Relationship between miR-92b expression and hypertension, the degree of heart disease and cerebral hemorrhage

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Research

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Abstract

Objective: To delve into the correlation between miR-92b expression in peripheral plasma and hypertension, heart disease and cerebral hemorrhage.

Methods: We enrolled 204 patients hospitalized in our institution from March 2016 to May 2017, including patients with hypertension (group B), hypertensive left ventricular hypertrophy (HTN-LVH) (group C), HTN-LVH complicated heart failure (group D), with 68 cases each group, and recruited another 60 healthy volunteers as control group (group A). Our team compared miR-92b level in peripheral plasma, and ultrasound indexes among the four groups and inquired into their correlation. The patients were followed up to assay miR-92b level in the peripheral plasma, cerebral edema volume and cerebral hematoma volume before and after treatment.

Results: (1) In contrast to group B, the LVDs and LVMI in group C, D waxed, whereas LVEF and E/A waned ($P<0.05$). In contrast to group C, group D owned increased LVDs and LVMI, and decreased LVEF (all $P<0.05$). (2) In contrast to group A, miR-92b expression decreased in groups B, C and D, among which group D were the lowest and group B were the highest (all $P<0.05$). (3) miR-92b held negative relationship with SBP, DBP, LVDd and LVMI (all $P<0.001$), and had positive link with LVEF ($r=0.649$, $P<0.001$). (4) In contrast to before treatment, miR-92b expression in plasma was up-regulated after treatment ($P<0.05$). miR-92b level in plasma after treatment possessed negative association with brain edema volume and hematoma volume ($P<0.001$), and no correlation with the edema/hematoma ratio.

Conclusion: miR-92b expression in peripheral plasma of patients with hypertension, myocardial hypertrophy and cerebral hemorrhage is down-regulated. miR-92b probably harbors a defensive impact and participates in the pathophysiological process of hypertension, heart disease and cerebral hemorrhage.

Introduction

Hypertension epidemiological research has evinced [1] that 23.2% (approximately 244.5 million) of the Chinese adult population aged > 18 years suffer from hypertension. 40.7% of patients are treated by taking antihypertensive drugs, whereas only 15.3% of patients have blood pressure under control. Hypertension is a risk factor for cardiovascular disease (CVD). What's more, CVD is the largest lethal cause across the globe, with 17.9 million people succumbing to it every year [2]. Patients with hypertension are in a state of pressure and volume overload for a long time, and patients whose blood pressure is not controlled are more serious. Hypertensive left ventricular hypertrophy (HTN-LVH), a usual hypertension complicated by heart disease, is an adaptive response of the heart to overload, and functions by a combination of multiple mechanisms, and is finally manifested by myocardial remodeling, ventricular wall thickening, etc. Research has projected that [3], the prevalence of LVH in hypertensive population is 20.1%. When myocardial hypertrophy is decompensated, the heart will develop into heart failure [4], which seriously jeopardizes the life and health of patients. Hypertensive intracerebral

hemorrhage (HICH), namely intraparenchymal hemorrhage, is the most grievous complication of hypertension. Thus, it is requisite to look into the emergence and progress of hypertension.

miRNAs are tightly connected to cardiovascular diseases, such as myocardial hypertrophy [5], myocardial fibrosis [6], cardiac remodeling, and heart failure [7]. A study [8] screened the differentially expressed miRNAs in patients with essential hypertension, and observed that hsa-miR-92b-3p expression in peripheral plasma was down-regulated. Nevertheless, miR-92b changes in the development of hypertension and its correlation with the disease remains equivocal. Hereby, we determined miR-92b level in peripheral plasma of patients with hypertension, HTN-LVH, HTN-LVH complicated heart failure, and cerebral hemorrhage for assessing the relationship between miR-92b and hypertension, heart disease and cerebral hemorrhage.

1 Methods

1.1 General data

We enrolled patients with hypertension (group B), HTN-LVH (group C), HTN-LVH complicated heart failure (group D) treated in our institution from March 2016 to May 2017, with 68 cases each group, and recruited another 60 healthy persons as control group (group A; 28 males and 32 females; mean age 56.44±5.68 years; range 38-68 years). Ethics committee of our hospital had approved this work. All the research subjects and family members had summited consent form.

Group B had 30 males and 38 females, aged 41-72 years, with mean age 56.09±5.77 years. Group C had 33 males and 35 females, aged 42-75 years, with mean age 55.83±5.82 years. Group D had 37 males and 31 females, aged 45-73 years, with mean age 55.79±5.60 years.

Inclusion criteria: (1) Patients aged > 18 years. (2) All patients satisfied the diagnostic standard for hypertension. Three outpatient blood pressures were higher than normal. SBP≥140mmHg and/or DBP≥90mmHg. (3) Hypertension: ECG detected IVSd or LVPWd<1.2cm, LVEF>40%, no other heart disease changes. (4) HTN-LVH: ECG detected IVSd/LVPWd ≥1.2cm, LVEF>40%. LVH was clinically diagnosed as being caused by long-term hypertension. (4) HTN-LVH complicated heart failure: LVEF<40%.

Exclusion criteria: (1) Female patients during pregnancy or lactation. (2) Combined with other diseases that can cause LVH, such as diabetes, aortic stenosis, and congenital heart disease; (3) Combined with malignant arrhythmia, other malignant tumors or other serious organic diseases outside the heart. (4) Patients failed to cooperate with the research or patients with incomplete clinical data.

1.2 Research methods

(1) Blood sample collection: Fasting for 12 hours was needed before blood collection. We used disposable vacuum blood collection needle to draw blood from the cubital vein of the subject in the morning, collected the blood sample into an EDTA anticoagulation tube, placed it at room temperature for 1 hour, used low-temperature high-speed centrifugation machine for centrifuging at 3000xg and 4℃ lasting 15 minutes, carefully aspirated the supernatant to be plasma, and stored the plasma at -80°C.

(2) ECG: Our crew applied the Philips iE33 color Doppler ultrasound diagnostic apparatus for detecting the research object, and set the probe frequency as 2.5-4.0 MHz. After the subject was in the left decubitus position, the probe was placed at the apex of the heart and connected M-mode ultrasonography. We continuously measured three cardiac cycles, recorded and calculated LVDd, LVDs, LVMI, LVEF.

(3) RT-PCR: Our member extracted total RNA from plasma employing BIOG plasma free RNA extraction kit (Changzhou Bio-generating Biotechnology Corp, China), quantified RNA, and utilized reverse transcription kit (Neobioscience, China) for reverse transcription. After that, we conducted RT-qPCR, used U6 as an endogenous control, and processed the data utilizing $2^{-\Delta\Delta Ct}$ method.

(4) CT examination: Our team adopted a CT machine (Siemens, Germany) for examining the subject's head. After the subject was in a supine position, the head was fixed, and the OM line was served as the baseline to perform a regular plain scan. After setting each parameter, we performed spiral scanning. Using stereology, the cerebral hematoma and surrounding edema were quantified and converted into the corresponding volume value (ml).

1.3 Observation indicators

(1) After the subjects were recruited, we applied color Doppler echocardiography for detecting the four groups, and recorded the dominating indicators for evaluating left ventricular function, involving LVDd, LVDs, LVMI, LVEF and E/A.

(2) We determined and compared miR-92b level in peripheral plasma of the four groups. (3) Using Pearson correlation analysis, miR-92b level in peripheral plasma was analyzed with blood pressure and ultrasound indexes (SBP, DBP, LVDd, LVMI, LVEF).

(4) Our team followed up the patients in groups B, C and D for one year, recorded the number of cerebral hemorrhage events in each group, and assayed miR-92b level before and after treatment.

(5) Making use of CT scanning, we calculated and compared cerebral edema volume, cerebral hematoma volume and edema/hematoma ratio before and after treatment. Ultimately, we carried out Pearson analysis on the relation between miR-92b level and cerebral edema volume, cerebral hematoma volume, and edema/hematoma ratio.

1.4 Statistical analysis

Taking advantage of SPSS 25.0 software, the data was statistically analyzed. We expressed the measurement data as mean ± SD (`X±S). If the data satisfied the normal distribution, single-factor ANOVA was performed for multi-group comparison; if not, non-parametric test was completed. The count data were recorded in the form of rate (%). The inter-group comparison was analyzed by chi-square test. Pearson analysis was utilized for the correlation analysis of bivariate. *P<0.05. We made use of Gradpad Prism 7.0 software for delineating.

2 Results

2.1 General clinical data of research objects

The study included 60 healthy controls (group A), 68 patients with hypertension (group B), 68 subjects with HTN-LVH (group C), and 68 patients with HTN-LVH complicated heart failure (group D). No significant difference was found in age, gender composition ratio and BMI among the groups (P>0.05). In contrast to group A, the SBP and DBP of patients in group B, C and D all heightened. **See Figure 1 and Table 1**

2.2 Comparison of echocardiographic indicators

We making use of Color Doppler echocardiography for detecting four groups, and recorded the primary indicators for evaluating left ventricular function. In comparison with group A, LVDd, LVDs and LVMI of group B augmented, whereas E/A dwindled; LVDd, LVDs, and LVMI of group C, D increased, whereas LVEF and E/A declined (P<0.05). In comparison with group B, LVDs and LVMI in group C amplified, while LVEF and E/A decreased; LVDd, LVDs and LVMI increased in group D, and LVEF and E/A ebbed (all P<0.05). Compared with group C, LVDs and LVMI of group D increased, while LVEF diminished (all P<0.05). **See Table 2, Figure 2**.

2.3 Comparison of the relative expression levels of miR-92b in circulating blood

We assayed miR-92b expression in the peripheral plasma of four groups via RT-PCR. Compared with group A, miR-92b expression in the plasma of patients in groups B, C, and D lessened (all P<0.05). Among group B, C, and D, group D held the lowest miR-92b expression, whereas group B possessed the highest miR-92b expression. See Figure 3.

2.4 Correlation of miR-92b with blood pressure and ultrasound indexes

We accomplished Pearson analysis on the correlation of miR-92b level in peripheral plasma with SBP, DBP, LVDd, LVMI, LVEF, and observed that miR-92b owned negative relation with SBP, DBP, LVDd and LVMI (all P<0.001), and positive relationship with LVEF (r=0.649, P<0.001). See Table 3, Figure 4.

2.5 Comparison of miR-92b level in the circulating blood

We followed up the patients in group B, C, and D for one year. In the three groups, there were 4, 6, and 13 cases of cerebral hemorrhage, respectively, with a total of 23 patients. We assayed the peripheral plasma of patients with cerebral hemorrhage for assessing the miR-92b changes in the plasma before and after treatment. Compared with before treatment, miR-92b expression was up-regulated after treatment (P<0.05). See Figure 5.

2.6 Comparison of cerebral edema and hematoma after cerebral hemorrhage

We compared cerebral edema volume, cerebral hematoma volume and edema/hematoma ratio before and after treatment by means of CT scan. The results evinced that compared with before treatment, brain edema volume, hematoma volume and edema/hematoma ratio abated after treatment (all P<0.05). Pearson analysis uncovered that after treatment of cerebral hemorrhage, miR-92b level in plasma owned negative relation with cerebral edema volume and hematoma volume (P<0.001), and had no link with the edema/hematoma ratio. See Table 4, Figure 6.

3 Discussion

The leading feature of hypertension is elevated systemic arterial pressure [9], and its risk factors include genetics, environmental changes, lifestyle and age [10, 11]. Hypertension is the most prominent risk factor for CVD. The heart and brain are both the target organs of its damage. Its disability and mortality rates are both high, which grievously influences the quality of life of patients. When the blood pressure of hypertensive patients is improperly controlled for a long time, it will cause hypertensive heart disease, and HTN-LVH is the most prevalent one. In the initial stage, in order to overcome the increased peripheral resistance, the cardiomyocytes are hypertrophy and compensatory work, which is conducive to maintaining heart function [12]. As the disease progresses, the oxygen consumption of cardiomyocytes increases, compliance decreases, and the heart chamber narrows, so that the decrease in left ventricular systolic function can be manifested as a decrease in LVEF. HTN-LVH will eventually develop into heart failure, increasing the mortality of patients. HICH is the most serious complication of hypertension, and rupture of cerebral blood vessels is one of the pathogenesis. Under long-term hypertension, the lipids of the arteriole walls in the brain tissue will appear hyaline degeneration, fibroblast proliferation and macrophage aggregation will replace vascular smooth muscle cells, and the vascular lumen will be narrowed [13]. When the patient's blood pressure rises suddenly, rupture bleeding occurs [14]. Hence, it is

indispensable to delve into the emergence and development of hypertension and thwart disease progression.

MicroRNA (miRNA) is a type of single-stranded non-coding small RNA with a nucleotide sequence length of 20–24 nt. miRNA can affect the stability of mRNA and protein translation, and take part in post-transcriptional gene modulation in diverse biological cells. The impact of miRNA on target mRNA relies on the degree of complementarity. When it is completely complementary to the target mRNA, it can cut the mRNA, and when it is only partially complementary, it can impede the translation of mRNA. miRNA exerts a vital modulatory part in the pathological process of hypertension, heart disease and cerebral hemorrhage. There are multiple mechanisms for the progression of hypertension to HTN-LVH, heart failure or cerebral hemorrhage. For instance, miR-19a/b-3p defenses the heart from pathological myocardial hypertrophy induced by hypertension via targeting PDE5A [15]. Up-regulated miR-133 can attenuate agonist-induced cell hypertrophy [16], balk myocardial fibrosis [17], and modulate heart development and normal heart function. There are various types of miRNAs involved, and there are also all sorts of signal pathways mediated. The target miRNA can be selected through the screening of the differential expression of miRNAs for further research. The target miRNA selected in this work was miR-92b.

In recent years, there has been scads of research on the role of miR-92b in cancer. miR-92b is capable of being utilized as a latent oncogene [18] or biomarker [19], and it has a means of enhancing tumor migration and invasion capabilities [20, 21]. In studies of cardiovascular disease, in the Uyghur population with essential hypertension, hsa-miR-92b-3p expression in peripheral plasma was down-regulated [8]. The expression level and role of miR-92b level and its role in different diseases are inconsistent. Research authenticated that [22], compared with control group, miR-92b expression in patients with cholangiocarcinoma was up-regulated, and highly expressed miR-92b was in correlation with disadvantageous prognosis. In Ang-II-induced neonatal mouse ventricular cell hypertrophy model [23], miR-92b-3p expression was dramatically increased, and miR-92b-3p can repress Ang-II-induced cardiomyocyte hypertrophy via targeting HAND2. The miR-92b-5p in serum exocrine of patients with dilated cardiomyopathy is an underlying biomarker for diagnosing acute heart failure [24].

Heart lesions are extensive, including a diversity of diseases, such as vascular disease [25], cardiomyopathy [26], arrhythmia [27] and valvular disease [28]. This study mainly focused on LVH in cardiomyopathy. In order to explore the relationship between miR-92b expression and the incidence of hypertension and the degree of heart disease. Patients was assigned to four groups, namely control group (group A), hypertension (group B), HTN-LVH (group C) and HTN-LVH complicated heart failure group (group D). The consequences unveiled that, compared with group A, miR-92b expression of the other three groups attenuated. Among the three groups B, C, and D, miR-92b expression was the lowest in group D and the highest in group B. For further probing into the correlation of miR-92b level with blood pressure (SBP, DBP) and ultrasound indexes (LVDd, LVMI, and LVEF), Pearson correlation analysis verified that miR-92b owned negative link with blood pressure, LVDd and LVMI, and held positive association with LVEF, implying that miR-92b was intimately connected to the onset of hypertension and different degrees

of heart disease (HTN-LVH, heart failure). We followed up patients in groups B, C, and D lasting one year, and observed that a total of 11.27% of patients had cerebral hemorrhage. Moreover, we assayed miR-92b level in peripheral plasma of patients with cerebral hemorrhage before and after treatment. After treatment, miR-92b expression was up-regulated and miR-92b level possessed negative association with cerebral edema volume and hematoma volume after treatment, suggesting that the up-regulated miR-92b was implicated in the improvement of cerebral hemorrhage.

4 Conclusion

To sum up, miR-92b expression in the peripheral plasma of hypertensive patients is down-regulated. As the hypertensive disease progresses to LVH or heart failure in the form of heart disease, miR-92b expression will be further down-regulated. Nonetheless, the mechanism of miR-92b is not yet transparent and can be further studied. It likely harbors a protective influence and takes part in the pathophysiological process of hypertension, heart disease and cerebral hemorrhage.

Declarations

Ethics approval and consent to participate

All experimental procedures conformed with institutional guidelines the

experiment was often approved by the Ethics Committee of the The First

Affiliated Hospital of Nanchang University NO.Z-20213 , and all patients

participating in this study provided written informed consent in accordance

with the“Helsinki Declaration”.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

Zi-Jun Tang conceived and designed the study. Jing Zhang，Jun-yi Zeng and Ze-qi Zheng analyzed the data. Wan Zhang，Lu Ding and Tong Wen contributed to literature review. Zi-Jun Tang， Jun-yi Zeng and Da-Song wrote the manuscript. Zi-Jun Tang and Jun-yi Zeng reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. General clinical data of study subjects

Classification	Group A (n=60)	Group B (n=68)	Group C (n=68)	Group D (n=68)
Age（years）	56.44±5.68	56.09±5.77	55.83±5.82	55.79±5.60
Gender n (%)				
Male	28(46.67)	30(44.12)	33(48.53)	37(54.41)
Female	32(53.33)	38(55.88)	35(51.47)	31(45.59)
BMI (kg/m^2)	22.53±1.89	22.66±1.94	22.74±1.85	22.71±1.90
SBP (mmHg)	113.83±6.50	148.56±8.80[a]	149.37±8.73[a]	150.44±9.65[a]
DBP (mmHg)	78.67±3.16	95.90±5.01[a]	94.96±4.60[a]	95.68±6.01[a]

Note: BMI is body mass index, SBP is systolic blood pressure, DBP is diastolic blood pressure, [a]$P<0.05$: vs group A.

Table 2. Comparison of ultrasound indexes

Indexes	Group A (n=60)	Group B (n=68)	Group C (n=68)	Group D (n=68)
LVDd (mm)	41.68±4.65	45.36±4.58[a]	46.15±5.61[a]	57.76±5.39[a,b,c]
LVDs (mm)	26.14±2.52	28.85±3.95[a]	32.94±4.21[a,b]	44.73±5.03[a,b,c]
LVMI (g/m^2)	86.99±6.00	96.00±7.22[a]	133.39±11.93[a,b]	144.22±11.91[a,b,c]
LVEF (%)	69.19±5.02	67.54±4.97	50.79±4.71[a,b]	40.55±3.79[a,b,c]
E/A	1.31±0.27	0.96±0.22[a]	0.79±0.24[a,b]	0.72±0.23[a,b]

Note：[a]$P<0.05$：vs group A；[b]$P<0.05$: vs group B；[c]$P<0.05$: vs group C.

Table 3. Correlation of miR-92b with blood pressure and ultrasound indexes

Indexes	r	95%CI	*P*
SBP (mmHg)	-0.499	(-0.601, -0.380)	<0.001
DBP (mmHg)	-0.475	(-0.581, -0.354)	<0.001
LVDd (mm)	-0.506	(-0.607, -0.388)	<0.001
LVMI (g/m^2)	-0.646	(-0.724, -0.552)	<0.001
LVEF (%)	0.649	(0.556, 0.727)	<0.001

Table 4. Comparison of cerebral edema volume and hematoma volume after cerebral hemorrhage

Indexes	Before treatment	After treatment
Cerebral edema volume (ml)	26.13±4.06	8.45±2.26[a]
Cerebral hematoma volume (ml)	18.86±3.95	7.90±1.80[a]
edema/hematoma	1.46±0.42	1.13±0.43[a]

Figures

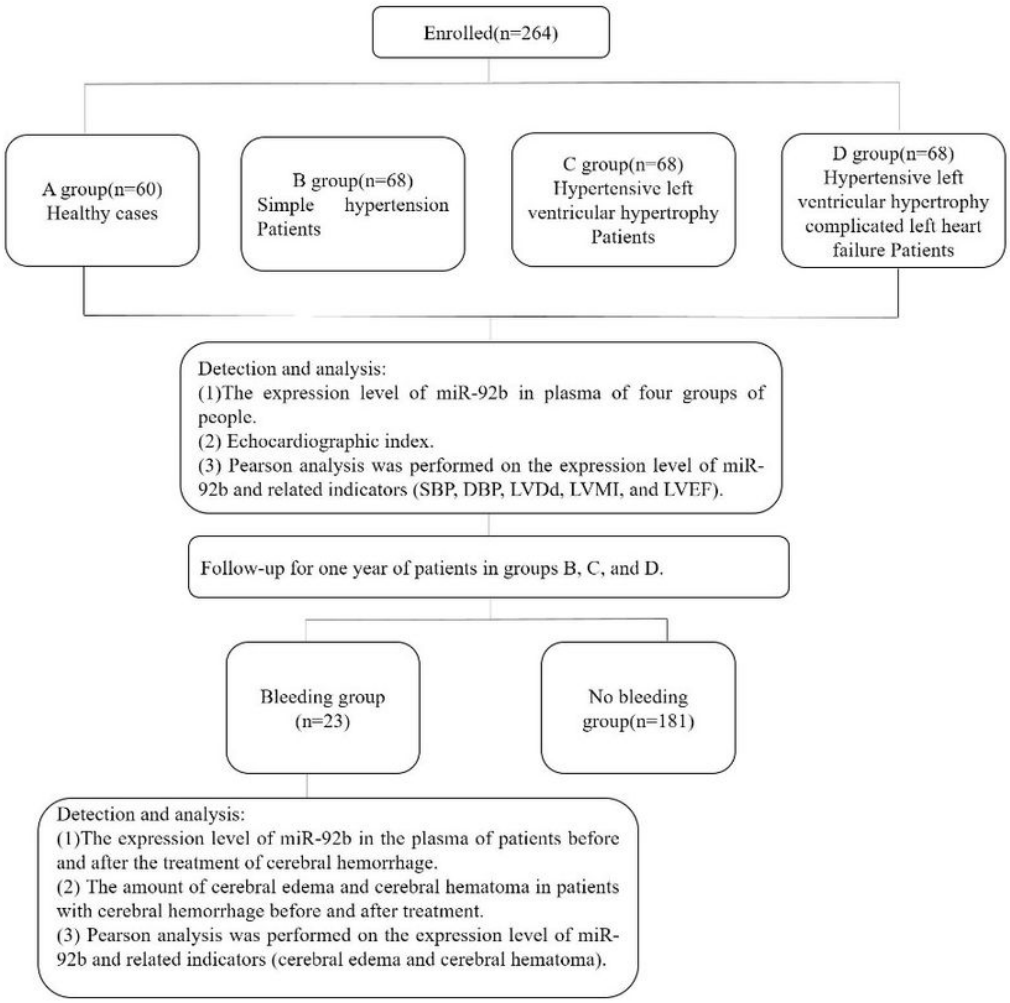

Figure 1

shows the combined diagram of the research process

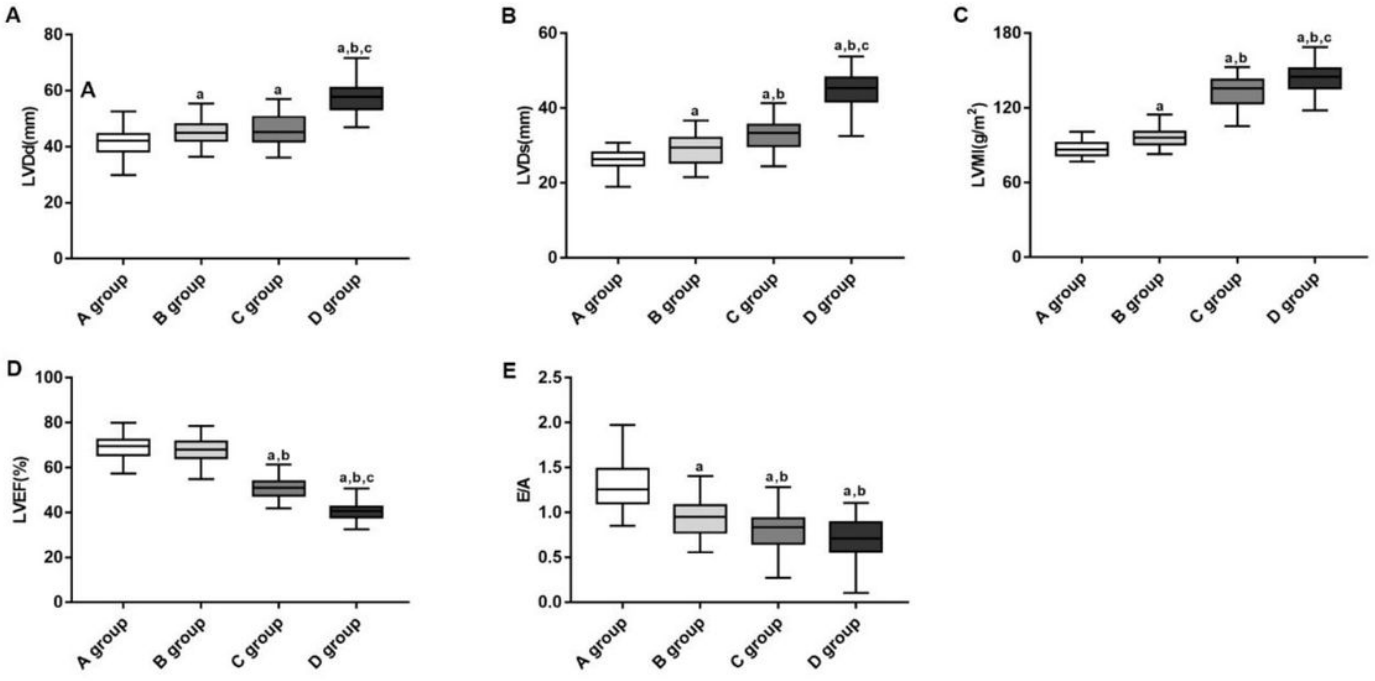

Figure 2

Comparison of ultrasound indexes. Color Doppler echocardiography was used for detecting four groups. The main indicators, namely LVDd (A), LVDs (B), LVMI (C), LVEF(D) and E/A(D) were recorded and compared. aP<0.05: vs group A, bP<0.05: vs group B, cP<0.05: vs group C.

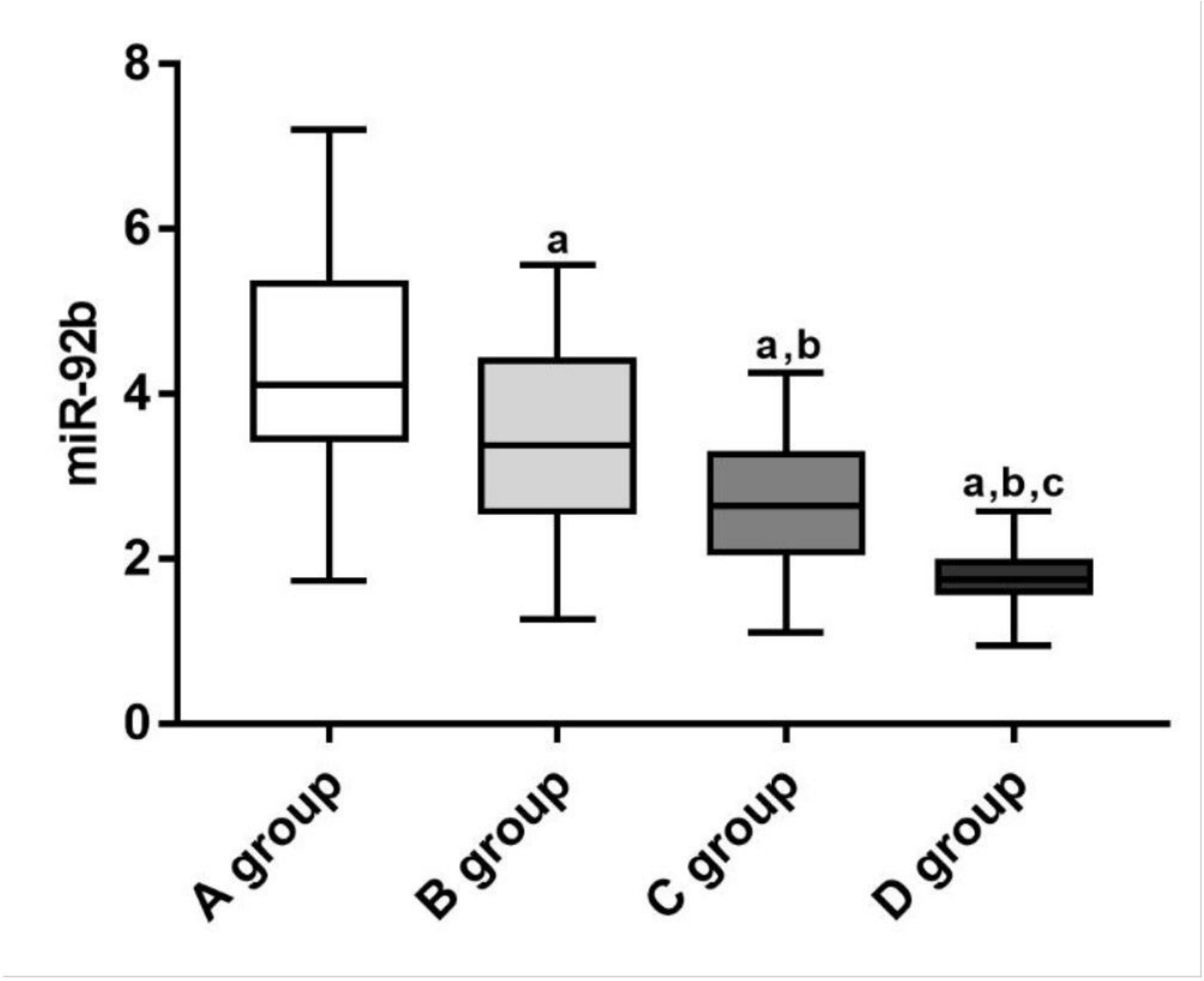

Figure 3

Comparison of miR-92b levels in circulating blood. RT-PCR to assay miR-92b expression in the peripheral plasma of the four groups. aP<0.05: vs group A, bP<0.05: vs group B, cP<0.05: vs group C.

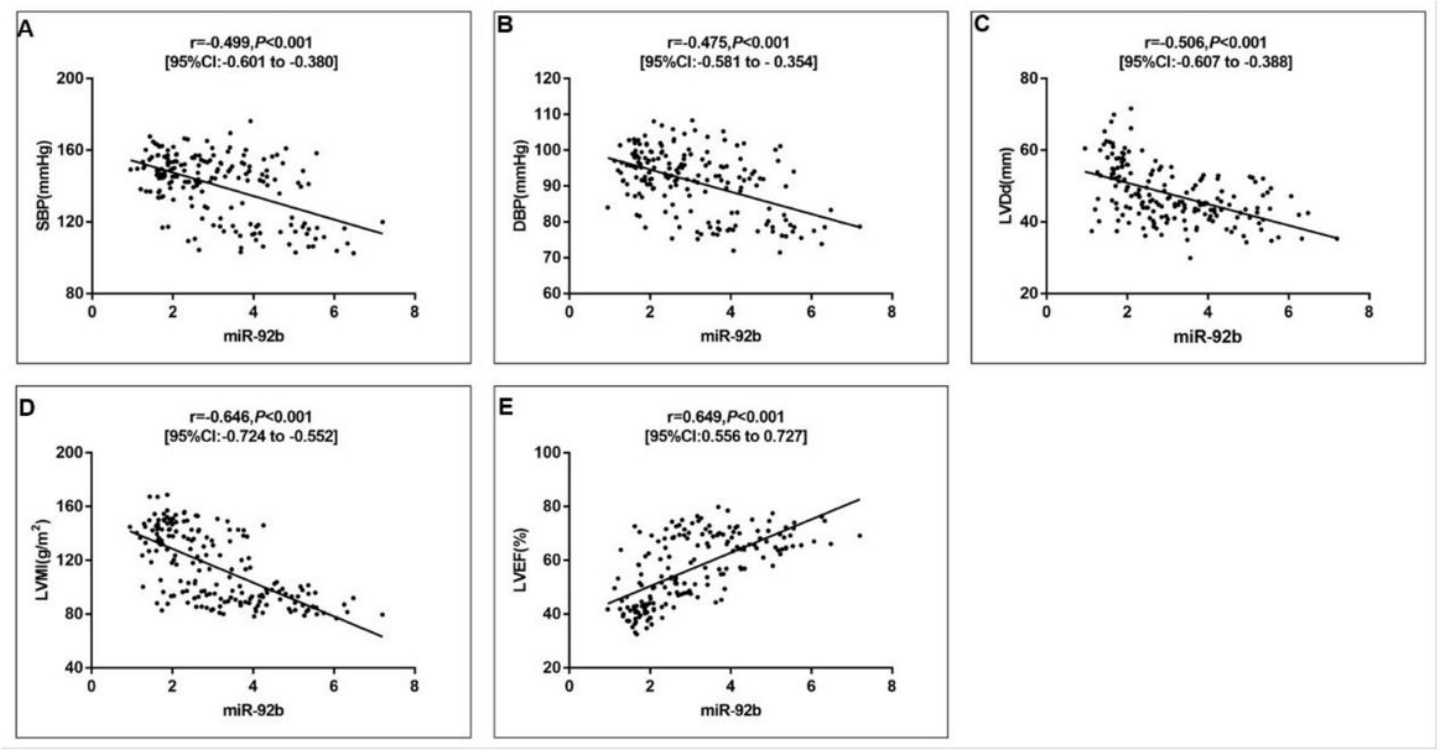

Figure 4

Correlation of miR-92b with blood pressure and ultrasound indexes. We performed bivariate correlation analysis. A: Correlation between miR-92b expression in peripheral plasma and SBP. B: correlation between miR-92b and DBP. C: correlation between miR-92b and LVDd. D: correlation between miR-92b and LVMI. E: correlation between miR-92b and LVEF.

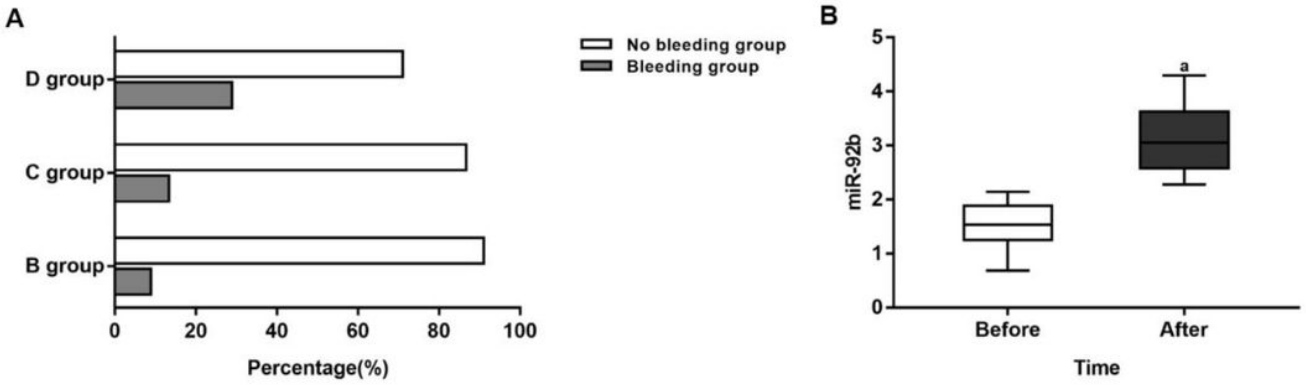

Figure 5

Comparison of miR-92b levels in the circulating blood of patients with cerebral hemorrhage after hemorrhage. A: We followed up patients in groups B, C and D for one year, and counted the proportion of cerebral hemorrhage in each group. B: RT-PCR to assay the changes in miR-92b level in plasma before and after treatment.

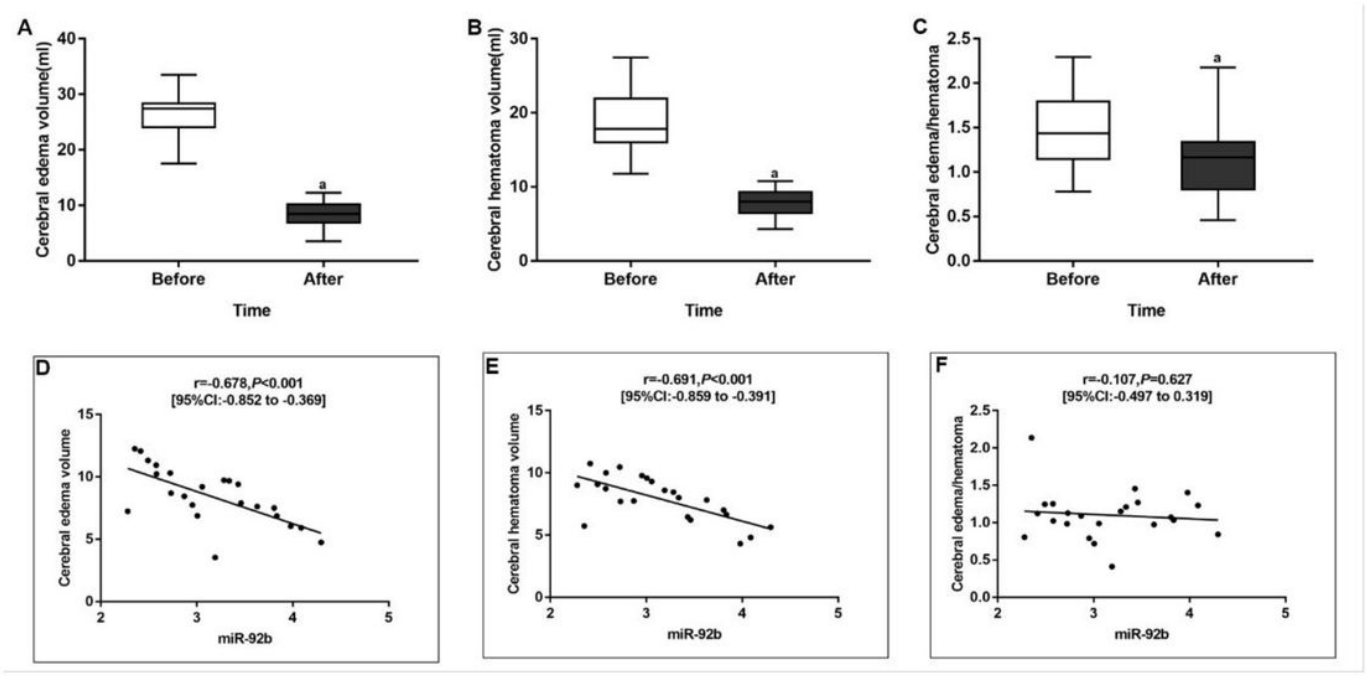

Figure 6

Comparison of cerebral edema volume and cerebral hematoma volume after cerebral hemorrhage. CT scan to assay cerebral edema volume (A), cerebral hematoma volume (B) and edema/hematoma ratio (C) of cerebral hemorrhage patients before and after treatment. Then we conducted a bivariate correlation analysis after treatment. D: Correlation between miR-92b level and cerebral edema volume. E: correlation of miR-92b level and cerebral hematoma volume. F: Correlation between miR-92b level and brain edema/hematoma ratio.