Safety of medical adjustment and confirmatory testing in the diagnostic work-up of primary aldosteronism

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Abstract

Objective: Saline infusion test (SIT) and captopril challenge test (CCT) are standard confirmatory procedures routinely used in the diagnostic work-up of primary aldosteronism (PA). However, side effects and complications during testing have not been systematically studied.

Design: We performed a cohort study with patients undergoing SIT and/or CCT in two centers from 2016 until 2018.

Methods: We studied 272 study participants with suspected PA enrolled at two outpatient centers in Germany. We assessed the frequency and severity of side effects during adjustment of blood pressure medication and during SIT and CCT.

Results: During the adjustment phase prior confirmatory testing, side effects including palpitations, headaches, edema and hypertensive episodes occurred in 18.4% of study participants. Side effects were associated with higher defined daily doses (DDD) ($r = 0.25$, $P < 0.005$), number of antihypertensive drugs ($r = 0.285$, $P < 0.005$) and higher blood pressure ($r = 0.145$, $P = 0.019$). During SIT, 17.5% of study participants had side effects, associated with higher blood pressure (systolic: $r = 0.541$, $P < 0.0005$; diastolic: $r = 0.426$, $P < 0.0005$) and DDDs ($r = 0.727$, $P < 0.0005$). During CCT, only 1.5% of study participants developed side effects.

Conclusions: In contrast to the high rate of side effects during SIT, CCT appears to be the safer test with a very low event rate. This makes CCT especially suitable for severely hypertensive patients.

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Introduction

Arterial hypertension is the most important underlying cause of mortality worldwide and international guidelines recommend screening and detection of potentially curable forms of high blood pressure (1, 2, 3, 4). Among these etiologies, primary aldosteronism (PA) is the most common endocrine form of arterial hypertension curable by surgery, with prevalences ranging from 5 to 13% among various studies and cohorts at tertiary teaching hospitals or primary care facilities (1, 5, 6, 7, 8). In accordance

with the intensified screening for PA, identification of more milder forms and more female patients occurs (9). Established confirmation tests during the assessment of PA patients include the saline infusion test (SIT) and captopril challenge test (CCT) (1, 10, 11), after adjustment of antihypertensive medication which may influence the aldosterone-to-renin ratios and results of confirmatory testings (12, 13). Other confirmatory tests include the oral sodium loading or fludrocortisone suppression testing (1).

With the widespread availability and use of these tests, more recent studies focused on the comparison of cut-off values and validation among various patient cohorts (14, 15, 16, 17). However, to the best of our knowledge, a comparative in-depth analysis of associated complications and side effects of the adjustment of antihypertensive medication prior to confirmatory testing and patient safety outcomes in relation to confirmatory testing have not been thoroughly performed. Therefore, we aimed at assessing the frequency and severity of potential complications and side effects before, during and after saline infusion and CCTs.

Subjects and methods

Description of the registry and patient cohort

Study participants undergoing SIT and CCT for suspected PA were prospectively enrolled in Berlin and Munich since 2016. For this analysis, 272 study participants were included (202 of the Munich center, 70 of the Berlin center). The ethics committees of the University of Munich and Berlin had approved the protocol and data protection laws were strictly adhered to. All study participants gave written informed consent and were included in the European Network for the Study of Adrenal Tumours (ENS@T). Study participants underwent standard procedures including collection of anthropometric data and laboratory testing.

Diagnostic work-up

The diagnostic work-up at both sites was performed in accordance with the Endocrine Society Practice Guidelines (1). The initial screening for PA was performed with the patients receiving their usual medication. In case of a high suspicion of PA, the patients were scheduled for confirmatory testing which then was done after adjustment of antihypertensive medication (1, 13, 18). Antihypertensive medication was stopped for at least 1 week (angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, beta blockers, calcium antagonists, low-dose thiazides, renin inhibitors) and 4 weeks (loop diuretics, mineralocorticoid antagonists) whenever possible, in accordance with the clinician's judgment, taking potential comorbidities into consideration. If not possible, hypertensive study participants received blood pressure-lowering medication with minimal effect on the ARR, such as an alpha receptor

blocker (doxazosin), slow-release calcium antagonists (verapamil) or low-dose dihydropyridine calcium antagonist amlodipine (Berlin center only). The diagnosis of PA was established as previously published (13, 18). In brief, PA was either confirmed by SIT and/or CCT. In accordance with the Endocrine Society Practice Guideline, patients were seated for 1 h before and during the infusion of 2 L of 0.9% saline over 4 h (8:00–12:00 h). Blood samples were drawn at time 0 and after 4 h, while vital parameters were monitored throughout the test (1). Saline infusion tests were considered diagnostic of PA, if post-test absolute aldosterone values would not be suppressed below 50 ng/L. Patients received 50 mg of captopril orally after sitting comfortably for at least 1 h. Blood samples were drawn before the beginning of the test, after 1 and 2 h after the challenge while being seated. CCTs were considered diagnostic of PA, if post-test absolute aldosterone suppression would be less than 30% of pre-test values (1). In case of a discrepancy between both test results, the urine excretion of aldosterone and its metabolites was taken into consideration in order to determine the final diagnosis (measured at Steroidlaboratorium Heidelberg, RIA (normal range): aldosterone 18-glucuronide: 3.5–17.7 µg/24 h, tetrahydroaldosterone: 10–70 µg/24 h, free urinary aldosterone: 0.1–0.4 µg/24 h). In 2016, saline infusion tests were performed as the first-line confirmatory testing. In case of contraindications to saline infusion testing (such as severe uncontrolled hypertension, cardiac arrhythmia, severe hypokalemia or severe chronic heart failure), CCTs were performed instead. From 2017 on, all study participants were scheduled for both tests sequentially, with the saline infusion tests followed by captopril challenge testing. Patients received a similar antihypertensive drug regimen during the tests. Aldosterone was measured in both centers using the DiaSorin Liaison CLIA, and plasma renin concentration (PRC) was measured in Berlin with the Diasorin Liaison and in Munich with the Diasorin Liaison Act, respectively. Since stress-induced ACTH (adrenocorticotrophic hormone) secretion might stimulate aldosterone secretion during testing, we measured serum cortisol levels during both tests.

Safety assessment and intervention during adjustment of medication phase

During the adjustment of medication phase, study participants were asked to monitor the blood pressure frequently (at least twice daily). They were asked to contact our medical staff by phone if new side effects

and/or complications occurred after the initiation of the adjustment of medication. The aim was to achieve systolic blood pressure values between 110 and 180 mmHg. We defined the lack of adequate pressure effect of the adjusted antihypertensive medication as a 'side effect'. According to the reported blood pressure values, the treating physicians recommended further dose adjustment of antihypertensive medication. Additionally, study participants were re-evaluated for the occurrence of high and low blood pressure episodes at the test day.

Safety assessment and intervention on the day of confirmatory testing

Study participants were advised to take the morning dose of antihypertensive medication at the day of the saline infusion test, but not on the day of the captopril challenge test. During both tests, a specialized endocrine nurse and a medical doctor closely monitored study participants. Blood pressure and pulse measurements were obtained before (at arrival, after 30 min of resting), during (after each hour) and after both tests. All information on side effects and medical interventions before, during and after the tests was documented by the staff. When systolic blood pressure was higher than 180 mmHg before, during or after a test, an extra dose of verapamil or doxazosin was applied. In the case of continued elevated blood pressure values, urapidil was administered intravenously. If systolic blood pressure was lowered to values below 180 mmHg, these episodes were considered resolved. If systolic blood pressure remained elevated >180 mmHg 1 h after the administration of antihypertensive medication, the test was terminated. The study participant was then monitored, and antihypertensive medication was administered until blood pressure values normalized. When systolic blood pressure was below 110 mmHg before the start of a CCT, captopril was not administered.

Statistical analysis

All values are expressed as median with 25th and 75th percentile in brackets, if not mentioned otherwise. Two-tailed probability values of <5% were considered to be statistically significant. To assess changes before and after the tests, we performed *t*-tests for dependent variables. Mann-Whitney *U* tests were used for independent variables. To compare frequencies, we performed Pearson chi-square test for categorical variables. We performed subgroup analysis for gender and post-test subtype classification. The comparison of quantitative variables

was performed using linear regression calculation and for categorical variables' logistic regression calculation. Correlation calculation was performed using Spearman coefficient for non-parametric analysis. Statistical analysis was performed using standard statistical software (SPSS 25, IBM). Figures and tables were generated using SPSS 25 or Microsoft Excel and Word for Mac, version 16.21.

Results

Key characteristics

In total, 272 study participants (159 females, 113 males) were analyzed. 269 of 272 underwent saline infusion tests (158 females, 111 males), 129 of 272 underwent CCT (72 females, 57 males) and 126 (71 females, 55 males) study participants underwent both tests. For 215/273 patients screening ARR values are available. In total, 33/215 patients had a negative screening test. In those 16 patients, it turned positive after the change of therapy. After the diagnostic work-up, eight patients had a final diagnosis of PA. SITs were positive for PA in 155/269 patients, while 110/269 had negative results. Four tests had to be terminated early. CCTs were positive for PA in 83/129, while 46/129 resulted negatively. Among those patients that completed both tests ($n=122/126$), 76 patients were classified to have PA. Both tests were positive for PA in 98/122 patients. 24/122 patients had divergent test results (10/24 positive SIT, 14/24 positive CCT). Taking urinary tests into consideration in these patients, 3/10 patients of the saline infusion-positive group were classified to have PA and 8/14 patients among the captopril challenge-positive group, respectively. Within our cohort, 53% were diagnosed with PA ($n=143$). Among the males, 67% ($n=76$) were diagnosed with PA, compared to 42% ($n=67$) of the females.

Safety during adjustment of medication

According to our standard operational procedure, hypertensive medication affecting the aldosterone-to-renin ratio was adjusted at least 1 week before the tests, as described in the 'Methods' section. The mean period of medication adjustment was 9.2 days (s.d. 6.4) for all patients. The occurrence of side effects during the adjustment of medication phase was not associated with the overall duration of this time period. No significant difference was seen when comparing patients who developed side effects to those who did not (with side

effects: 9.06 days vs no side effects 9.22 days; $P=0.883$, CI -2.334 to 2.009). Twenty-eight percent of all study participants were studied free of antihypertensive medication, while 45% received verapamil, 35% doxazosin, 4% urapidil and 16.5% amlodipine. 2.6% of all study participants received additional medications that might interfere with the ARR. Adjustment of medication was associated with side effects prior confirmatory testing in 50 study participants (18.4%) (Fig. 1). No patient had to discontinue the adjustment phase. Higher defined daily doses (DDDs) ($r=0.25$, $P<0.005$), higher overall number of antihypertensive drugs ($r=0.285$, $P<0.005$) and higher SBP at SIT ($r=0.145$, $P=0.019$) correlated with more side effects during the adjustment phase.

Saline infusion tests

Key baseline characteristics of study participants undergoing saline infusion tests are comprised in Fig. 2 and Table 1. As expected, serum cortisol levels dropped significantly during the test ($P<0.0005$), while 14/269 (5.2%, mean serum cortisol: pre-test $9.3\mu\text{g/dL}$ (s.d. 4.7), post-test $12.6\mu\text{g/dL}$ (s.d. 5.9)) of our patients did not have a cortisol reduction during the SIT. Interestingly, overall median SBP did not change significantly during SIT (2mmHg (-12 ; 11), $P=0.756$), while DBP (-2mmHg

Figure 1

Side effects during adjustment of medication phase. Overview of side effects reported during the adjustment of medication phase for both SIT and CCTs. Patients were asked to personally report side effects from the beginning of the adjustment of medication phase until the day of the testing. Hypertensive episode = episode with documented elevated systolic blood pressure ($>180\text{mmHg}$), hypotensive episode = episode with documented systolic blood pressure ($<110\text{mmHg}$), SE = side effects.

(-9 ; 5), $P=0.04$) and heart rates (-8beats/min (-14 ; 1), $P<0.0005$) decreased. Overall, median potassium levels marginally decreased (-0.06 (-0.1 ; 0.2), $P=0.01$), while 7.9% ($n=21$) received an additional dose of potassium supplementation, according to the baseline value at test day. Forty-seven study participants (17.5%) developed side effects during SITs (Fig. 3). Thirty-seven study participants (13.8%) required acute antihypertensive drug treatment

Figure 2

Pre- and post-test comparison according to subtype classification. Comparison of parameters (systolic blood pressure in mmHg, aldosterone in ng/L, cortisol in $\mu\text{g/dL}$ and potassium in mmol/L) before and after a confirmatory test according to the post-test subtype classification (primary aldosteronism (dark line) vs no primary aldosteronism (dotted line)). (A, B, C and D) Saline infusion test results of study participants with diagnosed PA (black line) and exclusion of PA (dotted line). (E, F, G and H) Captopril challenge test results of study participants with diagnosed PA (black line) and exclusion of PA (dotted line). Vertical indicators: 25th–75th percentile.

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Table 1 Saline infusion test: comparison of baseline characteristics of study participants on the day of the test.

	Men (n = 111)	Women (n = 158)	Combined (n = 269)	Significance P
Age	52.8 (44.8–61.6)	51.6 (42.3–58.7)	51.9 (42.7–60.5)	0.174
SBP in mmHg	153 (143–168)	144 (131–160)	149 (135–164)	<0.0005
DBP in mmHg	94 (85–104)	92 (83–101)	93 (84–102)	0.146
Pulse in beats/min	77 (68–85)	76 (68–85)	76 (68–85)	0.952
Aldosterone in ng/L	141 (109–210)	120 (80–183)	130 (87–192)	0.012
PRC in mU/L	4.3 (2–9.3)	3.4 (2–7.8)	3.9 (2–8.8)	0.126
ARR in ng/mU	29.1 (13.4–54.5)	33.2 (18.7–59.3)	31.5 (15.5–55)	0.523
Cortisol in µg/dL (pre-test)	12.6 (10.2–17.5)	12.2 (9.1–15.9)	12.5 (9.4–16.3)	0.178
Cortisol in µg/dL (post-test)	5.7 (4.5–7.6)	4.1 (3–5.7)	4.8 (3.5–6.4)	<0.0005
Potassium in mmol/L	3.9 (3.6–4.1)	4 (3.8–4.3)	4 (3.7–4.2)	0.001
DDD	1.5 (1–3)	0.5 (0–1)	1 (0–2)	<0.0005
DDD (morning)	1 (0.5–1.5)	0.25 (0–1)	0.5 (0–1)	<0.0005
Creatinine in mg/dL	1 (0.9–1.1)	0.8 (0.7–0.9)	0.9 (0.7–1)	<0.0005

Significance P calculated for the difference between the sexes.

ARR, aldosterone-to-renin ratio; DBP, diastolic blood pressure; DDD, defined daily dose; PRC, plasma renin concentration; SBP, systolic blood pressure.

during SIT (median DDD 1). 1.5% ($n=4$) of the tests were prematurely terminated because of uncontrolled hypertension. Side effects during the SIT correlated with higher in-hospital pre-test systolic and diastolic blood pressure values ($r=0.541$, $P<0.0005$ / $r=0.426$, $P<0.0005$) and at the end of test systolic blood pressure values ($r=0.29$, $P<0.0005$), as well as higher DDD administration ($r=0.727$, $P<0.0005$). Interestingly, lower pre- and post-test potassium values correlated with higher rates of side effects for all study participants undergoing saline infusion tests ($r=-0.184$, $P=0.003$; $r=-0.233$, $P=0.001$).

Captopril challenge tests

Key baseline characteristics of study participants undergoing CCTs are comprised in Fig. 2 and Table 2. Similar to SIT results, serum cortisol levels decreased significantly during the tests ($P<0.0005$), while 31/129 (24%, mean serum cortisol: pre-test 7.2 µg/dL (s.d. 3), post-test 10.7 µg/dL (s.d. 4.7)) of our patients had a mild increase of serum cortisol levels. As expected, overall median SBP/DBP was significantly lowered during CCT (−5 (−13.5; 3) and −3 mmHg (−9.5; 2), both $P<0.0005$). This effect was more pronounced in females (−9/−5 mmHg (−18.5; 0.5)/(−11; 0.5), $P=0.001$ / $P=0.029$). Overall, median potassium levels increased only marginally (0.06 (−0.1; 0.1), $P=0.045$), while 1.5% ($n=2$) received potassium supplementation during testing. Only 1.5% ($n=2$) required acute antihypertensive drug treatment (one male and one female patient). 2.3% ($n=3$, all females) of the CCTs were not performed because of hypotension prior to application of captopril. No other adverse effects were noted (Fig. 3). Higher DDDs during captopril challenge

test correlated with the occurrence of more side effects ($r=0.436$, $P<0.0005$).

Side effects – comparative subgroup analysis

As described earlier, 18.4% of study participants developed side effects during the adjustment of medication phase, significantly more men (24.3 vs 14.5%, $P=0.043$), independent of age ($P=0.05$). However, according to

Figure 3

Side effects during SIT and CCT. Overview of side effects that occurred during saline infusion and captopril challenge tests. Hypertensive episode (resolved) = episode with elevated systolic blood pressure (>180 mmHg) that was resolved by administration of oral and/or intravenous antihypertensive medication within 1 h. Hypertensive episode (test termination): episode with elevated systolic blood pressure that was not resolved within 1 h and led to test termination. SE = side effects, light gray columns indicate rates for saline infusion tests, black columns indicate rates for captopril challenge tests.

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Table 2 Captopril challenge test: comparison of baseline characteristics of study participants on the day of the test.

	Men (n = 57)	Women (n = 72)	Combined (n = 129)	Significance P
Age	52.8 (44.8–61.6)	51.6 (42.3–58.7)	51.9 (42.7–60.5)	0.174
SBP in mmHg	150 (140–159)	143 (132–154)	145 (137–155)	0.037
DBP in mmHg	93 (85–101)	91 (83–99)	92 (84–100)	0.084
Pulse in beats/min	70 (62–79)	70 (62–75)	70 (62–75)	0.518
Aldosterone in ng/L	119 (81–153)	82 (56.5–115)	92 (69–143)	0.001
PRC in mU/L	3.9 (2–8.6)	2 (2–3.7)	2 (2–5)	0.001
ARR in ng/mU	30.9 (14.7–43)	33 (20.4–45.8)	32.5 (17.5–44)	0.55
Cortisol in µg/dL (pre-test)	9.2 (7.1–12.8)	7.3 (6.3–10.2)	8.2 (6.6–10.9)	0.001
Cortisol in µg/dL (post-test)	7.6 (5.9–9.6)	5 (4–7.3)	6.4 (4.6–8.6)	<0.0005
Potassium in mmol/L	4 (3.7–4.2)	4 (3.7–4.3)	4 (3.7–4.3)	0.557
DDD	1.5 (0.75–3)	1 (0.25–2)	1 (0.5–2)	0.002

Significance P calculated for the difference between the sexes.

ARR, aldosterone-to-renin ratio; DBP, diastolic blood pressure; DDD, defined daily dose; PRC, plasma renin concentration; SBP, systolic blood pressure.

diagnosis (PA vs non-PA) no significant difference was identified ($P=0.234$). During saline infusion testing, significantly more men (25.2 vs 10.1%) experienced side effects, independent of age or diagnosis ($P=0.008$). However, these results remained no longer significant when adjusting for blood pressure values ($P=0.503$), indicating a gender-independent effect. Blood pressure at the start of testing remained, independent of sex, associated with side effects during SIT ($P<0.0005$, $P=0.019$). Interestingly, the underlying diagnosis (PA vs non-PA) was not linked to the incidence of side effects ($P=0.661$). The few side effects during captopril do not allow a meaningful analysis of subgroups. When comparing the study participants who underwent both tests ($n=126$), 1.6% ($n=2$) developed side effects during CCT and 20.6% ($n=26$) during saline infusion tests, with male sex being associated with side effects in a multivariate analysis ($P=0.015$).

Discussion

SIT and CCT are considered standard procedures in the diagnostic work-up for PA (1, 3). Both tests have been validated in multiple cohorts and most recently in studies conducted in China (14, 19). SITs have been associated retrospectively with higher incidence rates of cardiovascular and cerebrovascular events in PA patients (20). However, studies did not sufficiently address whether these procedures are equally safe. We, therefore, conducted a retrospective analysis of prospectively enrolled patients scheduled for PA work-up in two hypertension centers.

Our standard operational procedure for screening and confirmatory testing of PA comply with international recommendations to terminate interfering antihypertensive medications or to switch to medications

with little influence on the aldosterone-to-renin ratio. In general, adjustment or switching of antihypertensive medication is known to cause side effects mainly due to uncontrolled blood pressure (21). Almost 20% of our patients reported side effects during the adjustment of antihypertensive medication phase that did not prompt the discontinuation of the non-interfering medications. Especially men, independent of the underlying diagnosis, were more likely to develop side effects. As expected, these male patients had higher systolic blood pressure and needed more antihypertensive medications, identifying a high-risk group that warrants close and thorough monitoring by specialized medical staff. However, the interpretation of our results is limited, because it only included new side effects or complications that occurred after the adjustment of medication.

In total, 17.5% of all patients who underwent SITs developed side effects. The vast majority (78.7%) required additional antihypertensive medication due to high blood pressure during the test. Again, mostly men were affected, independent of age or the diagnosis following testing. Taking pre-test blood pressure values into account, according to logistic regression analysis, gender difference did not remain significant, indicating that elevated blood pressure is the main risk factor. These findings lead to the assumption that strict pre-test blood pressure control (SBP <180 mmHg) appears to be a key variable to target in order to prevent side effects during SIT. These side effects underline the necessity for close monitoring by specialized staff. Therefore, if careful systolic blood pressure control before the SIT can be obtained, the side effect rate might be further reduced. Whether lower systolic blood pressure cut-off values are safe has to be proven by a future study.

In contrast to the high incidence rate of side effects during SIT, CCT appears to be a safe test with very low

event rates. In addition, the CCT is a shorter, cheaper and less sophisticated test.

Other groups have compared both tests in terms of validity and reliability leading to the conclusion that they may be used interchangeably (15, 22). This study focused only on the safety of both tests in standardized settings. The SIT remains the preferred test in patients with controlled pre-test systolic blood pressure values. Our data demonstrate differences in the respective side effects, with the CCT being the safer test. We therefore prefer the CCT over the SIT in severely hypertensive patients with suspected PA.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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