Evaluation of Systolic Properties in Hypertensive Patients With Different Degrees of Diastolic Dysfunction and Normal Ejection Fraction

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BACKGROUND

Left ventricular (LV) diastolic dysfunction (DD) associated with a preserved ejection fraction (EF) is a frequent alteration in hypertensive patients, usually considered an impairment of the diastolic phase alone. However, because systole and diastole are strictly correlated to one another, it is possible that hypertensive patients with isolated DD may also present with initial abnormalities of LV systolic properties, particularly those presenting with a more severe degree of DD. We performed a multiparametric echocardiographic assessment of LV systolic properties in patients without cardiovascular diseases, with preserved EF and different degrees of DD.

METHODS

We evaluated 1,073 hypertensive subjects showing EF >55% and no overt heart disease.

RESULTS

A total of 362 patients had normal diastolic function (N), 609 displayed delayed relaxation pattern (DR), and 102 presented a pseudonormal filling pattern (PN). Albeit most of the subjects with DD (DR, PN) had systolic indexes within normal range, they presented a significant reduction of index stroke volume (SV) ($P < 0.0001$) and stroke work (SW) ($P < 0.0001$), EF ($P < 0.01$), midwall shortening (MFS) ($P < 0.0001$), circumferential end-systolic stress-corrected MFS (cESS-MFS) ($P < 0.001$), and tissue Doppler (TD) systolic velocity ($P < 0.0001$) as compared to the N group, particularly the PN group.

After adjustments, the reductions of LV systolic indexes were still significantly related to DD, particularly to PN.

CONCLUSIONS

Our results suggest a relation between LV systolic and diastolic properties in patients with normal EF. They also highlight the early onset of a preclinical reduction of systolic properties in patients with "isolated" DD, which is related to the degree of dysfunction.

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Arterial hypertension represents one of the most common causes predisposing to the development of left ventricular (LV) systolic dysfunction, which also occurs independently from the presence of coronary artery disease.[1] Most hypertensive patients, however, particularly those subjects with LV hypertrophy, may also present an impairment of LV relaxation and filling, which is widely recognized as LV diastolic dysfunction (DD).[2,3] LV DD is closely associated with the presence of an overt systolic dysfunction,[4] but a great proportion of hypertensive subjects with a preserved systolic function may also develop DD.[2] This latter condition is commonly defined as "isolated" DD, and it is usually considered an alteration of the diastolic phase alone without a concomitant initial decline of LV systolic properties.

Systole and diastole, however, are tightly coupled one to another, and several pathophysiological factors relate these two phases of the cardiac cycle, such as calcium-handling abnormalities and the "elastic recoil" phenomenon.[5] Therefore, it is unlikely that "isolated" DD represents an alteration of the diastolic phase alone, without a concomitant subtle impairment of systolic function. On the other hand, it might be possible that LV DD precedes the development of systolic dysfunction. Patients with an overt impairment of diastolic function and a clinically normal pump function may therefore present with an initial and preclinical reduction of LV systolic properties, particularly those subjects with a more severe degree of DD. These preclinical reductions of LV systolic properties could be better defined using more accurate echocardiographic techniques. Indeed, it should be pointed out that a normal systolic function in patients with "isolated" DD is usually defined by

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the presence of a preserved ejection fraction (EF), which is not a sensitive enough index to detect subtle systolic abnormalities, compared to estimates of midwall mechanics and tissue Doppler (TD) imaging indexes.[6–8]

Several clinical investigations, performed by using more accurate parameters of systolic function, were conducted over the past years to assess whether a pathophysiological continuum exists between diastolic and systolic dysfunction in patients with "isolated" DD.[9–17] Such studies, however, have provided discordant results. Most of these previous investigations were conducted in patients with diastolic heart failure and overt cardiovascular diseases,[9–13] or in hypertensive subjects with LV hypertrophy.[16,17] Moreover, these studies, including those investigations conducted in hypertensive patients, were performed by using inappropriate cutoff values to define a normal EF (<55%). Most remarkably, a multiparametric assessment of LV systolic properties (including TD assessment)—evaluating systolic performance, function, and contractility in hypertensive patients with different degrees of DD—has never been performed.

Thus, the aim of our study was to evaluate, through a multiparametric echocardiograph assessment, whether hypertensive patients without overt cardiovascular disease, but with DD and preserved EF, exhibit early abnormalities of LV systolic properties. In addition, we evaluated whether the extent of this decline of LV systolic properties is related to the severity of DD, independent from the influence of other confounding factors that may interfere with both systolic and diastolic function, such as LV hypertrophy.

METHODS

Selection of patients. We retrospectively evaluated 1,073 asymptomatic hypertensive subjects who were referred to the Echocardiography Laboratory of the St Andrea Hospital in Rome between the years 2003 and 2007 for the evaluation of left ventricular mass (LVM) and cardiac function. Inclusion criteria were the following: (i) age >25 years and (ii) EF >55%. Exclusion criteria were as follows: (i) coronary artery disease, based on clinical history and regional wall motion abnormalities at the echocardiogram; (ii) signs and symptoms of congestive heart failure; (iii) not in sinus rhythm on the electrocardiogram; (iv) bundle branch block; and (v) valvular or congenital heart disease or cardiomyopathies.

BP measurements. BP was measured before starting the echocardiograph exam by trained nurses using a mercury sphygmomanometer, with the patients in the sitting position. Three measurements were taken at 2 min intervals, and the mean value was used to define clinical systolic and diastolic blood pressures.

Echocardiography. Doppler-echocardiographic exams were performed with a phased array sector scan (Acuson Sequoia) using a multifrequence probe at 2.5, 3.5, or 5 MHz. All the examinations were supervised online by an expert sonographer (G.M.C.) and measures were taken using electronic proprietary markers.

End-diastolic and end-systolic LV diameters, end-diastolic and end-systolic interventricular septal thickness, and posterior wall thickness were measured according to the American Society of Echocardiography.[18] End-diastolic and end-systolic LV volumes were estimated using the *z*-derived method.[19] LVM was calculated using Devereux's formula[20] and normalized by height$^{2.7}$ (ref. 21,22). Relative wall thickness was calculated as (end-diastolic interventricular septal thickness + posterior wall thickness)/left ventricular end-diastolic diameter.

LV systolic properties were assessed by measuring indexes of systolic performance, function, and contractility, based on recent definitions.[13] Accordingly, indexes of LV systolic performance were SV and SW, calculated as the product of SV by mean blood pressure, then multiplied by 0.014 to convert in grammeters. Because both obesity and LV hypertrophy represent significant determinants of a higher systolic ventricular performance,[23–25] both SV and SW were normalized by body surface area (BSA) and LVM (indexed SV = SV/(BSA × LVM); indexed SW=SW/(BSA × LVM)) to obtain indexes of systolic myocardial performance. Normalization for BSA was used to exclude the effect of obesity on systolic performance indexes.[26]

LV systolic function was assessed by computation of EF, MFS,[27] and systolic velocity by TD (Sm). Myocardial contractility was assessed by cESS-MFS.[6,27] LV systolic stress was calculated as previously described.[27]

Cutoff of normality of indexed SV, indexed SW, MFS, Sm, and cESS-MFS were derived from a control group of 68 healthy, normotensive subjects with normal body weight (30 women, 38 men). Mean values − 2 s.d. were considered lower cut points. Indexed SV < 0.20 ml/(m^2 × g), indexed SW < 0.23 (g-m/beat)/(m^2 × g), MFS < 15.1%, cESS-MFS < 90.6%, Sm < 8.4 cm/s were considered subnormal.

LV filling was assessed by pulsed Doppler interrogation of transmitral inflow, and the following parameters were considered: early peak velocity (E), late peak velocity at atrial contraction (A), the ratio of early to late peak (E/A ratio), and deceleration time of E velocity (DTe). Because E/A ratio is strongly influenced by age and heart rate, its raw value was also normalized by age and heart rate as previously proposed.[28] LV DD was classified into four categories: (i) normal pattern (N; 10); (ii) delayed relaxation pattern (DR, normalized E/A ratio <1 or normalized E/A ratio between 1 and 2 with DTe > 240 ms (10)); (iii) pseudonormal filling (PN, apparent normal diastolic function (normalized E/A ratio between 1 and 2, DTe between 140 and 240 ms) with evidence of high E/Em ratio (>8 as previously reported),[29] or/and moderate or severe left atrium enlargement (left atrium diameter ≥43 mm for women, ≥47 for men as suggested),[30] as recommended by the American Society of Echocardiography);[31] and (iv) restrictive filling (normalized E/A ratio ≥2 and DTe <140 ms).

Myocardial velocities were recorded using pulsed-wave TD, according to reported methods.[8] TD spectral signal was acquired from the apical four-chamber view, with the sample volume placed along the myocardial lateral wall, 1 cm below the mitral annulus. Sm and lateral early (Em) and late diastolic

velocities were measured. E/Em ratio, an index of LV filling pressures, was also calculated.

Statistical analysis. Statistical analysis was performed using SPSS system (version 14.0; SPSS, Chicago, IL). Continuous variables are expressed as mean ± s.d. Means were compared using one-way ANOVA followed by Ryan–Einot–Gabriel–Welsch F post hoc test. Categorical variables are expressed as percentages and were compared using the χ^2-distribution.

The correlation between variables was tested by bivariate and multiple logistic and linear regression analyses. Multiple logistic and linear regression models were generated to assess the relationship between the indexes of systolic function, performance (raw values were included in the analysis), and contractility with DD, and then separately with DR and PN. All relevant potentially confounding factors that may influence both systolic and diastolic functions (age, gender, systolic and diastolic blood pressures, body mass index, E velocity, LVM, and different antihypertensive classes) were forced all together into the model with the enter method. In order to provide a reasonable estimation of the independent association between systolic and diastolic functions, raw values of all systolic parameters were divided by the standard deviation of each index (SV 16.6 ml, SW 25.8 g-m/beat, EF 6.3%, TD Sm 3.8 cm/s, MFS 2.6%, ESS-MFS 14.7%) in the whole population and the new values were then considered in the model. Normalization of systolic indexes raw values for their s.d. was performed because systolic indexes were considered in the

Table 1 | Clinical characteristics of the whole population subdivided into the different echocardiographic patterns of diastolic function

	Normal ($n = 362$)	Delayed relaxation ($n = 609$)	Pseudonormal ($n = 102$)	*P* value
Gender (male, %)	47.2	55.2	51.0	0.06
Age (years)	55.7 ± 14.1	59. 6 ± 13.2	64.8 ± 12.2	<0.001
BSA (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	<0.001
BMI (kg/m^2)	25.9 ± 4.9	26.7 ± 4.7	28.4 ± 4.8	<0.001
SBP (mm Hg)	132 ± 15	132 ± 14	135 ± 15	0.14
DBP (mm Hg)	81 ± 10	81 ± 9	81 ± 9	0.99
HR (beats/min)	74 ± 12	72 ± 12	72 ± 12	0.09
Untreated subjects (%)	30.1	26.1	25.5	0.36
RAAS inhibitors (%)	58.0	61.9	61.8	0.47
Beta-blockers (%)	11.0	12.8	13.7	0.72
Diuretics (%)	22.7	26.9	26.5	0.32
Calcium-channel blockers (%)	35.9	38.9	41.2	0.52

Values are expressed as mean ± s.d. *P* value refers to ANOVA test.
BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; HR, heart rate; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure.

Table 2 | LV geometry and diastolic function parameters of the whole population subdivided into the different echocardiographic patterns of diastolic function

	Normal ($n = 362$)	Delayed relaxation ($n = 609$)	Pseudonormal ($n = 102$)	*P* value
RWT	0.37 ± 0.05	0.39 ± 0.06	0.41 ± 0.05	<0.001
LVM/$h^{2.7}$ ($g/m^{2.7}$)	37.0 ± 9.1	41.2 ± 11.3	48.1 ± 11.6	<0.001
LVEDD (mm)	48.6 ± 4.8	49.5 ± 5.1	50.5 ± 4.9	<0.001
LAD (mm)	35.0 ± 4.1	36.2 ± 5.3	44.0 ± 5.2	<0.001
E-velocity	74.7 ± 16.5	61.6 ± 15.5	81.4 ± 19.2	<0.001
A-velocity	66.4 ± 16.5	78.3 ± 19.2	76.4 ± 18.6	<0.001
E/A Ratio	1.2 ± 0.4	0.8 ± 0.2	1.1 ± 0.3	<0.001
Normalized E/A ratio	1.3 ± 0.2	0.99 ± 0.2	1.4 ± 0.3	<0.001
DTe (ms)	192.1 ± 32.2	249.2 ± 63.1	191.2 ± 30.3	<0.001
Em (cm/s)	17.5 ± 4.3	14.5 ± 3.8	14.2 ± 4.0	<0.001
Am (cm/s)	15.8 ± 5.9	16.8 ± 4.5	15.7 ± 4.7	<0.001
E/Em ratio	4.4 ± 0.9	4.5 ± 1.6	6.2 ± 2.2	<0.001

Values are expressed as mean ± s.d. *P* value refers to ANOVA test.
Am, TD late-diastolic myocardial velocity; DTe, deceleration time of the E velocity; E/A ratio, ratio of early to late transmitral inflow velocities; Em, TD early-diastolic myocardial velocity by colour; E/Em ratio, ratio of early transmitral inflow velocities to TD early-diastolic myocardial velocity by colour Doppler myocardial imaging; LAD, left atrial diameter; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVM/$h^{2.7}$, left ventricular mass normalized by $height^{2.7}$; RWT, relative wall thickness; TD, tissue Doppler.

model as continuous variables, and the odds ratios resulting from changes of a single unit of each parameter would have not reflected the real effect size of the association.

A two-tailed *P* value <0.05 was considered the threshold to declare significance.

RESULTS

Characteristics of the study sample

Patients were divided into three groups: subjects with N, DR, or PN. Restrictive filling pattern was not observed in any patient in this population sample with preserved EF.

General characteristics of the three groups are reported in Table 1. Patients with DR or PN were older, more likely to be male, and had greater BSA and body mass index than N, with systolic and diastolic blood pressure comparable to N. Prevalence of untreated subjects was not different among the three groups as well as the prevalence of subjects taking renin–angiotensin system inhibitors, beta-blockers, diuretics, and calcium-channel blockers.

Echocardiographic parameters of cardiac geometry and function

Both DR and PN groups exhibited higher LV dimensions than N (Table 2). LVM and relative wall thickness were progressively greater in DR and PN groups as compared to N. Table 2 also shows that E velocity was lower in DR, and higher in PN, in parallel with the trend observed in E/A ratio. A-velocity was increased in both DD groups but less in the PN. TD Em was lower in both DR and PN groups compared to N. As a consequence of the combined alteration of E and Em velocities, the E/Em ratio was significantly higher in the PN group. No difference was found in end-systolic stress (N 130.06 ± 27.06 vs. DR 130.91 ± 31.10 vs. PN 135.09 ± 26.87 g/m^2, $P = 0.31$).

The three groups did not differ significantly with regards to SV and SW, which tended to be progressively higher in patients with DD (SV: N 75.02 ± 16.04 vs. DR 76.80 ± 17.30 vs. PN 78.42 ± 14.26 ml, $P = 0.12$; SW: N 103.07 ± 24.93 vs. DR 105.70 ± 26.83 vs. PN 108.73 ± 22.34 g-m/beat, $P = 0.10$). However, after normalization for BSA and LVM (to obtain indexes of systolic myocardial performance, as reported in the Methods), indexed SV and SW were found to be significantly lower in both groups with DD vs. the N group, but the impairment was more evident in the PN group (Figure 1).

Despite the fact the patients were selected on the basis of EF > 55%, MFS, cESS-MFS, Sm, and EF were also found to be significantly and proportionally lower depending on the severity of DD (Figure 1). However, when considering patients presenting with systolic indexes below the lower confidence

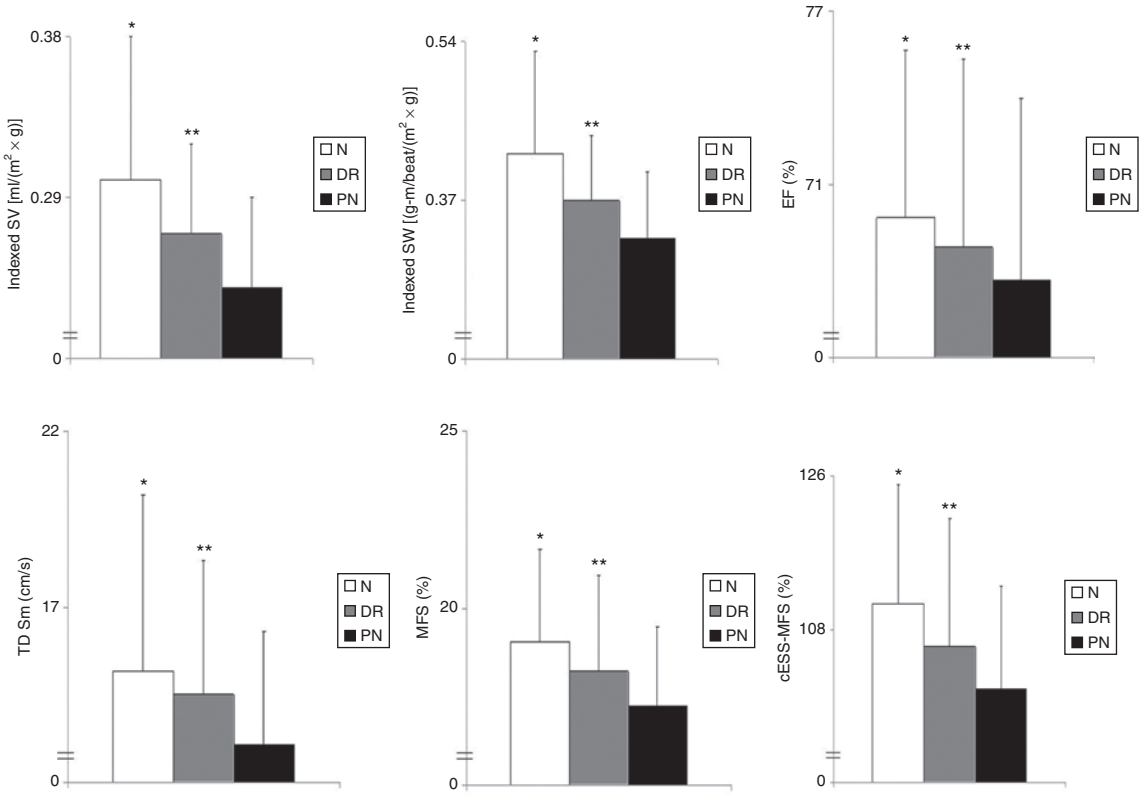

Figure 1 | Systolic performance, function, and contractility indexes in the different echocardiographic patterns of diastolic function. Variables are represented as mean value with their 95% confidence interval. *N significantly different from DR and PN; **DR significantly different from PN (RGWF *post hoc* test). cESS-MFS, end-systolic stress-corrected midwall shortening (N 111.1 ± 14.3 vs. DR 106.3 ± 14.9 vs. PN 101.3 ± 11.9%, $P < 0.001$); DR, delayed relaxation pattern; EF, ejection fraction (N 69.8 ± 5.8 vs. DR 68.8 ± 6.5 vs. PN 67.7 ± 6.3%, $P < 0.01$); Indexed SV, stroke volume indexed by body surface area (BSA) and left ventricular mass (LVM) (N 0.30 ± 0.08 vs. DR 0.27 ± 0.07 vs. PN 0.24 ± 0.05 ml/(m^2 × g), $P < 0.001$); Indexed SW, stroke work indexed by BSA and LVM (N 0.42 ± 0.11 vs. DR 0.37 ± 0.09 vs. PN 0.33 ± 0.07 (g-m/beat)/(m^2 × g), $P < 0.001$); MFS, midwall shortening (N 19.1 ± 2.6 vs. DR 18.2 ± 2.7 vs. PN 17.3 ± 2.2%, $P < 0.001$); N, normal diastolic function; PN, pseudonormal filling pattern; RGWF, Ryan–Einot–Gabriel–Welsch F; Sm, systolic velocity by TD (N 15.2 ± 3.8 vs. DR 14.5 ± 3.9 vs. PN 13.1 ± 3.2 cm/s, $P < 0.001$); TD, tissue Doppler.

Table 3 | Multiple logistic regression analysis, adjusted for age, gender, BMI, SBP, DBP, E velocity, LVM, and antihypertensive therapy to assess the relationship between systolic performance, function, and contractility, with presence of DD in general, and the presence of DR or PN of DD

	N vs. DD		N vs. DR		N vs. PN	
	OR	*P* value	OR	*P* value	OR	*P* value
SV (ml)	0.67 (CI 0.55–0.81)	<0.001	0.70 (CI 0.61–0.90)	<0.01	0.42 (CI 0.28–0.64)	<0.001
SW (g-m/beat)	0.64 (CI 0.52–0.80)	<0.001	0.69 (CI 0.61–0.88)	<0.01	0.40 (CI 0.25–0.63)	<0.001
EF (%)	0.86 (CI 0.74–0.98)	<0.05	0.89 (CI 0.85–1.07)	0.13	0.69 (CI 0.52–0.92)	<0.05
MFS (%)	0.74 (CI 0.65–0.86)	<0.001	0.80 (CI 0.69–0.93)	<0.01	0.52 (CI 0.38–0.71)	<0.001
cESS-MFS (%)	0.73 (CI 0.63–0.85)	<0.001	0.78 (CI 0.67–0.90)	<0.01	0.51 (CI 0.37–0.69)	<0.001
Sm (cm/s)	0.76 (CI 0.66–0.88)	<0.001	0.80 (CI 0.67–0.88)	<0.05	0.49 (CI 0.35–0.68)	<0.001

Indexes of LV systolic properties were included separately in the model.
BMI, body mass index; cESS-MFS, circumferential end-systolic stress-corrected midwall shortening; CI, confidence interval; DBP, diastolic blood pressure; DD, diastolic dysfunction; DR, delayed relaxation pattern; EF, ejection fraction; LV, left ventricular; LVM, left ventricular mass; MFS, midwall shortening; N, normal filling pattern; OR, odds ratio; PN, pseudonormal filling pattern; SBP, systolic blood pressure; Sm, systolic velocity by TD; SV, stroke volume (raw value); SW, stroke work (raw value), TD, tissue Doppler.

limit of normality, as defined in the Methods, only a small proportion of subjects showed a documented systolic dysfunction. Nonetheless, the proportion of subjects presenting systolic dysfunction, assessed with indexes different from EF, progressively increased from N to DR and further to PN (indexed SV: N 5.5%, DR 14.0%, PN 18.6%, $P < 0.001$; indexed SW: N 1,7%, DR 4.4%, PN 7.8%, $P < 0.001$; MFS: N 6.6%, DR 14,1%, PN 19.6%, $P < 0.001$; cESS/MFS: N 8.3%, DR 14.8%, PN 22.5%, $P < 0.001$; Sm: N 0.8%, DR 1.1%, PN 5.9%, $P < 0.05$).

A significant difference among the three groups with regards to systolic indexes was still observed even after the exclusion of these patients with a more evident reduction of systolic function from the analysis. We also assessed LV systolic properties indexes only in patients who were not under antihypertensive treatment (N 109, DR 159, PN 26). The previous observations were confirmed, being indexed SV (N 0.30 ± 0.07 vs. DR 0.26 ± 0.07 vs. PN 0.24 ± 0.05 ml/(m^2 × g), $P < 0.001$), indexed SW (N 0.41 ± 0.11 vs. DR 0.36 ± 0.09 vs. PN 0.34 ± 0.08 (g-m/beat)/(m^2 × g), $P < 0.001$), EF (N 69.3 ± 5.36 vs. DR 67.8 ± 6.57 vs. PN 67.4 ± 6.85%, $P = 0.11$), Sm (N 15.0 ± 3.3 vs. DR 14.9 ± 4.3 vs. PN 12.8 ± 2.8 cm/s, $P < 0.001$), MFS (N 18.9 ± 2.4 vs. DR 17.7 ± 2.7 vs. PN 17.2 ± 2.2%, $P < 0.001$), and cESS-MFS (N 110.4 ± 13.7 vs. DR 103.4 ± 15.4 vs. PN 102.9 ± 11.4%, $P < 0.001$) significantly lower in subjects with DD as compared to subjects with N.

Relationship between systolic performance, function, contractility, and DD

At multiple logistic regression analysis, all systolic function, performance, and contractility indexes were negatively associated with DD, which included both patients with DR and PN (Table 3). When separating patients with DR from those with PN, these results were confirmed for each pattern. Such correlations were stronger with regards to PN (Table 3).

In addition, following adjustments for previous variables, we performed a multiple linear regression analysis, to evaluate the relationship between indexes of systolic performance, function and contractility, and E/Em ratio, which is an index of LV filling pressure. A reduction of SV (β −0.09 (95% CI −0.01/−0.003), $P < 0.01$), SW (β −0.09 (95% CI −0.09/−0.002), $P < 0.01$), EF (β −0.04 (95% CI −0.02/0.001), $P = 0.074$), Sm (β −0.19 (95% CI −0.09/−0.06), $P < 0.001$), MFS (β −0.07 (95% CI −0.06/−0.02), $P < 0.01$), and cESS/MFS (β −0.07 (95% CI −0.01/−0.003), $P < 0.01$) resulted to be independently associated with a higher E/Em ratio.

DISCUSSION

In our study, a significant proportion of hypertensive subjects without overt cardiovascular disease and with a normal EF, presented with a mild to moderate degree of DD (DR, PN). In spite of the fact that most of LV systolic indexes were within the normal range, a decline of these indexes could be detected in subjects with DD. The degree of the reduction paralleled the severity of DD.

Previous studies have reported that LV DD is strongly associated with systolic dysfunction in patients with clinically relevant decline of LV systolic function.[3,4] Our results confirm this relationship between diastolic and systolic dysfunction also in hypertensive subjects with "isolated" DD. The latter is usually considered an alteration of the diastolic phase alone without a concomitant reduction of systolic properties.

Our study extends over a large population and further confirms previous observations of a relationship between a reduction of systolic function and an impairment of LV relaxation indexes in hypertensive patients.[14–17] In these previous studies, however, a multiparamentric assessment of LV systolic properties (including also TD assessment) was not performed, and systolic performance, function, and contractility were not evaluated in different patterns of DD. These studies observed a significant relationship of a reduced midwall fractional shortening with an impairment of several LV relaxation parameters. Of note, these studies considered also patients with an EF lower than 55%, which is the suggested cutoff to define a normal chamber function,[30] and some of them were conducted on subjects with LV hypertrophy.[16,17] Over the last few years, other studies have also investigated whether subjects with LV

DD and preserved EF may exhibit initial systolic abnormalities, by using more sensitive echocardiographic methods.[9–13] However, these studies provided discordant results and were in addition conducted on heterogeneous populations, mostly including subjects affected by diastolic heart failure or overt cardiovascular diseases.

In our study, which included a large cohort of subjects without cardiovascular disease and with normal LV systolic function (EF > 55%, as suggested by current guidelines for chamber quantification; 30), the presence of DD was associated with reductions of LV systolic indexes, particularly with regards to the midwall mechanics and TD indexes. However, only a proportion of subjects with DD had indexes of systolic properties lower than the cutoff values of normality as defined in the Methods section. Therefore, the presence of DD was associated with a significant reduction of systolic properties, which were mostly found to be within the normal range. Furthermore, the reduction of LV systolic properties was associated with DD, independently of other factors that could have contributed to a parallel impairment of both systolic and diastolic function, such as age, obesity, and LV hypertrophy. Of interest, we also demonstrated that this initial decline of LV systolic properties paralleled the degree of severity of DD. In fact, PN was associated with a more marked decline of systolic properties, as compared to DR. A reduction of systolic indexes was also significantly related to a higher E/Em ratio, i.e., increased LV filling pressures.

SV and SW, indexes of LV systolic ventricular performance, were not significantly different between patients with or without DD, despite the fact that they tended to be higher in the former. This might be a consequence of the greater prevalence of obesity, LV hypertrophy, and the increased preload recruitment in subjects with DD, especially in those with PN. Indeed, these factors could offset the intrinsic reduction of myocardial performance of these subjects, thus making it apparently normal. In fact, when SV and SW were adjusted by BSA and LVM, to obtain indexes of systolic myocardial performance, they became progressively lower in subjects with DD. As previously demonstrated and confirmed in our study, obesity and LV hypertrophy resulted to be significantly associated with an increased SV and SW,[23–25] mainly because of a higher preload recruitment and a reduction of wall stress. The above evidence is also supported by the multivariate analysis, showing that SV and SW raw values were inversely related to DD, especially to PN, after adjustment for obesity, LVM, and preload.

EF, midwall shortening, and Sm parameters of systolic function that are corrected for preload were also reduced in patients with DD. Also the stress-corrected midwall shortening showed a reduction of ventricular contractility in patients with DD, paralleling its severity.

Based on our results, "isolated" LV DD might, therefore, be considered as an intermediate pathway between a normal ventricular function and an overt systolic dysfunction. Moreover, as most of subjects with DD had a significant reduction of systolic indexes within the range of normality, it may be possible that overt clinical abnormalities in the filling phase develop earlier than those in the ejection phase. Further prospective studies are necessary and should be encouraged to demonstrate this hypothesis. Moreover, since the magnitude of the association between systolic and diastolic functions does not appear to be large, further investigations may be required to explore the real pathophysiological impact of this association in essential hypertension.

Our study might also have some clinical implications since hypertensive patients with a severe DD, despite being asymptomatic and presenting with a normal EF or a normal LV volume, may benefit from a more aggressive therapeutic approach, thus reducing the progression toward a clinically evident LV systolic dysfunction. Moreover, these patients may require more frequent and intensive outpatient controls.

A possible limitation of our study could be our associative experimental approach, which cannot directly address the potential pathophysiological mechanisms involved in the relationship between systolic and diastolic dysfunctions. We considered the absence of echocardiographic regional wall abnormalities and the lack of a clinical history as reasonable criteria to exclude subjects affected by coronary artery disease, and this could be considered a limitation of our study. The exclusion of subjects with wall motion abnormalities, in any case, allowed us to rule out the presence of cardiac functional and structural alterations which could affect our results.

CONCLUSIONS

This study demonstrates that in hypertensive patients with "isolated" LV DD, without clinical evidence of heart disease and heart failure, a reduction of LV systolic performance, function, and contractility could be detected. The extent of the reduction of LV systolic properties paralleled the degree of DD, this being more evident in patients with PN compared to DR. Remarkably, most of the subjects with DD had a reduction of these systolic indexes within the range of normality, although the reduction was in any case strictly and independently associated to DD.

Therefore, our study suggests the existence of a direct and preclinical pathophysiological relation between LV systolic and diastolic dysfunction in hypertensive patients with a clinically normal left ventricular pump function, which is more evident in the presence of a more advanced degree of LV DD.

LV DD might be considered an intermediate pathway between a normal ventricular function and an overt systolic dysfunction in essential hypertension.

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