

Diagnostic aspects of renovascular hypertension

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SUMMARY

After a brief introduction to the studies described in this thesis, in

Chapter II an overview of the epidemiology, clinical features and natural history, screening and diagnostic procedures, and therapeutic intervention in renovascular hypertension is given.

Chapter III to XI deal with the various studies that have been performed and the main questions that were addressed in these studies are formulated.

Chapter III

Is the fall in blood pressure during a 30 minute registration period with an automatic device different in patients with EH from the one in patients with renovascular hypertension?

It is known that casual (office) blood pressure readings are unreliable due to the so-called cuff response. To be better informed about a patient's blood pressure, automatically assessed recordings are often necessary. It is usually assumed that a cuff response occurs mainly in patients with essential hypertension (EH), but there is no compelling data to show that this phenomenon is less prevalent in subjects with renovascular hypertension, in whom a more sustained and higher blood pressure might be anticipated.

In a comparative study of automatically assessed blood pressure recordings in patients with EH (n=19) and renovascular hypertension (n=19), the difference between office and automatically assessed blood pressure during 30 min. appeared to be similar in both groups. The number of patients showing a pressure drop greater than 10 mmHg also was comparable in both groups. Blood pressure levels obtained in the office were found to overestimate "true" blood pressure not only in essential but also in renovascular hypertension.

Chapter IV

Can we identify hypertensive patients with renal artery stenosis by means of presenting clinical signs and symptoms or with combinations of these, and what is the value of renography as a screening test in such a selected population?

Selecting patients on the basis of clinical clues (as have been formulated by the Working Group on Renovascular Hypertension in their final report in 1987) resulted in a high prevalence (41%) of angiographically proven RAS. A history of smoking with a diastolic blood pressure above 110 mmHg was found to be a very sensitive clue for renovascular hypertension and the more clinical clues a hypertensive patient has the more likely a diagnosis of RAS is. All patients with more than 3 clinical clues had RAS and patients a "small kidney on ultra-sound" and an additional clinical clue had a 54% probability of RAS, while patients with a "small kidney on ultra-sound" and no additional clinical clue had a 100% probability of not having RAS.

Renography (both baseline and post-captopril) was of minimal value in this selected population. A positive renogram did have the best diagnostic accuracy in those patients who had signs of atherosclerotic disease with a post-test probability of a positive renogram of 78%.

Chapter V

What is the smallest degree of renal artery stenosis that may be associated with changes in renographic characteristics?

In the literature there is no consensus about what percentage of renal arterial narrowing should be considered hemodynamically significant in patients with renovascular disease.

From this point of view it would be of interest to relate the angiographic findings of different patients to their renographic characteristics in order to establish the smallest degree of renal artery stenosis that may be associated with changes in renographic characteristics.

We related the angiographic severity of luminal narrowing in renal artery stenosis to 131 I-hippuran

renographic characteristics in 72 patients who had been selected for renal angiography because a diagnosis of renovascular hypertension was suspected. Comparing non-stenotic kidneys with stenotic kidneys, significant differences in T_{max} , $T_{1/2}$ and counts under the curve to T_{max} were apparent already at 30% of arterial luminal narrowing. In patients with unilateral renal artery stenosis, the difference in counts under the curve to T_{max} between pairs of kidneys also was significantly different at 30% of stenosis.

The study also showed that patients with bilateral stenosis could not be differentiated well from patients with essential hypertension because the value of T_{max} on either side or the difference of T_{max} between the two kidneys and the values of the other parameters were similar except for the difference in counts to T_{max} . On the basis of these findings it seems that in renographic terms bilateral RAS does not "mimic" unilateral stenosis, but rather resembles a normal situation. Thus, in renal artery disease significant renographic changes can occur already at 30% of arterial luminal narrowing.

Chapter VI

What is the diagnostic performance of nuclear medicine physicians with respect to their interpretation of baseline, captopril and paired renograms and how do these results relate to renal angiography?

Numerous reports have documented a sensitivity and specificity ranging from 50%-95% for baseline and post-captopril renography as a screening test for renal artery stenosis.

Nuclear medicine physicians interpreting renograms base their conclusions on visual interpretation and on some established criteria for making a diagnosis of renal artery stenosis.

The diagnostic performance of experienced nuclear medicine physicians with respect to their interpretation of baseline, captopril and paired renograms, however, has not been prospectively assessed in relation to the results of renal angiography, the so-called "gold standard".

The results of our study showed that the concordance in the renographic diagnoses of 56 renograms between three experienced nuclear medicine physicians was reasonably good, with an intra-observer agreement and κ ranging from 64%-89% and from 0.52-0.75 respectively and an inter-observer agreement and κ ranging from 68%-86% and from 0.61-0.82 respectively. However, the sensitivity of their interpretation of paired baseline plus captopril renograms in relation to the angiographic diagnosis was poor and below 50%.

The post-test probability of RAS in case of a negative renographic study was found to be rather similar to the pre-test probability (prevalence) of 46%. The post-test probability of RAS when the paired renogram was positive increased to around 60% when the readers were blinded as to which renogram was the one after captopril but decreased below 25% when they were aware of which of the two renograms was obtained after captopril.

Chapter VII

Are measurements of renal blood flow from first-pass radionuclide angiography are performed in hypertensive patients in whom a diagnosis of renovascular hypertension is suspected helpful to detect renal artery stenosis?

In 1987, Peters and co-workers described a technique for noninvasive measurement of organ blood flow, which was based on the fractional distribution of cardiac output. When applied to the renal circulation, measurements of individual kidney blood flow may indicate whether a renal artery stenosis is present or not.

We performed measurements of renal blood flow from first-pass radionuclide angiography in 29 patients with EH and in 19 patients with RAS. In patients with normal kidneys the mean value of renal blood flow (RBF) measurements ranged from 10.5% to 10.9% of cardiac output. Only small stenotic and small kidneys with normal renal arteries showed a significant reduced baseline RBF as compared with normal kidneys; this difference disappeared after ACE-inhibition only for small kidneys with normal renal arteries.

In patients with stenosed kidneys RBF tended to be reduced both at baseline and after captopril, but the differences with normal kidneys were not statistically significant. After ACE-inhibition RBF increased in the majority of kidneys, but post-captopril RBF data did not differ significantly from those at baseline.

We conclude that RBF measurements using first-pass radionuclide angiography with $^{99m}\text{Tc-MAG-3}$ either before or after ACE-inhibition cannot reliably discriminate between patients with essential hypertension and patients with renal artery stenosis.

Chapter VIII

When hypertensive patients are selected on the basis of presenting clinical clues suggestive for renovascular hypertension, what will be the performance of the captopril test?

Since there is no pathognomonic sign or clinical clue identifying renal artery stenosis in hypertensive patients, a single noninvasive diagnostic test, easily performed in a outpatient facility and with a high predictive value would be the ideal screening test.

Angiotensin converting enzyme inhibitors given to hypertensive patients may enable the clinician to distinguish patients with EH from those with hypertension and renal artery stenosis. The so-called captopril test is a practical but controversial screening test studying the effect of ACE inhibition on blood pressure (magnitude and duration of fall in blood pressure) and changes in renin levels. From the results of the captopril test on these two parameters it may be possible to identify patients with renovascular hypertension.

After placebo and after captopril no significant changes (absolute or proportional) in blood pressure values were found between patients with EH ($n=26$) or RAS ($n=20$), either for all measurements or if only the fall in blood pressure was taken into account.

Receiver operator characteristic curves of both baseline and post-captopril peripheral renin levels were constructed, which indicate that the captopril test does not discriminate appropriately between patients with EH and RAS. Therefore, we would not advise the use of the captopril test as a screening test for RAS in hypertensive patients in whom a high level of clinical suspicion for RAS is already present.

Chapter IX

Are endothelin levels elevated in renovascular hypertension and is there a difference in renal extraction between kidneys of patients with essential hypertension compared to kidneys with a renal artery stenosis?

Circulating endothelin has been suggested to play a role in local vascular regulation.

As such it could be involved in the pathogenesis and maintenance of renovascular hypertension.

In our study endothelin levels and renal endothelin extraction were found to be comparable in EH and in hypertension associated with renal artery stenosis. Whereas renal uptake of endothelin was the rule, some kidneys, however, released this peptide irrespective of presence or absence of RAS. It is of interest that all kidneys with a normal blood supply released endothelin.

Chapter X

Are elevated levels of atrial natriuretic peptide in renovascular hypertension due solely to increased secretion or is an alternation in the renal extraction of this peptide responsible for this phenomena?

We studied the relationship between the renal fractional extraction of atrial natriuretic peptide (ANP) and renin in untreated patients under standardized conditions.

Arterial levels of ANP were found to be significantly higher in patients with unilateral or bilateral RAS than in patients with EH. Patients with EH and left ventricular hypertrophy (LVH) had a significantly higher arterial ANP level than those with no LVH but in patients with RAS, arterial ANP levels were similar between those with or without LVH.

Renal venous ANP levels were significantly higher in stenotic kidneys than in normal kidneys but

fractional extraction of ANP was similar around 0.50 (range from 0-0.83) in normal kidneys of patients with EH, and in stenotic and contralateral kidneys of patients with RAS. A significant correlation between arterial ANP and the arterio-venous difference of ANP was found. This relationship was similar for normal and for stenotic kidneys. The data of our study suggest that saturation of ANP extraction through the kidneys does not occur and probably is independent of renal blood flow.

Chapter XI

What is the diagnostic performance in terms of intra- and inter-observer agreement of experienced radiologists with respect to their interpretation of renal angiography?

Little is known about the accuracy of the interpretation of renal angiograms by radiologists. This is surprising as clinical decisions about surgical correction or angioplasty of a stenotic lesion in the renal artery often are based on the radiologist's interpretation of the angiogram. Can renal angiography really be considered the "gold standard"?

In this study on the diagnostic performance of three radiologists the difference between two estimates of the degree of stenosis ranged from 0 to 65% for the individual readers and from 0 to 75% between two readers.

Bland-Altman plots showed that, although the average difference between two estimates of individual readers or of pairs of readers is small and less than 10%, the standard deviation is considerable, ranging from 17-23%.

A post-hoc analysis using two different cut-off points of stenosis (50% or 75%) showed that intra- and inter-observer agreement ranged from 77-85% with a κ ranging from 0.71-0.78 when stenoses of more than 50% were considered abnormal, whereas, when a stenosis of more than 75% was considered to be abnormal, the intra-observer agreement ranged from 86-94% with a κ ranging from 0.86-0.91. In this case the inter-observer agreement ranged from 83-91% with a κ ranging from 0.74-0.81.

The results of our study on the diagnostic performance of these three experienced radiologists in their interpretation of renal artery angiograms indicate that the intra- and inter observer agreement with respect to their estimates of the degree of stenosis and the site of greatest stenosis are rather poor.

SAMENVATTING

Na een korte inleiding wordt in **hoofdstuk II** een overzicht gegeven van epidemiologie, natuurlijk beloop, klinische aspecten, screenings-testen en therapie van renovasculaire hypertensie.

Hoofdstuk III betreft een onderzoek waarin gekeken wordt naar bloeddruk patronen gedurende 30 min. automatische bloeddrukmetingen bij patiënten met essentiële hypertensie (EH) en patiënten met een stenose van de nierarterie (RAS). De resultaten tonen aan dat er geen significante verschillen in bloeddruk patronen zijn en dat het aantal patiënten met een bloeddruk daling van meer dan 10 mmHg tijdens automatische bloeddruk meting (een maat voor de zogenaamde cuff response?) vergelijkbaar is. Overigens blijken bij incidentele metingen van de bloeddruk hogere bloeddruk waarden te worden gevonden in beide groepen patiënten.

In **hoofdstuk IV** wordt een onderzoek beschreven waarbij is gekeken naar de waarde van klinische karakteristieken (zoals aangegeven door de Working Group on Renovascular Hypertension in 1987) bij de selectie van patiënten met hypertensie. In de groep van patiënten geselecteerd op basis van deze karakteristieken vinden wij een hoge prevalentie van RAS, nl. 46%. De meest gevoelige combinatie van karakteristieken blijkt te zijn: roken tezamen met een diastolische bloeddruk van meer dan 110 mmHg.

Verder blijken alle patiënten met meer dan drie karakteristieken RAS te hebben. In de groep van patiënten met "één kleine nier bij echografie" blijken diegenen die er nog een andere karakteristiek bij hadden een 54% waarschijnlijkheid op RAS te hebben, terwijl diegenen zonder een extra karakteristiek geen RAS te hebben.

Renografisch onderzoek heeft als screenings test dan ook vrijwel geen waarde bij deze patiënten. Aangezien niet goed bekend is bij welke mate van vernauwing van een nier-arterie significant hemodynamische veranderingen optreden, onderzochten we in **hoofdstuk V** bij 72 patiënten wanneer renografische veranderingen optreden.

Het blijkt dat significante renografische veranderingen al bij 30% vernauwing van een arterie kunnen optreden.

In **hoofdstuk VI** worden de resultaten van het onderzoek naar de diagnostische vaardigheden van drie nucleair geneeskundigen gegeven bij de beoordeling van 28 basale en 28 captopril renogrammen. Wat betreft de renografische diagnose blijken zij het redelijk goed met elkaar eens te zijn. Echter, als men hun renografische beoordeling vergelijkt met de resultaten van röntgenologisch onderzoek (angiografie), hetgeen als de gouden standaard kan worden beschouwd, dan blijken de beoordelingen van de nucleair geneeskundigen een sensitiviteit van minder dan 50% te hebben.

In 1987 werd een nieuwe methode beschreven voor het meten van de bloed-doorstroming door de nier met behulp van nucleaire angiografie. In **hoofdstuk VII** geven we de resultaten van metingen met deze techniek bij 48 patiënten met hoge bloeddruk. Metingen van de bloeddruurstroming van de nieren werden verricht om te zien of veranderingen in de doorstroming na toediening van captopril gebruikt kunnen worden voor de diagnostiek van vernauwing in de nier slagader.

Na toediening van captopril worden met deze techniek echter geen significante verschillen in de bloed doorstroming van de nieren tussen patiënten met EH en die met RAS waargenomen.

De captopril test is een test die gebruikt wordt om patiënten met hoge bloeddruk te screenen op de eventuele aanwezigheid van RAS. De vraagstelling in **hoofdstuk VIII** is of bij patiënten die geselecteerd zijn op grond van klinische karakteristieken zoals beschreven in hoofdstuk IV, de captopril test nog een aanvullende waarde heeft.

Het blijkt dat de captopril test (veranderingen in bloeddruk en in renine spiegels) bij deze patiënten van weinig waarde is.

Endotheline is een hormoon dat een (plaatselijke) werking heeft op de bloedvaten. Het is mogelijk dat endotheline een rol speelt bij hypertensie ten gevolge van RAS. Om beter inzicht in de werking van endotheline bij RAS (**hoofdstuk IX**) te verkrijgen onderzochten we de extractie van dit

hormoon in patiënten met RAS en met EH. De extractie van endotheline door de nieren bleek niet significant verschillend te zijn bij deze patiënten, echter alle kleine nieren van mensen met EH gaven endotheline af aan de circulatie.

Atriaal natriuretisch hormoon (ANP) is afkomstig uit de voorkamers van het hart en speelt een rol bij o.a. de vocht/volume regulatie. Het onderzoek naar de rol van ANP (**hoofdstuk X**) in RAS toont aan dat ANP spiegels verhoogd zijn bij patiënten met RAS in vergelijking met patiënten met EH. Bij de laatste groep hebben diegenen met linker hartkamer hypertrofie (LVH) hogere ANP spiegels dan diegene zonder LVH.

De extractie van ANP door de nieren is gelijk in alle onderzochte groepen patiënten (ongeveer 50%). We konden verder aantonen dat verzadiging van extractie niet optreedt en dat de extractie waarschijnlijk niet afhankelijk is van de bloed doorstroming door de nier.

In **hoofdstuk XI** worden de resultaten van het onderzoek naar de diagnostische vaardigheden van drie röntgenologen bij de beoordeling van 50 angiogrammen van de nieren beschreven. De intra- en inter-observator overeenstemming met betrekking tot de beoordeling van de angio's t.a.v de graad van vernauwing van een nier slagader varieert respectievelijk van 0-65% en van 0-75%.

In een post-hoc analyse, waarbij een graad van vernauwing groter dan 50% of groter dan 75% als klinisch significant wordt beschouwd bleek de intra- en inter-observator overeenkomst te variëren respectievelijk van 77-85% met een κ variërend van 0.71-0.78 en van 83-94% met een κ van 0.74-0.91. Deze gegevens wijzen erop dat de beoordeling van angio's door röntgenologen te wensen overlaat.