Acknowledgement

First great thanks to "Allah" who gave me the power to complete this work. Without his care nothing could be achieved.

I would like to express my greatest gratitude to **Prof. Dr.Mohammed El-Tayeb Nasser,** Professor of Internal Medicine and Nephrology – Ain Shams University, for his constant encouragement, unlimited help, stimulation, suggestions, excellent advice and constant support.

I am much thankful to **Prof. Dr.Mohammed Mahmoud Abdel Ghany,** Professor of Internal Medicine and Nephrology, Faculty of Medicine – Ain Shams University, for his kind supervision, valuable advices and continuous help throughout this work.

To ***My Daughter Malk,*** who is the sun of my life. To ***My Parents*** who have the great effect and support in all my life. To ***all My Family***.

RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY

Essay

Submitted For Partial Fulfillment of Master Degree in
Nephrology

By

Mahmoud Abdallah Mahmoud Amer
M.B.,B.Ch & M.Sc of Internal Medicine

Under Supervision Of

Prof. Dr.Mohammed El-Tayeb Nasser

Professor of Internal Medicine and Nephrology

Faculty of Medicine – Ain Shams University

Prof. Dr.Mohammed Mahmoud Abdel Ghany

Professor of Internal Medicine and Nephrology

Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2012

أرتفاع ضغط الدم الناتج عن انسداد شرايين الكلى والأعتلال الكلوى الناتج عن قصور الدورة الدموية للكلى

رسالة

توطئة للحصول على درجة الماجستير فى أمراض الكلى

مقدمة

من الطبيب / محمود عبدالله محمود عامر

بكالريوس الطب و الجراحه – ماجستير أمراض الباطنة العامة

تحت إشراف

الأستاذ الدكتور/ محمد الطيب ناصر

أستاذ أمراض الباطنة و الكلى

كلية الطب - جامعة عين شمس

الأستاذ الدكتور/محمد محمود عبد الغنى

أستاذ أمراض الباطنة والكلى

كلية الطب - جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠١٢

Introduction

Managing renovascular hypertension and ischemic nephropathy continues to present major clinical challenges to nephrologists. Aging population demographics coupled with advances in imaging technology and intensive medical therapy must be considered in the context of rapidly evolving techniques of renal revascularization. While recent trial data fail to provide compelling evidence in favor of endovascular stenting for many patients with atherosclerotic disease, experienced clinicians recognize that renal revascularization in these disorders sometimes should be undertaken to both improve hypertension and salvage renal function. Selecting patients and determining optimal timing for vascular intervention at reasonable risk is rarely simple ***(Textor, 2005).***

The study and treatment of renovascular disease overlaps many medical disciplines and subspecialties including nephrology, internal medicine, cardiovascular diseases, interventional radiology, and vascular surgery. These subspecialty groups often deal with widely different patient subgroups and clinical issues that shape different points of view. Cardiologists, for example, more commonly manage patients with refractory congestive heart failure at risk for flash pulmonary edema ***(Textor, 2005).***

In contrast, internists deal with established hypertensive patients with progressive hypertension or an increase in serum creatinine. Nephrologists may encounter declining kidney function with high-grade stenosis to a solitary functioning kidney. All of these conditions can represent clinical manifestations of renovascular disease but present different comorbid risk and management issues. Not surprisingly, perceptions related to renovascular hypertension and ischemic nephropathy sometimes differ even among informed clinicians ***(Textor, 2005).***

Initial results from prospective, randomized trials, such as the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) in the UnitedKingdom and Cardiovascular Outcomes in Renal Artery Lesions (CORAL) in the United States comparing optimal medical therapy with or without endovascular stent procedures continue to provoke controversy. The fact that National Institutes of Health review committees concluded that the role of stenting is in *equipoise*, such that randomization is ethical and appropriate, underscores the ambiguity clinicians encounter in practice ***(Textor, 2005).***

Ultimately, renovascular disease threatens blood flow to the kidney. The consequences of impaired blood flow not only affect blood pressure and cardiovascular risk, but also threaten the viability of the kidney. It can lead to irreversible loss of kidney function, sometimes designated *ischemic nephropathy*

or *azotemic renovascular disease*. Restoring blood flow and perfusion by relieving vascular occlusion intuitively offers a means to reverse this process ***(Textor, 2005).***

It must be recognized, however, that renal revascularization is a two-edged sword. The benefits include the potential to improve systemic arterial blood pressures and to preserve or salvage renal function. The potential risks of renal intervention are all too familiar to nephrologists. Endovascular procedures themselves may threaten the affected kidney through vascular thrombosis, dissection, restenosis, contrast exposure, or atheroemboli. These events sometimes precipitate the need for renal replacement therapy, including dialysis or transplantation. It is therefore important that nephrologists have a solid foundation related to the implications of reduced renal perfusion and the risks and benefits of both medical management and restoration of renal artery patency ***(Textor, 2005).***

Historical Perspective for Renovascular Diseases

Early observations regarding blood pressure regulation revealed important connections between fluid volume, renal arterial pressures, and vascular resistance.The sequence of these observations related to elaboration of the renin angiotensin-aldosterone system has been reviewed. In 1898, Tigerstedt and Bergman established that extracts of the kidney had pressor effects in the whole animal and are credited with the identification of renin. Identification of each component of the renin-angiotensin system represents a remarkable series of research ventures by investigators in many countries spanning a half-century ***(Basso N& Terragno, 2001).***

Goldblatt and others provided seminal experiments, published between 1932 and 1934, with the development of an animal model in which reduced renal perfusion regularly produced hypertension. Numerous investigators, thereafter, identified the peptide nature of angiotensin, the role of *renin-substrate* or angiotensinogen, the role of nephrectomy in sensitizing the animal to the pressor effects of angiotensin, and the sequential "phases" of renovascular hypertension. Hence, the renin-angiotensin system owes its initial discovery and nomenclature primarily to early studies related to regulation of blood pressure by the kidney ***(Textor, 2007).***

Only recently have many additional actions of angiotensin become evident regarding vascular remodeling, modulation of inflammatory pathways, and interaction with fibrogenic mechanisms. Understanding that reduced renal blood flow produces sustained elevations in arterial pressure led to broad study of the mechanisms underlying many forms of hypertension. Experimental models of two-kidney and one-kidney renal clip (two-kidney and one-kidney *Goldblatt hypertension*) represent some of the most extensively studied models of blood pressure and cardiovascular regulation ***(Textor, 2007).***

Extension of these studies into clinical medicine followed soon thereafter. Some forms of hypertension were designated as "malignant" in character during the late 1930s and 1940s based on poor survival if patients were untreated. Few antihypertensive agents were known until the 1950s, and intervention consisted mainly of lumbar sympathectomy and/or extremely low sodium intake diets ***(Textor, 2007).***

Recognition that some forms of severe hypertension were secondary to occlusive vascular disease in the kidney led surgeons to undertake unilateral nephrectomy for small kidneys in 1937.The fact that some of these were indeed "pressor" kidneys and blood pressure fell to normal levels provided "proof of concept" and led to more widespread use of nephrectomy. Unfortunately, achieving "cure" of hypertension

after nephrectomy was rare, and Homer Smith reviewed the poor results associated with nephrectomy in a 1956 paper. His overview of these collective findings discouraged this practice ***(Stanley, 1997).***

The 1960s marked the introduction of methods of vascular surgery to restore renal blood flow. These carried substantial morbidity, but offered an opportunity to improve renal circulation and potentially to reverse renovascular hypertension. One result of this development was a series of studies to characterize the functional role of each vascular lesion in producing hypertension, thereby allowing prediction of the outcomes of vascular surgery ***(Stanley, 1997).***

A large, Cooperative Study of Renovascular Hypertension, which included major vascular centers, reported on the results of more than 500 surgical procedures. These results provided limited support for vascular repair. Rather, the results identified relatively high associated morbidity and mortality with vascular repair, particularly in patients with atherosclerotic disease ***(Stanley, 1997).***

In the 1980s and 1990s further developments led to both improved medications and the introduction of endovascular procedures, including percutaneous angioplasty and stents. These both broadened the options for treating patients with vascular disease and raised new issues regarding timing and

overall goals of intervention. Recent developments highlight the need for intensive cardiovascular risk-factor reduction and more stringent standards of blood pressure control. Antihypertensive medications have improved dramatically, both with regards to efficacy and tolerability. As emphasized below, broad application of angiotensin converting enzyme inhibitors and angiotensin receptor antagonists, for reasons other than hypertension alone, changed the clinical presentation of disorders associated with renal artery stenosis ***(Garovic and Textor, 2005)***.

Uncontrollable hypertension is now an uncommon reason to intervene in renovascular disease. Often the main objective is the long-term preservation of renal function. In recent years, newer endovascular techniques make renal revascularization possible in patients previously considered unacceptable surgical candidates. The challenge for clinicians is how and when to apply these tools most effectively in the management of individual patients ***(Garovic and Textor, 2005).***

Pathophysiology of Renovascular Hypertension and Ischemic Nephropathy

As with most vascular lesions, the presence of a renovascular abnormality alone does not translate directly into functional importance. Some degree of renal artery stenosis can be identified in as many as 20% to 45% of patients undergoing vascular imaging for other reasons, such as coronary angiography or lower extremity peripheral vascular disease.Most of these incidentally detected stenoses are of little or no hemodynamic significance. Failure to limit treatment trials to patients with hemodynamically important lesions has been a serious barrier to understanding the role for renal revascularization ***(Conlon et al., 2000).***

The term *renovascular hypertension* refers to a rise in arterial pressure induced by reduced renal perfusion. A variety of lesions can lead to the syndrome of renovascular hypertension. Strictly speaking, the diagnosis of renovascular hypertension is established only in retrospect after successful reversal of hypertension with revascularization. Studies of vascular obstruction using latex rubber casts indicate that between 70% and 80% of lumen obstruction must occur before measurable changes in blood flow or pressure across the lesion can be detected ***(De Bruyne et al., 2006).***

Measurements of pressure gradients undergoing renal angiography confirm that a pressure gradient of at least 10 to 20 mm Hg between the aorta and the post stenotic renal artery is required before measurable release of renin develops. When advanced stenosis is present, the decrease in pressure and flow develops steeply. When lesions have reached a degree of hemodynamic significance, they are deemed to have reached *critical* stenosis ***(De Bruyne et al., 2006).***

When renal artery lesions reach critical dimensions, a series of events leads to a rise in systemic arterial pressure and restoration of renal perfusion pressure Hence, one can view the development of rising pressures in this context as an integrated renal response to maintain renal perfusion. It is important to distinguish between experimental models of clip stenosis, at which time a sudden change in renal perfusion is induced, and the more common clinical situation of gradually progressive lumen obstruction ***(Lerman et al., 1999).***

In the latter instance hemodynamic characteristics change slowly and are likely to produce hypertension over a prolonged time interval. The rise in systemic pressure restores normal renal perfusion, often with normal-sized kidneys and no discernible hemodynamic compromise ***(Lerman et al., 1999).***

If the renal artery lesion progresses further (or is experimentally advanced), the cycle of reduced perfusion and

rising arterial pressures recurs until malignant phase hypertension develops. Recent experimental swine models emphasize gradually progressing vascular lesions that mimic human renovascular disease.A corollary to critical arterial stenosis is that reduction of elevated systemic pressures to normal in renovascular hypertension reduces renal pressures beyond the stenotic lesion. Poststenotic pressures may fall below levels of autoregulation that maintain blood flow. This underperfusion of the kidney activates counter regulatory pathways and leads to a sequence of events directed toward restoring kidney perfusion ***(Lerman et al., 1999).***

Vascular Lesions Producing Renal Hypoperfusion and the Syndrome of Renovascular Hypertension. Unilateral Disease (Analogous to One-Clip–Two-Kidney Hypertension):

- Unilateral atherosclerotic renal artery stenosis
- Unilateral fibromuscular dysplasia (FMD)
- Medial fibroplasia
- Perimedial fibroplasia
- Intimal fibroplasia
- Medial hyperplasia
- Renal artery aneurysm
- Arterial embolus
- Arteriovenous fistula (congential/traumatic)
- Segmental arterial occlusion (posttraumatic)

- Extrinsic compression of renal artery, e.g., pheochromocytoma
- Renal compression, e.g., metastatic tumor

(Lerman et al., 1999).

Bilateral Disease or Solitary Functioning Kidney (Analogous to One-Clip–One-Kidney Model):

- Stenosis to a solitary functioning kidney
- Bilateral renal arterial stenosis
- Aortic coarctation
- Systemic vasculitis (e.g., Takayasu's arteritis, polyarteritis)
- Atheroembolic disease
- Vascular occlusion due to endovascular aortic stent graft

(Lerman et al., 1999).

Role of the Renin-Angiotensin System in One-Kidney and Two-Kidney Renovascular Hypertension

Reduction in renal perfusion pressures activates the release of renin from juxtaglomerular cells within the affected kidneys. Experimental studies indicate that hypertension in two-kidney– one-clip models can be delayed indefinitely so long as agents that block this system are administered, Animals

genetically modified to lack the angiotensin (AT1) receptor fail to develop two-kidney-one-clip hypertension. Experiments using kidney transplantation from AT1 receptor knockout mice indicate that both systemic and renal angiotensin receptors participate in an additive fashion to blood pressure regulation ***(Cervenka et al., 2002).***

Demonstration of the role of the renin-angiotensin axis in renovascular hypertension depends in part on whether or not a contralateral, nonstenotic kidney is present. Classically, human renovascular hypertension is considered analogous to two-kidney–one-clip experimental (Goldblatt) hypertension. The contralateral, nonstenotic kidney is subjected to elevated systemic perfusion pressures as shown in (table 1). Effects of rising perfusion pressure are to force natriuresis from the nonstenotic kidney and to suppress renin release. Hence, the nonstenotic kidney tends to prevent the rise in systemic pressures, thereby perpetuating reduced perfusion to the stenotic side and fostering continued renin release from the stenotic kidney ***(Crowley et al., 2005).***

Blood pressure in these models is demonstrably angiotensin-dependent and associated with elevated circulating levels of plasma renin activity. The two-kidney–one-clip model of renovascular hypertension provides the basis for many of the early functional studies of surgically curable hypertension in which side-to-side function was compared (e.g., glomerular