MAYO CLINIC

Diverse Cardiac Geometry and Cardiorenal Interaction in Heart Failure with Normal Ejection Fraction

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BACKGROUND

- The potential for diverse left ventricular (LV) geometric patterns in patients with hypertension has been recognized, as has the prognostic implication of altered LV geometry in these patients.
- Standardized recommendations for characterization of LV geometry have been issued by the American Society of Echocardiography (ASE).
- Patterns of LV remodeling may also provide insight into the pathophysiology of heart failure (HF), particularly HF with normal ejection fraction (HFnlEF).
- While normal or reduced LV size and LV hypertrophy (LVH) are considered *sine qua non* of diastolic heart failure, LV geometry may be more diverse in unselected HF cohorts with normal EF and no significant valve disease.

OBJECTIVES

1. Define distribution of LV geometric patterns (ASE criteria) in:
   A. Healthy population controls (CON)
   B. Hypertensive subjects (HTN) without HF
   C. HFnlEF patients within the community
2. Compare clinical features and vascular, LV systolic, LV diastolic and renal function in HFnlEF patients with different LV geometric patterns
3. Compare clinical features and vascular, LV systolic, LV diastolic and renal function between CON, HTN and HFnlEF within each LV geometric pattern

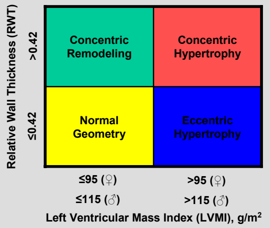
METHODS

- Subjects were Olmsted County, MN, residents selected from a prospective population-based cross-sectional echocardiographic study of a random sample of the population (A and B) and a prospective HF surveillance study of consecutive patients with HF (C).
- Subjects within each group who had measurements of LV dimension and wall thickness allowing geometric classification were included.

A. Non-obese subjects ≥45y without cardiovascular disease (CON) (n=530)
B. Hypertensive subjects ≥45y without HF (HTN) (n=549)
C. *Consecutive* patients with HF (Framingham criteria), echo within a median of 1 day of diagnosis and no significant valve disease (HFnlEF) (n=207)

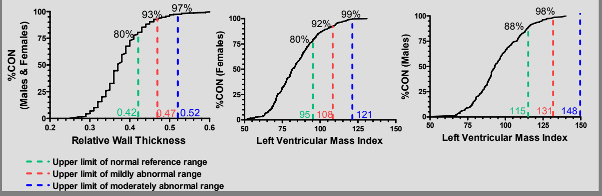
Assessment of LV geometry

ASE criteria (*Lang et al. J Am Soc Echocardiogr 2005*)



	Reference range	Mildly abnormal	Moderately abnormal	Severely abnormal
	Women			
LVMI	43-95	96-108	109-121	≥122
RWT	0.22-0.42	0.43-0.47	0.48-0.52	≥0.53
	Men			
LVMI	49-115	116-131	132-148	≥149
RWT	0.24-0.42	0.43-0.46	0.47-0.51	≥0.52

Application of ASE partition values for LVMI & RWT: Cumulative frequency distribution in CON group



Assessment of vascular function

- **Effective arterial elastance (Ea)** was estimated as end-systolic pressure (ESP)/ stroke volume (SV) where ESP was systolic pressure∗0.9 (*Kelly et al. Circulation 1992*)
- **Total arterial compliance (Ca)** was estimated by SV/pulse pressure ratio (*Chemla et al. Am J Physiol 1998*)
- **Systemic vascular resistance index (SVRI)** was estimated by [(mean arterial pressure/cardiac index)*80]

Assessment of ventricular function

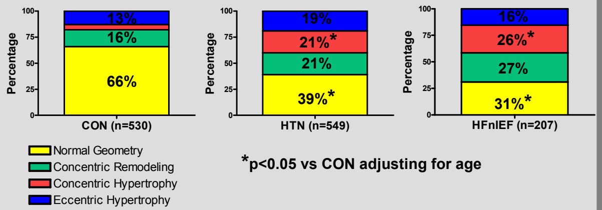
- **End-systolic elastance (Ees)** was estimated by the modified single-beat method using arm-cuff pressures, SV, pre-ejection and total systolic periods, EF, and an estimated normalized ventricular elastance at arterial end-diastole (*Chen et al. J Am Coll Cardiol 2001*)
- **The time constant of isovolumic relaxation (Tau)**, was derived by the formula [Tau = (14.70 – 100e') / 0.15] (*Sohn et al. J Am Coll Cardiol 1997;30:474*)
- **End-diastolic pressure (EDP)** was estimated as: [EDP = 11.96 + 0.596∗E/e'] (*Ommen et al. Circulation 2000*)
- The **end-diastolic pressure-volume relationship** (EDPVR, where **EDP = αEDV^{ß}**; α = curve fitting constant and ß = diastolic stiffness constant) was estimated using the single-beat approach (*Klotz et al. Am J Physiol Heart Circ Physiol 2006*). **LV capacitance (EDV at EDP of 20 mmHg, EDV_{20})** was calculated in each subject

Assessment of renal function

- **Glomerular filtration rate (GFR)** was estimated using the simplified Modification of Diet in Renal Disease Study equation

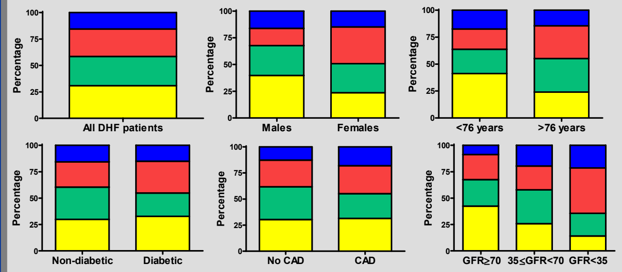
RESULTS

Distribution of LV geometry in subject groups



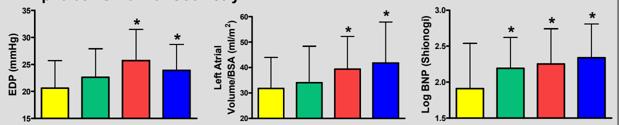
*p<0.05 vs CON adjusting for age

Clinical features by LV geometry in HFnlEF

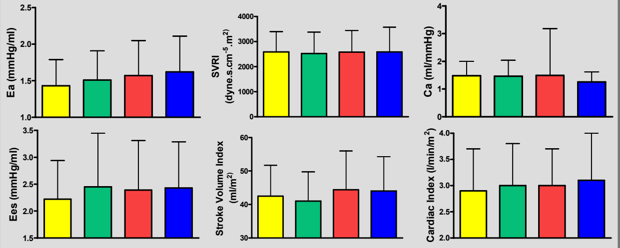


Distribution of LV geometric patterns in HFnlEF varied according to sex (p=0.01), age (p=0.03) and renal function (p=0.02) but was not associated with the presence of diabetes or coronary artery disease.

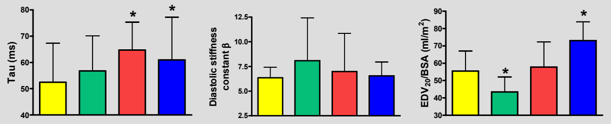
Ventricular-vascular function by LV geometry in HFnlEF



There was a trend towards increasing EDP across geometric subgroups in HFnlEF, corroborated by similar trends towards larger left atria and higher BNP levels. HFnlEF patients with LVH (concentric/eccentric LVH) had higher filling pressures than those without LVH.



There were no significant differences in vascular or LV systolic function among geometry subgroups in HFnlEF.



Compared to Normal Geometry, relaxation was more impaired in HFnlEF patients with concentric/eccentric LVH, while diastolic stiffness was most increased in concentric remodeling. Interestingly, despite higher EDP in the presence of LVH, diastolic stiffness was not increased compared to Normal Geometry.

Clinical features and vascular-ventricular function among subject groups within each geometric pattern

	Normal geometry			Concentric remodeling			Concentric hypertrophy			Eccentric hypertrophy		
	CON	HTN	HFnlEF	CON	HTN	HFnlEF	CON	HTN	HFnlEF	CON	HTN	HFnlEF
N (% of group)	349 (66%)	214 (39%)	64 (31%)	86 (16%)	113 (21%)	57 (27%)	24 (5%)	119 (21%)	54 (26%)	71 (13%)	103 (19%)	32 (16%)
Clinical Characteristics												
Age, y	55±7	62±9*	73±12*†	60±8	65±10*	79±11*†	64±11	68±10*	78±11*†	58±9	67±10*	76±18*†
Males, %	45	46	58	54	39*	46	42	33	28	24	34	47*
BSA, m²	1.85±0.21	1.98±0.25*	2.02±0.32*	1.85±0.20	1.94±0.24*	1.96±0.31*	1.84±0.22	1.92±0.26	1.90±0.28	1.78±0.18	1.90±0.27*	1.91±0.25*
GFR, ml/min/1.73 m²	74.8±13.5	79.5±61.0	72.4±26.1	73.9±13.7	72.9±18.9	67.7±30.6	74.3±12.2	70.1±19.4	57.4±26.3*†	72.0±16.2	73.1±20.2	56.7±28.8*†
Hypertension,%	0	100*	94*†	0	100*	97*	0	100*	98*	0	100*	97*
Diabetes,%	0	11*	38*†	0	12*	28*†	0	10	41*†	0	10*	34*†
CAD,%	0	15*	52*†	0	12*	44*†	0	11	52*†	0	16*	59*†
Heart rate, bpm	64±9	65±11	71±15*†	67±10	68±11	73±15*†	63±8	65±11	70±13	61±9	63±10	69±13*†
SBP, mmHg	116±12	139±21*	129±18*†	120±11	142±20*	128±26*†	120±11	147±26*	138±24*	117±13	145±20*	137±23*
DBP, mmHg	69±8	75±11*	68±14†	72±9	76±10*	68±15†	70±8	74±11	68±14†	68±8	75±9*	68±15†
LV filling pressure												
EDP, mmHg	16.4±1.3	17.6±2.0*	20.6±5.1*†	16.4±1.5	17.3±2.0	22.6±5.3*†	17.5±1.9	18.0±2.2	25.7±5.8*†	16.6±1.3	17.6±1.7	23.9±4.8*†
LAVI, ml/m²	22.0±5.2	25.3±7.6*	31.8±12.2*†	20.8±5.4	23.8±7.6	34.1±14.3*†	22.6±4.7	27.4±9.2	39.4±12.8*†	22.8±5.0	28.1±8.4*	41.8±16.1*†
BNP (Shionogi)	18.1±30.7	24.0±31.3*	186.2±187.6*†	19.0±32.2	26.2±40.0	235.7±205.3*†	45.3±134.5	38.9±45.0	317.9±469.8*†	20.6±18.4	31.9±33.6	379.4±389.5*†
LV structure												
EDVI, ml/m²	61.0±8.6	60.8±8.6	56.0±10.3*†	48.8±7.9	47.4±8.0	43.5±8.4*†	57.0±7.0	58.4±11.1	59.9±11.0	74.7±8.7	72.4±9.7	74.1±11.1
LVMI, g/m²	83.6±13.2	86.5±11.8*	84.5±16.8	86.4±12.7	87.9±12.7	84.1±14.8	112.8±13.1	121.5±22.0	131.6±27.1*†	109.3±11.2	117.5±18.5*	119.4±17.0*
RWT	0.36±0.03	0.36±0.04*	0.38±0.04*	0.47±0.05	0.48±0.05	0.50±0.09*	0.47±0.05	0.49±0.06	0.52±0.08*	0.36±0.04	0.38±0.03	0.38±0.04
Vascular function												
PP, mmHg	46±11	64±17*	61±17*	49±10	66±18*	60±19*	50±11	73±21*	70±22*	49±12	70±17*	68±15*
Ea, mmHg/ml	1.28±0.28	1.47±0.40*	1.43±0.36*	1.39±0.35	1.54±0.42*	1.51±0.40	1.28±0.28	1.51±0.41	1.57±0.48*	1.28±0.31	1.49±0.36*	1.62±0.49*
Ca, ml/mmHg	1.92±0.60	1.50±0.55*	1.48±0.52*	1.76±0.60	1.44±0.63*	1.46±0.58*	1.86±0.50	1.37±0.52	1.49±1.69	1.81±0.56	1.42±0.53*	1.25±0.37*
SVRI, dyne.s.cm⁻⁵. m²	2426±483	2780±663*	2587±808	2516±709	2695±651	2524±851	2349±493	2655±664	2578±860	2404±497	2696±556*	2584±983
LV systolic function												
EF, %	63±4	64±5	62±6*†	66±5	66±4	64±7†	67±5	66±6	64±6*†	62±5	64±6	59±6†
Ees, mmHg/ml	1.94±0.56	2.22±0.74*	2.22±0.72*	2.23±0.68	2.48±0.93	2.45±1.00	2.03±0.75	2.40±0.83	2.39±0.92	1.93±0.51	2.27±0.74*	2.43±0.86*
SVI, ml/m²	45.7±7.1	45.2±8.9	42.5±9.2*	44.5±9.3	44.9±8.0	41.0±8.8†	48.4±7.2	47.9±10.4	44.4±11.6	47.8±7.6	49.1±9.0	44.0±10.3†
Cardiac index, l/min/m²	2.9±0.5	2.9±0.6	2.9±0.8	3.0±0.7	3.0±0.6	3.0±0.8	3.1±0.6	3.1±0.7	3.0±0.7	2.9±0.6	3.0±0.7	3.1±0.9
LV diastolic function												
Tau, ms	32.9±21.3	45.6±15.1*	52.4±14.9*	35.4±31.6	41.2±53.3	56.8±13.3*	46.9±14.4	50.4±14.7	64.7±10.6*†	39.0±13.1	48.3±14.8*	60.9±16.3*†
β	5.96±0.05	6.07±0.57*	6.35±1.08*†	5.96±0.06	6.03±0.29	8.08±4.35*†	6.02±0.12	6.08±0.29	6.99±3.87	5.96±0.06	6.02±0.13	6.55±1.40*†
$EDVI_{20}$, ml/m²	62.4±8.8	60.9±8.8	55.4±11.7*†	49.9±8.1	48.3±8.1	43.4±8.6*†	57.8±8.0	58.1±10.1	57.8±14.5	76.5±9.3	72.6±9.8	73.1±10.8

*** p<0.05 vs CON; † p<0.05 vs HTN; Abbreviations**: BSA, body surface area; GFR, glomerular filtration rate; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; EDP, end-diastolic pressure; LAVI, indexed left atrial volume; BNP, B-type natriuretic peptide; EDVI, indexed end-diastolic volume; LVMI, left ventricular mass index; RWT, relative wall thickness; PP, pulse pressure; Ea, effective arterial elastance; Ca, arterial compliance; SVRI, systemic vascular resistance index; Ees, end-systolic elastance; SVI, stroke volume index; $EDVI_{20}$, EDV at common EDP of 20 mmHg/BSA

SUMMARY: HFnlEF

In unselected patients with HFnlEF in the community:

- LV geometry was variable
- LV geometry was more often abnormal in older persons, females and persons with renal dysfunction
- LV filling pressures were higher in concentric/ eccentric LVH
- Vascular and LV systolic function did not vary with geometry
- LV relaxation was more abnormal in concentric/ eccentric LVH
- Diastolic stiffness was most abnormal in concentric remodeling

SUMMARY: HFnlEF vs Controls

Within any LV geometry group, HFnlEF patients:

- were older, had more cardiovascular disease and had higher filling pressures, BNP and left atrial volumes than CON/HTN
- had lower GFR when geometry was concentric/eccentric LVH
- did not have increased vascular/LV systolic stiffness compared to HTN
- had more impaired relaxation than HTN when geometry was concentric/eccentric LVH
- had higher LV diastolic stiffness than CON/HTN when geometry was normal or concentric remodeling

CONCLUSIONS

1. HFnlEF is a heterogeneous disorder.
2. Patients with normal geometry or concentric remodeling display a "restrictive cardiomyopathy" picture with diastolic dysfunction in the absence of LVH or renal dysfunction.
3. HFnlEF patients with concentric/eccentric LVH have worse renal function and higher filling pressures without increased diastolic stiffness or LV dilatation suggesting decreased diastolic distensibility or the effect of enhanced extrinsic forces or impaired relaxation on diastolic pressures.
4. The renal impairment in patients with HFnlEF and LVH suggests an important cardiorenal connection with *concomitant* cardiac and renal end organ damage.