Abstract

**Background:** Renal artery stenosis (RAS) remains underdiagnosed because of nonspecific clinical manifestations, including in patients with coronary artery disease (CAD).

**Aims:** To estimate the prevalence and identify predictors of RAS in patients with CAD undergoing coronary angiography.

**Setting:** University-based medical centre.

**Methods:** We enrolled 650 consecutive patients (mean age=67±10 years, 80% men) with confirmed CAD. All patients underwent selective renal arteriography in the same procedure. We estimated the prevalence of RAS, defined as a >50% lesion. Multiple variable analysis of factors associated with presence of RAS was carried out using a logistic regression model. Variables that emerged as predictors by single-variable analysis were included in the model, along with variables that were tentatively associated with RAS, based on a literature review.

**Results:** RAS was detected in 94 patients (14.5%, 95% CI: 11.8–17.2%), including 20 (3.1%) with bilateral lesions. By single-variable analysis and presence and number of coronary artery stenoses \((P<.001)\), hypertension \((P=.001)\), and creatinine clearance \(<90\text{ ml/min} (P<.001)\) were associated with an increased risk of RAS. By multiple variable analysis, male sex \((P<.05)\), presence and number of coronary artery lesions \((P<.01)\), hypertension \((P=.001)\), and renal insufficiency \((P<.001)\) predicted the presence of RAS.

**Conclusions:** The main clinical predictors of RAS in patients with CAD were hypertension, renal insufficiency, and multivessel CAD. These observations might help defining a high-risk subgroup of patients in need of meticulous investigations of both CAD and RAS.

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**Keywords:** Renal artery stenosis; Coronary artery disease; Renal arteriography; Coronary angiography; Renal insufficiency

1. Background

Patients at high risk for adverse cardiovascular events are, in part, defined by the atherosclerotic involvement of multiple vascular territories, including the coronary, carotid, aortic, and peripheral arterial circulation. However, Conlon et al. [1,2] observed that the presence of...
atheromatous renal artery stenosis (RAS) is an independent predictor of death from a cardiovascular cause at 4 years. Likewise, De Silva et al. [3] found that RAS was an independent factor of risk of adverse health events and death at 3 years, in patients suffering from congestive heart failure. Therefore, in the process of evaluating atherosclerotic disease, or patients with cardiovascular disease, the presence of RAS appears to be an important observation. With a view to more precisely identify patients at very high risk for adverse cardiovascular events, we have systematically searched for the presence of stenotic disease of one or both renal arteries, among patients referred for coronary angiography at our medical centre. The objectives of this study were to (1) measure the prevalence of RAS in patients presenting with coronary artery disease (CAD) and (2) to further clarify predictive criteria of RAS in this population. Furthermore, to evaluate the potential adverse consequences of systematically studying the renal circulation at the time of coronary angiography, we compared patients included in this study with a group of patients who underwent coronary angiograms without renal arteriography, with a focus on (1) procedural duration, (2) duration of fluoroscopic exposure, and (3) amount of contrast material injected.

2. Methods

2.1. Inclusion criteria and data collection

Between May 2004 and May 2006, we prospectively performed selective renal arteriographies in all patients (n=650) who underwent coronary angiography at our medical centre and in whom CAD was confirmed during the procedure. All patients gave informed consent. Patients presenting with acute myocardial infarction, patients with angiographically normal coronary arteries, or patients hemodynamically unstable during the catheterisation procedure were excluded from this analysis. The CardioReport software (Biotronik, Berlin, Germany) was used to collect the data, including demographic and clinical characteristics, cardiovascular risk factors, patient’s personal and family medical history, and quality of renal function, evaluated by means of creatinine clearance (Clcr), calculated by the Gault and Cockcroft formula. Measurements of the systemic arterial pressures, from which the pulse pressure was derived, were made in the catheterisation laboratory.

2.2. Renal arteriography

Renal arteriography was performed immediately after coronary angiograms, using selective injections of iodized contrast material (Hexabrix 300, Hexabrix; Mallinckrodt Medical, St. Louis, MO, USA) via a right-sided Judkins catheter. Stenoses >50% of the reference vessel diameter were considered significant. When the significance of the lesion was uncertain, a semiautomatic quantitative analysis was performed, using the Cardiovascular Angiographic Analysis System software (Pie Medical Data, Maastricht, The Netherlands). The vascular access was femoral in 99% and radial in 1% of patients. A left ventriculogram was obtained in 276 patients (42.5%).

2.3. Renal protection

In presence of preexistent renal dysfunction, the patients received 1–2 ml/kg per hour of intravenous isotonic saline solution for 12–24 h, sometime along with N-acetylcysteine (NAC), (600 mg, three times a day, po). If the patient had not received a saline infusion before the procedure, intravenous rehydration was initiated immediately after coronary angiography, with a view to limit the risk of procedural complications. The postprocedural renal function was closely monitored in order to detect the development of renal insufficiency or worsening of preexistent renal dysfunction.

2.4. Analyzed variables and subgroups classifications

We used the following classification, based on the US National Kidney Foundation [4], for the analyses of subgroups according to the quality of renal function: (1) Clcr >90 ml/min=normal renal function; (2) Clcr between 60 and 90 ml/min=incipient renal insufficiency; (3) Clcr between 30 and 60 ml/min=moderate renal insufficiency; and (4) Clcr <30 ml/min=severe renal insufficiency, including end-stage renal failure.

Analyses of the measurements made in the catheterisation laboratory were based on threshold values for stages 1 and 2 of hypertension, defined by the European Society of Cardiology and European Society of Hypertension [5], i.e., 140 and 160 mmHg, respectively, for systolic and 90 and 100 mmHg, respectively, for diastolic arterial pressure. The threshold for pulse pressure (the difference between systolic and diastolic pressures) was set at 65 mmHg. Thresholds for body mass index (BMI) <20 (malnutrition), >25 (excess body weight), and >30 (obesity) kg/m² were entered in the analyses [6]. Analyses as a function of age were performed using a 70-year threshold, the median age of our population. For multiple variable analyses, age was treated as a continuous variable. Patients suffering from CAD were classified among (1) single-vessel, (2) two-vessel, and (3) triple-vessel disease groups and (4) no significant (>50%) CAD group. Patients presenting with isolated lesions of the left main coronary artery were assigned to the two-vessel disease subgroup. Chronic obstructive lung disease and asthma were grouped under the diagnosis of lung disease, and carotid and lower limb arterial diseases were grouped under peripheral artery disease. Patients who underwent left ventricular angiography were divided in a
group with and a group without left ventricular dysfunction, whether global or segmental.

2.5. Statistical analysis

Descriptive statistics are presented as numbers and percentages for discrete and as means±S.D. or median for continuous variables. Single-variable analysis comparing the clinical characteristics of patients presenting with versus without RAS was performed by means of the Chi-square and Fisher’s exact test for qualitative variables and by means of Student’s t test and Levene’s test for quantitative variables. For this latter analysis, several variables were reclassified, based on clinical observations and on review of the literature. Disease prevalence is expressed as percentages and 95% confidence interval (CI).

A multiple variable analysis of factors associated with presence of RAS was carried out using a logistic regression model (ascending/descending Wald method). Variables that emerged as significant predictors by single-variable analysis were included in the model, along with variables that were tentatively associated with RAS, based on a review of relevant literature, including (1) age; (2) sex; (3) BMI; (4) CrCl; (5) history of hypertension, smoking, diabetes, dyslipidaemia, and cerebral vascular accident; (6) presence of peripheral arterial disease; (7) systemic arterial pressure measured during cardiac catheterisation; and (8) number of diseased coronary arteries.

All analyses were made with the SPSS software (SPSS, Chicago, IL, USA). For all tests, A P value <.05 was considered statistically significant.

3. Results

3.1. Patients population

This study included 650 patients, of whom 1 patient was excluded because of nonvisualisation of the left renal artery, and persistent uncertainty, on subsequent analysis, with respect to its true congenital absence, versus pathologic occlusion. The indications to perform coronary angiography were acute coronary syndrome in 32.6%, stable angina in 46%, evaluation of nonvalvular heart disease in 8.6%, preoperative evaluation of valvular heart disease in 9.4%, and miscellaneous disorders, including mostly ventricular rhythm disturbances, in 3.4% of patients. Single-vessel disease was observed in 33.7%, two-vessel disease in 26.6%, three-vessel disease in 23.4%, and no significant stenosis in 16.2% of patients. The baseline characteristics of the overall population are presented in Table 1. A history of renal insufficiency was present at the time of inclusion in the study in 15.5% of patients. However, measurements of renal function revealed that 85% of patients had a CrCl <90 ml/min, i.e., at least incipient renal insufficiency.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of the overall patients population (n=650 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±10 (37–94)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>513 (80)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167±8 (145–192)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75.5±14 (40–120)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4±4 (16–41)</td>
</tr>
<tr>
<td>Number of coronary lesions</td>
<td>1.3±1 (0–3)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±14 (40–120)</td>
</tr>
<tr>
<td>Systemic arterial pressure, mmHg</td>
<td></td>
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<tr>
<td>Systolic</td>
<td>143±29 (75)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73±14 (19)</td>
</tr>
<tr>
<td>Mean</td>
<td>101±18 (56)</td>
</tr>
<tr>
<td>Creatinine clearance, ml/min</td>
<td>68±22 (14)</td>
</tr>
<tr>
<td>Serum creatinine before the procedure, μmol/l</td>
<td>103±37 (53)</td>
</tr>
<tr>
<td>Cardiovascular risk factors, number (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>423 (65)</td>
</tr>
<tr>
<td>Smoking</td>
<td>383 (59)</td>
</tr>
<tr>
<td>Insulin-dependent diabetes</td>
<td>45 (7)</td>
</tr>
<tr>
<td>Non-insulin-dependent diabetes</td>
<td>113 (17)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>486 (75)</td>
</tr>
<tr>
<td>Family history</td>
<td>211 (32)</td>
</tr>
<tr>
<td>Medical history, number (%) of patients</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>161 (25)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>79 (12)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>125 (19)</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>101 (15)</td>
</tr>
</tbody>
</table>

Unless specified otherwise, values are means±S.D. (range).

3.2. Estimated prevalence and factors predictive of renal artery stenosis

Among these 650 patients suffering from CAD, 94 presented with RAS, corresponding to an estimated prevalence of 14.5% (95% CI 11.8–17.2%), including 39 patients (6%) with left coronary artery stenoses, 35 (5.4%) with right coronary artery stenoses, and 20 patients (3.1%) with bilateral stenoses. The baseline characteristics of the 94 patients with versus 556 patients without RAS are compared in Table 2. Patients with RAS were more likely to (1) be >70 years of age, (2) be hypertensive, (3) suffer from renal insufficiency, and (4) present with disease of multiple coronary arteries. The proportion of patients presenting with RAS varied significantly according to the degree of CAD and renal dysfunction (Figs. 1, 2 and 3), between 7% among patients whose renal function was normal and 26.3% among patients with severe renal insufficiency, and between 3.3% among patients without significant coronary stenosis and 24.3% among patients with three-vessel disease. Furthermore, a trend was observed toward a relationship between RAS and age >70 years (P=.07).

By multivariate analysis, variables significantly associated with the presence of RAS included (1) male sex (P=.04), (2) history of hypertension (P=.001), (3) number of significant coronary lesions (P<.001), and (4) severity of renal insufficiency (P<.001).
3.3. Procedural characteristics and complications

No serious complication, such as haemorrhage requiring transfusion, renal insufficiency requiring dialysis, or renal artery dissection was observed during this study. Selected characteristics of the 409 procedures that included renal arteriograms, performed in this study, versus 460 other procedures limited to coronary angiograms, are compared in Table 3. Neither the mean duration of procedure nor the mean duration of fluoroscopic exposure was prolonged by the performance of renal arteriography. However, the mean amount of contrast material was increased by 33 ml by the selective injection of both renal arteries ($P<.005$).

4. Discussion

4.1. Predictors of renal artery stenosis

In this study of patients suffering from CAD, the estimated prevalence of RAS was 14.5% (95% CI 11.8-17.2), and its predictors, in single and multiple variable analysis, were 1) number of diseased coronary arteries, 2) severity of renal insufficiency, 3) male sex, and 4) history of systemic hypertension. These observations are concordant with those made in prior studies [7–12], where the prevalence of RAS varied between 4 and 59%. In patients with CAD, however, the reported prevalence was usually between 14 and 20%, depending on the study inclusion...
4.2. Risks associated with systematic renal angiography

In contrast with patients who were RAS-free, our patients who presented with RAS had no deterioration of renal function following renal arteriography. This observation must be interpreted cautiously. While serum creatinine concentration was measured in all patients before the procedure, it was available in only 339 of 556 RAS-free patients, and 57 of 94 patients with RAS, after the procedure. The absence of worsening of renal function among patients with RAS might be attributable to a more systematic intravenous hydration and NAC administration in presence of renal dysfunction (itself more often associated with presence of RAS) as well as immediately after the angiographic detection of RAS. While the methods of prevention of nephropathy caused by contrast material remain debated, the effectiveness of hydration with isotonic saline is well established [22], whereas that of NAC is uncertain [23]. Furthermore, the effects of the amount of contrast material on the risk of renal dysfunction remains controversial [24], while the main risk factor appears to be the severity of pre-existent renal dysfunction. The interpretation of these observations is challenging, particularly with regard to the safety of injecting additional contrast material with a view to opacify the renal arteries of patients whose renal function is abnormal. It is therefore imperative to select patients at high risk of RAS, on the basis of reliable and reproducible risk factors, such as those described in this report.

4.3. Merits of systematic detection of renal artery stenosis

Cardiovascular risk stratification currently relies on several factors, including (1) sex; (2) age; (3) BMI; (4) family history; (5) activity level; (6) history of diabetes, hypertension, dyslipidaemia, and smoking; (7) left ventricular function; and (8) presence of CAD. It does not include presence of RAS, viewed as an independent factor of risk of morbidity and mortality by some authors [1–3]. Therefore, the early detection of RAS is desirable, though its clinical manifestations are usually subtle, if not absent. Its diagnosis is often made late, in presence of unexplained renal insufficiency [12], or refractory hypertension, or episodes of unexplained cardiac decompenation. While various scoring systems have been proposed to predict the presence of RAS, they are rarely applied in clinical practice, as they are based on too many variables. For example, the scoring criteria, the sample size, and the definition of “significant” RAS (50% versus 70% diameter stenosis).

The strong association we found between systemic hypertension and RAS supports various hypothetic, self-perpetuating, pathophysiologic links between them, including activation of the renin-angiotensin system by RAS, hypertension triggered by ischemic nephropathy, and acceleration of renal atherosclerosis by hypertension [13]. In contrast, the systemic arterial pressures we measured in the catheterisation laboratory were not significantly associated with the presence of RAS, including systolic pressure, usually a predictor of RAS [11,12]. However, several factors interfere with the interpretation of these observations, including, among others, the variable degrees of anxiety caused by the procedures and the antihypertensive treatment that might have been prescribed on the day of catheterisation.

Our analysis as a function of severity of renal insufficiency confirmed the previously reported association between Clcr and presence of RAS [12,14,15]. Furthermore, RAS is increasingly recognised as the most common reversible cause of end-stage renal failure. However, while the pathophysiologic mechanisms of ischemic nephropathy caused by RAS are relatively well understood, the contributions of the latter to end-stage renal failure observed in elderly patients remain controversial [16–18]. The natural evolution of RAS toward progressively more severe disease or, ultimately, occlusion [7,10,19], supports a strategy of early detection, before renal insufficiency has become irreversible. This might explain the mixed results observed in studies of preservation of renal function after revascularisation, which might have been offered too late [20,20]. In addition, several studies support the link between chronic renal insufficiency and adverse cardiovascular events [13,21], strongly suggesting that patient management should include care of the kidneys as well as the cardiovascular system, since both contribute independently to an increased rate of death.

Table 3

<table>
<thead>
<tr>
<th>Characteristics of procedures with versus without renal arteriography</th>
<th>Without RA (n=460)</th>
<th>With RA (n=409)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure duration, min</td>
<td>25.2±14</td>
<td>25.3±13</td>
<td>ns</td>
</tr>
<tr>
<td>Contrast material, ml</td>
<td>133±53</td>
<td>166±58</td>
<td>.005</td>
</tr>
<tr>
<td>Fluoroscopic exposure, min</td>
<td>6.7±8</td>
<td>6.8±5</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are means±S.D. RA indicates renal arteriography; ns, nonsignificant.
system developed by Cohen et al. [25] is based on multiple criteria, including age, sex, blood pressure status, number of cardioactive medications, presence or absence of peripheral arterial disease, serum creatinine concentration, and presence of triple-vessel CAD or history of coronary artery bypass graft surgery.

In a recent US consensus conference [26], the systematic performance of renal arteriography at the time coronary angiograms was not recommended, except in presence of predefined indications for revascularisation [27]. While, in this study, the only inclusion criterion was presence of overt CAD, we identified patient subgroups with a RAS prevalence reaching approximately 25%. Since these patients are at highest cardiovascular (triple-vessel CAD) and renal (moderate or severe renal insufficiency) risk, they might be candidates for a systematic detection of RAS, with a view to improve their renal as well as cardiovascular prognosis. While this detection represents a first step, the merits of proceeding with subsequent revascularisation remains highly controversial [20,28]. The results of ongoing randomised trials, STAR and CORAL (CORAL trial: Cardiovascular Outcomes in Renal Atherosclerotic Lesions, STAR trial: STent placement for Atherosclerotic ostial Renal artery stenosis) in particular [29,30], will help identifying the patients that are likely to derive a benefit from renal revascularisation. Both trials have been designed to examine the benefits of renal artery angioplasty, based on a composite end point of adverse cardiovascular and renal events (CORAL) or adverse renal events only (STAR).

4.4. Limitations of our study

The results of our study and the predictive factors we identified are limited to a selected population of patients referred for coronary angiography, in whom the presence of CAD was confirmed. Therefore, these observations cannot be extrapolated to patients without CAD, including patients with overt peripheral arterial disease or renal insufficiency. Furthermore, since the study was carried out at a single medical centre, it might have suffered from biases related to patient enrolment.

The renal angiograms were usually interpreted by a single observer who had performed the coronary angiograms. While the interobserver variability of interpretation was not evaluated, measurement errors were limited by the use of semiautomatic quantitative analytic software. Detailed data pertaining to arterial hypertension, including number of antihypertensive medications prescribed, and stage and duration of the disease, were not collected, limiting the power of our analysis of relationships among RAS, severity of hypertension, and antihypertensive regimen. The nearly exclusive use of the femoral vascular access allowed the visualisation of the renal arteries of all but one patient. No conclusion can be drawn regarding the feasibility of systematic renal arteriography from other vascular accesses, radial in particular, despite the feasibility of renal angio-plasty from the radial artery, described in observational studies [31].

5. Conclusions

The presence of RAS in a patient suffering from CAD appears mostly determined by three factors, for which a statistical relationship is the strongest: 1) hypertension, 2) number of diseased coronary arteries, and 3) creatinine clearance. A systematic renal arteriographic detection of RAS at the time of coronary angiography might be justified in presence of 1) two- or three-vessel disease, 2) renal insufficiency, or 3) complicated hypertension, with a view to identify patients at highest cardiovascular risk. While these criteria allow the identification of patients very likely to suffer from RAS, they do not necessarily identify the best candidates for renal revascularisation. Ongoing trials will perhaps allow the selection of these optimal candidates, for whom detection of RAS is a priority.

References


