Atherosclerotic renovascular disease

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Atherosclerotic renovascular disease is a combination of renal artery stenosis and renal ischemia. Blood pressure does not rise until the stenosis is 60% or greater. Disease of both large and small blood vessels is often accompanied by the loss of glomerular filtration rate. Activation of the renin-angiotensin-aldosterone system leads to vasoconstriction and salt retention.

Risk factors for atherosclerotic renovascular disease include long-standing hypertension, diabetes, smoking and dyslipidemia. The prevalence of the condition in patients with hypertension resistant to two medications is 20%. As yet, there is no single ideal screening test or evidence-based recommended screening algorithm. Magnetic resonance angiography and computed tomography angiography are noninvasive and have high sensitivity and specificity, but also have high costs associated with them. The captopril renal scan has low sensitivity and specificity in people with renal disease (the population most likely to require the test). Doppler ultrasonography has high sensitivity and specificity in experienced hands, and the renal resistance index, which can easily be added to this test, can identify those with microvascular disease who may not benefit from revascularization.

The best determinant of patient outcome is not the degree of renal artery stenosis but the degree of renal parenchymal disease. To date, renal revascularization has not been associated with improved renal survival compared with medical treatment alone. Today, the approach to atherosclerotic renovascular disease is determined by the patient's blood pressure and renal function; possibly, in the future, it will be determined by the result of the renal resistance index as part of a screening algorithm. If the blood pressure is uncontrollable or the renal function is deteriorating, the patient should be considered for renal revascularization initially, with a percutaneous endovascular stent. The management of hypertension involves the use of combinations of antihypertensive agents at doses sufficient to control blood pressure. Medical management also includes aggressive lipid-lowering therapy.

Key Words: *Hypertension; Kidney disease; Renal artery stenosis; Renovascular disease; Resistant hypertension*

La maladie rénovasculaire athéroscléreuse

La maladie rénovasculaire athéroscléreuse est une association de sténose artérielle rénale et d'ischémie rénale. La tension artérielle n'augmente pas tant que la sténose n'a pas atteint au moins 60 %. La maladie des grands et des petits vaisseaux sanguins s'accompagne souvent de la perte du taux de filtration glomérulaire. L'activation du système rénine-angiotensine-aldostérone entraîne une vasoconstriction et une rétention de sel.

Les facteurs de risque de maladie rénovasculaire athéroscléreuse sont l'hypertension de longue date, le diabète, le tabagisme et la dyslipidémie. La prévalence de la maladie chez les patients atteints d'hypertension résistante à deux médicaments est de 20 %. Il n'existe pas encore de test de dépistage unique ou d'algorithme probant de dépistage recommandé. L'angiographie par résonance magnétique et l'angiographie tomodensitométrique sont non effractives et ont une sensibilité et une spécificité élevées, mais elles coûtent cher. La scintigraphie rénale avec Captopril est peu sensible et peu spécifique chez les personnes atteintes d'une maladie rénale (la population la plus susceptible de devoir subir le test). L'échographie Doppler est très sensible et très spécifique si elle est effectuée par quelqu'un d'expérimenté, et l'indice de résistance rénale qui peut facilement s'y associer peut permettre de repérer les personnes atteintes d'une maladie microvasculaire susceptibles de ne pas profiter de la revascularisation.

Le meilleur déterminant de l'issue des patients n'est pas le degré de sténose artérielle rénale, mais le degré de maladie du parenchyme rénal. Jusqu'à présent, la revascularisation rénale ne s'associe pas à une amélioration de la survie rénale par rapport à la médicothérapie seule. De nos jours, la démarche relative à la maladie rénovasculaire athéroscléreuse est déterminée par la tension artérielle et la fonction rénale du patient. À l'avenir, on pourrait peut-être la déterminer par le résultat de l'indice de résistance rénale intégré à un algorithme de dépistage. Si la tension artérielle est incontrôlable ou que la fonction rénale se détériore, il faudrait commencer par envisager la revascularisation rénale du patient au moyen d'une endoprothèse vasculaire percutanée. Pour prendre en charge l'hypertension, il faut utiliser une association d'antihypertenseurs à des doses suffisantes pour contrôler la tension artérielle. La prise en charge médicale inclut également un traitement agressif aux hypolipidémiants.

CASE PRESENTATION

A 74-year-old man with a 15-year history of hypertension and diabetes was reviewed for uncontrolled hypertension. The patient was taking six antihypertensive medications: a calcium channel blocker, an angiotensin-converting enzyme (ACE) inhibitor, a beta-blocker, an angiotensin receptor blocker, a thiazide diuretic and an alpha-blocker, all at maximally recommended doses. The patient had recently quit smoking, but had a 40-pack-year history. He had no history of cardiovascular disease. His low-density lipoprotein cholesterol was 3.3 mmol/L. His physical examination was unremarkable and no bruits were detected. His blood pressure was 152/76 mmHg. His serum creatinine concentration was 105 µmol/L, and serum potassium concentration was normal at 4.0 mmol/L. Abdominal ultrasound revealed that the right kidney was 9.5 cm and the left kidney was 9.3 cm in length, and the Doppler ultrasound was

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consistent with right renal artery stenosis (RAS). A magnetic resonance angiogram (MRA) revealed proximal RAS of the right kidney and a lesser degree of stenosis of the left main renal artery. The patient and his wife asked the following questions: what would the natural history of this disease be? What should his target blood pressure be? Were there any revascularization procedures that would allow him to reduce his medications and bring his blood pressure under better control? Which of these revascularization procedures would be best for him? What was his prognosis with and without revascularization?

ATHEROSCLEROTIC RENOVASCULAR DISEASE

RAS is defined as a narrowing of the lumen of the renal artery (1). Atherosclerotic renovascular disease is a combination of RAS and renal ischemia (2). The disease may be unilateral with a normal renal artery for the contralateral kidney, or it may be bilateral (or unilateral in the setting of one kidney). Atherosclerotic renovascular disease occurring in the elderly is most often due to atherosclerosis. Because of its systemic nature, atherosclerotic renovascular disease often leads to disease of both large and small arteries of both kidneys, leading ultimately to progressive impairment in renal function through ischemia of affected areas of the kidney, and potentially hypertensive damage to the parts of the kidney that had been perfused by relatively normal renal arteries. Fibromuscular disease, most often found in younger patients, is not the focus of the present paper and rarely progresses to complete occlusion. The term 'ischemic nephropathy' is used to describe the reduction in glomerular filtration rate (GFR) that is caused by hemodynamically significant RAS. Thus, a patient with atherosclerotic renovascular disease has both large and small vessel arterial disease and often has loss of GFR due to ischemic nephropathy.

Pathophysiology

Data on the pathophysiology of RAS come largely from animal experimentation. Renal perfusion pressure is not reduced until there is 50% stenosis (2). Blood pressure does not usually rise until the RAS is 60% to 70% (2). At this point, the renin-angiotensin-aldosterone system (RAAS) becomes active, leading to renin release, production of angiotensin II with vasoconstriction, release of aldosterone and salt retention. The resulting impact is both an increase in peripheral vascular resistance and an increase in vascular volume, leading to higher blood pressure unless the unaffected renal tissue is able to excrete the excess salt via a pressure naturiuresis. In addition to the activation of the RAAS, there is increased sympathetic nervous system activity and counter regulation through increased nitric oxide levels. Animal models of RAS were developed by clipping the renal artery unilaterally with two kidneys, the one clip-two kidney (1C:2K) model, or in an animal with one kidney removed, clipping the remaining kidney (1C:1K) (this latter model is the same as two kidneys-two clips). These 'Goldblatt' models (2) allowed for an assessment of pure unilateral or bilateral RAS.

In the 1C:2K model, activation of the RAAS leads to high levels of angiotensin II and generalized vasoconstriction. However, while high serum aldosterone levels should lead to sodium retention, the normal unclipped kidney responds to the increased blood pressure by excreting most of the sodium load via pressure natriuresis. This leaves blood pressure elevation that is purely vasoconstrictive, or a 'renin-dependent' hypertension. In these cases, blockade of the RAAS effectively with an ACE inhibitor or an angiotensin receptor blocker will dramatically lower blood pressure. Over time, if this condition persists, hypertension will damage the 'normal', unclipped kidney, leading to persistent hypertension because the pressure natriuresis will not occur.

In the 1C:1K model of hypertension, or what is more commonly seen as bilateral RAS, activation of the RAAS leads to vasoconstriction as well as salt and water retention. The rise in intravascular volume and blood pressure may eventually restore renal perfusion enough to lower plasma renin levels. However, hypervolemia leads to persistent hypertension – a 'volume-dependent' hypertension. This hypertension is resistant to blockade of the RAAS.

However, in most patients with atherosclerotic renovascular disease, there is disease in both kidneys. Because this disease occurs asymmetrically, patients will be somewhere along the spectrum from a pure renin-mediated to a pure volume-mediated hypertension. This is further modified by the degree of ischemic damage that has occurred to both kidneys. In patients with bilateral disease on therapy to block the RAAS, lowering the blood pressure below the critical pressure needed to perfuse the kidneys will result in a drop of renal function (3).

The sodium retention that occurs in the setting of bilateral RAS explains in part the predisposition these patients have to develop flash pulmonary edema. Affected patients have a history of long-standing hypertension and usually have left ventricular hypertrophy. This hypertrophy both increases myocardial oxygen demand and limits myocardial oxygen delivery during diastole, because coronary perfusion of the thickened myocardium occurs only during diastole. With an accompanying degree of coronary artery disease, not uncommon in these vasculopathic patients, an increase in heart rate or run of atrial fibrillation may be all that is required to tip the balance of myocardial oxygen delivery and demand, leading to myocardial ischemia, rising pulmonary artery pressures and, ultimately, pulmonary edema. Risk factors for atherosclerotic RAS include long-standing hypertension, diabetes, smoking and dyslipidemia; these are also risk factors for premature coronary artery disease.

Prevalence

The prevalence of atherosclerotic renovascular disease is unknown in the general hypertensive population, but is likely around 1% (2). In a substudy (4) in 834 participants with and without hypertension in the Cardiovascular Health Study of people older than 65 years, atherosclerotic renovascular disease was diagnosed by Doppler ultrasound in 6.8%. In a study (5) of hypertensive Japanese older than 40 years with dyslipidemia or diabetes, the prevalence of RAS greater than 50% by MRA was 20%. In patients with hypertension resistant to two medications, the prevalence was found to be 20% (6). The prevalence was found to be 50% in a study of 44 participants with chronic kidney disease and atherosclerotic disease of another target organ when evaluated by magnetic resonance imaging (7). In an autopsy study of 346 consecutive stroke patients older than 40 years, the prevalence of RAS 75% or greater was 10.4% overall, and 14.7% in hypertensive patients (8). Thus, while atherosclerotic RAS is prevalent in patients with uncontrolled hypertension or vascular disease in target organs, it is also present in many patients without hypertension. In a prospective study (9) of 843 consecutive patients undergoing cardiac catheterization who were able to

have an aortogram, the prevalence of RAS 50% or greater was 18.3%, and the prevalence of RAS 75% or greater was 11.7%. Hypertension was present in 78.6% of those with RAS 50% or greater, and 81.8% of those with RAS 75% or greater (9). Thus, while RAS is prevalent in hypertension, particularly in patients complicated by other atherosclerotic disease, the presence of the anatomical renal artery narrowing is not always associated with hypertension. This may explain one of the reasons why renal revascularization does not lower blood pressure in all patients with atherosclerotic renovascular disease.

Diagnosis

The ideal single screening test for atherosclerotic renovascular disease would be accurate, have low technical failure, high sensitivity and specificity, and should be noninvasive and inexpensive (10,11). MRA and computed tomography (CT) angiography are noninvasive and have high sensitivity and specificity, but also have high costs and carry a risk for acute renal dysfunction related to the dyes that are used (contrast media for CT scan and radiation exposure or gadolinium for MRA). MRA is also contraindicated for patients with claustrophobia, metallic implants, obesity or for the seriously ill. The best performance statistics in detecting radiographic RAS were found through the use of MRA and CT angiography, followed by Doppler ultrasound and captopril-enhanced radioisotope renal scanning. This is based on a meta-analysis (12) using renal angiography as the gold standard and the area under the receiver operating curve as a measure of the diagnostic performance of the test.

Early reports of the captopril-enhanced renal scan suggested that it could detect atherosclerotic renovascular disease with high sensitivity and reasonable specificity (13). It may also play a role in predicting the benefits of renal artery revascularization (14). More recent reports of the test as a screen have found a much lower sensitivity and specificity (15). This test is limited in that it cannot locate the stenosis or determine its severity. Furthermore, the sensitivity of this test is reduced in patients with renal insufficiency, bilateral stenoses or a single kidney with vascular stenosis, clinical scenarios common enough to exclude this test alone as a screening tool (16).

Doppler ultrasonography has been demonstrated to have high sensitivity and specificity in experienced hands for the diagnosis of anatomical lesions (17). It can detect unilateral and bilateral lesions and accessory RAS, it is noninvasive and is not expensive. Obesity, excessive bowel gas or poor blood flow in the main renal artery can interfere with direct visualization. The renal resistance index (RRI) performed as part of a Doppler ultrasound examination is a powerful tool for identifying patients that may not benefit from revascularization. It is easy to learn and can effectively be applied to all patients referred for a simple abdominal ultrasound as part of the initial investigation for atherosclerotic renal arterial disease.

Simple measurements of serum renin levels have been investigated to predict the potential success of surgical revascularization but the frequency of false-negative and false-positive results make this screening test unhelpful (18). Even when the accuracy of the serum renin test is enhanced by the addition of an ACE inhibitor, the test still has insufficient specificity and sensitivity to be recommended (19). Also, renin-based diagnostic tests are limited by antihypertensive drugs that interfere with plasma renin activity.

Prognosis

The best determinant of patient outcome is not the degree of RAS, but the degree of renal parenchymal disease. Damage to the nephrons has been found to be more important in the pathogenesis of renal dysfunction than the presence of renal artery stenoses greater than 50% of the vessel lumen (20). Furthermore, evidence of ischemic nephropathy is also a marker of cardiovascular and renal risk. In a observational study of 105 patients with angiographically proven atherosclerotic renovascular disease followed an average of 4.5 years, 20% of patients had cardiovascular death, 10% developed end-stage renal disease and 20% had increases in serum creatinine levels of more than one-third (21). Renal revascularization was not associated with improved mortality or renal survival compared with medical treatment alone (21). With medical management alone, progression to total renal artery occlusion is not frequent (3% to 5%) and occurs only in those with 60% or greater stenosis (22). No completed trial has compared aggressive medical management combining multiple risk factor modification (high-dose statin therapy, blood pressure and blood glucose control, and antiplatelet therapy) to renal revascularization.

One method of determining the impact of renal parenchymal disease caused by small vessel atherosclerosis is the RRI, which can be performed during Doppler ultrasonography. The RRI was described by Radermacher in 2001 (11). It describes the amount of renal arterial impedance and is calculated as:

$$([\text{peak systolic velocity} - \text{end diastolic velocity}]/\text{peak systolic velocity}) \times 100$$

averaged over four to six measures in the upper, middle and lower kidney (11). In univariate analysis, the RRI was found to have a very high odds ratio for detecting those patients who would have worsening of renal function after renal revascularization in orders of magnitude greater than the other known predictive factors, including low GFR, proteinuria and lack of response to captopril in renal scintography (11). In both univariate and multivariate analyses, the RRI was shown to be the only reliable predictor of progression of renal disease in patients with RAS and identified those whose blood pressure and renal function was unlikely to improve with intervention (11,23,24). However, this diagnostic test has not yet been tested in a randomized prospective study, and its role in the management of atherosclerotic renovascular disease is therefore still uncertain.

Revascularization

Angiographic endovascular procedures are increasingly replacing surgery for revascularization of atherosclerotic renovascular disease (25). Three studies of percutaneous renal angioplasty (PTRA) were not able to show improvements in blood pressure control (26-28). However, a meta-analysis of these studies was able to show an 8 mmHg reduction in blood pressure with PTRA but could not show improvement in renal function compared with conservative strategies (29). Factors associated with a lower likelihood of response to revascularization are listed in Table 1. The restenosis rate for PTRA is high for ostial lesions, and 80% to 85% of all atherosclerotic RAS is ostial. PTRA with stenting (PTRAS) may circumvent this problem. While it seems logical that greater patency following PTRAS would lead to improved blood pressure control and preservation

TABLE 1
Factors associated with a lower likelihood of response to renal revascularization

Urinary protein excretion ≥1 g/day
Hyperuricemia
Glomerular filtration rate <40 mL/min
Age >65 years
Pulse pressure of ≥70 mmHg
Diastolic blood pressure <80 mmHg, systolic blood pressure <160 mmHg
Male sex
No abrupt onset of higher blood pressure
Duration of hypertension >10 years
Diabetes mellitus
No history of smoking
Coronary artery disease
Cerebrovascular disease
Peripheral arterial disease

TABLE 2
Clues suggesting the need for assessment of renovascular hypertension*

Sudden onset or worsening of hypertension and age greater than 55 years or less than 30 years
The presence of an abdominal bruit
Hypertension resistant to three or more drugs
A rise in creatinine associated with use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist
Other atherosclerotic vascular disease, particularly in patients who smoke or have dyslipidemia
Recurrent pulmonary edema associated with hypertensive surges

**Patients presenting with two or more of the clinical clues listed above, suggesting renovascular hypertension, should be investigated*

of renal function, no study has yet been conducted to prove this. A meta-analysis of PTRA with stenting compared with PTRA found that surrogate markers of stenting were improved with a higher technical success rate for opening stenoses and a lower restenosis rate than PTRA (98% versus 77% and 17% versus 26%, respectively) (30). In general, studies of PTRA for atherosclerotic renovascular disease have shown that renal function is improved in approximately 25%, stabilizes in approximately 40%, but worsens in approximately 25% of patients (31).

Approach

The approach to atherosclerotic renovascular disease must therefore deal with two distinct population groups: those with known RAS, and those with a high likelihood of disease (Table 2). When RAS has already been diagnosed, management will be determined by the patient's blood pressure and renal function. If the blood pressure is uncontrollable or the renal function is deteriorating, the patient should be considered for renal revascularization, initially with PTRAS. For those with a high likelihood of atherosclerotic renovascular disease (Table 2), the following tests are recommended, when available, to screen for RAS: captopril-enhanced radioisotope renal scan, Doppler sonography, MRA and CT angiography. The optimal test for diagnosing renovascular hypertension depends on local radiological expertise and the underlying clinical situation. Given the published sensitivities and specificities, a cost-benefit analysis found that Doppler sonography was marginally more cost-effective than renal scintigraphy and MRA, and that combining the Doppler with a positive RRI was the most cost-efficient strategy (32). However, MRA, despite the extra cost, may be preferred to avoid false-negative examinations (32).

The dilemma faced by the clinician is that resistant hypertension is common and atherosclerotic renovascular disease may be found in 20% of this large population. However, because atherosclerotic renovascular disease may also be found in normotensive patients, this may explain in part why finding the disease and treating it in resistant hypertension does not always lead to better blood pressure control. Furthermore, if there is already renal parenchymal damage, renal revascularization may not lead to improvement in blood pressure or to the preservation of renal function.

Management of hypertension and kidney disease

The management of hypertension in this condition involves the use of combinations of antihypertensive agents at doses sufficient to control blood pressure. Most patients with atherosclerotic renovascular disease will have associated isolated systolic hypertension consistent with their vasculopathic state. Blockers of the RAAS must be used with close monitoring of renal function and serum potassium level, preferably with an existing baseline result and another within a week of initiating therapy. Diuretics and long-acting calcium channel blockers are common mainstays of therapy. Adding beta-blockers and their antirenin effect may be beneficial, but will also increase the risk for hyperkalemia; the beta-blockers will also help to control heart rate and cardiac output but may possibly worsen peripheral arterial insufficiency symptoms from unopposed alpha-adrenergic effects. Adding an alpha-adrenergic blocking agent is often necessary to help bring the blood pressure to target. Medical management also includes aggressive blood sugar- and lipid-lowering therapy with high-dose statins, or possibly the combination of a lower dose of statin in the setting of chronic kidney disease and a cholesterol absorption inhibitor drug such as ezetimibe, the use of antiplatelet therapy, smoking cessation as well as diet and lifestyle counselling. The recommendations for the management of hypertension in atherosclerotic renovascular disease are found in Table 3. Acute renal failure can occur when significant reduction of blood pressure is effected with any antihypertensive agents in patients with a hemodynamically significant stenosis(ses) of the arteries, leading to the functioning kidney(s); the significant reduction in blood pressure can embarrass renal blood flow across the stenosis(ses) and cause a reduction in GFR.

UPCOMING STUDIES

New evidence will be forthcoming over the next three years from a number of clinical trials. The STent placement and blood pressure and lipid-lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery (STAR) study (33) aims to compare the effects of renal artery stent placement together with medical risk reduction strategies versus the risk reduction strategies alone. One hundred forty patients with atherosclerotic renovascular disease (RAS 50% or greater and GFR less than 80 mL/min) will be randomly assigned to either therapy and followed for two to five years (33). The Cardiovascular Outcomes in Renal Athersosclerotic Lesions (CORAL) study

TABLE 3
Recommendations for the management of hypertension in atherosclerotic renovascular disease

Renovascular hypertension should be treated in the same manner as uncomplicated hypertension, except for caution in the use of angiotesin-converting enzyme inhibitors or angiotensin receptor blockers due to the risk of acute renal failure in bilateral disease or unilateral disease with a solitary kidney
Close follow-up and early intervention (angioplasty and stenting or surgery) should be considered for patients with uncontrolled hypertension despite therapy with three or more drugs, deteriorating kidney function, bilateral atherosclerotic renal artery lesions (or tight atherosclerotic stenosis in a single kidney), or recurrent episodes of flash pulmonary edema

(34) is a National Institutes of Health study designed to test the hypothesis that medical therapy with PTRAS of RAS greater than 60% with evidence of hemodynamically significance on angiography in hypertensive patients will reduce the incidence of adverse cardiovascular and renal events compared with medical therapy alone. One thousand eighty patients will be followed for three to 5.5 years. The Renal Atherosclerotic Vascular Evaluation (RAVE) study (35) is a single-centre pilot study designed to assess the prevalence of renovascular disease in consecutive patients referred for resistant hypertension and in the cohort with RAS to test the role of the RRI in determining who should not be a candidate for renal revascularization. Currently in the pilot phase, this study will screen 180 patients with resistant hypertension and is expected to follow 30 with renovascular disease over a 3.5-year period.

CASE REVISITED

The patient and his wife recognized that renovascular disease was a marker for cardiovascular risk and focused on risk reduction strategies, including lifestyle modification and medication changes. The blood pressure target was systolic less than 130 mmHg, if tolerated. Despite maximum medical therapy, his blood pressure could not be controlled and renal angiography was arranged. An ostial lesion was found in the right renal artery, which was successfully stented. His blood pressure improved to 128/70 mmHg on his current medications. His blood pressure and renal function were followed every three months for possible recurrence.

SUMMARY

Renovascular disease is common, and is often associated with hypertension and ischemic nephropathy as well as a greater risk for adverse cardiovascular and renal outcomes. Screening strategies for high-risk patients can identify patients with reasonable accuracy. PTRAS can treat the anatomical lesions of even ostial RAS. It is presently unknown whether the addition of the RRI can help identify patients who will not benefit from revascularization, or whether revascularization can improve hard outcomes compared with medical therapy alone.

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