高度医療技術開発室

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近年における医療を取り巻く情報処理や画像処理の技術革新により、診断、治療における医用画像診断装置の利用範囲は拡大しており、著しいイノベーションを引き起こしています。医用画像診断装置の技術開発により低侵襲化、従来視覚化困難であった部位や現象の画像化が可能になりつつあり、そこから新たな治療が生まれる可能性があります。これらの技術開発には医工連携すなわち病院、大学、企業との連携体制の構築が必要ですが、米国における産学連携の仕組みや組織と比較すると本邦ではまだまだ発展の余地が多いと言えるでしょう。本研究室では病院における医療現場のニーズを、企業が保有している技術開発力や大学の基礎医学研究能力に結び付けながら、常に新しい高度医療技術（特に医用画像診断装置）の開発に取り組んでいきます。

現在、当研究室の主要な課題は、コントラスト剤を用いた心エコーによる心腔内血流イメージングです。心腔内のコントラストバブルを Particle Image Velocimetry (PIV 法)という画像解析手法を用いて心腔内血流を可視化しています。PIV 法は流体工学の分野で流体解析に用いられている手法であり、これを医用画像に応用することによって、心腔内血流動態というこれまで観察出来なかったものを観察することにより、心疾患の新たな病態解明の手段になればと考えて研究を行っています。

この新たな心エコーによる PIV 法を確立するためには動物実験が必要であり、大阪大学大学院医学系研究科保健学専攻機能診断科学講座の中谷敏教授とともに基礎研究を行っています。

さらにコントラスト剤を用いずにカラードプラ情報やスペックルパターンから得られる心筋の移動情報から心腔内の血流を可視化することは、非侵襲という点で極めて重要な課題であり、日立アロカメディカル社の Vector Flow Mapping 開発に協力している。

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Original Article

Early impairment of left ventricular function in patients with systemic hypertension: New insights with 2-dimensional speckle tracking echocardiography

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ABSTRACT

Background: Two-dimensional strain imaging allows rapid and accurate analysis of regional left ventricular (LV) principal strains in the longitudinal, radial, and circumferential directions. The aim of this study was to assess the ability of subtle differences in LV principal strains to characterize features of subclinical LV dysfunction in patients with systemic hypertension and apparently preserved LV systolic function.

Methods: 2-dimensional echocardiographic (2DE) images of the LV were acquired in apical 4-chamber and parasternal short-axis at the basal, mid, and apical levels in 59 subjects, including 25 healthy controls (33 ± 4 yrs, 14 male) and 34 patients with systemic hypertension (36 ± 3 yrs, 24 male). Longitudinal (LS), circumferential (CS) and radial strains (RS) were quantified in an 18-segment model using a novel speckle tracking system (2D Cardiac Performance Analysis, TomTec Imaging System, Munich, Germany).

Results: In comparison with normal controls, peak LS was markedly attenuated in the subendocardial and subepicardial regions in patients with systemic hypertension. However, circumferential strain was reduced only in subepicardial region; radial strain was not significantly different in the two groups. The subendocardial-to-subepicardial gradient of circumferential deformation correlated with the radial strains in both controls and hypertensive patients ($R = 0.87$, $p < 0.001$).

Conclusions: Despite reduced longitudinal shortening, LV wall thickening in patients with systemic hypertension remains unaltered due to relatively preserved circumferential shortening. Characterizing the disparities in LV principal strains reveals the presence of subclinical LV dysfunction and provides unique insights into functional adaptations that maintain global LV ejection fraction in patients with systemic hypertension.

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1. Background

Development of left ventricular hypertrophy (LVH) in patients with systemic hypertension is an established risk factor for the development of asymptomatic left ventricular (LV) dysfunction and congestive heart failure.[1] Moreover, while conventional echocardiography can detect changes in LV diastolic dysfunction associated with LVH, global LV systolic function often remains preserved until late in the course of the disease, making subtle changes in LV contractile function difficult to interpret in the early stages.[2,3]

Subclinical changes in LV function can be identified by quantifying myocardial strain, a dimensionless measurement of deformation, expressed as a fractional or percentage change from an object's original dimension. Two-dimensional (2D) speckle tracking has recently emerged as a novel echocardiographic technique for rapid, offline, bedside analysis of regional LV strains in the longitudinal, radial, and circumferential directions.[1,4–6] This technique analyzes myocardial motion by tracking natural acoustic reflections and interference patterns seen in two-dimensional echoardiographic images and has been validated with measurements obtained by sonomicrometry and magnetic resonance imaging.[7] The aim of this study was to assess the ability of subtle differences in the LV strain patterns in the longitudinal, radial and circumferential directions to characterize features of subclinical LV dysfunction in patients with systemic hypertension and preserved LV ejection fraction (LVEF).

2. Methods

2.1. *Study subjects*

We included 34 young consecutive patients with systemic hypertension (36 ± 3 yrs, 24 male) and 25 age and sex matched healthy controls (33 ± 4 yrs, 14 male). Patients with established coronary artery disease, echocardiographic evidence of either regional or global wall motion abnormalities, valvular heart disease, diabetes mellitus and hypertrophic cardiomyopathy were excluded. Each study participant gave written, informed consent.

2.2. *Echocardiography*

A complete 2DE was performed in all patients, using a commercially available ultrasound transducer and equipment (S4-2 probe, HD7, Philips). All acquisitions were performed by the same experienced operator with the patients in the left lateral position. Basic measurements included LV wall thickness by M-mode and LV diameter by 2D. LV volumes and LVEF were measured using the modified biplane Simpson method as recommended by the American Society of Echocardiography.[8] To determine the timing of cardiac events, mitral inflow and LV outflow were recorded using pulsed Doppler echocardiography. 2DE images of the LV were acquired in apical 4-chamber (A4C), apical 3-chamber (A3C), apical 2-chamber (A2C) and parasternal short-axis at the basal, mid, and apical levels with same ultrasound machine. Three consecutive cardiac cycles loops were recorded at end expiration. The frame rate was kept between 70 Hz and 100 Hz. Longitudinal, circumferential and radial strains were quantified in an 18-segment model using a novel speckle tracking system (2D Cardiac Performance Analysis (2D CPA), TomTec Imaging System, Munich, Germany). LS was measured in all 3 views, A4C, A3C and A2C. Peak systolic strain was measured. 2D CPA is a speckle tracking based analysis tool that can analyze 2D data from various ultrasound machines and is an extension of velocity vector imaging software that has been previously validated with sonomicrometry[4,9] and magnetic resonance imaging.[1,10] 2D CPA, similar to velocity vector imaging, determines myocardial motion from a user-defined tracing along the endocardial border. Endocardial and automated subepicardial borders are traced throughout one cardiac cycle by successive application of a series of tracking steps. From this motion, the myocardial velocity, longitudinal and radial strain are calculated for both endocardial and subepicardial regions along the trace. Longitudinal systolic strain from endocardial and subepicardial regions respectively was obtained from 6 segments and from lateral and septal wall segments in apical 4-chamber, three and two chamber views. Circumferential strain and radial strain were obtained from 6 segments in short-axis views of the LV. Offline analyses were independently performed by one observer who was not involved in image acquisition nor had knowledge of other echocardiographic measures of LV function. The intra-observer variabilities for endocardial longitudinal strain, epicardial longitudinal strain, endocardial circumferential strain and epicardial circumferential strain were found to be 10 ± 7%, 8 ± 7%, 11 ± 10%, 25 ± 22%, and 24 ± 20%, respectively. Also interobserver variabilities reported by us for the same measurement were −13.6 ± 6.3%, −12.6 ± 7.9%, 16 ± 15%, 26 ± 21%, and 28 ± 29%, respectively.[11]

2.3. *Statistics*

Continuous variables were expressed as mean ± SD. The differences between groups were analyzed by independent samples student *t* tests (MedCalc 11.2 software MariaKerke, Belgium). Annova and paired *t* test were used to assess the level of significance in the follow up group. Correlations between variables were tested by Pearson or Spearman correlation tests where appropriate. A *p*-value <0.05 was considered to be significant.

3. Results

The study population consisted of 59 subjects, including 34 patients of systemic hypertension (36 ± 3 yrs, 24 male) and 25 age and sex matched healthy controls (33 ± 4 yrs, 14 male). Clinical and echocardiography data of patients with systemic hypertension and controls are shown in Table 1. No significant differences were found between the two groups in terms of age, sex or height. Patients with systemic hypertension weighed significantly more than the control group ($p < 0.001$). There was a significant higher systolic and diastolic blood pressure in patients with systemic hypertension than the

Table 1 – Clinical and echocardiographic characters between two groups.

Characteristic	Controls ($n = 25$)	Systemic hypertension ($n = 34$)	p
Age (yrs)	33 ± 4	36 ± 3	NS
Men/women (n)	14/11	24/10	NS
Height (cm)	168.2 ± 11	166.7 ± 10	NS
Weight (kg)	63.8 ± 8.6	75.2 ± 12.8	<0.001
Systolic blood pressure (mmHg)	120 ± 7	164 ± 8	<0.001
Diastolic blood pressure (mmHg)	78 ± 4	100 ± 8	<0.001
Ao (cm)	2.3 ± 0.1	2.66 ± 0.3	<0.001
LA (cm)	2.6 ± 0.1	3.24 ± 0.3	<0.001
LVDd (cm)	5.0 ± 1.8	4.54 ± 0.6	0.008
LVDs (cm)	27 ± 1	2.66 ± 0.3	NS
LV mass index g/m^2	53 ± 8	62 ± 2	NS
Septum wall thickness (cm)	0.8 ± 0.2	1.5 ± 0.2	<0.001
Global ejection fraction %	65 ± 5	67 ± 5	NS
E peak velocity (cm/s)	72 ± 14	84 ± 16	<0.001
A peak velocity (cm/s)	61 ± 13	65 ± 15	NS
e' (septal) cm/s	11.7 ± 0.8	9.7 ± 2.8	<0.001
A' (septal), cm/s	11.0 ± 0.3	10.8 ± 2.5	NS
S' (Septal), cm/s	13.4 ± 0.4	9.3 ± 2.3	<0.001
e'(lateral), cm/s	12.4 ± 0.5	13.2 ± 2.8	NS
A' (lateral), cm/s	10.8 ± 1.9	11.6 ± 2.9	NS
S' (lateral), cm/s	14.1 ± 0.5	11.41 ± 2.6	<0.001

control group ($p < 0.001$). Echocardiography parameters revealed significant septal wall thickness in hypertensive patients ($p < 0.001$). However there was no significant difference in LV mass in both the groups. There was no significant difference in the LV global ejection fraction between groups.

In comparison with normal controls, peak LS was markedly attenuated in the subendocardial and subepicardial regions in patients with systemic hypertension as shown in Table 2 and Fig. 1. However, circumferential strain was reduced only in the subepicardial region. Radial strain in hypertensive patients was less than controls but it was not statistically significant (Fig. 2). The subendocardial-to-subepicardial gradient of circumferential deformation correlated with the radial strains in both controls and hypertensive patients ($R = 0.87$, $p < 0.001$). The comparison of LV mechanics between controls and systemic hypertension is shown as a graph in Fig. 3.

Table 2 – Comparison of left ventricular mechanics between two groups.

Characteristic	Controls ($n = 25$)	Systemic hypertension ($n = 34$)	P
Longitudinal strain			
Subendocardial (%)	−20.2 ± 4.7	−13.4 ± 5.8	<0.001
Subepicardial (%)	−17.5 ± 4.4	−11.3 ± 5.6	<0.001
Circumferential strain			
Subendocardial (%)	−23.5 ± 8.8	−19.0 ± 9.6	0.06
Subepicardial (%)	−6.6 ± 2.1	−5.1 ± 3.4	0.03
Radial strain (%)	20.3 ± 11.3	17.2 ± 10.3	0.23

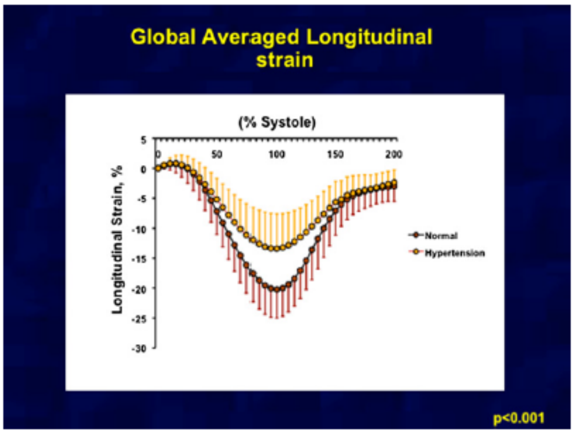


Fig. 1 – Showing average of subendocardial longitudinal strain in two groups. There is significant difference in longitudinal strain in both groups.

4. Discussion

In hypertensive patients with abnormal diastolic LV filling, LV systolic function is commonly considered normal if the global ejection fraction (GEF) and fractional shortening (FS) are normal.[12,13] However, the GEF and FS only reflect the global cardiac contractile function and do not take regional systolic abnormalities into consideration. The above results show that 2D speckle tracking is able to detect sub-clinical myocardial dysfunction in hypertensive patients with LVH despite normal global systolic parameters.

2D speckle tracking echocardiography is a relatively new technique that can be used in conjunction with two or three-dimensional echocardiography to detect the multidirectional components of LV deformation. The tracking system is based on gray-scale B-mode images and is obtained by automatic measurement of the distance between two pixels of an LV segment during the cardiac cycle, independent of the angle of insonation. The integration of 2D speckle tracking with real-

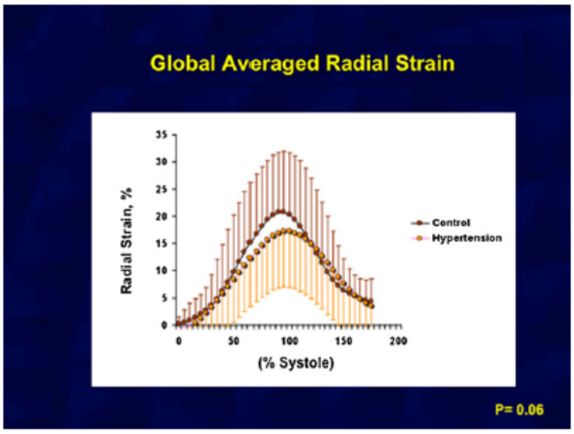
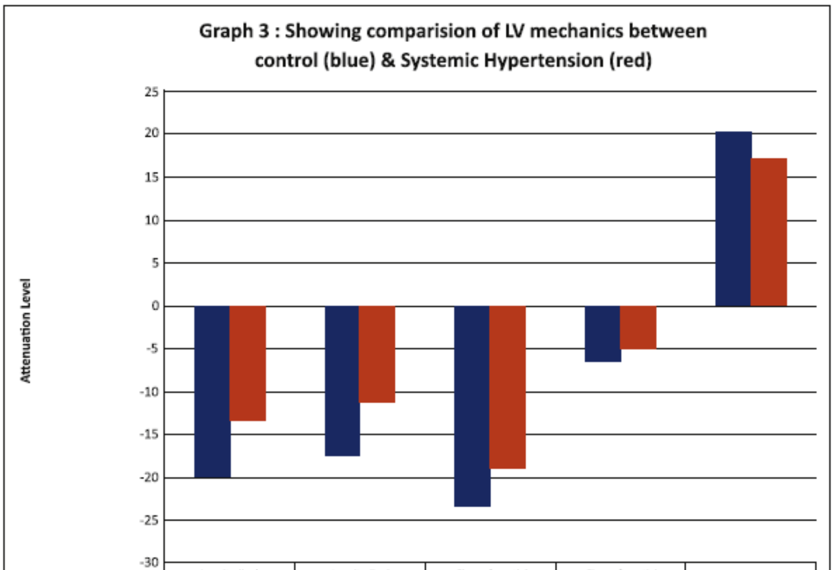


Fig. 2 – Showing average of radial strain in two groups. No significant difference in radial strain seen in two groups.



	Longitudinal Subendocardial strain (%)	Longitudinal Subepicardial strain (%)	Circumferential Subendocardial strain (%)	Circumferential Subepicardial strain (%)	Radial strain (%)
Controls (n=25)	-20.2	-17.5	-23.5	-6.6	20.3
Systemic Hypertension (n=34)	-13.4	-11.3	-19	-5.1	17.2

Fig. 3 – Graph showing comparison of LV mechanics between control (blue) and systemic hypertension (red).

time cardiac ultrasound imaging overcomes some of the limitations of previous work in the field and has the potential to provide a unified framework to more accurately quantify the regional and global function of the LV. 2D speckle tracking holds promise to reduce inter- and intra-observer variability in assessing regional LV function and improve patient care while reducing health care costs by early identification of subclinical disease.[14]

The longitudinal fiber shortening was less in the LVH group with normal GEF and FS than the corresponding segments in the control group, a finding that was consistent with the results of Poulsen et al.[15] The subendocardial longitudinal-oriented myocardial fibers have shown to be particularly vulnerable to ischemia leading to a dominant decrease in shortening in the longitudinal axis.[16,17] Manaka et al found that myocardial systolic impairment in hypertensive LVH may originate at the endocardial side and significantly move to the epicardium compared with control, and the impairment may progress with increased LVH, but this study was limited to the longitudinal direction.[18] Our findings in patients with hypertension and decreased tissue tracking values in the longitudinal fibers might be explained by the presence of regional subendocardial myocardial ischemia and increased perivascular and interstitial fibrosis, which was previously demonstrated in patients with hypertension.[19] It is also possible that the level of end-systolic wall stress is different between the groups, affecting the subendocardial fiber shortening. Furthermore, the hypertrophic myocardium itself may impede contraction. These pathophysiologic changes are likely to lead to decreased longitudinal systolic contraction and might also result in a heterogeneous segmental diastolic impairment affecting the global diastolic function. There was no significant difference in circumferential strain values in both the groups. Radial strain was reduced, although it was not significant reduction as compared to controls. Kosmala et al[20] and Imbalazano et al[21] have reported reduced radial strain in hypertensive patients along with reduced longitudinal study. 2D strain has a limitation of through plane motion, although least in longitudinal direction.

Hypertension and LVH are important risk factors for developing chronic congestive heart failure and, although patients with congestive heart failure and a normal LVEF have a lower mortality risk than those with reduced EF, the mortality risk is still significantly increased over control patients.[22] The assessment of LV systolic longitudinal contraction by 2D speckle tracking gives new insight in myocardial function in hypertension that might improve pathophysiologic understanding and identify patients at high risk who would benefit from regression of LV hypertrophy following a more aggressive antihypertensive treatment program. The combination of depressed longitudinal systolic contraction and abnormal diastolic LV filling may play a key role in the development of acute and chronic heart failure in patients with hypertension.

4.1. *Study limitations*

The present study is a single-center observational study. It is limited by the relative small sample size. Also torsion and rotational characteristics have not been discussed.

5. Conclusion

Despite reduced longitudinal shortening, LV wall thickening in patients with systemic hypertension remains unaltered because of relatively preserved circumferential shortening. Characterizing the disparities in LV principal strains unmasks presence of subclinical LV dysfunction and provides unique insights regarding functional adaptations that maintain global LV ejection fraction in patients with systemic hypertension.

Conflicts of interest

All authors have none to declare.

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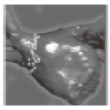


Visualization of blood flow with echocardiography: the future for heart failure diagnosis

> *"…in the human heart … [blood] flow is redirected within the cardiac chambers through vortex formation, which avoids excessive dissipation of energy and facilitates the efficient passage of blood … visualizing multidirectional [intracavity blood] flow using echocardiographic techniques may open up new possibilities in assessing cardiac blood transport efficiency in health and disease."*

KEYWORDS: blood flow ▪ heart failure ▪ hemodynamic efficiency ▪ vortex

The prognosis of heart failure (HF) after hospital discharge remains dismal, with high readmission rates and mortality [1,2]. Transthoracic echocardiography is commonly used to follow up with HF patients for serial assessment of cardiac chamber size, function and for noninvasive estimation of chamber filling pressures. In particular, estimation of left atrial pressure may allow earlier identification of incipient cardiac decompensation and guide adjustment of vasodilator and diuretic dosing [3]. Doppler-derived indices of diastolic dysfunction, particularly the ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity (E/e′), is considered a noninvasive estimate of left ventricular filling pressure [4]. However, nearly half of patients displaying symptoms of HF have preserved left ventricular ejection fraction (HFpEF) and E/e′ may not be reliable in patients with HFpEF [5]. Moreover E/e′ may not be an appropriate measurement for evaluating HF patients with pacemakers and cardiac resynchronization therapy [6]. The search for alternative echocardiography indices continues. Some investigators have suggested that flow of the blood may be immediately affected by changes in left ventricular (LV) morphology and intracavity filling pressures. Therefore, flow can be a more robust marker for characterizing chamber filling dynamics [7].

Vortex formation: a marker hemodynamic efficiency

More than 500 years ago, Leonardo da Vinci introduced the concept of circular flow formation in the sinus of Valsalva [8]. Such a fluid structure that possesses circular or swirling motion is defined as a vortex. Vortices are considered as reservoirs of kinetic energy. Theoretically, in an ideal fluid this energy can never be dissipated and the vortex would persist forever. However, in reality, the resistance of the fluid (viscosity) reduces the energy. *In vitro* experiments have demonstrated that fluid transport can be laminar, vortical or turbulent. Within these patterns, vortex ring formation is the most efficient for periodic changes in the direction of the flow [9,10].

Pattern of blood flow in a normal heart

The pattern of flow in the human heart changes dramatically during one cardiac cycle. However, flow is redirected within the cardiac chambers through vortex formation, which avoids excessive dissipation of energy and facilitates the efficient passage of blood [11]. Inside the ventricle, just after ejection, the direction of flow reverses towards the apex, which initiates early diastolic filling. During early diastolic filling, an asymmetric vortex ring is formed, with a larger anterior vortex ring and a small posterior ring. This vortex continues to enlarge anteriorly during diastasis, and overall rotation of flow is further accentuated during atrial contraction. The specific geometry and anatomical location of the vortex formed during diastolic filling are critical determinants of directed blood flow during ejection [9]. After the mitral valve closes and before the aortic valve opens, the vortex changes direction of flow towards LV outflow tract. This maintains the transfer of kinetic energy from diastolic filling into ejection. Lastly, at the LV end-ejection phase, the vortex diminishes in size as the flow is ejected across the aortic valve [12,13].

Vortex formation in decompensated heart failure

The formation of abnormal vortices relates to the underlying fluid dynamics in LV dysfunction [14,15].


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When this geometric arrangement is broken, for example in dilated left ventricles, undesirable vortices develop and there is an increase in the dissipated energy [9]. In end-stage systolic HF, ventricular dilatation decreases the strength of the diastolic vortex [16].

Noninvasive assessment of vortex formation

The term fluid velocity commonly describes the fluid motion. However, flow is multidirectional and vortical, with a tendency to curl or spin in the cardiac chambers [11]. In this respect, dynamical structure of a flow cannot be described by velocity alone. Therefore, investigators have attempted different approaches in characterizing vortex formation, ranging from mathematical indices to real-time visualization of vortices using parametric imaging in 2D or 3D.

In the experimental model, vortex rings develop from fluid ejected from a nozzle. The starting jet is typically produced by a piston-cylinder mechanism, which is commonly expressed through the stroke ratio as the ejected jet length divided by the effective jet diameter. This length-to-diameter ratio is often referred to as vortex formation time (VFT). VFT is a dimensionless measure of the time needed for optimal vortex ring formation [17,18].

> *"In end-stage systolic heart failure, ventricular dilatation decreases the strength of the diastolic vortex."*

In the human heart, VFT can be calculated by transmitral flow and ejection fraction (EF) using the formula: $VFT = 4 \times (1-\beta)/\pi \times \alpha^3 \times LVEF$ (β is the fraction of stroke volume contributed from the atrial component of LV filling obtained from the velocity-time integral of A-wave, the effective diameter of mitral geometric orifice area (GOA) and EDV. The parameter α^3 is a nondimensional volumetric parameter for the LV, obtained by dividing the EDV by cubic power of GOA) [19]. Other indices, such as vortex circulation and vortex dissipation [20], are known to represent the strength of the vortex. However, these indices have not yet been validated in clinical practice.

VFT in myocardial dysfunction

VFT has been previously shown to be an index of cardiac function [19]. In patients with acute myocardial infarction, LV diastolic VFT was shown to be strongly associated with the infarct size and LV untwisting rate, indicating that the mechanical sequence of diastolic restoration played a key role in early diastolic vortex ring formation [21]. VFT has also been used as a predictor of adverse events in HF patients. Poh *et al.* analyzed an adapted VFT (VFTa), where the β was measured from mitral annulus [22]. VFTa was markedly reduced in HF with reduced EF, and mildly abnormal in HFpEF compared with non-HF patients. VFTa of <1.32 was associated with significantly reduced event-free survival. In multivariate analyses, only E' and LA volume are significant independent determinants of VFTa, demonstrating that VFT is related to mitral annular recoil. However, since VFT is derived by EF, it is strongly influenced by EF. In addition, the feasibility of obtaining component parameters of VFT, such as the mitral diameter, has yet to be resolved.

Flow visualization

Flow visualization can be achieved by cardiac MRI [10] and echocardiography [23]. With respect to cardiac MRI, blood flow can be measured in any direction by the phase-contrast technique, without using contrast agents [24–26]. However, this technique is time-consuming and costly. By contrast, flow visualization using echocardiography is relative low cost and is suitable for routine clinical use. There are two methods for assessing flow pattern, color Doppler and echo-particle image velocimetry (PIV). Although color Doppler measurement has advantages in spatial resolution and has no need of contrast, it has some limitations. One limitation is that color Doppler is easily affected by noise. Another limitation is that it cannot measure flow velocities perpendicular to the Doppler angle. Alternatively, echo-PIV using contrast echocardiography tracks particle patterns in the field frame-by-frame and, the displacement data are converted to velocity using the time duration between the frames. PIV does not track individual particles. Rather, it tracks the patterns produced by groups of contrast particles.

> *"...vortex rings may help diastolic–systolic coupling for maintaining left ventricular cardiac output in remodeled hearts."*

We recently performed a study to explore echo-PIV-derived measures of blood flow in 31 patients with HF [27]. LV vortex strength, defined as the amount of curl in the flow (vorticity), was significantly lower in patients with reduced LV ejection fraction (<50%) and related to the extent of LV spherical remodeling. LV late diastolic vortex strength was related to LV systolic longitudinal strain, suggesting that vortex rings may help diastolic–systolic coupling for maintaining LV cardiac output in remodeled hearts.

In summary, visualizing multidirectional flow using echocardiographic techniques may open up new possibilities in assessing cardiac blood transport efficiency in health and disease. Vortex flow influences stroke output and efficiency of the LV through optimum redirection of intraventricular flow. Increasing access to noninvasive hemodynamic assessment of LV fluid mechanics may therefore be a key to understanding the physiological drivers of stroke work in a remodeled LV. This may lead us to better understand how hemodynamics correlates to symptom status in HF patients.

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