Pediatr Nephrol (2004) 19:66–70
DOI 10.1007/s00467-003-1285-z

ORIGINAL ARTICLE

Edda Lagomarsino · Pilar Orellana · Jaime Muñoz · Claudia Velásquez · Felipe Cavagnaro · Francisco Valdés

Captopril scintigraphy in the study of arterial hypertension in pediatrics

Received: 29 July 2002 / Revised: 14 July 2003 / Accepted: 14 July 2003 / Published online: 25 November 2003

Abstract Renovascular hypertension (RVH) is responsible for 10% of arterial hypertension in children. The early diagnosis of RVH permits specific treatment leading to the cure of hypertension and avoidance of parenchymal damage. Captopril renal scintigraphy (CRS) provides information on the renovascular cause of the arterial hypertension. To validate the usefulness of CRS in hypertensive children, clinical, scintigraphic, and radiological data from 20 patients (mean age 6.1±5.5 years) were reviewed. Two patients were newborns. All had renal ultrasound scans and 9 had aortograms. In 7 children, RVH was confirmed by angiography, and CRS was positive for RVH in 6 of these. CRS was negative for RVH in 12 of 13 children without RVH. CRS was non-diagnostic in 3 children with abnormal baseline renal scintigraphy and severely decreased relative renal function (<35%), 1 of whom had RVH. No side effects of captopril renography were observed. Captopril renography provides a logical, non-invasive, safe, and cost-effective approach in the evaluation of children suspected of having RVH.

E. Lagomarsino · P. Orellana · J. Muñoz · F. Cavagnaro
Department of Pediatrics, School of Medicine,
Catholic University of Chile,
Santiago, Chile

P. Orellana · C. Velásquez
Department of Radiology, Nuclear Medicine Section,
School of Medicine,
Catholic University of Chile,
Santiago, Chile

F. Valdés
Cardiovascular Section, Surgery Division, School of Medicine,
Catholic University of Chile,
Santiago, Chile

P. Orellana (✉)
Nuclear Medicine Section,
Catholic University Hospital,
Marcoleta 347, Santiago, Chile
e-mail: pilar@med.puc.cl
Tel.: +56-2-3543277
Fax: +56-2-6333266

Keywords Pediatric arterial hypertension · Renovascular hypertension · Renal scintigraphy · Captopril

Introduction

Arterial hypertension in children has a prevalence of 1%–3% and is caused mainly by renal disease [1]. Renovascular hypertension (RVH), defined as arterial hypertension in association with renal artery stenosis and hypertension, improves when the morphological abnormality is repaired. It is an important cause of infantile arterial hypertension and accounts for 5%–25% of all cases studied by arteriograms [2, 3, 4]. The most frequent cause of hypertension in newborns is renal vascular thrombosis [5]. Much attention has been focused on this form of secondary hypertension because it is potentially curable. The early diagnosis of RVH permits specific treatment to cure arterial hypertension. Therapy with beta-blockers, calcium antagonists, and angiotensin-converting enzyme inhibitors (ACEI) has also facilitated pharmacological control of this entity [1, 2, 4].

Many tests are available for the evaluation of RVH. Conventional angiography has traditionally been used to diagnose renal artery stenosis in adults. However, this invasive test usually requires hospitalization and general anesthesia or deep sedation is often necessary in younger patients. For these reasons, it is not universally performed for the evaluation of pediatric hypertension [6].

Several non-invasive techniques have been advocated for the diagnosis of RVH, but their accuracy varies widely [7, 8, 9, 10]. Renal scintigraphy evaluates perfusion and renal function, and when associated with ACEI suggests a renovascular cause of arterial hypertension. Renal scintigraphy with ACEI is now recognized as having a high sensitivity and specificity in the diagnosis of RVH [7, 8, 9, 10, 11].

Most isotopic studies with ACEI have been performed in adults, and these indicate sensitivity and specificity in the range of 60%–100% and 70%–100%, respectively, in the detection of renovascular disease [7, 8, 9, 10, 11].

There is scarce experience in the use of these procedures in the pediatric population and especially in newborn patients [12, 13, 14, 15].

The purpose of this retrospective case series was to describe our experience with the use of captopril renal scintigraphy (CRS) in the evaluation of hypertension in the pediatric population: newborns, infants, and children.

Patients and methods

Among 29 CRS procedures performed in children from 1995 to 2000, we retrospectively evaluated 20 hypertensive children [16 males, 4 females, mean age 6.1 years (range 12 days to 15 years)] suspected of having RVH, all presenting with blood pressure readings equal to or greater than the 95th percentile for age- and gender-adjusted standards in patients less than 1 year of age, and age-, height-, and gender- adjusted standards for older children [16]. Clinical examination, hematological analysis, biochemical analysis, urinalysis, renal ultrasonography, and CRS were performed in all patients. Arteriography was performed in 9 children with sustained and severe hypertension, in whom no other cause was identified, and/or in children with a high index of clinical suspicion of RVH [1]. The children not included in this evaluation did not have a complete follow-up.

In the classification of patients, their clinical antecedents, presence of significant renovascular stenosis, and post-therapy outcome was considered. We considered a diagnosis of RVH when there was hypertension associated with an anatomical lesion and decreased blood pressure after revascularization. In patients who remained on drug therapy after correction of their lesions, clinical improvement was considered when they were on fewer hypertensive medications or lower doses of the same medicine. In those children without arteriography, RVH was ruled out according to their clinical antecedents and evolution.

Captopril renal scintigraphy

Antihypertensive drugs were not discontinued prior to CRS, except for diuretics (48 h) and ACEI drugs (72 h). No child was on angiotensin II blockers. Patients were orally hydrated (10 ml/kg of body weight) 30 min before the scintigraphic study. The patient was placed in the supine position and 99m-technetium diethylene triamine penta-acetic acid (Tc99m DTPA) or Tc99m mertitatide (MAG3) was injected, at a dose according to an international scale [17]. A baseline renal scintigraphic study was performed; 2–24 h later captopril scintigraphy was done. Captopril was administered orally at a dose of 0.5–0.7 mg/kg. With the patient in the supine position, blood pressure was recorded at baseline and every 15 min for 1 h after captopril administration, with the patient continuing fluid intake (10 ml/kg of body weight). The radiopharmaceutical was administered 1 h after the captopril dose, followed by standard image acquisition. Both studies were performed with the gamma camera facing the lower back of the supine patient. Kidneys and bladder were in the field of view. Scintigraphic sequential images were acquired; 30 s/image per 20 min. No sedation was used, but motion was restricted.

The scintigraphic parameters analyzed at baseline and post captopril scintigraphy were: visual assessment of kidney size, time to peak activity, urinary excretion, parenchymal retention (MAG3), relative renal function, and overall pattern of the renographic curve.

The general interpretative criteria of scintigraphic study associated with RVH included: worsening of the renogram curve, reduction in relative renal uptake (>10%), prolongation of the time to peak activity time of at least 2 min, increase in the time of parenchymatous transit, and abolition or decrease of urinary excretion [18].

Scintigraphic results were interpreted as consistent with high or low probability of disease or non-diagnostic [18]:

Low probability (<10%):
normal findings post captopril scintigraphy or abnormal baseline findings that improve after ACEI.

Non-diagnostic (intermediate probability):
abnormal baseline findings without modification after ACEI; decreased renal function; small kidney with severely decreased function (relative renal function <35%).

High probability (>90%):
marked change of the renogram after ACEI compared with baseline findings.

No statistical analysis was performed because of the small number of children evaluated.

Results

Clinical data for the 20 subjects included in the review are summarized in Table 1. Asymptomatic hypertension was found in 50% of the population studied. In the rest, the main clinical symptom was headache, which was present in 33% of the group. Other clinical symptoms were vascular bruits and epistaxis. It is important to mention that 1 child presented in the emergency room with congestive cardiac insufficiency and another child presented with cardiac arrest. Neither had previous clinical symptoms. Symptoms were more frequent in children with RVH (85.7%) than children with non-RVH (30.7%).

Doppler renal ultrasonography was performed in 4 children. It was positive in 1 child with left renal artery stenosis. In 3 children without RVH, it was normal in 1, non-diagnostic in 1, and abnormal in 1. The remaining 16 children had standard renal ultrasonography that showed a small hypoplastic kidney in 3.

A renovascular origin of hypertension was confirmed in 7 of 20 hypertensive patients (Table 1). CRS showed a high probability for RVH in 6 (Table 2). The child with RVH and a non-diagnostic CRS had an abnormal baseline study without modification after captopril administration, with severely diminished relative renal function. The angiogram showed fibromuscular dysplasia associated with renal atrophy.

Among the 13 children without RVH, CRS indicated low probability in 10, high probability in 1, and was non-diagnostic in the remaining 2. In 2 newborns, CRS was normal and RVH was excluded in both. Only 1 normal kidney without RVH showed abnormal findings on CRS.

Analyzing by number of kidneys, among the 39 kidneys (1 patient with a single kidney) there were 11 kidneys with RVH confirmed by angiography. CRS showed a high probability for RVH in 10 and was non-diagnostic in the remaining kidney. In 28 kidneys without RVH, CRS was negative in 25, non-diagnostic in 2, and positive in 1. The 3 kidneys with non-diagnostic CRS had a decreased relative renal function of less than 35%. No side effects or complications secondary to the use of captopril were observed.

In the group of children with RVH, surgical revascularization was performed in 6 children and 1 child underwent balloon angioplasty. During follow-up (over 5 years), arterial pressure readings were equal to or lower

Table 1 Clinical data of 20 hypertensive children evaluated with captopril renal scintigraphy (CRS) (*RVH* renovascular hypertension, *NA* not applicable, *LK* left kidney, *RK* right kidney, *BP* blood pressure, *HP* high probability of RVH, *LP* low probability of RVH)

Age	Sex	Diagnosis	Side[a]	CRS	Treatment	Follow-up	Final diagnosis
5 years	M	Takayasu arteritis	LK	HP LK	Surgery	Normal BP with drugs[b]	RVH
6 years	F	Aortic coarctation	Bilateral	HP Bilateral	Surgery	Normal BP with drugs[b]	RVH
3 months	F	Unclassified arteritis	Bilateral	HP Bilateral	Surgery	Normal BP	RVH
6 years	M	Post-traumatic thrombus	LK	HP LK	Medical	Normal BP with drugs[b]	RVH
14 years	M	Takayasu arteritis	Bilateral	HP Bilateral	Surgery	Normal BP	RVH
9 years	M	Fibromuscular dysplasia	Bilateral	HP Bilateral	Surgery	Normal BP with drugs[b]	RVH
14 years	M	Fibromuscular dysplasia	RK	Non-diagnostic RK	Surgery	Normal BP	RVH
25 days	M	Reflux nephropathy LK	NA	LP Bilateral	Surgery[c]	Normal BP	Non RVH
15 years	M	Transient hypertension	NA	LP Bilateral	Medical	Normal BP	Non RVH
5 years	F	Acute tubular necrosis	NA	LP Bilateral	Medical	Normal BP	Non RVH
2 months	M	Transient hypertension, bronchopulmonary dysplasia	NA	LP Bilateral	Medical	Normal BP	Non RVH
12 days	F	Pulmonary hypertension, sepsis	NA	LP Bilateral	Medical	Normal BP	Non RVH
15 years	M	Chronic renal failure	NA	LP Bilateral	Medical	Normal BP	Non RVH
11 years	F	Glomerulonephritis	NA	LP Bilateral	Medical	Normal BP	Non RVH
8 years	M	Intramedullary tumor	NA	LP Bilateral	Medical	Normal BP	Non RVH
4 months	M	Transient hypertension	NA	LP Bilateral	Medical	Normal BP	Non RVH
2 months	M	Nephrocalcinosis	NA	LP Bilateral	Medical	Normal BP	Non RVH
2 months	M	Freeman Sheldan syndrome, multiple congenital anomalies	NA	HP LK	Medical	Normal BP	Non RVH
4 years	M	Hypoplasia LK	NA	Non-diagnostic LK	Medical	Normal BP	Non RVH
9 years	F	Hypoplasia LK, chronic renal failure	NA	Non-diagnostic LK	Medical	Normal BP with drugs	Non RVH

[a] According to angiography
[b] With fewer antihypertensives or lower doses of the same medications
[c] Left kidney nephrectomy due to reflux nephropathy

Table 2 CRS in children suspected of having RVH

CRS	RVH		Total
	Present	Absent	
High probability	6	1	7
Low probability	0	10	10
Non-diagnostic	1	2	3
Total	7	13	20

than the 90th percentile normal for age, height, and gender in 3 children. The other 4 children remained on fewer antihypertensive drugs or on lower doses of the same medicine.

Discussion

Renovascular disease is a frequent cause of severe secondary hypertension in children and may result in significant morbidity or mortality [1, 2, 3, 4]. However, the precise frequency of RVH is unknown, because not all hypertensive children are systematically evaluated. Since it is potentially treatable either by balloon angioplasty or surgical revascularization, it is important to identify these patients. In this regard, imaging techniques have an important role to play. The underlying principle of such tests, particularly in the pediatric population, is that they should be the least invasive and carry the least possible radiation burden.

Most children presenting with RVH have few if any symptoms. However, devastating neurological injuries and congestive heart failure are still too often observed [1]. In spite of its importance as a vital sign and as an indicator of clinical stability, blood pressure is not routinely measured in the pediatric population. It is important to measure blood pressure at least once a year in all children in the outpatient clinic [16]. As with other studies [4, 19], our experience indicates that the evolution of hypertension is asymptomatic over a long period of time. Over 50% of our group were asymptomatic and hypertension was discovered only during physical examination. Among the group of symptomatic patients, 2 had severe complications of the disease.

Hypertension was rarely reported in the newborn infant prior to 1970 [20, 21]. During the last 30 years an increasing number of cases of neonatal hypertension have been reported [5]. This increase has been associated with the use of indwelling umbilical catheters, the more frequent survival of very sick neonates, and the administration of potential hypertensive drugs (steroids, theophylline), but probably also reflects an improvement in the monitoring of arterial pressure in infants [5]. In our study none of the newborns studied with CRS had RVH. The dose of captopril used in this procedure (0.5–0.7 mg/kg) could be considered high when compared with the

usual therapeutic starting dose in this age group (0.01–0.5 mg/kg) [5]. However, adverse side effects with the former dose are uncommon despite the generalized use of this dose among nuclear medicine specialists. Further evaluation of the safest and most useful dose of captopril for this age group should be considered.

There is no simple clinical test for identifying RVH. Conventional and digital subtraction angiography is considered the gold standard in diagnosing renovascular disease [7, 10]. Unfortunately, the presence of renal artery stenosis does not necessarily imply that it is the cause of hypertension. A 50% stenosis is often considered significant, although perfusion pressure in a large artery may not be affected until stenosis exceeds 70% [22]. Essentially, the only way to judge its significance is to treat the stenosis and see if blood pressure falls [4, 22]. Angiographic studies are invasive, relatively expensive, and expose the kidney to a contrast load. Thus, they are less useful as screening examinations, especially in patients with poor renal function and in children [6, 7]. A number of screening tests has been developed in recent years, including magnetic resonance (MR) angiography, CRS, and Doppler ultrasonography. It is suggested that renal scintigraphy and Doppler ultrasonography should be considered the primary techniques in screening for RVH [8, 13]. Duplex sonography is non-invasive, but the test can be quite time-consuming and has achieved reliability only at certain dedicated centers. There are difficulties inherent in performing and interpreting the examination that depend on the technical skill of the radiologist [7, 8, 9, 10]. MR angiography, with its higher cost and more restricted availability, is gaining wider appeal due to its non-invasive nature and lack of iodinated contrast [7, 8,10]. However, MR angiography does not appear to be sensitive to segmental or distal renal artery stenosis. It may be more useful in the evaluation of the proximal main renal arteries and it is best suited for patients with suspected atherosclerotic disease [7, 8, 10]. Measurement of peripheral plasma renin activity and its reactive rise after captopril (captopril test) are screening tests that assess the renin dependency of hypertension and so indicate the hypertensive patients who need subsequent investigation. Available data suggest that the captopril test has a limited diagnostic accuracy as a screening test for the detection of RVH [23].

The main role of radioisotopic studies is to provide functional information that can be correlated with morphological data from other radiological techniques. RVH depends on secretion of renin from the juxtaglomerular apparatus of the underperfused kidney. ACEI interrupt the renin-angiotensin system by preventing the conversion of angiotensin I to angiotensin II, therefore blocking the vasoconstrictor and aldosterone-stimulating effects of angiotensin II. Within the ischemic kidney, inhibition of the enzyme reduces the angiotensin II-dependent constriction of the postglomerular arteriole, thereby lowering the transcapillary forces that maintain glomerular filtration [22]. This decrease in individual kidney glomerular filtration can be assessed non-invasively by radionuclide renography [7, 8, 9, 10, 11, 18, 22].

Baseline renal scintigraphy alone is not useful in the evaluation of RVH, because a normal result does not exclude the existence of RVH and an abnormal result can be due to parenchymatous lesions [11, 13]. In our experience, as with other studies [13, 14], CRS is a useful procedure for the diagnosis of RVH in pediatrics patients.

As in other diagnostic tests for RVH, the existing renal function at the time of the scintigraphic procedure is important in the evaluation of the results [11, 18, 22, 24, 25, 26]. Patients with decreased renal function have a high percentage of non-diagnostic test results [18, 22, 25]. In our study, CRS was non-diagnostic in 3 kidneys with decreased renal function, 1 of them with RVH. A non-diagnostic test is not necessarily a problem if the referring physician understands the likelihood of this outcome when referring such a patient for ACEI renography. A non-diagnostic test, in the appropriate clinical setting, may be sufficient to refer a patient for angiography or another diagnostic procedure. False-negative results are uncommon, but when they do occur, they are more likely in azotemic patients with bilateral disease, probably due to pressure natriuresis with suppression of the renin-angiotensin system [25, 26]. Dehydration, a severe hypotensive response, and the use of calcium antagonists can cause false-positive captopril renograms [25, 27, 28]. Physicians should be aware of these possible causes of false-positive results if bilateral symmetrical alteration of renal function is seen on a patient's captopril renograms.

Diagnostic imaging procedures used in the evaluation of RVH possess a high specificity and sensitivity in selected hypertensive populations, but if applied to a general population of hypertensive patients their positive predictive values are necessarily low because of the low prevalence of the disease. Accordingly, it is mandatory for the physician to pre-select those who, on the basis of a thorough clinical examination, are more likely to harbor a renal artery stenosis, before sending patients for these procedures.

If a patient has a moderate-to-high likelihood of RVH and normal renal function, ACEI renography provides a logical, non-invasive, safe, and cost-effective approach to patient management. A normal ACEI renography obviates the need for further work-up, except if a patient has renal failure. Conversely, an abnormal study should lead to referral for angiography and revascularization. More research is needed to determine the optimal dose of captopril, especially in newborns.

In conclusion, captopril renography provides a logical, non-invasive, safe, and cost-effective approach in the evaluation of children suspected of having RVH. It is a useful screening method for RVH in hypertensive children with an increased likelihood of renovascular disease.

References

1. Hiner LB, Falkner B (1993) Renovascular hypertension in children. Pediatr Clin North Am 40:122–140
2. Deal JE, Snell MF, Barratt TM, Dillon NJ (1992) Renovascular disease in childhood. J Pediatr 121:378–384
3. Dillon MJ (1997) The diagnosis of renovascular disease. Pediatr Nephrol 11:366–372
4. Wells TG, Belsha CW (1996) Pediatric renovascular hypertension. Curr Opin Pediatr 8:128–134
5. Flynn JT (2000) Neonatal hypertension: diagnosis and management. Pediatr Nephrol 14:332–341
6. Shahdadpuri J, Frank R, Gauthier BG, Siegel DN, Trachtman H (2000) Yield of renal arteriography in the evaluation of pediatric hypertension. Pediatr Nephrol 14:816–819
7. Rankin SC, Saunders AJ, Cook GJ, Scoble JE (2000) Renovascular disease. Clin Radiol 55:1–12
8. Soulez G, Oliva VL, Turpin S, Lambert R, Nicolet V, Therasse E (2000) Imaging of renovascular hypertension: respective values of renal scintigraphy, renal Doppler US and MR angiography. Radiographics 20:1355–1368
9. Johansson M, Jensen G, Aurell M, Friberg P, Herlitz H, Klingenstierna H, Volkmann R (2000) Evaluation of duplex ultrasound and captopril renography for detection of renovascular hypertension. Kidney Int 58:774–782
10. Mitty HA, Shapiro RS, Parsons RB, Silberzweig JE (1996) Renovascular hypertension. Radiol Clin North Am 34:1017–1036
11. Orellana P, Jalil R, Valdes F, Fava M, Olea E, Fernández M, Valdés G, Contreras O, Fontbote C (1993) Renal scintigraphy with captopril in the evaluation of renovascular hypertension. Rev Med Chil 121:762–767
12. Minty I, Lythgoe MF, Gordon I (1993) Hypertension in paediatrics: can pre- and post-captopril technetium-99m dimercaptosuccinic acid renal scans exclude renovascular disease? Eur J Nucl Med 20:699–702
13. Estepa R, Gallego N, Orte L, Puras E, Aracil E, Ortuño J (2001) Renovascular hypertension in children. Scand J Urol Nephrol 35:388–392
14. Chandar JJ, Sfakianakis GN, Zilleruelo GE, Guerra JJ, Georgiou MF, Abitbol CL, Montane BS, Strauss J (1999) ACE inhibition scintigraphy in the management of hypertension in children. Pediatr Nephrol 13:493–500
15. Ng CS, Bruyn R de, Gordon I (1997) The investigation of renovascular hypertension in children: the accuracy of radioisotopes in detecting renovascular disease. Nucl Med Commun 18:1017–1028
16. National High Blood Pressure Education Program of Hypertension Control in Children and Adolescents (1996) Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. Pediatrics 98:649–658
17. Piepz A, Hahn K, Roca I, Ciofetta G, Toth G, Gordon I, Kolinska J, Gwidlet J Paediatric Task Group European Association Nuclear Medicine Members (1990) A radiopharmaceuticals schedule for imaging in paediatrics. Eur J Nucl Med 17:127–129
18. Taylor A, Nally J, Aurell M, Blaufox D, Dondi M, Dubovsky E, Fine E, Fommei E, Geyskes G, Granerus G, Kahn D, Morton K, Oey HY, Russell C, Sfakianakis G, Fletcher J (1996) Consensus report on ACE inhibitor renography for detecting renovascular hypertension. J Nucl Med 37:1876–1882
19. Daniels SR, Loggie JM, McEnery PT, Towbin RB (1987) Clinical spectrum of intrinsic renovasuclar hypertension in children. Pediatrics 80:698–704
20. Adelman RD (1988) The hypertensive neonate. Clin Perinatol 15:567–585
21. Lagomarsino E, Tapia JR, Ventura-Junca P (eds) (2000) Arterial hypertension: manual de neonatología, 2nd edn. Publicaciones Técnicas Mediterráneas, Santiago, Chile, pp 505–510
22. Prigent A (1993) The diagnosis of renovascular hypertension: the role of captopril renal scintigraphy and related issues. Eur J Nucl Med 20:625–644
23. Lenz T, Kia T, Rupprecht G, Schulte KL, Geiger H (1999) Captopril test: time over? J Hum Hypertens 13:431–435
24. Shamlou KK, Drane WE, Hawkins IF, Fennell RS (1994) Captopril renography and the hypertensive renal transplant patient: a predictive test of therapeutic outcome. Radiology 190:153–159
25. Taylor A (1999) Radionuclide renography: a personal approach. Semin Nucl Med 29:102–127
26. Van de Wiele C, Brans B, Vanholder R, Hoeben H, Van Laere K, Dierckx RA (1999) Predictive value of 99 Tcm-DTPA captopril scintigraphy in patients with a solitary kidney and reduced kidney function. Nucl Med Commun 20:263–266
27. Levey CS, Schraml FV, Abreu SH, Silverman ED (1999) False positive result of captopril-enhanced radionuclide renogram in a child secondary to dehydration. Clin Nucl Med 24:6–8
28. Claveau-Tremblay R, Turpin S, De Braekeleer M, Brassard A, Leblond R (1998) False-positive captopril renography in patients taking calcium antagonists. J Nucl Med 39:1621–1626