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Review

Management of Renovascular Disease

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Abstract

Introduction: Renal artery stenosis (RAS) is not rare, but is often asymptomatic. In older individuals, atherosclerosis is the most common cause of RAS. Atherosclerotic RAS is usually one manifestation of wide spread atherosclerotic disease, and its presence increases the morbidity and mortality of other manifestations of atherosclerotic disease.

Review: Renal arterial disease discovered incidentally can be managed expectantly as long as blood pressure and kidney function are well maintained. Revascularization can be considered with the prospect of improving blood pressure control or impaired kidney function, but its outcomes are heterogeneous. The potential for serious deterioration in kidney function after revascularization underscores the need to select patients carefully for vascular procedures in the kidney.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are effective in treating most cases of hypertension in atherosclerotic RAS. In addition, clinical data suggest that the survival of patients with renovascular hypertension is better when ACE inhibitors are part of therapy than when they are not. This benefit may be in part due to the fact that ACE inhibitors reduce morbidity and mortality in congestive heart failure which is common co-morbidity in patients with RAS. Withdrawal of the ACE inhibitor in such patients should occur only when the rise in serum creatinine level exceeds 30% above baseline within the first two months of ACE inhibitor initiation, or if hyperkalemia develops.

Conclusion: Renovascular hypertension is best managed with ACE inhibitors or ARBs as long as blood pressure and renal function are well maintained. Revascularization should be considered if blood pressure control is not adequate or if renal function deteriorates.

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Introduction

Renal vascular disease manifesting as renal artery stenosis (RAS) is not a rare entity, but is quite often asymptomatic. Among 716 potential living kidney donors who underwent conventional arteriography in a single center, 6.6% had renovascular disease due to fibromuscular dysplasia and 1.7% had renovascular disease due to atherosclerosis [1].

Atherosclerosis is by far the most common cause of RAS in older individuals. Population based studies have shown that hemodynamically significant RAS affects up to 6.8% of individuals above 65 years of age and that its presence is significantly and independently associated with increasing age, low high-density lipoprotein cholesterol levels and increasing systolic blood pressure [2]. RAS is also reported to affect 1-5% of all patients with hypertension [3], and this percentage increases to 17% in case of coexistent diabetes mellitus [4].

Atherosclerotic RAS rarely occurs in isolation, but is usually one manifestation of wide spread atherosclerotic disease. This is reflected by the fact that up to 26% of patients referred for evaluation of peripheral vascular disease [5], 10.4% of autopsy patients with stroke [6] and 4.8-15% of patients undergoing abdominal aortography immediately following coronary angiography [7, 8] have significant RAS.

The complex interaction between atherosclerotic RAS and hypertension is further enhanced by the deleterious effect of RAS on renal perfusion and kidney function. This may explain, at least in part, the negative impact of RAS on the morbidity and mortality of other manifestations of atherosclerotic disease.

In a retrospective analysis of patients with hypertension and renovascular disease, their 5 and 10 year survival rates were found to be 83% and 67% respectively, which was greatly reduced in comparison with that of matched controls in the general population, and was also less than

that of matched hypertensive patients. Age, cigarette smoking and the presence of atheromatous disease were significantly and independently related to outcome among these patients [9].

The prospective Cardiovascular Health Study has also shown that the presence of renovascular disease conferred an increased risk of adverse coronary events, which was not dependent on the effects of associated atherosclerotic risk factors, other prevalent cardiovascular disease, or high blood pressure [10].

In another cohort of patients who underwent abdominal aortography immediately following coronary angiography, the presence of significant RAS was found to be a strong independent predictor of mortality, with an unadjusted 4-year survival rate of 57% compared to 89% in patients without RAS. In addition, bilateral disease was associated with a 4-year survival rate of 47%, compared to 59% in patients with unilateral disease [7].

Also, in a large cohort of patients who underwent intra-arterial digital subtraction angiography for peripheral vascular disease (PVD) in a single center, RAS was an independent predictor of mortality. The estimated 5-year survival probability was 37% for patients with RAS as compared with 72% for patients without RAS [5].

Regarding end stage renal disease (ESRD) patients, renovascular disease was characterized clinically in 83 of 683 dialysis patients in a single center. Their 2-year, 5-year and 10-year survival rates were 56%, 18%, and 5% respectively, which was significantly worse than other diagnostic groups [11].

Review

Atherosclerotic RAS is progressive in nature. However, the rate of progression is quite variable, and this can have a great impact on management decisions.

In a prospective study among a group of hypertensive patients that used duplex scanning to document the natural history of atherosclerotic RAS, the 2-year cumulative incidence of renal atrophy (a reduction in kidney length of greater than 1 cm) was 5.5%, 11.7%, and 20.8% in kidneys with a baseline renal artery disease classification of normal, less than 60% stenosis, and 60% or more stenosis respectively. Also, there was a significant risk of renal atrophy among kidneys exposed to elevated systolic blood pressure and among those with low renal cortical blood flow velocity as assessed by renal duplex scanning. The occurrence of renal atrophy was well correlated with changes in the serum creatinine concentration [12]. Also, in the DRASTIC trial, 9% of patients who were randomized to receive medical treatment experienced total occlusion of the affected renal artery by 12 months [13].

However, in a prospective population-based study that estimated the incidence of new RAS and the progression of established RAS among elderly Americans with a low rate of clinical hypertension who were followed up for 8 years, progression to significant RAS was observed in only 4% of kidneys, and no case of RAS diagnosed at baseline progressed to occlusion [14].

This demonstrates that renal arterial disease discovered incidentally can pose no problem for either kidney function or blood pressure for several years, and as long as blood pressure and kidney function are well maintained, expectant management appears to be entirely appropriate.

Nevertheless, revascularization of RAS is often considered with the prospect of improving blood pressure control or impaired kidney function. The potential of revascularization to prevent or delay further decline in kidney function in some patients with RAS was documented by a number of observational studies. Impressive early results in this respect were reported by Morris and colleagues, who noted that renal function recovered in eight patients who underwent surgical revascularization at a time before the general availability of dialysis, six of whom returned to essentially normal renal function [15].

Surprisingly, randomized controlled trials comparing percutaneous transluminal renal angioplasty (PTRA) with medical therapy in the treatment of RAS failed to demonstrate any long term benefit on the preservation of renal function in the PTRA group, even though angioplasty was slightly more effective in improving blood pressure control in some studies. Overall, the evidence from these studies was not sufficiently robust to determine the comparative effectiveness of angioplasty and medical treatment in the management of RAS [16, 17].

The failure of these studies to detect a meaningful overall improvement in serum creatinine level may be explained by the heterogeneous outcomes of revascularization. Overall, among RAS patients who underwent PTRA with stenting, 26% had an improvement in glomerular filtration rate (GFR), 48% had a stable GFR, whereas 26% had a decline in GFR [18].

The rapid deterioration in renal function that occurs in some patients after revascularization may be due to the relatively high risk of complications of revascularization. Apart from contrast nephropathy, possible complications of PTRA include hemorrhage, injury to the femoral, iliac or renal arteries, stent thrombosis, distal renal embolism,

septicemia, and cholesterol embolism to the lower limbs [18].

As expected, the risk is even higher for surgical revascularization. In a retrospective analysis that compared surgical revascularization and PTRA in the management of RAS, both procedures had similar efficacy; however, surgical revascularization had a higher complication rate and higher thirty-day mortality than PTRA (9% versus 2%) [19].

The potential for serious deterioration in kidney function after revascularization, percutaneous or surgical, and the possibility of serious complications underscore the need to select patients carefully for vascular procedures in the kidney.

Several factors were explored for the potential of predicting which patient is most likely to benefit from revascularization. A shrunken kidney, a kidney with cortical necrosis or a kidney proven by biopsy to have irreversible damage is not likely to benefit from revascularization. In addition, a duplex ultrasound scan revealing renal resistance index greater than 80 indicates small vessel and large vessel disease. Such findings predict poor response to either percutaneous or surgical revascularization with respect to improvement in hypertension, renal function, or kidney survival [20].

In a secondary analysis of the DRASTIC study, only patients with bilateral RAS had a substantial benefit on creatinine clearance, and they also seemed to benefit most with regard to blood pressure control [21].

In a study of 105 patients with hemodynamically significant atherosclerotic RAS who underwent PTRA with stenting, it was found that the subgroup of patients which initially had a moderately or severely impaired GFR had a significant increase in the calculated GFR one year after the procedure despite no significant change in blood pressure. In contrast, the subgroup which had normal or mildly impaired GFR, had significant reductions in systolic and diastolic blood pressure, but no significant change in the calculated GFR [22].

Among 59 chronic renal failure patients who underwent PTRA for hemodynamically significant RAS, it was found that a rapidly progressive decline in renal function prior to the procedure was associated with a more favorable response to PTRA regarding renal failure progression [23].

Timing of revascularization is also of paramount importance. In a cohort of 241 patients who were treated with PTRA and stent implantation for significant RAS, the long term survival was found to depend largely on renal function and left ventricular function at the time of the procedure; the 5-year survival rates for patients with baseline serum creatinine of more than 2.5 mg/dl, 1.2-2.5 mg/dl and less than 1.2 mg/dl were 29.6%, 89.1%, and 95.4% respectively [24]. Hence, revascularization should not be delayed for a suitable candidate in order to spare him/her the development of advanced ischemic nephropathy or congestive heart failure.

The American College of Cardiology and the American Heart Association have recently published guidelines for the management of patients with peripheral arterial disease, including RAS [25]. According to these guidelines, percutaneous revascularization is indicated for patients with hemodynamically significant unilateral or bilateral RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, hypertension with intolerance to medication, recurrent unexplained congestive heart failure or sudden unexplained pulmonary edema, or unstable angina. It is also indicated for patients with bilateral RAS or RAS to a solitary functioning kidney and progressive chronic kidney disease, and may be considered for patients with unilateral RAS and chronic renal insufficiency. Vascular surgical reconstruction is indicated for patients with RAS who have a clinical indication for revascularization when percutaneous revascularization is not feasible or has been unsuccessful [25].

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are effective in treating 86 – 92% of cases of hypertension and atherosclerotic RAS [26]. As a result of the wider use of these agents for the treatment of hypertension, it is likely that many individuals with renovascular hypertension are never detected but are simply treated.

In addition, clinical data suggest that the survival of patients with renovascular hypertension is better when ACE inhibitors are part of therapy than when they are not [27]. This benefit may be in part due to the fact that ACE inhibitors reduce morbidity and mortality in congestive heart failure [28], which is common co-morbidity in patients with RAS.

However, a major concern regarding the use of ACE inhibitors for renovascular hypertension is their potential to cause functional acute renal failure. A rise in serum creatinine of up to 30% above baseline following the initiation of ACE inhibitors in patients with heart failure is a normal hemodynamic response, and a strong association exists between this acute increase in serum creatinine and long term preservation of renal function; withdrawal of the ACE inhibitor in such patients should occur only when the rise in serum creatinine level exceeds

30% above baseline within the first 2 months of ACE inhibitor initiation, or hyperkalemia develops [29].

The benefits of revascularization for such patient are not limited to restoration of kidney function and improved blood pressure control, but extend to an improvement in heart failure symptoms [40]. Renal revascularization also has the potential to ameliorate the increased risk of adverse coronary events which is associated with renovascular disease [9]. This issue will be addressed by a prospective trial, Cardiovascular Outcomes in Renal Artery Lesions (CORAL), which will examine the effect of intensive medical management versus revascularization with or without stenting on cardiovascular events in patients with RAS [41].

Conclusion

Renal arterial disease discovered incidentally can be managed expectantly as long as blood pressure and kidney function are well maintained. Renovascular hypertension is best managed with ACE inhibitors or ARBs. Revascularization can be considered for a select group of patients with the prospect of improving blood pressure control or impaired kidney function.

References

1. Neymark E, LaBerge JM, Hirose R, Melzer JS, Kerlan RK Jr, Wilson MW, Gordon RL. Arteriographic detection of renovascular disease in potential renal donors: incidence and effect on donor surgery. Radiology. 2000 Mar; 214(3):755-60.

2. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, Burke GL, Dean RH. Prevalence of renovascular disease in the elderly: a population based study. J Vasc Surg. 2002 Sep;36(3): 443–51.

3. Derkx FHM Sc,halekamp MA. Renal artery stenosis and hypertension. Lancet. 1994 Jul;344(8917):237–9.

4. Valabhji J, Robinson S, Poulter C, Robinson AC, Kong C, Henzen C, Gedroyc WM, Feher MD, Elkeles RS. Prevalence of renal artery stenosis in subjects with type 2 diabetes and coexistent hypertension. Diabetes Care. 2000 Apr;23(4):539–43.

5. Mui K, Sleeswijk M, van den Hout H, van Baal J, Navis G, Woittiez AJ. Incidental renal artery stenosis is an independent predictor of mortality in patients with peripheral vascular disease. J Am Soc Nephrol. 2006 Jul;17(7):2069-74.

6. Kuroda S, Nishida N, Uzu T, Takeji M, Nishimura M, Fujii T, Nakamura S, Inenaga T, Yutani C, Kimura G. Prevalence of renal artery stenosis in autopsy patients with stroke. Stroke. 2000 Jan;31(1):61-5.

7. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. Kidney Int. 2001 Oct;60(4):1490-7.

8. Harding MB, Smith LR, Himmelstein SI, Harrison K, Phillips HR, Schwab SJ, Hermiller JB, Davidson CJ, Bashore TM. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. J Am Soc Nephrol. 1992 May;2(11):1608-16.

9. Isles C, Main J, O'Connell J, Brown I, Findlay J, Stewart R, Wilkinson R. Survival associated with renovascular disease in Glasgow and Newcastle. Scot Med J. 1990 Jun;35(3):70–3.

10. Edwards MS, Craven TE, Burke GL, Dean RH, Hansen KJ. Renovascular disease and the risk of adverse coronary events in the elderly: a prospective, population-based study. Arch Intern Med. 2005 Jan 24;165(2):207-13.

11. Mailloux LU, Napolitano B, Bellucci AG, Vernace M, Wilkes BM, Mossey RT. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: A 20-year clinical experience. Am J Kidney. Dis 1994 Oct;24(4):622−9.

12. Caps MT, Zierler RE, Polissar NL, Bergelin RO, Beach KW, Cantwell-Gab K, Casadei A, Davidson RC, Strandness DE Jr. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. Kidney Int. 1998 Mar;53(3):735–42.

13. van Jaarsveld BC, Krijnen P, Pieterman H, Derkx FH, Deinum J, Postma CT, Dees A, Woittiez AJ, Bartelink AK, Man in't Veld AJ, Schalekamp MA. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. N Engl J Med. 2000 Apr;342(14):1007–14.

14. Pearce JD, Craven BL, Craven TE, Piercy KT, Stafford JM, Edwards MS, Hansen KJ. Progression of atherosclerotic renovascular disease: A prospective population-based study. J Vasc Surg. 2006 Nov;44(5):955-62.

15. Morris GC Jr, DeBakey ME, Cooley DA. Surgical treatment of renal failure of renovascular origin. JAMA. 1962;182:609-12.

16. Ives NJ, Wheatley K, Stowe RL, Krijnen P, Plouin PF, van Jaarsveld BC, Gray R. Continuing uncertainty about the value of percutaneous revascularization in atherosclerotic renovascular disease: a meta-analysis of randomized trials. Nephrol Dial Transplant. 2003 Feb;18(2):298–304.

17. Nordmann AJ, Woo K, Parkes R, Logan AG. Balloon angioplasty or medical therapy for hypertensive patients with atherosclerotic renal artery stenosis? A meta-analysis of randomized controlled trials. Am J Med. 2003 Jan;114(1):44–50.

18. Isles CG, Robertson S, Hill D. Management of renovascular disease. A review of renal artery stenting in ten studies. QJM. 1999 Mar;92(3):159–67.

19. Alhadad A, Ahle M, Ivancev K, Gottsäter A, Lindblad B. Percutaneous transluminal renal angioplasty (PTRA) and surgical revascularisation in renovascular disease: a retrospective comparison of results, complications, and mortality. Eur J Vasc Endovasc Surg. 2004 Feb;27(2):151-6.

20. Radermacher J, Weinkove R and Haller H. Techniques for predicting a favourable response to renal angioplasty in patients with renovascular disease. Curr Opin Nephrol Hypertens. 2001 Nov;10(6):799–805.

21. Krijnen P, van Jaarsveld BC, Deinum J, Steyerberg EW and Habbema JD. Which patients with hypertension and atherosclerotic renal artery stenosis benefit from immediate intervention? J Hum Hypertens 2004. Feb;18(2):91-6.

22. Ramos F, Kotliar C, Alvarez D, Baglivo H, Rafaelle P, Londero H, Sánchez R and Wilcox CS. Renal function and outcome of PTRA and stenting for atherosclerotic renal artery stenosis. Kidney Int. 2003 Jan;63(1):276–82.

23. Muray S, Martín M, Amoedo ML, García C, Jornet AR, Vera M, Oliveras A, Gómez X, Craver L, Real MI, García L, Botey A, Montanyà X and Fernández E. Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. Am J Kidney Dis. 2002 Jan;39(1):60-6.

24. Zeller T, Müller C, Frank U, Bürgelin K, Schwarzwälder U, Horn B, Roskamm H and Neumann FJ. Survival after stenting of severe atherosclerotic ostial renal artery stenoses. J Endovasc Ther. 2003 Jun;10(3):539-45.

25. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr, White CJ, White J, White RA, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B; American Association for Vascular Surgery; Society for Vascular Surgery; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology; ACC/AHA Task Force on Practice Guidelines; American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; Vascular Disease Foundation. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol. 2006 Mar 21;47(6):1239-312.

26. Textor SC. ACE inhibitors in renovascular hypertension. Cardiovasc Drugs Ther. 1990 Feb;4(1):229-35.

27. Losito A, Gaburri M, Errico R, Parente B, Cao PG. Survival of patients with renovascular disease and ACE inhibition. Clin Nephrol. 1999;52:339–43.

28. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril on morbidity and mortality in chronic heart failure. Circulation. 1999 Dec 7;100(23):2312–8.

29. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med. 2000 Mar 13;160(5):685–93.

30. Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS; Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Circulation. 2001 Oct 16;104(16):1985–91.

31. Schneider JR, Wright A, Mitchell RS. Successful percutaneous balloon catheter treatment of renal artery occlusion and anuria. Ann Vasc Surg. 1992 Nov;6(6):533-6.

32. Sezer M, Nisanci Y, Ozsaruhan O, Olcay A, Ecder T. Stenting for bilateral renal artery occlusion: a

report of two cases. Nephrol Dial Transplant. 2003 Dec;18(12):2663-4.

33. Rehan A, Almanaseer Y, Desai DM, Ali A, Yamasaki H. Complete resolution of acute renal failure after left renal artery angioplasty and stent placement for total renal artery occlusion. Cardiology. 2007;108(1):51-4.

34. Fernandez-Fresnedo G, Piña T, Mateos Chaparro F, Sanz de Castro S, González-Tutor A, Bustamante M, de Francisco AL, Arias M. Revascularization of total renal artery occlusion by angioplasty and stent placement. Nefrologia. 2005;25(4):434-7.

35. Han BG, Kim JY, Choi JU, Lee SH, Choi SO. An acute renal failure patient successfully stented for bilateral renal artery occlusion with a distal embolism protection device. Nephrol Dial Transplant. 2004 Jun;19(6):1662-3.

36. Ascer E, Gennaro M, Rogers D. Unilateral renal artery revascularization can salvage renal function and terminate dialysis in selected patients with uremia. J Vasc Surg. 1993 Dec;18(6):1012-8.

37. Perona PG, Baker WH, Fresco R, Hano JE. Successful revascularization of an occluded renal artery after prolonged anuria. J Vasc Surg. 1989 Jun;9(6):817-21.

38. Cohen DL, Townsend RR, Kobrin S, Genega EM, Tomaszewski JE, Fairman R. Dramatic recovery of renal function after 6 months of dialysis dependence following surgical correction of total renal artery occlusion in a solitary functioning kidney. Am J Kidney Dis. 2001 Jan;37(1):E7.

39. Patterson LT, Bock GH, Guzzetta PC, Ruley EJ. Restoration of kidney function after prolonged renal artery occlusion. Pediatr Nephrol. 1990 Mar;4(2):163-5.

40. Messina LM, Zelenock GB, Yao KA, Stanley JC. Renal revascularization for recurrent pulmonary edema in patients with poorly controlled hypertension and renal insufficiency: a distinct subgroup of patients with arteriosclerotic renal artery occlusive disease. J Vasc Surg. 1992 Jan;15(1):73–82.

41. Cooper CJ, Murphy TP, Matsumoto A, Steffes M, Cohen DJ, Jaff M, Kuntz R, Jamerson K, Reid D, Rosenfield K, Rundback J, D'Agostino R, Henrich W, Dworkin L. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. Am Heart J. 2006 Jul;152(1):59-66.