and hard cardiac events either unadjusted or adjusted for age and clinical variables with univariate significance, i.e. prior MI, prior CABG, prior PCI, CHF, diabetes, hypertension,
Table 2. DSE results according to renal function

<table>
<thead>
<tr>
<th></th>
<th>Normal renal function (729 patients)</th>
<th>Mild renal dysfunction (933 patients)</th>
<th>Moderate renal dysfunction (502 patients)</th>
<th>Severe renal dysfunction (128 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest WMAa</td>
<td>432 (59%)</td>
<td>578 (62%)</td>
<td>374 (74%)</td>
<td>85 (66%)</td>
</tr>
<tr>
<td>NWMAb</td>
<td>453 (62%)</td>
<td>616 (66%)</td>
<td>390 (78%)</td>
<td>87 (68%)</td>
</tr>
<tr>
<td>WMSF at rest</td>
<td>1.39 ± 0.53</td>
<td>1.45 ± 0.59</td>
<td>1.62 ± 0.64</td>
<td>1.53 ± 0.61</td>
</tr>
<tr>
<td>WMSF at peak</td>
<td>1.46 ± 0.60</td>
<td>1.53 ± 0.66</td>
<td>1.71 ± 0.70</td>
<td>1.61 ± 0.69</td>
</tr>
</tbody>
</table>

aWMA: wall motion abnormalities.
bNWMA: new wall motion abnormalities.
cWMSI: wall motion score index.
*p: significant (< 0.001) (chi-square test).

Table 3. Multivariate analysis for the end points of all-cause mortality, cardiac death and hard cardiac events (cardiac death or non-fatal MI)a

<table>
<thead>
<tr>
<th>End point</th>
<th>HRs (95%CI) Unadjusted</th>
<th>Adjustedb</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NWMA during DSE</td>
<td>1.4 (1.5–2.1)</td>
<td>1.5 (1.2–1.8)</td>
</tr>
<tr>
<td>Normal CrCl</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mildly abnormal CrCl</td>
<td>1.9 (1.5–2.5)</td>
<td>1.3 (1.1–1.7)</td>
</tr>
<tr>
<td>Moderately abnormal CrCl</td>
<td>4.5 (3.5–5.9)</td>
<td>2.4 (1.8–3.3)</td>
</tr>
<tr>
<td>Severely abnormal CrCl</td>
<td>6.2 (4.5–8.5)</td>
<td>4.1 (2.9–5.8)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NWMA during DSE</td>
<td>2.7 (2.1–3.6)</td>
<td>1.8 (1.3–2.4)</td>
</tr>
<tr>
<td>Normal CrCl</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mildly abnormal CrCl</td>
<td>2.2 (1.5–3.1)</td>
<td>1.4 (1.0–2.1)</td>
</tr>
<tr>
<td>Moderately abnormal CrCl</td>
<td>5.9 (5.7–6.1)</td>
<td>2.9 (1.9–4.3)</td>
</tr>
<tr>
<td>Severely abnormal CrCl</td>
<td>6.1 (3.9–9.8)</td>
<td>4.3 (2.6–6.9)</td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NWMA during DSE</td>
<td>2.3 (1.8–3.0)</td>
<td>1.6 (1.2–2.0)</td>
</tr>
<tr>
<td>Normal CrCl</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mildly abnormal CrCl</td>
<td>1.8 (1.4–2.4)</td>
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<td>Moderately abnormal CrCl</td>
<td>4.2 (3.1–5.7)</td>
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<tr>
<td>Severely abnormal CrCl</td>
<td>4.7 (3.2–7.1)</td>
<td>3.5 (2.3–5.4)</td>
</tr>
</tbody>
</table>

aHR associated with levels of the CrCl in 2292 patients.
bAdjusted for age, prior MI, prior CABG, prior PCI, CHF, diabetes, hypertension, high cholesterol and smoking.

Discussion

This study showed the predictive value of renal function relative to DSE findings during a long-term mean follow-up of 8 years. Ischemia during DSE was an independent predictor of mortality and hard cardiac events among the entire strata of renal function (Table 2). The global χ² increased significantly when CrCl was added to the model (Figure 1). The degree of renal dysfunction was an additional determinant of survival and hard events among patients with normal as well as those with abnormal DSE (Figures 2–4). Based on survival curves, we suggest that patients with moderate renal dysfunction and normal DSE at baseline represent the highest risk group and should repeat the DSE every 15 and 36 months. This suggestion derives from the Kaplan–Meier curve (Figure 3) showing that 10% of patients with moderate renal dysfunction in 15 months and 20% of these patients in 36 months do have a cardiac event, i.e. cardiac death alone or hard cardiac event.

However, regarding all-cause mortality patients with both moderate and severe renal dysfunction and normal DSE represent similar high-risk groups (Figure 2).
Comparison to previous studies

The American Society of Transplantation has reported guidelines for the pre-transplant evaluation of patients with severe renal dysfunction [13]. They included the use of non-invasive cardiac stress testing; however, it remained unclear which test to use due to the lack of firm support for a single test. Some studies have suggested that DSE is superior to exercise ECG for diagnosis of CAD in patients with renal dysfunction [14] and also has prognostic value in this setting [15–17]. We also demonstrated the prognostic value of DSE among the entire strata of renal function. In addition, patients with significant renal dysfunction are often unable to perform treadmill exercise testing. Furthermore, the presence of left ventricular hypertrophy makes any ST-segment interpretation on ECG less reliable [14].

Survival in patients with normal DSE according to creatinine clearance

Fig. 2. Kaplan–Meier curves for all-cause mortality in patients with normal DSE, rest WMA, NWMA and more than four abnormal segments in DSE and according to renal function, for a period of 8 years.

Fig. 3. Kaplan–Meier curves for cardiac death and hard cardiac events in patients with normal DSE and according to renal function, for a period of 8 years. Patients with normal DSE and renal dysfunction have greater probability for both cardiac death and hard cardiac events compared to those with normal renal function. The warranty of a normal DSE in the presence of moderate renal dysfunction was 15 and 36 months for 10 and 20% risk, respectively.
The theoretical advantages of DSE in renal dysfunction include maintained sensitivity and specificity in hypertension \[18\] and bundle branch block \[19\].

It is known that early renal failure is associated with changes in traditional and non-traditional cardiovascular risk factors \[1,2\]. Moreover, patients with renal dysfunction may have only atypical or no symptoms of CAD, due to limited activity levels \[2\]. The avoidance of coronary angiography and potentially nephrotoxic contrast material is also critical in these patients. Therefore, given its safety and low cost, DSE could be used as a screening tool in detecting occult CAD before the development of MI or sudden cardiac death in patients with renal dysfunction \[20\].

A previous study has shown that the accuracy for detecting CAD and the prognostic implications of positive results of DSE in patients with renal dysfunction appear similar to the general population \[20\]. We similarly found that new WMA during DSE were independent predictors for decreased survival but the addition of CrCl added significantly to the power of the predictive model (Table 2, Figure 1).

Although the prognosis of patients with renal dysfunction and normal DSE was better than for patients with new WMA, the event rate remained substantial for all end points. This could be explained by the high-risk profile of our population and by the known high prevalence of cardiac events in patients with renal failure even in the absence of CAD at baseline because uremia itself provides an atherogenic milieu \[17\].

In two of the largest prognostic series, the prognostic value of a normal DSE in renal dysfunction appears to be limited to about 2 years \[4,21\]. We have shown in an even larger study population with a longer follow-up period that the predictive value of a normal DSE in the presence of moderate renal dysfunction is limited to 15 and 36 months for 10 and 20% risk for cardiac event respectively.

In conclusion, we found that renal dysfunction has additional independent prognostic value over DSE findings, irrespective of the presence and severity of WMA. The low-risk period after a normal DSE is determined by the presence of moderate mainly renal dysfunction.

Conflict of interest statement. None declared.

References


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