H-type Hypertension is a risk factor for Cerebral Small Vessel Disease: a retrospective study

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Abstract

Background: The correlation between H-type hypertension and cerebral small-vessel diseases (CSVD) remains uncertain. The present study was designed to explore the possible relationship between H-type hypertension and CSVD spectrum and total burden. Methods: We included 329 patients in the present study and divided them into four groups: H-type hypertension group, the isolated hypertension group, the isolated hyperhomocysteinemia (HHcy) group and the control group. Clinical variables of interest and the MR examination sequences were obtained. We count the presence of each CSVD feature and rated the total burden of CSVD on an ordinal scale from 0 to 4 according to a recent described score rule. Results: The results showed that H-type hypertension was associated with the presence of CMB and the severity of WMH and PVS. CSVD total burden was significantly related to age (OR: 1.059, 95% CI: 1.037-1.082), systolic pressure (OR: 1.122, 95% CI: 1.007-1.136), triglycerides (OR: 1.386, 95% CI: 1.037-1.854), isolated HHcy (OR: 4.154, 95% CI 1.836–9.401) and H-type hypertension (OR: 5.028, 95% CI 2.323-10.883). And we further observed hypertension and HHcy had a synergistic effect on CSVD total burden (OR: 2.776, 95% CI 1.564-4.927). Conclusions: H-type hypertension may act as an independent risk factor of CSVD and cause increased susceptibility to CSVD total burden and CSVD spectrum, which deserved further prevention measures.

Background

Cerebral small-vessel diseases (CSVD) is an intrinsic disorder of small arteries, arterioles, venules and capillaries of the brain(1). From a clinical point of view, CSVD contributes to a risk of cognitive decline, dementia and stroke, and causes considerable worsening of cognitive function, gait, and balance(2). In recent years, the development of neuroimaging has improved the diagnostic rate of CSVD. The recognized neuroimaging spectrum ascribable to CSVD has been expanded including leukoaraiosis, cerebral microbleeds, lacunar infarcts, perivascular spaces and brain atrophy currently(1). Magnetic resonance (MR) is the gold standard imaging for CSVD, and four closely correlated features are markers on brain MR: white hyperintensities (WHM), lacunes, cerebral microbleeds (CMBs), and perivascular spaces (PVS).

Recently, a total SVD burden score was proposed(3-5), which capture the global effect of cerebral SVD and quantified the global burden with a combined score. In this score, one point is allocated to each of the following: presence of lacunes, presence of microbleeds, moderate to severe WHM, PVS grated. The score has been tested partly for association with vascular risk factors or stroke subtype in few studies(6, 7).

H-type hypertension, which refers to concurrence of primary hypertension and elevated homocysteine levels, is a special hypertension type. In China, approximately 75% of the hypertensive patients simultaneously have hyperhomocysteinemia (HHcy). Previous studies suggested that H-type hypertension could be a significant risk factor for cardio-cerebrovascular disease and that their effects are synergistic(8, 9). Thus, H-type hypertension has received increasing attention over the years and has

become a hot-spot. However, few studies have assessed the association between H-type hypertension and CSVD.

This retrospective study was designed to investigate the impact of H-type hypertension on CSVD spectrum and CSVD total burden. And we aimed to screen the risk factors of CSVD and prevent CSVD at an early stage.

Methods

2.1 Study design and subjects: The present study was performed in Stroke Center of First Hospital Affiliated to Soochow University, and included 329 patients diagnosed with ischemic stroke who were admitted to our hospital between October 2015 to February 2018. The patients who underwent admission and finished MR-based imaging were included. The participants were divided into four groups: the control group (patients with neither hypertension nor HHcy), the isolated hypertension group, the isolated HHcy group and the H-type hypertension group. At least 2 trained neurologists from our stroke center evaluated the clinical features and diagnostic test results. All data were analyzed anonymously. Ethical approval for this study was obtained from the ethics committees of the First Hospital Affiliated to Soochow University and informed consent was obtained from all of our participants

2.2 Clinical information and indexes determination：Clinical variables of interest included age (calculated according to the ID birth date), gender, education level, marital status were collected. Lifestyle factors including smoking and alcohol consumption, past medical history, family history, disease history of hypertension history, diabetes history, stroke history, hyperlipidemia history and coronary heart disease history were obtained. Hypertension was defined as the presence any of the following: systolic blood pressure ≥ 140 mmHg, or diastolic pressure ≥ 90 mmHg for twice in quiet conditions or having self-reported history of hypertension. Diabetes mellitus was defined as the presence any of the following: fasting serum glucose > 7.0 mmol/L or postprandial 2h plasma glucose > 11.1 mmol/L or having previous history of diabetes. Hyperlipidemia was defined as having elevated level of one of triglyceride, total cholesterol or low density lipoprotein. Venous blood samples from the participants were collected on an empty stomach the second day after admission. The serum Hcy level were measured within 24h of hospitalization using enzymatic cycling method. HHcy was defined as Hcy concentration ≥12.0 umol/L. Full neurological examination, brain CT or MRI scan and carotid ultrasonography were also recorded.

2.3 Brain MRI acquisition and Analysis: The MR examination was performed within 48 hours after admission and sequences included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), axial diffusion-weighted imaging (DWI), and TOF-MRA sequences. MR was rated for the presence of lacunes, white matter hyperintensities, cerebral microbleeds, and perivascular spaces independently. Lacunes was defined as rounded or ovoid shaped lesions, >3- and <20-mm diameter on T1, T2 or FLAIR sequences in basal ganglia, the white matter or brainstem. We defined microbleeds as small (<5 mm), homogeneous, round foci of low signal intensity on gradient echo images in basal ganglia, white matter, cerebellum, brainstem or cortico-subcortical junction(10). EPVS was defined as small (<3 mm) round or

linear hyperintensities in the basal ganglia or centrum semiovale on T2 images, and they were rated using a five-point ordinal scale12 as follows: 0=no EPVS, 1=1-10 EPVS, 2=11-20, EPVS, 3=21-40 EPVS, and 4=>40 EPVS. Three trained neurologists and 2 neuroradiologists, each of whom was blinded to clinical information rated all the available scans for the presence and severity of SVD features. Deep and periventricular WMH were both coded according to the Fazekas scale from 0 to 3(11).

Based on the recent described score(4), we count the presence of each SVD feature and rated the total burden of SVD on an ordinal scale from 0 to 4. The MR manifestation of WMHs graded 2-3 according to Fazekas grading was recorded as 1 point, presence of CMBs or lacunes was recorded 1 point respectively, PVS graded 2-4 (≧11) was counted 1 point (Table 1). The severity of total SVD burden score were divided into three categories: mild (0 or 1 point), moderate (2 points), severe (3 or 4 points)(3, 12).

2.4 Statistical analysis: Statistical analysis was performed with SPSS13.0 (SPSS, Inc., Chicago, IL, USA). Normally distributed variables were presented as the mean ± Standard Deviation (SD) and categorical data were presented as frequency or ratio. Kolmogorov–Smirnov was used for the test of normality of quantitative data. Levene's test was used to test homogeneity of variance. T test or one-way ANOVA was performed to compare the distribution of quantitative variables. χ^2 test was used to compare the distribution of classification index. To determine the independent factors related to CSVD, we performed one variable analysis and multiple logistic regression analysis by using a backward elimination method and set the probability at 0.10 for removal. The statistical significance level was set at $p < 0.05$ in the present study.

Results

3.1 Baseline characteristics. A total of 329 (220 males and 109 females) participants were finally included and they were divided into four groups. There were 76 participants (23.10%) in the control group, 112 participants (34.04%) in the isolated HBP group, 53 participants (16.11%) in the isolated HHcy group and 88 participants (26.75%) in the H-type hypertension group at baseline. Table 2 summarized the clinical characteristics of patients with H-type hypertension. Participants with H-type hypertension were more likely to be eldly, male, have higher systolic pressure, have a higher level of uric acid and Hcy, have a medical history of diabetes mellitus than the control participants. When compared the isolated hypertension group to the H-type hypertension group, the higher Hs-CRP (4.24±4.69 vs 6.12±6.77) level were observed in H-type hypertension participants ($P<0.05$), as well as gender, uric acid (283.55±78.97 vs 344.58±106.09) and Hcy level (8.81±2.49 vs 22.46±27.68) had significant difference between the two groups ($P<0.01$). Diabetes (1.9% vs 22.7%) and systolic pressure (134.39±14.42 vs 147.19±19.24) had a significant difference between the isolated HHcy group and the H-type hypertension group (all $P<0.01$).

3.2 Correlation between H-type hypertension and CSVD spectrum. CSVD spectrum included WMH, LI, CMB and PVS. We analysed the correlation between H-type hypertension and these subtypes, and our results showed that the H-type hypertension participants were more likely susceptible to the presence of CMB, more serious WMH and PVS, higher CSVD burden score than the control group. When it came to the H-

type hypertension group and the isolated HBP group, more serious WMH, higher frequency of CMB occurrence, and higher CSVD total burden score could be observed in the H-type hypertension participants. More patients suffered from moderate-severe WMH and CMB presence in the H-type hypertension group compared with the isolated HHcy group (Table 3 & Figure 1).

3.3 The association of risk factors with CSVD total burden. A number of predictors of CSVD were shown in the logistic regression model (Table 4). Single factor analysis indicated that age, systolic pressure and diastolic pressure were contributed to the high CSVD total burden. However, after the multivariate adjustment, CSVD total burden was significantly related to age (OR: 1.059, 95% CI: 1.037-1.082), systolic pressure (OR: 1.122, 95% CI: 1.007-1.136), triglycerides (OR: 1.386, 95% CI: 1.037-1.854).

3.4 The association of H-type hypertension with CSVD total burden. In univariate analysis, baseline isolated hypertension (OR: 3.339, 95% CI: 1.751-6.369), isolated HHcy (OR: 5.317, 95% CI: 2.469-11.447) and H-type hypertension (OR: 9.667, 95% CI: 4.725-19.778) were all associated with the CSVD total burden. In multivariate analysis, we adjusted for age, systolic pressure and triglycerides and found that isolated HHcy (multivariate-adjusted OR: 4.154, 95% CI 1.836–9.401) and H-type hypertension (multivariate-adjusted OR: 5.028, 95% CI 2.323–10.883) were indicators of CSVD total burden. Finally, we investigated whether there were synergistic association between hypertension and HHcy, the results showed that after the multivariate adjustment of age, systolic pressure and triglycerides, hypertension and HHcy had a synergistic effect on CSVD total burden (OR: 2.776, 95% CI 1.564-4.927). The results were shown in table 5.

Discussion

A direct relationship between Hcy and CSVD spectrum has been observed in several studies. One study reported that patients suffered from CSVD with confluent leukoaraiosis had the highest serum Hcy level compared with other TOAST subtypes of stroke(13). Another study found that in Japanese patients elevated Hcy level is independently associated with leukoaraiosis, but not with the incidence of microbleeds(14). Lin et. al reported both smoking and total HCY levels were shown to be risk factors for LA occurrence(15). Wang et al observed an independent association between Hcy level and severity of the CMBs(16). Miwa et al reported that serum Hcy was associated with lacunas, CMBs, and strictly deep CMBs(17). Elevated Hcy level increases hypercogulability(18) and oxidative stress(3), induces endothelial dysfunction and smooth muscle cell proliferation(19), increases hypercoagulability, and thus contributed to the damage of blood brain barrier.

Our study is the first to focus on the predictive impact of H-type hypertension on CSVD. In our research population, we studied the relationship between H-type hypertension and CSVD spectrum, and observed that H-type hypertension was associated with the presence of CMB and the severity of WMH and PVS.

However, CSVD imaging features usually occur together, a relative study showed that signs of two or more severe CSVD features may appear in around one-third of the patients suffered acute ischemic stroke. A number of researches indicated that quantification of global burden of CSVD is feasible,

meaningful and has clinical relevance(20, 21). The total CSVD burden may provide a more comprehensive view of the global impact of CSVD than do the single feature separately. Thus, in the present study, we aimed to study the effect of H-type hypertension on the CSVD total burden. We observed that isolated homocysteine and H-type hypertension were associated with CSVD total burden. Like other traditional risk factors, such as age, systolic pressure and triglycerides, H-type hypertension is an independent risk factor for CSVD total burden. Our study is the first to focus on the predictive impact of H-type hypertension on CSVD spectrum and CSVD total burden.

In the present study, CSVD total burden was significantly related to age, systolic pressure, triglycerides, isolated HHcy and H-type hypertension. And we further observed hypertension and HHcy had a synergistic effect on CSVD total burden (OR: 2.776, 95% CI 1.564-4.927).

The certain synergistic effect of hypertension and HHcy can be observed in some recent studies(22, 23). A large population-based study showed that H-type hypertension contributed to a remarkable increase of stroke incidence compared with isolated HBP(24). Another study that enrolled 750 subjects of cardiac, cerebral, and peripheralreported disease reported that the incidence of atherosclerotic vascular diseases was about five times higher than that of the patients who suffered from the isolated hypertension(25). The primary mechanisms may be explained by the fact that HHcy activates the angiotensin-converting enzyme by inhibiting the production of endogenous hydrogen sulfide to aggravate hypertension(26-28). Another study discovered that reduction of Treg cells percentage might be an important cause of immune disorders in H-type hypertension patients. According to their results, HHcy oxidized to peroxide causing T-cell subsets imbalance and vascular injury aggravation(29). Thus, when hypertension and HHcy are combined, the adverse effects may be increased.

The potential limitations in the study need to be acknowledged. First, vitamin B12, pyridoxal-5-phosphate and some medicines are related to Hcy metabolism and may affect the results. However, in our study, we only tested the plasma homocysteine level and did not record patients' medications at baseline. In future follow-up studies, we will add these parameters and expect to further interpreted the relationship between H-type hypertension and CSVD. Subsequently, we only detected blood pressure and the level of plasm Hcy at one time-point and have no data on possible changes in the long-term. Finally, the sample size in our study was relatively small that might have an impact on the overall assessment of the results.

5. Conclusions

In conclusion, our study indicated that H-type hypertension may cause increased susceptibility to CSVD total burden and CSVD spectrum, which deserved further prevention measures.

Conclusions

In conclusion, our study indicated that H-type hypertension may cause increased susceptibility to CSVD total burden and CSVD spectrum, which deserved further prevention measures

Abbreviations

CSVD: Cerebral small-vessel diseases; MR: Magnetic resonance;

WHM: White hyperintensities; CMBs: cerebral Microbleeds;

PVS: Perivascular spaces; HHcy: Hyperhomocysteinemia;

FLAIR: Fluid-attenuated inversion recovery; DWI: Diffusion-weighted imaging;

SD: Standard Deviation

Declarations

Ethics approval and consent to participate:

The present study was approved by the ethics committees of the First Hospital Affiliated to Soochow University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee, and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all of our participants

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

CXY and FQ devised the study. LT and LXY collected and analyzed data, and drafted the manuscript. DSS and KY participated in the clinical evaluation of the patients, and performed MRI data analysis and

interpretation. DXY, YS and LSJ conceived of the study, and helped to draft and revise the manuscript. All authors provided intellectual input to the study and approved the final version of the manuscript.

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Consent for publication:

A written consent form was obtained from all participants for potentially publishing their clinical data and images while protecting their personal information.

References

1. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol. 2013;12(5):483-97.
2. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9(7):689-701.
3. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. Neurology. 2014;83(14):1228-34.
4. Klarenbeek P, van Oostenbrugge RJ, Rouhl RP, Knottnerus IL, Staals J. Ambulatory blood pressure in patients with lacunar stroke: association with total MRI burden of cerebral small vessel disease. Stroke. 2013;44(11):2995-9.
5. Huijts M, Duits A, van Oostenbrugge RJ, Kroon AA, de Leeuw PW, Staals J. Accumulation of MRI Markers of Cerebral Small Vessel Disease is Associated with Decreased Cognitive Function. A Study in First-Ever Lacunar Stroke and Hypertensive Patients. Front Aging Neurosci. 2013;5:72.
6. Brenner D, Labreuche J, Pico F, Scheltens P, Poirier O, Cambien F, et al. The renin-angiotensin-aldosterone system in cerebral small vessel disease. J Neurol. 2008;255(7):993-1000.
7. Pico F, Labreuche J, Touboul PJ, Leys D, Amarenco P. Intracranial arterial dolichoectasia and small-vessel disease in stroke patients. Ann Neurol. 2005;57(4):472-9.
8. Trabetti E. Homocysteine, MTHFR gene polymorphisms, and cardio-cerebrovascular risk. J Appl Genet. 2008;49(3):267-82.
9. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. Nutr J. 2015;14:6.
10. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12(8):822-38.
11. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol. 1987;149(2):351-6.

12. Nighoghossian N, Abbas F, Cho TH, Geraldo AF, Cottaz V, Janecek E, et al. Impact of leukoaraiosis on parenchymal hemorrhage in elderly patients treated with thrombolysis. Neuroradiology. 2016;58(10):961-7.
13. Ma Y, Zhao X, Zhang W, Liu L, Wang Y, Fang R, et al. Homocysteine and ischemic stroke subtype: a relationship study in Chinese patients. Neurol Res. 2010;32(6):636-41.
14. Naka H, Nomura E, Takahashi T, Wakabayashi S, Kajikawa H, Kohriyama T, et al. Plasma total homocysteine levels are associated with advanced leukoaraiosis but not with asymptomatic microbleeds on T2*-weighted MRI in patients with stroke. Eur J Neurol. 2006;13(3):261-5.
15. Lin Q, Huang WQ, Ma QL, Lu CX, Tong SJ, Ye JH, et al. Incidence and risk factors of leukoaraiosis from 4683 hospitalized patients: A cross-sectional study. Medicine (Baltimore). 2017;96(39):e7682.
16. Wang BR, Ou Z, Jiang T, Zhang YD, Zhao HD, Tian YY, et al. Independent Correlation of Serum Homocysteine with Cerebral Microbleeds in Patients with Acute Ischemic Stroke due to Large-Artery Atherosclerosis. J Stroke Cerebrovasc Dis. 2016;25(11):2746-51.
17. Miwa K, Tanaka M, Okazaki S, Yagita Y, Sakaguchi M, Mochizuki H, et al. Increased Total Homocysteine Levels Predict the Risk of Incident Dementia Independent of Cerebral Small-Vessel Diseases and Vascular Risk Factors. J Alzheimers Dis. 2016;49(2):503-13.
18. Durand P, Lussier-Cacan S, Blache D. Acute methionine load-induced hyperhomocysteinemia enhances platelet aggregation, thromboxane biosynthesis, and macrophage-derived tissue factor activity in rats. FASEB J. 1997;11(13):1157-68.
19. Zhang C, Cai Y, Adachi MT, Oshiro S, Aso T, Kaufman RJ, et al. Homocysteine induces programmed cell death in human vascular endothelial cells through activation of the unfolded protein response. J Biol Chem. 2001;276(38):35867-74.
20. Staals J, Booth T, Morris Z, Bastin ME, Gow AJ, Corley J, et al. Total MRI load of cerebral small vessel disease and cognitive ability in older people. Neurobiol Aging. 2015;36(10):2806-11.
21. Arba F, Inzitari D, Ali M, Warach SJ, Luby M, Lees KR, et al. Small vessel disease and clinical outcomes after IV rt-PA treatment. Acta Neurol Scand. 2017;136(1):72-7.
22. Zhang W, Sun K, Chen J, Liao Y, Qin Q, Ma A, et al. High plasma homocysteine levels contribute to the risk of stroke recurrence and all-cause mortality in a large prospective stroke population. Clin Sci (Lond). 2009;118(3):187-94.
23. Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E, Heart Outcomes Prevention Evaluation I. Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial. Stroke. 2009;40(4):1365-72.
24. Pang H, Han B, Fu Q, Zong Z. Association of High Homocysteine Levels With the Risk Stratification in Hypertensive Patients at Risk of Stroke. Clin Ther. 2016;38(5):1184-92.
25. Graham IM, Daly LE, Refsum HM, Robinson K, Brattstrom LE, Ueland PM, et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. JAMA. 1997;277(22):1775-81.

26. Mendis S, Athauda SB, Naser M, Takahashi K. Association between hyperhomocysteinaemia and hypertension in Sri Lankans. J Int Med Res. 1999;27(1):38-44.
27. Laggner H, Hermann M, Esterbauer H, Muellner MK, Exner M, Gmeiner BM, et al. The novel gaseous vasorelaxant hydrogen sulfide inhibits angiotensin-converting enzyme activity of endothelial cells. J Hypertens. 2007;25(10):2100-4.
28. Antoniades C, Antonopoulos AS, Tousoulis D, Marinou K, Stefanadis C. Homocysteine and coronary atherosclerosis: from folate fortification to the recent clinical trials. Eur Heart J. 2009;30(1):6-15.
29. Li T, Zhu J, Fang Q, Duan X, Zhang M, Diao S, et al. Association of H-Type Hypertension with Stroke Severity and Prognosis. Biomed Res Int. 2018;2018:8725908.

Tables

Table1. The scale of CSVD total burden

CSVD MRI spectrum	White matter hyperintensities	Perivascular space	Microbleeds	Lacunes
Visual assessment	Fazekas scale	Semiquantitative scale	Consensus definition	Consensus definition
Grade	Perivebtricular WMH Fazekas 3 and/or deep WMH Fazekas 2-3	Semiquantitative scale 2-4	≥ 1 Microbleed	≥ 1 Lacune
Score	1 point	1 point	1 point	1 point

Table 2. Clinical baseline characteristics of participants according to H-type hypertension

Variables	Control group (n=76)	Isolated HBP (n=112)	Isolated HHcy (n=53)	H-type HBP group (n=88)	c2/F	P
Age	55.78±13.36	63.35±12.82**	63.45±13.03*	66.44±13.15**	9.624	0.000
Male	49(64.5%)	65(58.0%)	36(67.9%)	70(79.5%)*##	10.551	0.014
Diabetes melitus	7(9.3%)	32(28.6%)**	1(1.9%)##	20(22.7%)*DD	22.647	0.000
Cardiac diseases	12(15.8%)	16(14.3%)	11(21.2%)	19(21.6%)	2.429	0.488
Systolic pressure	132.33±13.04	148.80±17.86**	134.39±14.42##	147.19±19.24**DD	21.022	0.000
Diastolic pressure	79.08±9.69	85.78±11.75**	79.66±10.74##	82.98±14.48	5.900	0.001
TC (mmol/l)	4.11±0.92	4.28±1.08	3.99±0.83	4.39±1.02	2.274	0.080
TG (mmol/l)	1.34±0.60	1.72±1.28	1.17±0.46##	1.64±1.19	4.453	0.004
HDL-C (mmol/l)	1.19±0.28	1.25±0.34	1.17±0.30	1.21±0.29	1.222	0.302
LDL-C (mmol/l)	2.38±0.80	2.54±0.89	2.31±0.70	2.63±0.75	2.347	0.073
Glucose (mmol/l)	5.80±2.28	6.90±2.70*	5.24±0.99##	6.27±1.91	7.876	0.000
Urid acid (U/L)	281.40±74.02	283.55±78.97	313.71±90.11	344.58±106.09**##	10.187	0.000
Hs-CRP (mg/L)	4.19±6.27	4.24±4.69	4.18±4.65	6.12±6.77#	2.441	0.064
Hcy (umol/l)	8.00±2.29	8.81±2.49	22.60±20.86**#	22.46±27.68**##	19.049	0.000

NOTE: **P＜0.01，*P＜0.05 vs control group；##P＜0.01，#P＜0.05 vs isolated hypertension group；DDP＜0.001，DP＜0.005 vs isolated HHcy group. HBP is the abbreviation of hypertension.

Table 3. Correlation between H-type hypertension and CSVD spectrum.

CSVD spectrum	Control group	Isolated HBP	Isolated HHcy	H-type HBP group	c2/F	P
Moderate-Severe WMH	9(11.8%)	36(32.1%)**	16(30.2%)*	55(62.5%)**##DD	47.938	0.000
LI presence	41(53.9%)	78(69.6%)**	34(64.2%)	56(63.6%)	4.827	0.185
CMB presence	6(7.9%)	21(18.8%)	16(30.2%)*	45(51.1%)**##D	44.478	0.000
PVS grade 2-4	17(22.4%)	39(34.8%)	25(47.2%)*	51(58.0%)*	14.696	0.002
Moderate-Severe CSVD burden score	18(23.7%)	57(50.9%)**	33(62.3%)**	66(75%)**#	45.331	0.000

NOTE: **P<0.01,*P<0.05 vs control group,##P<0.01,#P<0.05 vs isolated hypertension group,DDP<0.001,DP<0.05 vs isolated HHcy group. HBP is the abbreviation of hypertension.

Table 4. The association of risk factors with CSVD total burden

	Single factor analysis		Multiple analysis	
Risk factors	OR	95%CI	OR	95%CI
Age	1.048	1.029-1.067	1.059	1.037-1.082
Gender	0.913	0.577-1.446	0.632	0.373-1.071
Diabetes melitus	1.413	0.800-2.497	1.387	0.694-2.770
Cardiac diseases	1.456	0.819-2.594	1.068	0.544-2.096
Systolic pressure	1.026	1.013-1.040	1.122	1.007-1.136
Diastolic pressure	1.020	1.001-1.039	1.014	0.989-1.041
Total cholesterol	1.018	0.819-1.266	0.823	0.631-1.073
Triglycerides	1.200	0.948-1.518	1.386	1.037-1.854
LDL	1.046	0.800-1.368	1.123	0.549-2.296
HDL	0.798	0.394-1.617	0.657	0.251-1.720
Glucose	1.040	0.944-1.145	0.957	0.854-1.073
Uric acid	1.001	0.999-1.004	1.001	0.998-1.004
Hs-CRP	1.020	0.982-1.061	1.010	0.964-1.059

Table 5. The association of H-type hypertension with CSVD total burden

	Single factor analysis		Multiple factor analysis	
Variables	OR	95%CI	OR	95%CI
Control	1.000		1.000	
Isolated hypertension	3.339	1.751-6.369	1.611	0.779-3.333
Isolated HHcy	5.317	2.469-11.447	4.154	1.836-9.401
H-type hypertension	9.667	4.725-19.778	5.028	2.323-10.883
HBP by Hcy	3.694	2.142-6.373	2.776	1.564-4.927

Figures

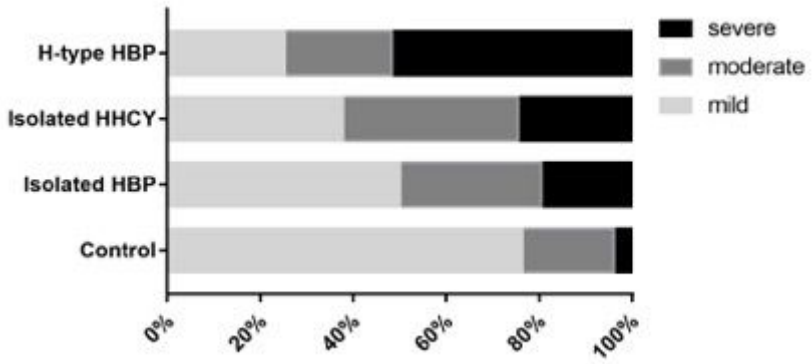

Figure 1

The comparison of CSVD total burden among the four groups. Mild CSVD total burden: 0 or 1 point, moderate CSVD total burden: 2 points, severe CSVD total burden :3 or 4 points.