

The relation of hypertension and aldosterone-renin ratio with the severity of coronary artery disease in non-diabetic patients

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Abstract

Background: The aim of this study was to assess the relationship between hypertension and aldosterone-renin ratio (ARR) with the severity of coronary artery disease (CAD).

Methods: This cross-sectional study was performed on non-diabetic patients who were candidate for coronary angiography in Shafa hospital in Kerman in 2017. The levels of active renin and aldosterone were measured by the radioimmunoassay (RIA) method before angiography. All patients underwent coronary angiography to determine the severity of CAD. The CAD severity was described by the Gensini score.

Results: Of the 306 patients, 174 (55.1%) were hypertensive. The overall prevalence of CAD in hypertensive and normotensive groups was not statistically different (39.7% versus 38.9%, $p = 0.898$). In groups with and without hypertension, normal coronary arteries were found in 60.3% and 60.8%, single-vessel disease in 15.5% and 17.7%, two-vessel disease in 14.4% and 11.5%, and three-vessel disease in 9.8% and 10.0%, respectively. The differences were not significant ($p = 0.880$). The average Gensini scores in hypertensive and normotensive groups were 29.27 ± 28.42 and 33.74 ± 33.05 , respectively with no significant differences ($p = 0.370$). The mean ARR in those with normal coronaries, one, two, and three-vessel diseases was 3.17 ± 7.63 , 2.51 ± 4.21 , 1.93 ± 1.57 , and 1.20 ± 0.68 , respectively with no significant difference ($p = 0.696$). We did not observe any association between the Gensini score and ARR ($r = -0.126$, $p = 0.263$). In multivariable linear regression model (Table 3), ARR could not predict the severity of CAD assessed by determining the Gensini score (Beta = -0.463 , $p = 0.636$).

Conclusion: There was no significant relation between hypertension and ARR to the severity of CAD.

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Introduction

Over the past two centuries, the prevalence of ischemic heart disease (IHD) has been increasing in the world,

accounting for 50% of the total mortality in advanced countries and more than 25% of deaths in developing countries. IHD is the leading cause of death world wide (1).

CAD is a multifactorial disease characterized by a series of risk factors including hyperlipidemia, hypertension, diabetes mellitus and smoking (2-5). Risk factors are important targets for reducing the risk of disease. For instance, many studies have shown that hypertension treatment can effectively reduce acute cerebrovascular accidents, coronary artery disease, and heart failure, where poor hypertension treatment and control can contribute to the growing epidemic of cardiovascular disease (6, 8). Although hypertension is a well-known risk factor for CAD; however, the extent to which the presence of hypertension affects the severity of CAD is not clear (9, 10). Of all risk factors associated with CAD, high blood pressure plays an important role because of its high prevalence in society and due to its pathogenesis. Blood pressure also increases the risk of CAD not only in the at-risk populations, but also in the general population (11).

Renin-Angiotensin-Aldosterone System (RAAS) is a group of dependent hormones for the regulation of blood pressure. In other words, this system is actually used to regulate long-term blood pressure in the body (12). Angiotensin is a peptide hormone that causes vasoconstriction and an increase in blood pressure. In addition, it can stimulate the release of aldosterone from the adrenal cortex. Aldosterone helps to absorb water and salt and increases the accumulation of water in the body and causes an increase in blood pressure (13). Also, aldosterone can increase the blood pressure independently to RAS. However, it can be assumed that increasing aldosterone leads to the development of various diseases, including high blood pressure, congestive heart failure, chronic kidney disease, coronary artery disease, and stroke.

Aldosteronism was previously considered as a rare condition; however, employing developed assessment tools could reveal that its incidence in patients with hypertension is about 6%. Aldosteronism affects 14%-21% of patients with

resistant hypertension and is, thus, the most common cause of secondary hypertension in this subgroup. The best initial test for diagnosing primary aldosteronism is to measure the aldosterone to renin ratio (ARR), which is the most sensitive test for the diagnosis of disease, because in about 25% of people with primary aldosteronism, aldosterone levels are normal (14-15).

Considering the fact that there has been no study concerning the relation between ARR to the severity of CAD, the aim of this study was to assess the relationship between hypertension and ARR with the severity of CAD.

Materials and Methods

This cross-sectional study was performed on non-diabetic patients who were candidate for coronary angiography in Shafa hospital in Kerman in 2017. After receiving informed consent, all patients were interviewed to assess their baseline characteristics including demographics, medical history, and medications. The patients with the history of diabetes mellitus, renal failure, respiratory or immunological disorders were not included. Along with interviewing and medical examination, venous blood samples were also extracted to determine the serum values of blood sugar, lipid profiles as well as the plasma levels of renin and aldosterone. The levels of active renin and aldosterone were measured (only in hypertensive group) by the RIA method, after an overnight fasting and without any medication for at least 12 hours. AAR more than 15 ng /dl was considered abnormal. Blood pressure was determined as the mean of two pressures after a sitting position for at least five minutes. Systolic and diastolic readings, in the left arm of the subject, were taken with a mercurial sphygmomanometer. Hypertension was defined as a systolic blood pressure (SBP) of 140 mm Hg or a diastolic blood pressure (DBP) of 90 mm Hg or those who were receiving antihypertensive therapy at the time of the examination. All patients underwent coronary

angiography to determine the severity of CAD. The involvement of coronary arteries was stratified as normal, one, two, and three-vessel diseases as well as the left main lesion. The CAD severity was also described by the Gensini score. In this scoring system, the percentage of involvement in each vessel is estimated obviously and then the score which is assigned to the percentage of the involvement of the corresponding vessel is multiplied in a score called Functional Sig-Score to achieve the final Gensini score. The Gensini Score spectrum is wide from zero for normal coronaries to even higher than 100 according to the severity of coronary involvement. Also, the Gensini Score less than or equal to twenty is considered as mild CAD and greater than twenty as severe involvement. The study endpoint was to test the association between ARR and CAD severity in hypertensive patients.

Quantitative data were presented as mean \pm standard deviation and qualitative data were reported as percentages and frequencies. Normality of the data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with an expected count of less than 5 were observed. Quantitative variables were also compared with ANOVA test or Kruskal-Wallis H test. The role of ARR and also blood pressure for predicting CAD severity was tested by the multivariate regression modeling with the presence of baseline variables as the confounders. For the statistical analysis, SPSS software version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

The patients were categorized into four groups including the hypertensive group with normal coronaries (n = 79),

hypertensive group with CAD (n = 95), normotensive group with CAD (n = 62), and normotensive group with normal coronaries (n = 70). Comparing baseline variables across the four groups (Table 1) showed a significant difference in some parameters including gender, age, body mass index (BMI), serum creatinine, and using some drugs such as aspirin, Plavix, metoral, nitrocontin, and lozar. In this regard, those groups with CAD regardless of the presence of a hypertensive status had higher male to female ratio, higher mean age, and higher serum creatinine level. Also, the use of above-mentioned drugs was more reported in hypertensive groups with and without CAD. To assess the relationship between hypertension and severity of CAD, we observed that the overall prevalence of CAD in hypertensive and normotensive groups was not statistically different (39.7% versus 38.9%, $p = 0.898$). In this regard, in the groups with and without hypertension, normal coronary condition was found in 60.3% and 60.8%, single-vessel disease in 15.5% and 17.7%, two-vessel disease in 14.4% and 11.5%, and three-vessel disease in 9.8% and 10.0%, respectively without a significant difference ($p = 0.880$). The average Gensini score in hypertensive and normotensive groups was 29.27 ± 28.42 and 33.74 ± 33.05 , respectively with no significant difference ($p = 0.370$). In this regard, no significant linear association was also found between Gensini score and systolic blood pressure ($r = -0.055$, $p = 0.498$) and diastolic blood pressure ($r = 0.001$, $p = 0.998$). Using multivariable logistic regression model (Table 2), HTN could not predict the severity of CAD in non-diabetic patients (OR = 1.566, $P = 0.398$). In the two hypertensive groups with and without CAD, the mean serum level of renin was 98.99 ± 64.34 and 100.93 ± 66.50 ($p = 0.855$), the mean level of aldosterone was 119.04 ± 51.45 and 108.30 ± 54.55 ($p = 0.214$), and the mean ARR was 3.32 ± 8.51 and 2.27 ± 3.48 ($p = 0.310$) indicating no difference between the two groups in terms of these biomarkers. The mean

of ARR in those with normal coronaries, one, two, and three-vessel diseases was 3.17 ± 7.63 , 2.51 ± 4.21 , 1.93 ± 1.57 , and 1.20 ± 0.68 , respectively with no significant difference ($p = 0.696$). Also, we did not observe an association between

Gensini score and ARR ($r = -0.126$, $p = 0.263$). In multivariable linear regression model (Table 3), ARR could not predict the severity of CAD assessed by determining the Gensini score (Beta = -0.463 , $p = 0.636$).

Table 1. Baseline characteristics of study subjects

ITEM	HTN(+).CAD(-) (N=79)	HTN(+).CAD(+) (N=95)	HTN(-).CAD(+) (N=62)	HTN(-).CAD(-) (N=70)	P VALUE
MALE, GENDER	36 (45.6)	61 (64.2)	44 (72.1)	29 (41.4)	< 0.001
AGE, YEAR	53.32±9.50	58.27±9.51	57.23±9.66	52.93±11.17	0.001
BMI	26.31±5.16	24.63±4.58	24.18±4.28	25.17±4.71	0.068
FBS, MG/DL	94.08±11.51	91.91±10.25	92.26±10.57	94.67±12.64	0.341
CR, MG/DL	0.96±0.02	1.07±0.22	1.11±0.19	1.00±0.21	< 0.001
CHOL, MG/DL	145.25±32.41	138.12±39.19	145.03±42.65	140.98±41.57	0.590
TG, MG/DL	112.71±53.89	114.64±70.89	109.11±47.03	104.40±36.10	0.672
HDL, MG/DL	38.39±9.04	37.49±11.32	38.92±12.19	40.73±10.07	0.284
LDL, MG/DL	83.86±32.20	77.79±33.44	84.20±35.47	78.00±37.53	0.598
SBP, MMHG	125.10±16.31	120.84±13.50	115.33±11.61	121.64±13.95	0.001
DBP, MMHG	75.30±9.35	72.72±10.83	70.08±8.03	75.72±8.00	0.001
ASA USE	59 (74.7)	79 (83.2)	12 (19.7)	3 (4.3)	< 0.001
PLAVIX USE	12 (15.2)	26 (27.4)	54 (88.5)	43 (61.4)	< 0.001
ATORVASTATIN	48 (60.8)	68 (71.6)	43 (70.5)	41 (58.6)	0.212
METORAL	46 (58.2)	49 (51.6)	2 (3.3)	2 (2.9)	< 0.001
NITROCANTIN	45 (57.0)	60 (63.2)	4 (6.6)	4 (5.7)	< 0.001
LOZAR	38 (48.1)	45 (47.4)	2 (3.3)	5 (7.1)	< 0.001
CAPTOPRIL	11 (13.9)	20 (21.1)	6 (9.8)	6 (8.6)	0.091
CARVEDILOL	3 (3.8)	6 (6.3)	0 (0.0)	1 (1.4)	0.130

Table 2. Multivariate logistic regression model to determine the association between hypertension state and the severity of CAD

Item	B	S.E.	Wald	P value	Odd ratio	95.0% CI for OR	
						Lower	Upper
HTN	0.449	0.531	0.715	0.398	1.566	0.554	4.432
age	0.029	0.014	4.160	0.041	1.029	1.001	1.058
sex	-0.630	0.269	5.488	0.019	0.532	0.314	0.902
BMI	-0.087	0.031	7.806	0.005	0.917	0.863	0.974
FBS	-0.010	0.012	0.678	0.410	0.990	0.967	1.014
Cr	2.645	0.679	15.151	0.000	14.079	3.717	53.320
Chol	-0.025	0.027	0.867	0.352	0.975	0.925	1.028
TG	0.006	0.006	1.132	0.287	1.006	0.995	1.018
HDL	0.039	0.030	1.684	0.194	1.040	0.980	1.104
LDL	0.029	0.027	1.188	0.276	1.030	0.977	1.085
ASA	-0.588	0.401	2.150	0.143	0.555	0.253	1.219
Plavix	-0.711	0.356	3.986	0.046	0.491	0.244	0.987
Atorvastatin	-0.389	0.305	1.628	0.202	0.678	0.373	1.232
Metoral	-0.507	0.357	2.021	0.155	0.602	0.299	1.212
Nitrocantfin	-0.369	0.343	1.157	0.282	0.691	0.353	1.354
Lozar	-0.113	0.356	0.102	0.750	0.893	0.445	1.792
Captopril	-0.136	0.408	0.110	0.740	0.873	0.393	1.942
Carvediol	0.067	0.769	0.008	0.931	1.069	0.237	4.828
Constant	1.877	2.604	.519	0.471	6.534		

Hosmer-Leme show goodness of fit: Chi-Square: 4.144, p = 0.844

Table 3. Multivariate linear regression model to determine the association between ARR and gensini score

Item	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Std. Error	Beta		
(Constant)	-6.382	59.482		-0.107	0.915
ARR	-0.463	0.973	-0.060	-0.476	0.636
age	-0.169	0.402	-0.057	-0.420	0.676
sex	0.042	7.139	0.001	0.006	0.995
BMI	0.415	0.768	0.068	0.541	0.591
FBS	-0.245	0.334	-0.096	-0.733	0.466
Cr	26.507	17.805	0.203	1.489	0.142
Chol	-0.440	1.922	-0.651	-0.229	0.820
TG	0.068	0.383	0.142	0.178	0.859
HDL	0.310	1.970	0.130	0.157	0.875
LDL	0.504	1.920	0.640	0.262	0.794
ASA	1.218	9.897	0.017	0.123	0.902
Osvix	-1.720	8.814	-0.028	-0.195	0.846
Plavix	1.343	12.474	0.016	0.108	0.915
Plavix	-5.595	7.795	-0.096	-0.718	0.476
Metoral	-7.084	6.885	-0.132	-1.029	0.308
Nitrocantín	-14.167	7.799	-0.256	-1.816	0.074
Lozar	10.986	7.954	0.205	1.381	0.172
Captopril	16.401	10.250	0.239	1.600	0.115
Carvediol	10.097	15.743	0.091	0.641	0.524

R-square = 0.209

Discussion

In the present study the relationship between hypertension and the severity of CAD was investigated in non-diabetic patients. Also, the difference in ARR was evaluated between hypertensive and normotensive groups. According to the results, there was no significant correlation between hypertension and the severity of CAD. Evidence shows that hypertension is a powerful risk factor for the development of CAD (16). In fact, linking hypertension with other traditional risk factors such as diabetes, hyperlipidemia and smoking along with the critical role of familial tendency can powerfully increase the likelihood of CAD in suspected patients; however, this issue remains as an important challenge in non-diabetic patients. This insignificant association can be explained by some suggestions. First, the majority of our hypertensive patients were under treatment with anti-hypertensive drugs. For these patients the mean of systolic and diastolic blood pressure was in the controlled range and therefore the triggering effects of hypertension on the progression of coronary atherosclerosis might be masked by anti-hypertensive medications. Additionally, a strong link between diabetes and raised blood pressure may be the main factor for developing CAD and therefore the presence of isolated hypertension without any evidence of diabetes may not have enough power to flare coronary atherosclerosis (17).

As the second hypothesis and due to the strong association between RAAS with hypertension and CAD, we hypothesized that the increase in ARR might predict the severity of CAD even in non-diabetic patients. However, we could not see this causality. In other words, ARR cannot be useful to predict CAD severity in hypertensive non-diabetic patients. It might be also

referred to the controlled condition of hypertension using medications. As previously shown by Bhandari et al., higher plasma renin activity levels demonstrated an increased risk for ischemic heart events and congestive heart failure. In addition, a trend toward higher mortality among individuals with raised systolic blood pressure was seen but this trend was not observed among those with SBP less than 140 mmHg (18). In fact, it seems that plasma activation of renin is a reflection of physiological compensation in normotensive state, while higher plasma renin activity levels in those with elevated blood pressure denote a pathophysiologic state. In another study performed by Erne et al., findings showed that renin was significantly elevated in patients with either hypertension or CAD, but the ARR was elevated only in atrial fibrillation patients and in patients with hypertensive cardiomyopathy, but not in CAD subgroups (19). This finding is consistent with our study. Ali IA et al., showed that aging, duration and magnitude of hypertension and left ventricular hypertrophy have a strong and frequent association with CAD (20). These findings prompt a recommendation for the clinical practice to consider and search for the presence of hyperaldosteronism in patients with resistant hypertension and hypertensive heart disease with atrial fibrillation rhythm.

Conclusion

It can be concluded that the history of hypertension may not be a powerful predictor of the severity of CAD in non-diabetic patients. Also, the change in ARR may not predict CAD severity in hypertensive non-diabetic patients. It should be considered that controlling the hypertensive state in our patients may explain these insignificant relations.

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