Diagnosis and management of renovascular disease

Summary report

In 1983 the National Heart, Lung, and Blood Institute (NHLBI), on the recommendation of the Cardiology Advisory Committee that advises the Division of Heart and Vascular Diseases, concluded that there was a need to review the current status, future needs, and potential for detection and therapy of renovascular disease. A workshop was convened March 5 and 6, 1984 with the goals of assessing current knowledge regarding pathology and pathophysiology, diagnostic procedures, patient management, and the incidence and economic impact of the disease. The participants were also charged with identifying future research and clinical needs that will be brought to the attention of the NHLBI and its advisory committees. To develop this report a planning committee was formed of the following participants: Robert Barnes, M.D., Chairman, (Department of Surgery, University of Arkansas, Little Rock, Ark.), Alan Berson, Ph.D., (NHLBI, National Institutes of Health, Bethesda, Md.), Richard Dean, M.D., (Department of Surgery, Vanderbilt University, Nashville, Tenn.), Calvin Ernst, M.D., (Department of Surgery, Baltimore City Hospital, Baltimore, Md.), James Hunt, M.D., (Center for Health Sciences, University of Tennessee, Memphis, Tenn.), Lawrence Krakoff, M.D., (Department of Medicine, Mt. Sinai Hospital, New York, N.Y.), Morton Maxwell, M.D., (Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, Calif.), Mr. Armando Sandoval, (NHLBI, National Institutes of Health, Bethesda, Md.), James Stanley, M.D., (Department of Surgery, University of Michigan, Ann Arbor, Mich.), Jack Thornbury, M.D., (Department of Radiology, University of Rochester, Rochester, N.Y.), and John Watson, Ph.D., (NHLBI, National Institutes of Health, Bethesda, Md.).

Renal artery disease in human beings is a pathologic process, often with serious consequences. In both atherosclerotic disease and fibromuscular dysplasia, the disease is usually characterized by irregular narrowing of the arterial lumen and loss of elasticity of vessel walls. The resultant impairment of renal blood flow may lead to hypertension, reduced kidney function, or renal failure. The currently acceptable clinical method for providing the best quantitative measures of the presence and extent of arterial lesions is angiography, which when appropriately accomplished is of high sensitivity and specificity but is also subject to considerable inter- and intraobserver variability. It is also expensive and time-consuming and carries a small but significant risk to the patient. Save for the presence of a systolic-diastolic abdominal bruit, no symptom or sign at physical examination will assist in the detection of renal artery disease; however, screening tests of variable but proven value include saralasin acetate infusion tests, intravenous urography, renal venous renin activity studies, and radionuclide scanning. Minimally invasive techniques less often used but having potential for quantitative assessments include ultrasound Doppler flow studies and ultrasound B-mode imaging, nuclear magnetic resonance (NMR) imaging, and digital subtraction angiography (DSA) in conjunction with intravenous administration of contrast material. Traditionally acceptable management modes include both medical treatment and surgical reconstruction. Percutaneous transluminal angioplasty (PTA) is a technique more recently utilized and is rapidly gaining acceptance. Generally, conclusive data in the areas of detection and treatment are lacking to permit optimization of diagnostic procedures in identifying patients having hypertension caused by renal artery stenosis as well as in making a clinical decision as to surgical or medical treatment.

The NHLBI convened a workshop on March 5 and 6, 1984 on Detection and Treatment of Renovascular Disease. Presentations and discussions included the potentials and limitations of the various
diagnostic techniques of intravenous urography, renal vein renin activity measurements, saralasin acetate testing, split renal function, converting enzyme inhibitors, angiography, DSA, ultrasound, nuclear medicine, and NMR. Medical, surgical, and PTA treatments and costs were discussed. Pathophysiologic features of the disease process, lesion morphology, and animal models were also discussed. This article is a synopsis of the workshop discussions and recommendations, highlighting important recent advances and defining areas having high potential for success in broadening the base of knowledge in detection and treatment of renovascular disease.

PATHOPHYSIOLOGY AND MORPHOLOGY

Several pathogenetic mechanisms are associated with the development of renovascular hypertension. When a renal artery is acutely occluded, both peripheral vascular resistance and blood pressure increase, with associated changes in the renin-angiotensin and sympathetic nervous systems. Hemodynamic alterations result from changes in plasma angiotensin activity, which can often be reversed or prevented by converting enzyme inhibition. The one-kidney, one-clip and the two-kidney, one-clip rat experimental models have been used to demonstrate both renin-dependent and sodium-dependent mechanisms and the reciprocal relation between the two mechanisms. These models provide the rationale for diagnostic procedures used to predict reversibility of the disease after anatomic correction.

The histologic and anatomic characteristics of renal artery stenotic lesions are also important in defining the natural history and clinical significance of renovascular hypertension. Two major forms of renal artery disease exist: arterial fibrodysplasia and atherosclerosis.

Arterial fibrodysplasia is classified by the specific region of the vessel wall affected, that is, intimal, medial, or perimedial-adventitial regions. Intimal fibrodysplasia accounts for 5% of dysplastic disease, usually with hillocks of tissues encroaching on the lumen. The etiology of intimal disease may relate to embryonic cushions, sequela of intrauterine or early neonatal injuries, as well as thrombotic events associated with infectious diseases such as rubella. Medial hyperplasia is an uncommon entity reflected in actual increases in the amount of medial smooth muscle tissue. The existence of this particular entity is controversial. Medial fibrodysplasia accounts for approximately 85% of dysplastic disease, and it occurs in women more frequently than in men. This dysplastic disease often presents as a series of stenoses alternating with thinned areas, the latter representing true aneurysms. Perimedial dysplasia, a fourth dysplastic process accounting for less than 10% of this group of renal artery stenoses, is often associated with medial fibrodysplasia. Excessive accumulations of elastic tissue in the subadventitial-perimedial region characterize these lesions.

Arteriosclerosis is the most common cause of renal artery occlusive disease, affecting men twice as often as women. The natural history of this particular disease entity is poorly defined although progression seems to parallel that noted in the coronary, carotid, and peripheral extremity arteries. The etiology of certain localized atherosclerotic lesions appears to be secondary, with an underlying developmental or intimal stenosis occurring first. This latter group of patients appears to have better long-term survival than have others with generalized disease. These differences have been inadequately defined.

Many gaps continue to occur in our understanding of renal artery disease, including a more precise definition of the anatomic-histologic classification of these lesions. Experimental models of renal artery fibrodysplasia and atherosclerosis need to be developed to better study the late (third) phases of experimental renovascular hypertension (RVHT). The progression of both fibrodysplastic as well as atherosclerotic lesions occurs at unpredictable rates, and risk factors should be better defined if clear therapeutic choices are to be forthcoming in the clinical setting.

Animal models for renal hypertension have emphasized the one kidney—two kidney—one clip Goldblatt experiments. These models allow study of blood pressure and blood volume changes associated with changes in renal plasma renin activity. Responses to sodium overload and angiotensin antagonists can also be studied. Further development of genetically inbred rats such as Dahl salt-sensitive and salt-resistant rats is potentially valuable for exploring the involvement of the kidney in hypertension. It may be possible to inbred rats for specific disturbed renal responses, tubular function, and humoral mechanisms. New experimental models are needed to reproduce lesions that occur in fibromuscular dysplasia.

CLINICAL MANIFESTATIONS

During the past 30 years, many clinical features have been suggested to identify RVHT. Early reports
were limited by small numbers of patients or by inclusion of patients with hypertension not related to renal artery stenosis. The Cooperative Study of Renovascular Hypertension (1972) provided the first multi-institutional attempt to define the clinical characteristics of this type of hypertension. For analysis 339 patients with essential hypertension (EHT) were compared with 175 patients with RVHT who had been successfully treated by revascularization or nephrectomy. The nonatherosclerotic group included all subtypes of fibrous dysplasia.

Patients with EHT were younger (mean 40.8 years) than those with atherosclerotic renovascular hypertension (AS) (49.7 years) yet were older than those with fibromuscular dysplastic renovascular hypertension (FM) (34.9 years). The mean duration of high blood pressure in patients with EHT was more than 1 year longer than in patients with RVHT. Onset of hypertension after the age of 50 years was present in 39% of patients with AS as opposed to only 7% of patients with EHT and only 3% of patients with FM. In contrast, early onset (before the age of 20 years) was seen in only 2% of patients with AS as opposed to 12% (EHT) and 16% (FM). Patients with EHT and AS were predominantly men whereas 81% of patients with FM were women. Blacks comprised 30% of patients studied, yet only 8% of 175 patients with RVHT were black. Accelerated hypertension was seen in 23% of patients with AS compared with 13% and 14% in patients with EHT and FM, respectively.

Abdominal or flank bruits were seen six to nine times more commonly in patients with RVHT (both AS and FM). Flank bruits were less common but the discrepancy between groups was even greater with bruits in this location. Abdominal bruits are found in only 7% of patients with EHT, a much lower frequency than in patients with RVHT. However, the diagnostic value of systolic abdominal bruits in patients with RVHT is limited by the much greater frequency of EHT. The correlation between a systolic-diastolic abdominal bruit and renovascular hypertension is exceedingly high and this finding is of greater predictability than any other single sign. There is an increased frequency of cardiac and cerebrovascular disease in patients with atheromatous renal artery stenosis and hypertension in comparison with patients with EHT.

Workshop participants expressed concern regarding integration of the various diagnostic tests and their ability to predict surgical responses. They noted that the power of clinical observations to predict the response to surgical revascularization appears important and warrants reappraisal.

**DIAGNOSTIC INSTRUMENTATION TECHNIQUES**

Conventional arteriography with selective injection and magnification techniques provides the most accurate means for evaluating the presence and severity of main and intrarenal artery stenoses. A more recently introduced method involves injection of epinephrine or acetylcholine with a selectively placed renal artery catheter for assessment of clinical and hemodynamic consequences of renal artery stenosis (pharmacoangiography). Studies have shown that pharmacoangiography is moderately sensitive and very specific for evaluation of hemodynamic significance of renal artery stenosis, but the technique has not been widely employed and its potential risks have not been assessed. The costs and risks of conventional angiography have precluded its use as a screening test.

Although rapid sequence filming (hypertensive urography has been used for more than two decades, it is neither a satisfactory test for renal artery stenosis nor a reliable predictor of surgical cure or improvement. False negative rates are on the order of 22%, false positive rates 13%, and predictive value is about 31% for the diagnosis of renal artery stenosis.

DSA in conjunction with intravenous administration of contrast material is a relative newcomer to this field. It appears to be a safe and effective screening alternative to arteriography in a large proportion of cases but data are lacking regarding sensitivity and specificity in detecting and quantifying lesions in renal arteries. Risks to patients are reduced compared with conventional arteriography, and DSA may be performed on an outpatient basis with associated decreased costs. A study comparing this technique with conventional arteriography and intra-arterial DSA or outcome after interventional therapy would be most useful.

Ultrasonic examination for renovascular disease is feasible with real-time B-mode ultrasonic imaging of the kidney or renal artery and vein, continuous-wave or pulsed Doppler ultrasonic detection of flow velocity in the renal artery or vein or the renal parenchyma, and combined echo-Doppler (duplex) scanning of the renal artery and vein. Real-time B-mode ultrasonic imaging of the kidney parenchyma enjoys widespread application. B-mode imaging of the renal artery and vein permits detection of advanced atherosclerotic stenosis or arterial or venous
thrombi. The potential also exists for imaging and quantifying vessel wall thickness with B-mode, an advantage for following the time course of early atherosclerotic disease. However, current resolution of real-time imaging equipment, particularly at the depth of renal arteries, fails to permit sensitive detection of small, localized, nonobstructing plaques and does not provide information about renal blood flow. Continuous-wave or pulsed Doppler ultrasound permits assessment of renal artery and venous blood flow and information about both extrarenal and intrarenal vascular occlusive disease. When combined with real-time B-mode imaging, so-called duplex scanners permit detection of arterial or venous lesions that may be partially or totally occlusive. In addition, flow velocity perturbations occur, which correlate with peripheral vascular resistance.

Although CT scanning times ordinarily are relatively long, at least one new CT scanner has been produced that generates a scan in 50 msec. With such an instrument, scans of the kidney can be generated at sufficiently short intervals and for a long enough duration after intravenous bolus injection of contrast media to generate density-vs.-time curves. These curves can be produced for various regions of the kidney and thereby provide an estimate of regional perfusion of the kidney(s). Preliminary studies in dogs show a good correlation between regional blood flow and parameters derived from these density-time curves. This technique may, with some additional refinement and validation, evolve as a minimally invasive means for evaluating renal ischemia.

NMR techniques have been applied to imaging of various vascular structures and to quantifying blood flow in vessels. Few studies have been directed toward renal arteries but the potential for obtaining both anatomic and flow information of high quality warrants experimental and clinical investigations. Investigations should include animal models that most closely mimic the disease in human beings. Blood flow measurements through the renal arteries as well as the aorta should be performed in those models. In addition to analysis of blood vessels, NMR researchers should be directed toward the analysis of the renal parenchyma with respect to ischemic changes. Clinical investigations should be aimed toward sensitivity and specificity of NMR compared with the current standard, angiography. For NMR to become clinically useful, several technologic advancements will be needed, such as improvements in three-dimensional reconstruction methods, greater precision in quantifying blood flow, and capability for imaging thinner sections of tissue.

Nuclear medicine techniques are potentially useful in studies of functional renal derangements. Examinations commonly used include renal perfusion studies, renal imaging studies performed solely for morphologic purposes, and renal imaging studies combined with estimates of renal function. They are not usually first-line procedures but may be performed when intravenous urogram results indicate a need for additional evaluation. The two most important applications are in urinary tract obstruction and in serial studies of the kidney when some intervention is planned or there is a prospect of progressive loss of renal function.

Many nuclear medicine studies yield inconclusive results. This may not necessarily be a failure of the test but rather a reflection of the wide spectrum of disease that is found among patients and the inability to control such basic modulating factors as the patient's state of hydration. Nuclear medicine tests, with their great sensitivity to changes in renal function, frequently make follow-up studies extremely valuable. The ongoing problem in nuclear medicine methodology is the multiplicity of techniques that have been reported in the literature. A well-planned study of the various approaches should be directed toward the goal of optimizing the techniques. A study of clinical efficacy and cost benefit in relation to the various other screening and diagnostic procedures may prove useful.

Renin activity is often measured to assess the hemodynamic significance of renal artery stenoses. Renal vein renin activity studies have been considered valuable in this respect because (1) the renin-angiotension system is the only generally accepted pathophysiologic mechanism underlying renovascular hypertension and (2) renal vein renin levels have been good predictors of the response to surgery. Unfortunately, renal vein renin sampling is fraught with analytic problems that may be a major reason for the insensitivity and lack of specificity in a significant proportion of cases. A need exists for standardization of both sampling procedures and assay methodologies.

In the evaluation of diagnostic techniques in the past, emphasis has been concentrated on "making the diagnosis" of renal artery stenosis. As more information has been documented on the outcomes of patients from surgery and medical treatment, attention is being shifted from "making the diagnosis" to identifying patient selection criteria for use of tests. The selection strategy is aimed at identifying patients who have a high likelihood of surgical cure or improvement. Thus, the optimum use of a test is linked
to its contribution toward the determination of whether a patient is, or is not, a surgical candidate from the standpoint of likelihood of cure or improvement. New imaging technology needs to be evaluated on this basis, just as traditional testing for renal artery stenosis has begun to be evaluated in this fashion.

**CLINICAL MANAGEMENT**

RVHT encompasses two different disease processes with different etiologies and natural histories. The choice of treatment depends on two principal considerations: control of blood pressure and preservation of renal function. Outcomes related to the surgical therapy of renal artery disease causing secondary renin-mediated hypertension depend on: (1) accurate diagnosis, (2) a technically successful operation, and (3) the specific type of renal artery disease being treated. Outcomes, in general, parallel the type of disease being treated, with more favorable results in patients with fibrodysplastic disease, and less favorable results in patients with atheromatous stenosis. This may relate to the recurrence of atherosclerotic lesions as contrasted with rarely recurring restenoses in patients treated for fibrodysplastic disease as well as to the ever-increasing incidence of EHT in the atherosclerotic age group compared with the younger fibrodysplastic patients.

The most frequently used criteria regarding blood pressure outcome in surgically reported series represent a modification of criteria from the Cooperative Study on Renovascular Hypertension. Cured adult patients are those with blood pressures less than 150/90 mm Hg without drug therapy for a minimal 6-month period. Improved patients are those with blood pressures less than 150/90 mm Hg but at least 15% below preoperative levels. Those not improved are patients in whom diastolic blood pressure is greater than 90 mm Hg with less than a 15% decrease from the preoperative level and in all cases when diastolic pressures exceed 110 mm Hg.

A major gap in these criteria is the difficulty of defining outcome with the recent introduction of angiotension II–converting enzyme inhibitors. The latter may cause many patients to be moved from the failure to the improved group, a move that would not have occurred in the past. A better system might incorporate some form of scoring system related to drug therapy. Furthermore, it would be advantageous to include some statement regarding long-term success (beyond 6 months) of surgical therapy in the definition of surgical outcome. Any consideration of outcome related to blood pressure must take into account the risks of nephrectomy and long-term effect on renal function. Last, long-term mortality data in the literature are controversial with respect to medical vs. surgical intervention.

Differentiation of patients with atherosclerotic disease into those with clinically overt extrarenal atherosclerotic disease and those exhibiting secondary hypertension as a consequence of focal renal arterial atherosclerosis deserves scrutiny. Although this has been a useful clinical categorization in the past, redefinition of these subgroups may identify more accurately those patients most likely to benefit and those least likely to benefit from operative intervention.

The long-term success of conventional reconstructive procedures appears well accepted, although the number of series reporting such data is limited. Outcome by year of follow-up in specified subgroups needs to be compared by treatment undertaken. Clearly, any comparison of surgical therapy to other forms of treatment needs to be made within specific subgroups of patients with long enough follow-up to evaluate the success of the procedure and patient survival.

In about 90% of patients having fibromuscular dysplasia, blood pressure is improved following reconstructive surgery. PTA, an alternative to reconstructive surgery, has recently been applied to treatment of renal artery stenosis. Also, PTA has been attempted at the time of initial arteriography. When PTA is successful, open operation becomes unnecessary and when unsuccessful, surgical repair can still be performed. Costs associated with PTA are considerably less than those of reconstructive surgery. High success rates have been reported for PTA but there are not enough data to demonstrate convincingly that PTA is as good as surgical intervention. Many series may have been preselected, and therefore a properly randomized trial to compare differing therapies would be an appropriate undertaking.

**RECOMMENDATIONS**

Renovascular disease, with RVHT, affects a relatively small number of those people with hypertension. In 1971 the annual rate for deaths caused by hypertensive disease related to renal disease was estimated as 9.6 per 100,000 population. Estimates of prevalence vary over a wide range, from 100,000 to perhaps 1,200,000 in the United States. Improved detection techniques might reveal this number to be considerably higher. Current assumptions about prevalence and distribution based on highly biased
samples are too imprecise. A first objective must be to obtain reliable population-based data to define the prevalence of RVHT and variables (clinical, demographic, or historic) associated with its occurrence. More sensitive and specific diagnostic tests are needed to establish better estimates of prevalence.

A prospective study appears timely for evaluating the effectiveness of surgery, PTA, and medical treatment. A randomized study should examine not only the technical success of dilating the stenotic artery by PTA but also the clinical success of relieving the patient’s hypertension. Such a study would ideally include a protocol to determine the relative value of various techniques for detection of renovascular stenosis and assessment of renal function. The accuracy of detection of renal artery stenosis with the use of modalities such as intravenous DSA, ultrasound Doppler and B-mode imaging, NMR, and the hypertensive urogram should be evaluated against conventional arteriographic techniques. The efficacy of nuclear medicine methods for evaluating renal function should be considered as one component of any prospective study. The presence of a renal artery stenosis and hypertension does not necessarily imply a causal relationship, and renin determinations may be a useful mechanism to identify this relationship. A reliable method is needed to identify the subset of patients who will benefit from correction of renal artery obstruction. Any prospective study should pay particular attention to standardization of procedures. Finally, the study design should attempt to answer the question of how to optimize the diagnostic evaluation of adult hypertensive patients.

There is a need for better understanding of basic mechanisms accounting for the appearance of renovascular disease in its various forms, why patients with similar anatomic findings do not all have correctable RVHT, and why some do not have hypertension at all. Studies should be directed toward a better understanding of the cellular biology of the arterial wall. This biology as it relates to the development of the arterial wall may reveal a great deal about dysplastic diseases and arteriosclerosis of the renal artery. The relationship between salt, water, renin, and sympathetic tone is a complex one and is ultimately controlled at the cellular level. Clinical data demonstrating male/female differences in atherosclerotic disease and fibromuscular dysplasia should be considered in developing hypotheses and experimental plans.

Development of improved animal models that better mimic the human conditions in RVHT is an area of research that could help contribute to basic knowledge. Such models would ideally be specific to disturbed renal responses, including tubular function and humoral mechanisms. Of special value would be a cellular biologic component capable of elucidating the role of pressor and depressor hormones at the cellular and tissue levels.

When noting these important problem areas, the workshop participants recognized that the areas were too complex to do much more than identify them in general terms. Their strongest recommendation, therefore, was for a continued multidisciplinary assessment and discussion of the areas identified by workshop participants, which may lead to specific recommendations for future research opportunities.

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