ABSTRACT

The prevalence of “primary aldosteronism” (PAL) cannot be precisely determined at this time, given 1) lack of a universally accepted definition, and 2) normotensive as well as normokalemic phases in the evolutionary development of a disease eventually characterized by hypertension and hypokalemia. The exception is fully genetically characterised forms such as glucocorticoid-suppressible hyperaldosteronism, the true prevalence of which could be proven today by universal screening using a single blood sample, but this is neither practical nor appropriate. Controversy has arisen regarding the rareness, or otherwise, of PAL because of 1) rediscovery in the last 12 years of the normokalemic phase described by Conn, 2) application of widely available methods for measurement of aldosterone and renin to “screening”, 3) variable quality of these methods, and of their application, and 4) lack of the necessary “diagnostic”, in addition to “screening”, tests in some studies. PAL is significantly more common than previously thought, and a very important potentially curable form of hypertension. Early diagnosis and specific treatment avoids morbidity. The current focus on increased detection is essential, and will help to resolve the question of prevalence. (Arq Bras Endocrinol Metab 2004;48/5:666-673)

Keywords: Aldosterone; Renin; Aldosterone-renin ratio; Primary aldosteronism; Hypertension

RESUMO

Hiperaldosteronismo Primário – Uma Epidemiologia Verdadeira ou Alarme Falso?

A prevalência de “hiperaldosteronismo primário” (HAP) não pode ser determinada atualmente com precisão, uma vez que 1) não há uma definição aceita universalmente, e 2) existem fases tanto de normotensão como de normocalemia durante o desenvolvimento evolutivo desta doença eventualmente caracterizada por hipertensão e hipocalemia. A exceção são as formas totalmente caracterizadas geneticamente, como o hiperaldosteronismo supressível por glicocorticóides, cuja real prevalência pode ser comprovada hoje em dia por rastreamento universal, usando uma única amostra de sangue, embora isto não seja nem prático nem apropriado. Controvérsias têm sido levantadas com relação à rariade, ou o contrário, do HAP, devido à 1) redescoberta, nos últimos 12 anos, da fase normocalemica descrita por Conn, 2) aplicação de métodos amplamente disponíveis para mensuração da aldosterona e renina para “rastreamento”, 3) a variável qualidade destes métodos, e sua aplicação, e 4) ausência dos necessários testes “diagnósticos”, em adição ao “screening”, em alguns estudos. HAP é significativamente mais comum do que previamente imaginado, e uma forma muito importante de hipertensão potencialmente curável. O diagnóstico precocce e o tratamento específico evitam a morbidade. O foco atual no aumento da detecção do HAP é essencial, e irá auxiliar a resolver a questão de sua prevalência. (Arq
INTRODUCTION AND BACKGROUND

“Epidemic” is an emotive term, evoking images of plague, pestilence and death. “False alarm” suggests that we can all relax again and get back to our real work. While neither term can be readily applied to primary aldosteronism, I was very happy to accept this title when offered to me, because it correctly implies two opposing schools of thought. Not surprisingly, the term epidemic has been used by those who believe that the “conventional wisdom” has been unnecessarily brought into question, without adequate evidence (1,2). Epidemic is an inappropriate term, because epidemics are evanescent, while normokalemic primary aldosteronism has been known for 50 years, always there, but not recognized because patients were not tested for it. Robust debate and discussion are necessary in most areas of human endeavour for worthwhile advances in thinking and knowledge, and this of course applies to science and medicine. The current debate on primary aldosteronism (PAL) will help to crystallize our evolving understanding of that condition, with benefit to patients and to our own peace of mind.

Insights into the mind of a very gifted clinical investigator are provided by Conn’s description, in his Harvey Lecture delivered on April 20, 1967 (3), of how, in 1954, he determined the pathophysiological basis and successful treatment of a new patient presenting with severe hypertension and hypokalemia. Right adrenalectomy on December 9, 1954 disclosed a 3.75 cm diameter cortical adenoma, and resulted in cure. How did he achieve this?

Conn had used the concentration of sodium in sweat as an index of excessive desoxy-corticosterone activity. The long-suspected but elusive salt-retaining, potassium-excreting hormone had been detected biologically, isolated chromatographically and named “electrocorin” in 1952, isolated in pure crystalline form in 1953, named aldosterone in 1954, synthesized in 1955 and a method devised for its measurement in urine only in 1956. Conn’s monumental achievement in 1954 should be seen in this context. He named the condition Primary Aldosteronism in 1955, in his first detailed report of the syndrome (4). Over the next ten years he methodically elucidated the pathophysiological basis of its clinical presentation and evolution. Importantly, in the context of the current debate, he discovered the normokalemic form. A quotation from his Harvey Lecture in 1967 (3) is illuminating: “While we were theorizing about the possible existence of normokalemic primary aldosteronism (5) and before we had actually described it (6), we had suggested on the basis of autopsy reports and other indirect evidence, that primary aldosteronism could actually involve as many as 20 percent of people with “essential” hypertension. Although our own work in this regard is far from complete, it appears that the determined value will not be as high as predicted. At present 10 percent appears to be more realistic.” At that time, Conn had diagnosed 14 (7.6%) of 184 normokalemic essential hypertensives with PAL on the basis of renin and aldosterone levels, and had found and removed an adrenal adenoma in each of them.

He pointed out that renin and aldosterone levels represented a more sensitive criterion than potassium, anticipating the use of the aldosterone/renin ratio (ARR). He conceded that his sample of hypertensives might not be representative of the general hypertensive population. He made another important observation, very relevant today as we seek firm criteria for correct diagnosis on which to base assessments of sensitivity and specificity of diagnostic tests (receiver-operator curves): “We have observed that blood pressure may not begin to descend for as long as eight months after operation”.

How can we establish whether primary aldosteronism is common or rare among “essential hypertensives”?

This task requires at least the following:

1. Selecting an appropriate hypertensive population. What would that be? Should mild or intermittent or “white coat” hypertension be excluded? Should “resistant hypertension”, possibly with PAL highly represented, be excluded? Would 24-hour ambulatory monitoring be required to establish satisfaction with selection criteria? Would any patient already receiving antihypertensive medication be assumed (perhaps incorrectly) to have been hypertensive? Should it be derived from a “primary care” or “family medicine” setting, rather than from a hospital clinic setting? Should thorough screening be performed to exclude other identifiable causes of hypertension such as parenchymal renal disease, renal artery stenosis, pheochromocytoma, Cushing’s syndrome and aortic coarctation? Should there be age limits, since hypertension in children is likely to have an identifiable cause, while up to 30% of adults over the age of 50 years have hypertension (depending on definition) in
some societies?

(2) Establishing a firm diagnostic criterion for PAL. Should this be cure of excessive, autonomous aldosterone production rather than “cure” of hypertension following removal of an adrenal containing a cortical adenoma, bearing in mind that the patient might also have “essential hypertension”? Is cure of hypertension achieving a BP level, which never exceeds an arbitrary level after withdrawal of medications? Is there a minimum or a maximum limit on the time elapsing after surgery before this decision is made? Should the population be screened by peripheral blood DNA analysis for the hybrid gene of glucocorticoid-suppressible hyperaldosteronism?

While these represent criteria against which any screening test or diagnostic test could be assessed, they ignore the more common problem of bilateral hyperplasia causing PAL. Also, discovery of an adrenal mass in a patient with raised ARR is insufficient to establish that it is an aldosterone-secreting adenoma. It could be a non-functioning nodule, not uncommonly discovered on organ imaging of the abdomen ("incidentaloma").

(3) “Screening” the population with a safe, non-invasive test, which has few false positives or false negatives. This would reduce the numbers subjected to more complicated tests such as salt loading or adrenal venous sampling. The above requirements are very difficult to achieve and probably impractical at present. In the real world we are often faced with the task of making a decision based on imperfect data. This is not unusual in clinical medicine. So we must look at some of the very reasonable attempts, which have been made to examine this question, and without unreal expectations of a definitive answer just yet. It would be helpful if they could be standardized, but different Units have established there own criteria and based their patient management on their experience with their use, and will be reluctant to change. It will be a matter for debate, which are the most informative studies. However, it seems clear that when aldosterone secretion becomes autonomous and then excessive, the first recognizable biochemical alteration is that its normal regulator, renin, begins to turn off, resulting in an increase in the aldosterone/renin ratio. Hence the most sensitive screening test is measurement of the ARR, and measurement of aldosterone, looking for clearly raised levels, is much less sensitive. Least sensitive are serum potassium levels, which lag behind total body potassium decrements. It is a matter for debate whether aldosterone and renin should be measured after overnight recumbency, after two to four hours upright in the morning, or after a period of recumbency following upright posture. These different approaches may explain some of the discrepant results (see later).

What Progress Has There Been to Date?

Between 1993 and 2000, reports (7-13) appeared from five different continents of raised ARK (approximately 15 to 30 percent) in apparent “essential” hypertensives screened for the presence of PAL, whether normokalemic (7,8,13) or a mixture of normokalemic and hypokalemic (9-12). If a suppression test to demonstrate “autonomy” of aldosterone production was then performed (oral fludrocortisone or intravenous saline infusion), in order to establish the diagnosis, percentages of patients with PAL fell to 4.6 to 12 percent (7,8,13). This represented a much higher prevalence of PAL than the less than one percent indicated in authoritative texts (14,15) in the early 1990’s. Young from the Mayo Clinic also reported a large (ten-fold) increase in diagnosis of PAL since introduction of screening using the ARR (16). The spectrum of PAL of course includes a solitary “adenoma”, several adenomas or nodules in the same gland, unilateral macro- or micro-nodular hyperplasia and unilateral or bilateral diffuse hyperplasia. Unless adrenal venous sampling is performed, however, leading to unilateral adrenalectomy in those patients who “later-alize” and choose to have it, the prevalence of classic unilateral, solitary adenoma is not forthcoming. There were also reports during the same period, which suggested a low prevalence for PAL, and/or questioned the validity of the ARR as a screening test, and these have been recently summarized by Kaplan (1), providing the basis for a genuine controversy. We will now trace in some detail, how the possibility of a higher incidence than previously supposed arose, and stimulated closer examination by various groups.

Why suspect that PAL may be uncommon?

When Conn suggested that primary aldosteronism might be common (see above), a number of investigators set out to test his hypothesis using the methodology available at the time, and came up with “negative” results. I was involved in one such study (17) from Grant Liddle’s group at Vanderbilt University Hospital, which excluded hypertensives with hypokalemia, pheochromocytoma, Cushing’s syndrome, renal artery stenosis (by renal angiography), raised creatinine or retinal hemorrhages or exudates. Medications were ceased at least 10 days before the study. Plasma renin activity was measured after three to four hours upright on the fourth or fifth day of a low sodium diet, achieving a 24-hour urine sodium less than 10mmol.per day. Aldosterone secretion rate was determined while
the patient received a diet containing either exactly 100mmol sodium per day, or more than 100mmol per day. Only seven of 90 patients had aldosterone secretion rates in excess of 160mcg per day, and the three who also had distinctly subnormal PRA were considered to have PAL (an incidence of 3.3%). Two more had levels of PRA near the lower limit of normal (and hence incidence could rise to 5.6%) and were considered to merit continued observation. Five of 24 patients with aldosterone secretion less than 130mcg per day had markedly suppressed levels of PRA. These patients, if studied today, would also be considered “worthy of further interest”. There will always be a large degree of arbitrariness about cut-off points, which aim to separate normal from abnormal and indicate the need for further, more intensive investigation. No test for suppressibility of aldosterone secretion was performed. This study, performed in a reputable centre, illustrates the difficulties in the late 1960’s of determining the incidence of PAL among normokalemic “essential hypertensives”. Many of these difficulties remain today. It was regarded as negative, even though it suggested an incidence higher than the incidence of less than one percent, which was in favour at that time.

The Endocrine Hypertension Research Unit at Greenslopes Hospital in Brisbane had been diagnosing approximately five patients per year with PAL between 1970 and 1990, in hypertensive patients with unprovoked hypokalemia, plasma renin activity which remained suppressed after five days of a less than 10mmol per day sodium diet (collected between 10am and noon on an ambulatory day) and failure of suppression of urinary or plasma aldosterone after five to seven days (subsequently shortened to four days) of high salt diet and fludrocortisone 0.1mg six-hourly, with supplemental oral slow-release potassium chloride in sufficient dosage to maintain normal plasma potassium levels, in samples collected without stasis (18-21). Adrenal venous sampling (AVS) with comparison of aldosterone/cortisol ratios in each adrenal vein and a peripheral vein was always performed before surgical removal of an adrenal, in order to show that in one gland aldosterone production was appropriately suppressed, and not autonomous, and that the condition should therefore be correctable by removal of the abnormal, unsuppressed gland. These were conventional techniques, reviewed weekly and rigorously performed according to strict protocols. The Unit (also known as the Greenslopes Hospital Hypertension Unit, GHHU) had no particular views about the incidence of PAL in the general hypertensive population, except that it seemed to be low. In 1987 the GHHU reported (22) its experience with a form of APA identifiable by AVS but otherwise missed because of biochemical behaviour resembling BAH, with plasma aldosterone responsive to upright posture and to angiotensin infusion. Thereafter, every patient with PAL not suppressible with glucocorticoid had AVS, and angiotensin-responsive APA (AII-R APA) was found by the GHHU to be equal in frequency with the classical form (plasma aldosterone unresponsive to upright posture or to angiotensin infusion, AII-U APA). The rate of recognition of APA by the GHHU doubled. Measuring ARR midmorning upright may be important for recognition of angiotensin-responsive forms of PAL (20).

Hiramatsu and coworkers described in 1981 how their use of the aldosterone to renin ratio (ARR) in screening for PAL disclosed a surprisingly high incidence of 2.6% of patients with APA among 348 hypertensives (23). Six of the nine patients who had an APA removed were normokalemic. The methods used would have missed small APAs and all patients with hyperplasia, and might thus have halved the incidence of PAL. Because of these unexpected findings, the GHHU in 1985 studied 18 patients with hypokalemic PAL (12 had APAs, four had BAH and two had FH-1) after cessation of angiotensin converting enzyme inhibitors (ACEIs) and aldosterone antagonists, but continuation of other antihypertensives (24). In comparison with normal subjects and other hypertensives, a cut-off point of 25 for plasma aldosterone (ng%) divided by PRA (ng/ml/hr) appeared to discriminate well. We concluded that the ARR appeared promising as a screening test for PAL, but we noted that consistency, effects of sodium and potassium balance and the effects of antihypertensive medications required further study. Not surprisingly, with increasing and eventually very large experience, the ratio proved to have significant limitations unless performed with great care. Our recommendations regarding conditions of sampling have evolved continuously since that time (18-20). Some of these considerations are shown in table 1, but for greater detail see references 20 and 21.

Mulatero and coworkers (25) have demonstrated very convincingly the confounding effects of currently used medications on the ARR, yet Gallay and coworkers (26) found the ARR useful in identifying PAL among a group of resistant hypertensive patients in whom it would be dangerous to cease medications, employing a higher “cut-off point” than usual for the ARR. This is an important question, since PAL eventually causes resistant hyperten-
Table 1. Guidelines in screening for and diagnosing primary aldosteronism (PAL).

1. Hypokalemia with hypertension is very suggestive of PAL, but waiting for this stage to develop delays (in 50 percent of patients) the specific treatment, which protects from the cardiovascular morbidity, which accompanies PAL.

2. A decrease in renin without a corresponding decrease in aldosterone is the first recognizable biochemical change in PAL, making a rise in the aldosterone/renin ratio (ARR), the most sensitive screening test. Hypokalemia is the least sensitive. When present, it lowers aldosterone, and should be corrected before measuring the ARR.

3. Medications which affect renin (and/or aldosterone) levels should be either withdrawn or their effects taken into account, replacing them when necessary with medications with little or no interference in interpretation of the ARR (see references 20 and 21 for suggestions).

4. Effects of posture, duration of that posture and time of day must be taken into account in interpreting aldosterone and renin levels. Midmorning upright levels may be most sensitive, while recumbent levels may miss angiotensin-unresponsive forms of PAL (20,21).

5. Because of spontaneous fluctuations in renin and aldosterone levels, a single ARR will neither rule in nor rule out PAL. Always measure the ratio more than once before going on to a suppression test of aldosterone.

6. Demonstration of lack of normal suppressibility of aldosterone by salt loading is necessary to establish the diagnosis of PAL. Hypokalemia developing during either saline infusion or oral administration of fludrocortisone will lower aldosterone and lead to false negative suppression tests. It must be prevented or taken into account.

7. Appropriate treatment of PAL depends on diagnosis of the subtype by hybrid gene testing and adrenal venous sampling when this is negative. The presence or absence of an adrenal mass on imaging neither proves nor disproves the diagnosis of PAL due to aldosterone-producing adenoma.

8. Be aware that the accurate measurement of aldosterone (which circulates in concentrations roughly one 1000th those of cortisol) and of renin (which circulates in both an inactive and an active form) is very difficult. Laboratory and clinical quality control is essential. Some commercially available “rapid” assays have significant problems still to overcome, limiting the reliability of both screening and diagnostic tests, which employ them.

The number of patients diagnosed each year with PAL then rose from five to 50 or more (a ten-fold increase), and the number with lateralizing PAL going onto adrenalectomy went up to 15-25 per year (a four-fold increase). In 1992, we proposed (27) that PAL might not be uncommon, might always have a genetic basis, and that genetic and morphological diversity might explain the varied biochemical and clinical manifestations of PAL. This was based on 1) discovery that normokalemic PAL was more common than expected; 2) recognition in 1990 (28) that there was a variety of familial PAL which was not glucocorticoid-suppressible, which we named (29) Familial Hyperaldosteronism type II, in order to distinguish it from the glucocorticoid-suppressible variety, which we labeled FH-I (29); and 3) by Lifton’s elucidation of the genetic basis of FH-I (30).

In 1993, we reported (7) the unexpected finding that six of 52 volunteers (newspaper advertisement) for an antihypertensive drug trial conducted by the GHHU and screened for PAL by ARR had positive ratios on repeated testing and positive FSTs, an incidence of almost 12%. None had unprovoked hypokalemia. In 1994, we reported the results of screening 199 consecutive, newly referred, normokalemic hypertensive patients using ARR, repeating it at least once if positive, and going on to FST only if it...
was consistently positive, planning to follow the remainder long term if possible (8). There were 40 with an initial raised ratio, but 14 of them had a normal second ratio, were excluded from further immediate study, and listed for follow-up. Definitive FST testing was reserved for the 22 of the remaining 26 who had two further positive ratios (that is four positive ratios in all, or “consistently raised ratios”), a conservative approach by anybody’s criteria. At the time of the report, FSTs had been completed in 17, all positive. It seemed not unreasonable to conclude that the incidence of PAL in this normokalemic cohort was at least 8.5%. In his paper (1) discussing the inappropriate nature of using the ARR to screen for PAL in all hypertensive patients, Kaplan includes the above study in a meta-analysis, which he uses as a basis for calculating the cost of curing one patient with PAL. Unfortunately, the reference to our study (Kaplan’s reference 5) has been the subject of an unrecognized typographical error, making it untraceable by those unfamiliar with the literature on PAL. Compounding the problem, Kaplan misinterpreted the criterion used by us for selection of patients for FST in this study, which was four consecutive positive ratios, with only 11% going on to FST, rather than 20%, which Kaplan included in his subsequent calculations of cost-effectiveness.

In some reports of a very low incidence for PAL using screening by ARR, exclusion of PAL has depended on absence of an obvious mass on CT of the adrenals. The experience of both the GHHU (31) and, more recently (32), the Princess Alexandra Hospital Hypertension Unit (PAHHU), in Brisbane has been that less than half the patients cured of PAL by unilateral adrenalectomy have identifiable masses on CT, yet an identifiable adenoma on sectioning the removed adrenal. In some studies, sampling for ARR has taken place after a period of remission, which would lead to low aldosterone levels in those with angiotensin-responsive PAL, and false negative ratios (20). However, there have been other studies using remnant sampling, which have reported a significant incidence of PAL, and so this is not the complete answer.

If the ARR is correctly viewed as a screening test and not as a definitive test for PAL, if it performed very carefully with all possible confounding factors in mind (20,21), if it is repeated enough to be consistently raised before a suppression test (of aldosterone) is performed, then it can be an appropriate first test in the search for PAL. Neither renin nor aldosterone are simple to measure reliably, and current commercially available methods which depend on “kits” or a pre-programmed machine require significant further work before they will be satisfactory for widespread application to screening (20). If these problems can be solved, however, we can look forward to an era in which results can be compared between laboratories, and a large collective experience can be accumulated and analyzed. Appropriate analysis will depend on a satisfactory definitive test for PAL (a subject still requiring discussion), application of a hybrid gene test and adrenal venous sampling to differentiate subtypes, and on appropriate follow up and restudy of patients treated surgically, such as postoperative suppression testing (31). Further work on the non-glucocorticoid suppressible form of familial PAL (FH-II) which we have been studying from a genetic point of view (32,33) may one day provide a genetic test or tests requiring only a single blood sample, which would enable a firm diagnosis (of a predisposition to PAL, already expressed, if hypertensive) simply and effectively. We now have three families (two Australian and one Central American) showing linkage of PAL to chromosome 7p22, are further examining the genes at that locus. The affected members of the 32 families with FH-II identified so far can not be distinguished clinically or biochemically from the large population with apparently non-familial PAL, leading to the reasonable assumption that some of the latter group also harbour the same genetic mutation or mutations (32,33). If patients with PAL have hypertensive relatives, it is important to think of the possibility that these relatives may also have PAL.

**CONCLUSION**

An increased incidence of primary aldosteronism (in comparison with the incidence of less than 1%, which was accepted for 30 years) has been noted by most workers who have looked for it. It is not “an epidemic”, because it has presumably always been there, unnoticed. It is there when screening is conducted with the utmost rigour, and backed by careful tests which prove the autonomy of aldosterone secretion in regard to its normal prime regulator, renin-angiotensin. It remains there when the diagnosis is restricted to those whose excess aldosterone secretion is confined to one adrenal on adrenal venous sampling, and whose hypertension (and hypokalemia when present) is cured by unilateral adrenalectomy. Its apparent increase in incidence is clearly not a “false alarm”, but a call to those who wish their hypertensive patients to avoid the unpleasant sequelae of longstanding, unsuspected and therefore undetected exposure to excessive levels of aldosterone, now thought to be more insidious and pervasive than previously suspected. The apparently “recent” increase in incidence of primary
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The controversy, which has been thus aroused by those daring to question the conventional wisdom, will serve the vital purpose of alerting clinicians to the presence of this eminently treatable (and sometimes curable) condition, clearly a major contributor to “resistant” hypertension with its poor prognosis. It should also lead to essential, long overdue critical examination of available aldosterone and renin methodology, and, hopefully, to simplification of diagnostic testing and subtype differentiation. If the genetic basis or bases of the more common familial variety not suppressible with glucocorticoids can be defined, it is possible that diagnostic testing for many patients might become very simple indeed.

The opinions expressed here clearly represent a very personal view, which will continue to change and evolve. A deliberate attempt has been made to place today’s questions into an historical perspective, in the belief that this can provide some balance and some measure of the progress which has been made.

Finally, cure his or her hypertension and you have one very grateful patient. Cure 100 hypertensives and you have many very grateful patients. Yes, screening your next normokalemic hypertensive patient for PAL is definitely worthwhile.

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