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Evaluation of left ventricular functions in patients with retinal vein occlusion

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Abstract

The aim of this study was to evaluate cardiac functions in patients with retinal vein occlusion (RVO) by both conventional and speckle tracking echocardiography (STE). We included 54 consecutive RVO patients, 47 patients with systemic arterial hypertension (SAH), and 52 healthy controls. Two-dimensional echocardiography (2DE) and STE were performed to all patients and healthy subjects in order to assess left ventricle (LV) systolic and diastolic functions. There was no statistically significant differences among-group in clinical data. RVO and hypertensive patients had LV diastolic dysfunction in conventional echocardiographic measurements. The RVO patients had lower LV global longitudinal, radial, circumferential strain measurements than hypertensive patients and healthy controls. LV subclinical dysfunction might be determined by STE in patients with RVO, independent of whether or not they have SAH.

Keywords: Retinal vein occlusion, left ventricle, speckle tracking echocardiography

Introduction

Retinal vein occlusion (RVO) is common vascular disease of retina and large studies revealed that RVO is the second most frequent retinal vascular disease after the diabetic retinopathy [1,2]. Depending on the site of occlusion, RVO can be classified as either branch or central RVO. However, the physio pathogenesis of RVO is not yet clear, it may be due to a combination of three pathological conditions: compression of the venous wall by an adjacent sclerotic retinal arteriole [3] degeneration of the vessel wall [4] thrombosis of the retinal vein [1]. Classic cardiovascular (CV) risk factors [such as diabetes mellitus (DM), systemic arterial hypertension (SAH), dyslipidaemia, obesity and haemostatic factors] are reported to play a role in the development of RVOs [5]. Several conditions known to cause atherosclerosis have been associated with RVO [6,7]. Chen et al. revealed that patients with RVO were at a significantly greater risk of developing ischemic

and hemorrhagic stroke [8]. Moreover, current studies with long-term follow-up have reported that the group differences between the RVOs and non-RVOs were also found to be significant in atrial fibrillation, hyperlipidemia, DM, obesity, and also major adverse cardiac and cerebrovascular events (MACCE) and these findings was also found related with mortality in patients with RVO [9-11]. These studies suggest that ophthalmologists should be aware of the possible increased risk of CV diseases and patients with RVO should be referred to physicians for early diagnosis of MACCE.

With advances in ultrasound deformation imaging techniques, speckle tracking echocardiography (STE) has been proposed for detecting myocardial dysfunction as an alternative to ejection fraction [12]. STE is less dependent on Doppler beam angle and loading conditions, which decreases intra- and interobserver variability. Moreover, it provides a global approach, including information on the three spatial dimensions of cardiac contraction, to myocardial mechanics [13]. In this study, we aim to assess left ventricle (LV) function using the STE in patients with RVO, and compare results with evaluations in patients with SAH and healthy subjects.

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Material and Methods

Study population

In this cross-sectional study, 54 patients with RVO and 47 patients with SAH, and 42 healthy subjects were included consecutively. Demographic and clinical data were noted for all participants. Patients with systolic BP \geq 140 mmHg and diastolic BP \geq 90 mmHg were classified as hypertensive. Patients who were taking antihypertensive drugs for more than 6 months prior to the start of the study were also defined as hypertensive [14]. Patients with SAH and healthy controls underwent ophthalmic examination to exclude any retinal vascular occlusion. The same cardiologist and ophthalmologist systemically evaluated all study participants.

Exclusion criteria comprised participants with inflammatory RVO, a history of RVO more than three months, retinal vascular disease other than RVO. Patients with LV systolic dysfunction (ejection fraction $<$ 50%), coronary artery disease, moderate or severe valvular heart disease, diabetes mellitus, atrial fibrillation, acute or chronic renal failure and connective tissue disease were also excluded. All patients and healthy controls provided written informed consent prior to their participation in the study. The procedures in our study followed the tenets of the Declaration of Helsinki and were approved from the Ethical Committee.

Echocardiographic assessments

In our study, we used an ultrasound system (Philips Healthcare Medical Imaging System, Andover, MA, USA) which had a 3.5-Hz probe. Moreover, the basic two-dimensional echocardiography (2DE) evaluations were performed according to the American Society of Echocardiography guideline [15].

Two independent cardiologist performed STE analysis using the QLAB Philips off-line software (Philips Healthcare Medical Imaging System performed the STE analysis, Andover, MA, USA). Moreover, they recorded three consecutive cardiac cycles in DICOM format for each view with a frame rate above 50 per second and automatically traced myocardial contour after determination of baso-septal, baso-lateral and apical landmarks [15].

The region of interest was adjusted to cover at least 90% of the myocardial wall thickness. If first tracking is thought to be suboptimal, other retracings were manually or semi-automatically performed. However, after three retracings the non-tracking segments were excluded. If more than three of six segments had poor tracking quality, the study was excluded. 3.7% of the segments were excluded from STE analysis due to inadequate endocardial border tracking in our study. LV longitudinal strain analysis [global longitudinal strain (GLS), early diastolic GLS rate (GLSRe), late diastolic GLS rate (GLSRa), systolic GLS rate (GLSs)] was calculated using the apical views (4-chamber, 3-chamber, and 2-chamber). Short-axis views at the basal, midpapillary, and apical levels were obtained for circumferential (C) and radial strain (RS) analysis as recommended.[16].

Segmental data were not analyzed. Strain is negative values; the more negative the value is, the greater the deformation and

LV function are [17,18]. The STE analysis of randomly selected 20 patients was repeated 3 months later to determine intra- and interobserver variability, which were calculated as the average difference between the 20 measurements assessed by the same observer or a second independent observer, respectively. The intra- and interobserver variability were 9.2% and 11.5%, respectively, in our study.

Statistical analysis

Statistical analyses were performed using the SPSS statistical software version 22.0 (SPSS Inc., for MAC, Chicago, IL, USA). The variables were investigated using (histograms, probability plots) analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. In sample size calculation, we calculated that we would need 54 RVO and 47 hypertensive patients and 52 healthy subjects in each group to detect a 2 point difference in DAN scale with 80% power and at 1% significance. Continuous variables were presented as mean \pm standard deviation. Between-group differences in categorical variables were compared with χ^2 -test. Between-group differences in continuous variables were compared with independent-samples t-test and one-way analysis of variance testing. An overall p-value of less than 0.05 was considered to show a statistically significant result. When an overall significance was observed, pairwise post-hoc tests were performed using Tukey's test. Kappa coefficients were calculated to estimate inter-observer as well as intra-observer correlation in both STE examinations [19].

Results

The present study comprised 54 patients with RVO (26 female, 56.2 \pm 9.3 years), 47 patients with systemic hypertension (26 female, 55.9 \pm 8.3) and 52 healthy controls (26 female, 54.9 \pm 6.2 years). The clinical and demographic characteristics of the patients are shown in Table 1. Age, sex and smoking were similar in all groups. There were significant differences between three groups in systolic and diastolic blood pressure. RVO patients and hypertensive patients had higher systolic and diastolic blood pressure than healthy controls. In RVO group, 28 patients had SAH (18 patients had already SAH diagnosis but 10 were newly diagnosed with SAH at the time of RVO diagnoses).

Conventional and speckle tracking echocardiographic data are shown in table 2. LV end diastolic and systolic diameters, and LV ejection fraction were all within normal limits. RVO and hypertensive patients had thicker interventricular septum than healthy controls. In the analyses of the diastolic dysfunction determining parameters, RVO and hypertensive patients had higher deceleration time, E/A, and E/e' ratios. In conventional echocardiographic measurements, there was no statistically significant difference between RVO and hypertensive patients.

The patients with RVO had lower LV GLS, RS, and CS than hypertensive patients and healthy controls. In speckle tracking echocardiographic measurements, there was no statistically significant difference between hypertensive patients and healthy controls.

Table 1. Clinical, demographic, and laboratory characteristics of RVO, hypertension, and control group

	RVO group (n=54)	Hypertension group (n=47)	Healthy control group (n=52)	p value
Age (years)	56.2±9.3	55.9±8.3	54.9±6.2	0.24
Sex (female/male)	26/29	26/21	26/26	0.33
BMI (kg/m ²)	28.1±3.9	28.5±4.0	27.2±3.9	0.29
Systolic BP (mmHg)	148.4±25.3 ^a	144.7±22.9 ^b	126.9±16.5	0.03
Diastolic BP (mmHg)	89.1±16.3 ^a	86.2±12.7 ^b	77.2±12.6	0.02
Smoking (%)	25(46.2%)	21(44.6%)	22(42.3%)	0.19
Total cholesterol	215.3±32.4	219.4±31.2	208.4±30.5	0.15
LDL cholesterol	114.8±10.2	112.5±9.9	107.3±10.9	0.22
Hemoglobin (g/dL)	13.8±2.5	14.1±3.9	12.9±3.4	0.17
Creatinine (mg/dL)	1.02±0.8	1.09±1.1	0.92±0.6	0.35

BMI: body mass index; BP: blood pressure; RVO: retinal vein occlusion; LDL: low-density lipoprotein.

^a p < 0.05, RVO group versus healthy controls (Tukey's HSD post hoc test).

^b p < 0.05, Hypertension group versus healthy controls (Tukey's HSD post hoc test).

^c p < 0.05, RVO group versus hypertension group (Tukey's HSD post hoc test).

Table 2. Conventional echocardiographic measurements of RVO, hypertension, and control groups

	RVO group (n=54)	Hypertension group (n=47)	Healthy control group (n=52)	p value
LV end diastolic diameter (mm)	45.9±6.3	45.3±5.4	44.2±4.9	0.14
LV end systolic diameter (mm)	32.3±7.4	31.2±6.4	30.4±5.8	0.21
IVS thickness (mm)	12.3±3.4 ^a	11.5±2.1 ^b	8.1±1.9	0.01
PW thickness (mm)	10.9±2.6	9.8±2.4	7.8±2.0	0.07
LV Ejection fraction (%)	64.2±4.5	63.1±4.1	62.6±3.9	0.25
E/A ratio	0.84±0.3 ^a	0.89±0.2 ^b	1.31±0.2	0.02
Deceleration time (ms)	224±69 ^a	217±64 ^b	158±48	0.03
E/e' ratio	13.0±2.7 ^a	12.4±2.4 ^b	9.6±1.9	0.01
Speckle tracking echocardiography				
LV global longitudinal strain (-%)	18.1±3.8 ^{a,c}	23.4±3.9	24.5±3.5	<0.001
LV circumferential strain (%)	21.2±4.5 ^{a,c}	25.7±4.0	26.9±3.4	<0.001
LV radial strain (%)	32.3±5.2 ^{a,c}	39.1±4.1	40.1±4.5	<0.001
LV global SRS (-1/s)	1.9±0.2	2.0±0.2	2.2±0.3	0.24
LV global SRE (1/s)	1.6±0.1	1.7±0.2	2.0±0.3	0.32
LV global SRA (1/s)	2.2±0.4	2.3±0.4	1.9±0.2	0.26

IVS: interventricular septum; PW: posterior wall; SRA = Late diastolic strain rate; SRE = Early diastolic strain rate; SRS = systolic strain rate; LV: left ventricle.

^a p < 0.05, RVO group versus healthy controls (Tukey's HSD post hoc test).

^b p < 0.05, Hypertension group versus healthy controls (Tukey's HSD post hoc test).

^c p < 0.05, RVO group versus hypertension group (Tukey's HSD post hoc test).

Discussion

In this study, we compared the LV systolic and diastolic functions using conventional and STE among patients with RVO and SAH, and healthy controls. The primary results of our study are as follows: (1) RVO patients had lower LV GLS, CS, and RS compare to hypertensive patients and healthy controls. (2) STE might detect LV dysfunction earlier than conventional echocardiographic measurements. (3) RVO and hypertensive patients had diastolic dysfunction in the conventional echocardiographic measurements.

As far as current studies are concerned, retinal vascular events are associated with the burden of cardiovascular (CV) disease [20]. Although most of the RVO patients have no evidence of CV disease at the time of the diagnosis, RVO can be the first sign of atherosclerosis and microvascular dysfunction. One meta-analyses

revealed that frequency of CV disease in patients with RVO was higher than in aged matched healthy subjects and this review indicated that RVO patients had higher MACCE risk at ten years follow-up [21]. In addition, Martin et al. explored that there was an increased mortality from CV disease in patients with RVO at the end of the long-term follow-up [22].

In a recent pulsed wave Doppler echocardiography based study, Kaderli et al. revealed that LV myocardial performance index and diastolic function were impaired in RVO patients, independent of whether or not they have SAH [23]. In our study, we explored that RVO and hypertension are associated with left ventricular hypertrophy and diastolic dysfunction in 2DE measurements. Moreover, RVO Patients group had higher left ventricular mass and increased E/e' ratio independent of whether or not they have SAH, which is associated with diastolic dysfunction due to RVO.

Rim et al. [24]. showed that RVO is associated with an increased risk of the incidence of ischemic heart failure. In a 2DE based study Rauh et al. demonstrated the increase of the LV mass index in RVO patients compare with healthy subjects [25]. To the best of our knowledge, this is the first study showed the LV subclinical systolic dysfunction using STE in patients with RVO.

Today, LV GLS measured by STE is an independent predictor of cardiac mortality due to various diseases and also it might detect subclinical LV dysfunction [26,27]. LV subclinical dysfunction is associated with an increased risk of MACCE in some disorders such as systemic HT, DM, insulin resistance [28-30]. In the present study, the LV GLS, CS, and RS were significantly lower in RVO patients compared with hypertensive patients and healthy controls, although LV ejection fraction was normal in all three groups. These findings might be the early detection of the global decrease of myocardial performance in patients with RVO compare to conventional echocardiography. Because, STE has some advantages in daily practice compare with conventional 2DE. For instance, STE is independent of cardiac translation, and it is angle- and load-independent, thereby allowing more accurate quantification and categorization of myocardial function [28].

As known as, SAH is a major cause of LV systolic and diastolic dysfunction as an end-organ damage [29]. SAH is an agreed predisposing factor for RVO although some patients with RVO are normotensive. CV abnormalities in patients with RVO might result from SAH [30]. Nevertheless, our study suggest that some systemic abnormalities other than HT (such as LV dysfunction in STE measurements) may play role in the increase of the burden of CV diseases in patients with RVO.

Study limitations

Our study has some limitations. First of all it was a single-center and relatively restrictive sized study. Further studies with larger patient numbers are needed to verify our findings. Second, we did not compare our results with cardiac magnetic resonance imaging that is the gold standard for evaluation of LV myocardial function and structure. However, magnetic resonance imaging is currently limited by cost and availability and is deemed unsuitable after the implantation of a cardiac pacemaker.

Conclusion

The results of our study revealed that patients with RVO have impaired LV subclinical dysfunction independent of the presence of HT using STE. In daily practice, RVO patients would generally present to ophthalmologists, their high burden of CV disease should include a referral for CV assessment as part of their clinical approach. Ophthalmologists should be aware of the importance of RVO as a sign of progressive CV and refer to cardiologist. Further studies are needed, to confirm the results of our study and to determine the overall prognostic significance of LV subclinical dysfunction in patients with RVO.

Competing interests

The authors declare that they have no competing interest.

Financial Disclosure

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Ethical approval

Consent of ethics was approved by the local ethics committee.

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