Clinical Study

NP-59 SPECT/CT Imaging in Stage 1 Hypertensive and Atypical Primary Aldosteronism: A 5-Year Retrospective Analysis of Clinicolaboratory and Imaging Features

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Objective. We retrospectively analyzed all primary aldosteronism (PA) patients undergoing NP-59 SPECT/CT imaging with regard to their clinirolaboratory and imaging features, investigation, and outcomes. Material and Methods. 11 PA patients who presented to our hospital for NP-59 SPECT/CT imaging between April 2007 and March 2012 and managed here were analyzed. Results. Among 11 PA patients, eight (73%) had stage 1 hypertension, three (27%) stage 2 hypertension, four (36%) normal plasma aldosterone concentration, nine (82%) nonsuppressed plasma renin activity (PRA), six (55%) normal aldosterone-renin-ratio (ARR), eight (73%) serum potassium \( \geq 3 \) mEq/L, seven (64%) subclinical presentation, seven (64%) negative confirmatory testing, and four (36%) inconclusive results on CT scan and seven (64%) on planar NP-59 scan. All 11 (100%) patients had positive results on NP-59 SPECT/CT scan. Two (18%) met typical triad and nine (82%) atypical triad. Among nine atypical PA patients, three (33%) had clinical presentation, six (67%) subclinical presentation, six (67%) negative confirmatory testing, and four (44%) inconclusive results on CT scan and six (67%) on planar NP-59 scan. All patients had improved outcomes. Significant differences between typical and atypical PA existed in PRA and ARR. Conclusions. NP-59 SPECT/CT may provide diagnostic potential in stage 1 hypertensive and atypical PA.

1. Introduction

Primary aldosteronism (PA) is the most common surgically curable form of secondary hypertension and has also been documented to trigger harmful cardiovascular events independent of hypertension [1]. PA classically presents with typical triad of elevated plasma aldosterone concentration (PAC), suppressed plasma renin activity (PRA), and high aldosterone-renin-ratio (ARR). Saline infusion or captopril tests are used to confirm the diagnosis. It has been shown that PA reaches at least 11.2% prevalence among newly diagnosed hypertensive patients [2], when determinations of ARR, PAC, and PRA are used as screening tools.

Screening for PA is generally recommended in subjects with drug-resistant hypertension or stage 2 hypertension [3] according to JNC 7 [4], despite hypokalemia or normokalemia, because of a high frequency (∼21%) of PA in stage 2 essential hypertension [5]. However, recent data have shown that PA is not uncommon in normotensive, prehypertensive, and stage 1 hypertensive patients [6–9]. Patients with normotensive and subclinical PA may represent as an early, milder form of PA which may subsequently develop into hypertension on followup and lead to more aldosterone-dependent cardiovascular morbidity than essential hypertension [7, 8, 10]. Emerging evidence also has shown that PA patients may vary widely in their clinirolaboratory features...
information were reviewed from the medical notes and analyzed.

2.3. Definitions. The severity of hypertension was staged according to JNC 7 criteria [4] with stage 1 equivalent to 140 to 159 mm Hg systolic over 90 to 99 mm Hg diastolic and stage 2 as >160/100 mm Hg. Clinical PA was defined by stage 1 or 2 hypertension with serum potassium less than 3 mEq/L or stage 2 hypertension with serum potassium greater than 3 mEq/L. Subclinical PA was defined by stage 1 hypertension with serum potassium greater than 3 mEq/L or normokalemia (serum potassium > 3.5 mEq/L). PAC and PRA were measured by radioimmunoassay using commercially available kits (Diasorin Inc., MN, USA). Normal ranges for PAC and PRA were 3.7–24 ng/dl and 0.15–2.33 ng/mL/h, respectively. An ARR >30 was considered elevated [17]. All drugs that might affect the ARR were discontinued 2 weeks before performing confirmatory testing. Confirmatory testing included an IV saline load (2 L of 0.9% NaCl infused over 4 h), which was considered positive if posttest PAC was greater than 10 ng/dl [3]. Alternatively, a captopril test (25 mg of captopril) was performed and considered positive if posttest PAC suppression after 2 hours was greater than 30% [3]. Kaliuria was defined by transtubular potassium concentration gradient (TTKG) > 4. Typical PA was defined as PA patients who met the triad of elevated PAC, suppressed PRA, and high ARR. Atypical PA was defined as PA patients who had normal PAC, or nonsuppressed PRA, or normal ARR.

2.4. NP-59 Planar and SPECT/CT Imaging. A dexamethasone suppression regimen (1 mg orally four times daily) was initiated seven days prior to tracer injection and was continued throughout the imaging procedure and for five days postinjection [22]. In order to block thyroid uptake of free I-131, subjects were also given five drops daily of Lugol’s solution three days before the start of imaging and daily until the end of the imaging period. All drugs that might interfere with NP-59 uptake were discontinued for four weeks prior to imaging [22]. NP-59 scanning was performed on days 1 through 5 to obtain planar images after intravenous injection of 1.5 mCi (56 MBq) of NP-59. SPECT/CT scanning was performed on days 2 through 5 with a dual-head gamma camera and a low-dose nondiagnostic CT (Infinia Hawkeye 4, GE Healthcare, Milwaukee, WI, USA) to obtain merged SPECT/CT images. This low-dose nondiagnostic CT operates at 140 mV–2.5 mA.

2.5. Imaging and Pathological Interpretation. The NP-59 planar and SPECT/CT images were interpreted after a consensus reading by two board-certified nuclear medicine physicians who were unaware of the clinical data. Aldosteronism on the affected side(s) was diagnosed if there was early visualization of the tracer before the fifth postinjection day and if intense uptake (greater than that seen in the liver) was noted on the image [2]. Adrenal CT imaging with 3 mm thin cuts was interpreted by a board-certified radiologist unaware of clinical data. Ten patients underwent laparoscopic adrenalectomy and one was treated with spironolactone. Histopathological
3.1. Analysis according to Hypertension Stage. Among 11 PA patients (6 men and 5 women, median age: 55 years; range: 27–75 years) using NP-59 SPECT/CT imaging were shown in detail in Table 1. Eight patients had adrenal adenoma, one adrenal micronodule, one focal nodular hyperplasia, and one bilateral adrenal hyperplasia without surgery.

3.2. Analysis according to Typical versus Atypical Triad. Integrated and quantitative analyses of all PA cases according to typical versus atypical triad can be gained from Tables 3 and 4. Among 11 PA patients, two (18%) had typical triad and nine (82%) atypical triad. Among atypical PA patients, three (33%) had clinical presentation, six (67%) subclinical presentation, six (67%) negative confirmatory testing, and four (44%) inconclusive results on CT scan and six (67%) on planar NP-59 scan. All atypical PA patients had positive results on NP-59 SPECT/CT scan and improved outcomes. Benefit of NP-59 SPECT/CT could be summarized as one point, that is, the disclosure of adrenal lesions in typical or atypical PA with clinical or subclinical presentation despite negative confirmatory testing and/or inconclusive results on traditional lateralization modalities. Among 11 PA patients using NP-59 SPECT/CT imaging, median systolic BP was 150 mm Hg, median diastolic BP 90 mm Hg, median PAC 26.8 ng/dL, median PRA 1.31 ng/mL/h, median ARR 18, and median serum potassium 3.4 mEq/L. There were significant differences in PRA and ARR between typical and atypical PA.

3.3. Outcome Followup. On followup (Table 1), eight stage 1 hypertensive PA patients were cured of their hypertension following treatment and three stage 2 hypertensive PA patients had improvement in hypertension. It is worth noting that patient 4 (Figure 1) shared a clinical presentation similar to essential hypertension, which made it difficult to access the subject for PA but was ultimately diagnosed with PA by a positive NP-59 SPECT/CT result.

4. Discussion
A methodology to detect atypical PA and stage 1 hypertensive PA using NP-59 SPECT/CT imaging against general screening for typical PA has been presented. This strength of this approach lies in its higher sensitivity and diagnostic accuracy, as well as its safety with no contrast exposure and very little radiation exposure from the nondiagnostic CT scanner. Our preliminary results indicated three clinical benefits of NP-59 SPECT/CT in PA. The first is to discover stage 1 hypertensive PA despite the presence of atypical triad or/and negative confirmatory testing. The second is to confirm the diagnosis of atypical PA when there is clinical suspicion. The third is to detect invisible adrenal lesions not found by conventional imaging.

In the present study, PA patients using NP-59 SPECT/CT imaging were featured as stage 1 hypertension, atypical triad, subclinical presentation, serum potassium \( \geq 3 \) mEq/L (normokalemia, 46%), negative confirmatory testing, and inconclusive results on CT and planar NP-59 scanning (Tables 1 and 3). It seems reasonable to expect that clinical presentation and typical triad predominate in stage 2 hypertensive PA. However, a significant proportion of stage 1 hypertensive PA was accompanied with subclinical and atypical PA and seemed to be less easy access because of the obstacle to negative confirmatory testing, inconclusive results on CT and planar NP-59 scanning (Table 2). These findings were consistent with the prevailing concept that most PA patients exhibit an attenuated form of the disease and normokalemia, and only a minority exhibit typical triad and hypokalemia [5, 7]. This could lead to marked underdiagnosis of PA. Emerging circumstantial evidence has also supported the notion of neurohormonal heterogeneity and progression over time in PA until the “autonomous” nature of aldosterone secretion results in hypertension [12, 13] and that PA should be considered as a continuum of pathological disorders [5].

Given that normokalemic or mildly hypertensive PA may have low positive yield on confirmatory testing [23, 24], this would explain why up to 63% of stage 1 hypertensive PA patients in this study had negative confirmatory testing. Given that adrenal CT or planar NP-59 findings alone are insufficient for lateralization due to their low accuracy in detecting subtle hyperfunctioning nodules or hyperplasia [15], this would explain a significant proportion of inconclusive results on these traditional modalities in stage 1.
Table 1: Detailed profile of all PA cases using NP-59 SPECT/CT imaging between April 2007 and March 2012 ($n = 11$).

| Case | Age (year) | Sex | BP (mm Hg) | Class of anti-hypertensives | HTN Stage | K (mEq/L) | PAC (ng/dL) | PRA (ng/mL/hr) | ARR | TTKG | Confirmatory testing | CT (site, mm) | NP-59 Planar SPECT/CT | Pathology | Improved outcomes |
|------|------------|-----|------------|-----------------------------|-----------|-----------|------------|----------------|------|------|---------------------|--------------|--------------------|------------|-------------------|
| 1    | 55         | F   | 140/90     | 1                           | 1         | 3.24      | 31.9       | 2.52           | 13   | 8.8  | Saline loading (N)  | Normal       | N                  | R          | PAC, K, BP         |
| 2    | 48         | F   | 145/80     | 2                           | 1         | 4.01      | 26.8       | 0.06           | 447  | ND   | Saline loading (N)  | L (17)       | L                  | L          | Adenoma (17)       |
| 3‡   | 57         | M   | 170/100    | 4                           | 2         | 2.79      | 37.2       | 0.32           | 116  | 6.2  | Saline loading (N)  | L (puffy, 9) | N                  | L          | Focal nodular Hyperplasia |
| 4    | 56         | M   | 144/90     | 1                           | 1         | 4.14      | 25.3       | 1.31           | 12   | ND   | Saline loading (N)  | L (12)       | N                  | L          | Adenoma (12)       |
| 5    | 39         | M   | 206/115    | 4                           | 2         | 2.2       | 27.5       | 1.68           | 16   | 8.2  | Saline loading (N)  | R (14)       | N                  | R          | Adenoma (26)       |
| 6‡   | 27         | F   | 150/88     | 2                           | 1         | 4.32      | 29.3       | 1.62           | 18   | ND   | Captopril (N)       | Normal       | Faint              | Bil         | No operation‡       |
| 7    | 53         | M   | 145/63     | 2                           | 1         | 2.95      | 37.7       | 0.02           | 1885 | ND   | Saline loading (P)  | L (20)       | N                  | L          | Adenoma (18)       |
| 8    | 61         | F   | 150/93     | 1                           | 1         | 3.84      | 19.9       | 0.39           | 51   | ND   | Captopril (N)       | L (29)       | L                  | L          | Adenoma (22)       |
| 9    | 63         | M   | 136/79     | 1                           | 1         | 3.4       | 17.4       | 1.39           | 13   | ND   | Saline loading (N)  | L (21)       | L                  | L          | Adenoma (20)       |
| 10   | 40         | F   | 150/90     | 1                           | 1         | 3.1       | 5.36       | 1.99           | 2.7  | 6.3  | Captopril (N)       | R (20)       | R                  | R          | Adenoma (20)       |
| 11   | 75         | M   | 181/92     | 6                           | 2         | 3.9       | 8.42       | 0.21           | 39   | ND   | Captopril (N)       | L (puffy, 10)| N                  | L          | Adenoma (10)       |

Abbreviations: BP: blood pressure; HTN: hypertension; K: potassium; PAC: plasma aldosterone concentration; PRA: plasma renin activity; ARR: aldosterone-renin-ratio; TTKG: transtubular potassium gradient; F: female; M: male; ND: not done; P: positive; N: negative; L: left; R: right; Bil: bilateral.

‡Normal range of PAC, PRA, and serum K is 3.7–24 ng/dL, 0.15–2.33 ng/mL/hr, and 3.5 to 5.0 mEq/L, respectively.

‡HTN stage according to JNC7 report.

‡Only spironolactone therapy.

‡Patient 3 had stage 3 chronic kidney disease and patient 6 had stage 4 chronic kidney disease.
### Table 2: Qualitative analysis by HTN stage (n = 11).

| Characteristics                          | All (n = 11) | Stage 1 HTN (n = 8) | Stage 2 HTN (n = 3) |
|-----------------------------------------|-------------|---------------------|---------------------|
| Class of antihypertensives              |             |                     |                     |
| ≥ 3                                     | 3 (27)      | 0 (0)               | 3 (100)             |
| <3                                      | 8 (73)      | 8 (100)             | 0 (0)               |
| PAC                                     |             |                     |                     |
| Elevated                                | 7 (64)      | 5 (63)              | 2 (67)              |
| Normal                                  | 4 (36)      | 3 (37)              | 1 (33)              |
| PRA                                     |             |                     |                     |
| Suppressed                              | 2 (18)      | 2 (25)              | 0 (0)               |
| Nonsuppressed                           | 9 (82)      | 6 (75)              | 3 (100)             |
| ARR                                     |             |                     |                     |
| Elevated                                | 5 (45)      | 3 (37)              | 2 (67)              |
| Normal                                  | 6 (55)      | 5 (63)              | 1 (33)              |
| Serum K (mEq/L)                         |             |                     |                     |
| Normal (>3.5)                           | 5 (46)      | 4 (50)              | 1 (33)              |
| 3 ≤ Serum K < 3.5                      | 3 (27)      | 3 (38)              | 0 (0)               |
| 2 ≤ Serum K < 3                        | 3 (27)      | 1 (12)              | 2 (67)              |
| Presentations                           |             |                     |                     |
| Clinical                                | 4 (36)      | —                   | 2 (cases 14, 16)    |
| Stage 2 HTN + 2 ≤ Serum K < 3          | —           | —                   | 1 (case 22)         |
| Stage 1 HTN + 2 ≤ Serum K < 3          | —           | 1 (case 18)         | —                   |
| Subclinical                             | 7 (64)      | —                   | —                   |
| Stage 1 HTN + 3 ≤ Serum K < 3          | 3 (cases 12, 20, 21) | — |                     |
| Stage 1 HTN + Serum K > 3.5            | 4 (cases 13, 15, 17, 19) | — |                     |
| Confirmatory testing                    |             |                     |                     |
| Positive                                | 1 (9)       | 1 (12)              | 0 (0)               |
| Negative                                | 7 (64)      | 5 (63)              | 2 (67)              |
| Not done                                | 3 (27)      | 2 (25)              | 1 (33)              |
| CT lesion                               |             |                     |                     |
| Positive (nodule)                       | 7 (64)      | 6 (75)              | 1 (33)              |
| Adrenal puffiness                       | 2 (18)      | 0 (0)               | 2 (67)              |
| Negative                                | 2 (18)      | 2 (25)              | 0 (0)               |
| NP-59 Planar                            |             |                     |                     |
| Positive                                | 4 (36)      | 4 (50)              | 0 (0)               |
| Faint                                   | 1 (9)       | 1 (12)              | 0 (0)               |
| Negative                                | 6 (55)      | 3 (38)              | 3 (100)             |
| NP-59 SPECT/CT                          |             |                     |                     |
| Positive                                | 11 (100)    | 8 (100)             | 3 (100)             |

Abbreviations are the same as Table 1. Data are expressed as number (percentage).

### Table 3: Quantitative analysis between typical and atypical PA cases (n = 11).

| Variable       | All (n = 11) | Typical (n = 2) | Atypical (n = 9) | P* |
|----------------|-------------|-----------------|------------------|----|
| SBP (mm Hg)    | 150 (135–206) | 145 (145)       | 150 (136–206)    | 0.58 |
| DBP (mm Hg)    | 90 (63–115)  | 72 (63–80)      | 90 (63–115)      | 0.07 |
| PAC (ng/dL)    | 26.8 (5.36–37.7) | 32.2 (26.8–37.7) | 25.3 (5.36–37.2) | 0.33 |
| PRA (ng/mL/h)  | 1.31 (0.02–2.52) | 0.04 (0.02–0.06) | 1.39 (0.21–2.52) | 0.036 |
| ARR            | 18 (2.7–1885) | 1165 (447–1885) | 16 (2.7–116)     | 0.036 |
| Serum K (mEq/L)| 3.4 (2.2–4.32) | 3.4 (2.95–4.01) | 3.4 (2.2–4.32)   | 1.00 |

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure. Other abbreviations are the same as Table 1. Data are expressed as median (range).

*P < 0.05 as significant.
| Triad | Presentation | Confirmatory Testing | Case | CT | Planar | SPECT/CT | Improved outcome |
|-------|--------------|---------------------|------|----|--------|----------|------------------|
|       | Serum K      | HTN stage           |      |    |        |          |                  |
|       |              |                     |      |    |        |          |                  |
| Typical (n = 2) |  |  |  |  |  |  |  |
| PAC↑, PRA↓, ARR↑ | Clinical | <3 | 1 | P | Case 7 | ✓ | ✓ | ✓ | ✓ |
| Subclinical | >3.5 | 1 | N | Case 2 | ✓ | ✓ | ✓ | ✓ |
| Atypical (n = 9) |  |  |  |  |  |  |  |
| PAC↑, PRA−, ARR↑ | Clinical | <3 | 2 | N | Case 3 (Kaliuria) | ✓ | ✓ | ✓ | ✓ |
| Subclinical | <3 | 2 | ND | Case 5 (Kaliuria) | ✓ | ✓ | ✓ | ✓ |
| PAC↑, PRA−, ARR− | 3–3.5 | 1 | N | Case 1 (Kaliuria) | ✓ | ✓ | ✓ | ✓ |
| PAC−, PRA−, ARR↑ | Clinical | >3.5 | 1 | ND | Case 4 | ✓ | ✓ | ✓ | ✓ |
| Subclinical | >3.5 | 2 | N | Case 11 | ✓ | ✓ | ✓ | ✓ |
| PAC−, PRA−, ARR− | 3–3.5 | 1 | N | Case 8 | ✓ | ✓ | ✓ | ✓ |
| Subclinical | 3–3.5 | 1 | ND | Case 9 | ✓ | ✓ | ✓ | ✓ |

**Abbreviations are the same as Table 1.**

1 Indicates either saline loading or captopril testing.
2 Indicates adrenal nodule.
hypertensive PA in this study. Given that normotensive PA may reflect an early or milder form of PA [7, 9], NP-59 SPECT/CT appears feasible for the diagnosis of stage 1 hypertensive PA, which was not documented in the literature.

Next, we analyzed the differences between typical and atypical PA (Tables 3 and 4). Subclinical presentation, stage 1 hypertension, and negative confirmatory testing seemed to predominate in atypical PA. If traditional imaging fails to support the clinical suspicion of PA, NP-59 SPECT/CT seems to provide diagnostic potential for atypical PA. In addition, significant differences between typical and atypical PA existed in PRA and ARR.

Stage 1 hypertensive PA and atypical PA seem to be not uncommon. The number of stage 1 hypertensive and atypical PA patients increased from four and five, respectively, in 2007–2010 [24] to eight and nine, respectively, till March 2012 in our hospital. Given the higher prevalence of PA among prehypertensive and stage 1 hypertensive patients [8, 9], NP-59 SPECT/CT appears to provide significant improvement in diagnosis. It remains unclear, however, whether it is cost effective to screen for normotensive and mildly hypertensive PA using NP-59 SPECT/CT. Given that modest adrenal hormonal autonomy, as exhibited in clinically silent normokalemic PA, is associated with significant morbidity [25] and that hyperaldosteronism is fairly common in hypertension [14] and is associated with aldosterone-dependent cardiovascular morbidity, long-term care with antihypertensives, and cardiovascular complications, increased efforts to identify such cases appear justified [26, 27]. In this study, eight stage 1 hypertensive patients were cured of their hypertension.

In the SPECT/CT systems currently commercially available, we adopted the GE Hawkeye hybrid system with a low-dose nondiagnostic CT scan that is a low cost option [28] and aids the diagnosis and therapeutic planning in various clinical situations [18, 19]. The radiation exposure from this 2.5 mA CT scan of an abdomen nondiagnostic localization is small (about 0.5 mSv) compared with the dose received from the use of spiral CT [29]. Therefore, SPECT/CT may be suited to play a major role in noninvasive and safe characterization of subtle adrenal lesions.

This study had some limitations. First, this was a retrospective analysis. Second, AVS was not available for all patients. Despite its usefulness, successful sampling of both adrenal veins remains technically demanding and potentially harmful and thus has been limited largely to major tertiary centers. Despite these limitations, our findings are clinically significant. It is increasingly being recognized that PA is not confined to stage 2 hypertensive patients but also common in stage 1 or mildly hypertensive patients and that atypical PA is common. This evidence poses a challenge for the clinicians to the existed guideline that screening for PA should image be recommended to stage 2 hypertensive patients. Noninvasive NP-59 SPECT/CT appears to have promising potential in identifying stage 1 hypertensive and atypical PA.

5. Conclusion
In conclusion, this study demonstrates diagnostic potential of noninvasive NP-59 SPECT/CT in the diagnosis of stage 1 hypertensive and atypical PA. A prospective scale-up study is warranted to validate our findings in the future.

Conflict of Interests
All authors declare that there is no conflict of interests.

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