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Tesi di Dottorato

Effects of high-normal and mildly increased arterial blood pressure on right ventricular function: application of new echocardiographic techniques

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ANNO ACCADEMICO 2008/2009

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SUMM ARY

***Purpose*:** To analyze the relationship between increasing systemic blood pressure and right ventricular function by means of Tissue-Doppler Imaging (TDI) and Two-dimesional Strain echocardiographic techniques.

***Subjects and methods*:** Ninety-eight never-treated, nonobese patients with blood pressure values varying from the optimal to the mild hypertensive range were recruited. Peak early (Em) and late (Am) diastolic and systolic (Sm) velocities were recorded at the tricuspid and mitral annuli by TDI. Longitudinal peak strain and strain rate (SR) were sampled by speckle-tracking methodology at the right ventricle (RV) free wall and interventricular septum (IVS) and RV and left ventricular (LV) structure and function were evaluated by conventional echo-Doppler sonography. Insulin sensitivity was tested by homeostasis model assessment (HOMA) index. Data were analyzed by 24-h systolic BP (SBP) (cut-offs 117 and 130 mmHg), thus partitioning an optimal BP from an intermediate high-normal and an upper mildly increased BP stratum.

***Results*:** Em decreased in the mid-third and decelerated further in association with reduced Sm in the upper BP tertile; both correlated negatively to septal thickness and positively to homologous TDI-derived LV indices. RV peak systolic strain and early diastolic SR decreased in the mid-BP third without further changes in the upper tertile. IVS thickened gradedly by increasing systemic 24-h SBP; posterior wall remodelled to a lesser extent and poorly related to BP load and LV mass index did not change. RV and IVS systolic and diastolic strain indices associated inversely with increasing septal thickness. RV and LV indices of global ventricular function, estimated pulmonary pressure, HOMA did not differ by systemic BP.

***Conclusion*:** TDI and 2D-strain echocardiography showed a RV diastolic and systolic function impairment in response to slightly increased systemic BP. The process

paralleled homologous changes at the LV side and was driven by interventricular septum remodeling, perhaps as a reflection of its role in RV function and biventricular interdependence. Insulin sensitivity seemed to play no relevant role.

INTRODUCTION

II. *The right ventricle in systemic hypertension*

Chronically elevated systemic blood pressure (BP) has profound consequences on the heart and systemic vessels. Through the activation of a complex and interrelated series of biological mechanisms [1,2], the left ventricle (LV) undergoes geometric remodelling [3] and hypertrophies [4] while decreased compliance and delayed isometric relaxation impair left ventricular diastolic function, this latter occurring even in early hypertensive stages and in absence of left ventricular hypertrophy (LVH) [5]. Arterial hypertension also reshapes the more distal sites of the peripheral vasculature through faster vascular growth, eutrophic remodelling and changed distensibility [6]. As a consequence, resistance-sized arterioles increase their wall/lumen ratio, a structural modification that, on one hand, amplifies nonspecifically vasoconstrictor responses and, on the other, initiates and maintains a vicious circle heading towards a stable increase in peripheral vascular resistance, the hallmark of hypertensive disease [7]. The wide-ranging effects of BP elevation on the leftsided cardiovascular system, as above capsulized, are documented by a huge amount of basic and clinical research. However, sparser data scattered across at least 3 decades also point out to the presence of abnormalities of the right-sided cardiovascular system during the course of systemic hypertension, an important and rather overlooked body of information [8].

II.a *A synopsis of the anatomy and the function of the right-sided cardiovascular system*

The right ventricle (RV) is a thin-walled, crescent-like chamber originating from the juxtaposition of a concave anterior free wall with a convex interventricular septum (Fig. 1) [9]. The RV mass is about one-sixth of the LV and performs about one-quarter of its stroke work to propel blood across a vascular circuit whose resistance is about one-tenth

of the systemic values due to the large cross-sectional area of the pulmonary circulation [10].

Anatomically, the RV is separated in an inflow and an outflow tract, the latter being responsible for the systolic ejection of the stroke volume. Because of the lower intraventricular pressure regimens and in contrast with the phasic perfusion of the LV, blood flows across the RV during both systole and diastole through the right coronary artery and its main branches, the conus artery, the acute marginal branches and the posterior descending artery with an additional contribution of the left anterior descending coronary artery to the right anterior wall [10]. As compared with its left counterpart, the RV has a lower volume-to-surface area ratio in agreement with its highly compliant nature adapted to accept large volumes of blood with negligible changes in pressure. Not surprisingly, therefore, the acutely overloaded right ventricular chamber first dilates to compensate for the reduced cardiac output and, eventually, fails. On the contrary, chronic pulmonary pressure overload stimulates a rather stereotyped adaptive response consisting of compensatory RV hypertrophy (RVH) characterized by a thicker wall and flattened interventricular septum with a relative impairment of coronary perfusion [11]. Independent of the underlying causal mechanism, long-term increase in pulmonary resistance originates from both functional components due to an unbalanced production of endothelium- derived vasoactive mediators (e.g. nitric oxide, prostacyclin, endothelin-1) and structural remodelling of pulmonary arterioles caused by proliferating endothelial cells, vascular smooth muscle cells and fibroblasts [11]. RV and LV are functionally and structurally interdependent [12] with the ultimate goal to provide sufficient lung/peripheral perfusion during rapidly changing physiological conditions. That goal is reached by a shared anatomic array of spiral muscle bundles encircling both ventricles [13] with the interventricular septum acting as a sort of ‘motor of biventricular function’ thanks to its endowment of fibres arising from both

ventricular chambers [14]. Because of ventricular interdependence, force is transmitted from one to the other ventricle through the myocardium independently from neural, humoral and haemodynamic influences, so that about 20–40% of the beat-to-beat right ventricular systolic pressure and volume outflow is conditioned by left ventricular contraction [12]. Not surprisingly, therefore, in the light of their intimate anatomic and functional connections, pressor stimuli exerted on one ventricular chamber are transmitted to the nonstressed counterpart. For example, LV haemodynamic overloading in experimental animals was accompanied by biventricular hypertrophy with augmented biochemical and haemodynamic function of the nonstressed RV [15]. Reciprocally, pulmonary banding increased mass and stiffness [16], augmented connective tissue synthesis [17] and reduced beta-adrenergic receptor density [18] not only in the overloaded RV but also in the haemodynamically uninvolved LV.

II.b *Pulmonary haemodynamics in systemic hypertension*

Following very early reports [19–21], the interest towards the behaviour of pulmonary haemodynamics in systemic hypertension was revived in 1977 by Atkins et al. [22] who showed increased pulmonary vascular resistance in 62% of 110 hypertensive patients on a variety of antihypertensive drug in presence of a positive correlation between pulmonary and systemic resistance suggestive of a common vasoconstrictor mechanism in the two vascular beds. A more detailed description of pulmonary haemodynamics in systemic hypertension was provided in 1978 by Olivari et al. [23] who showed higher pulmonary pressure and increased capillary wedge pressure in a group of hypertensive patients with LVH and strain at the electrocardiogram (EKG) as compared with normotensive controls. That finding was confirmed by Ferlinz [24] in 1980 in reporting both higher pressures in the right-sided heart (Fig. 2) and depressed RV function. However, both sets of data [23,24], consistent with increased pulmonary resistance

secondary to backward transmission of increased diastolic ventricular pressure in poorly compliant or failing LV (Fig. 3), resented of the inclusion of patients with more severe hypertension and advanced hypertensive cardiac damage. Consistent with that interpretation, studies in patients with atrial fibrillation showed larger ostial pulmonary vein diameter in hypertensive – than in normotensive patients (1.55±0.32 vs 1.43±0.26 cm, $P<0.01$), a pattern worsened by coexisting LVH (1.66±0.37 cm) [25]. Highlighting further the importance of the clinical characteristics and stage of progression of hypertensive disease, the depressed RV ejection fraction reported by Ferlinz [24] through haemodynamic techniques contrasts with the normal RV function documented in subsequent studies by either radionuclide ventriculography [26] or echocardiography [27] including tricuspid annular plane systolic excursion (TAPSE) evaluation [28]. Interestingly, however, subtle disturbances of contractility emerged when tested by sophisticated echocardiographic techniques, such as strain/strain rate imaging [29], not influenced by global heart translation and adjacent myocardial segments tethering [30]. In addition, pulmonary resistance was normal in mildly hypertensive patients [31,32] implying normal left ventricular compliance and performance but also that –whatever hypertensinogenic factor affected the systemic circulation did not similarly affect the pulmonary circuit. Still, other studies [33,34] identified an elevated pulmonary resistance in absence of venous hypertension, an intriguing pattern compatible with the action of vasoconstrictor factors acting on both sides of the circulation. Thus, systemic hypertension may coexist with an apparently primary form of vasoconstriction in the lesser circulation in a subset of hypertensive patients, possibly under the influence of enhanced sympathetic tone, increased delivery of blood-borne vasoconstrictor substances or abnormal local release of vasoactive factors [7], perhaps promoted by an underlying insulin-resistant state [35]. Hyperreactivity to vasoactive stimuli is an additional feature of pulmonary arterioles in the presence of systemically elevated BP,

an evidence generated by Guazzi et al. [34] who reported greater pulmonary vasomotor responses evoked by both exogenous (Fig. 4, left panel) and endogenous sympathetic activation in response to cold, mental stress [36] and caval obstruction [32]. That hyperreactive pattern did not differ by baseline pulmonary resistance level [32 vs. 34] and could also be elicited by hypoxia [37] (Fig. 4, right panel), a nonadrenergicmediated vasoconstrictor stimulus [38]. That overall picture is compatible with the presence of early structural readaptation of pulmonary arterioles whose increased wall/lumen ratio can have a progressive pressor effect and accentuate nonspecifically the response to superimposed vasoconstrictor stimuli [7]. Exaggerated reactivity [39] and increased wall/lumen ratio [40] in the vascular bed of animal models of hypertension support that possibility though relevant human data are missing. Therefore, the question of whether the augmented vasoconstrictor reaction of pulmonary arterioles in human hypertension has a structural background or derives from functional abnormalities, for example, a systemically altered calcium ion metabolism of vascular smooth muscle cells [41], remains unanswered.

II.c *Echocardiographic evaluation of the right ventricle in systemic hypertension*

The application of M-mode echocardiography, though hampered by the geometric configuration of the RV and its heavily trabeculated anatomic structure with muscle bands, papillary muscle and chordae tendineae lying proximal to the right ventricular free wall [8], allowed Nunez et al. [27] in 1987 to show an increased right anterior wall thickness in patients with systemic hypertension and LVH (see Table 1 [26–29,42–46] for a synopsis of the available results). To that preliminary observation, Gottdiener et al. [42] added the important pathophysiological observation of RVH in conditions such as aortic stenosis in which left ventricular overload develops independent of heightened systemic BP levels. In that series, increased RV wall thickness exceeded the cut-off for

RVH in a large portion of the hypertensive group without relationship with right ventricular systolic pressure (Fig. 5, left panel). In agreement with Nunez et al. [27], a statistically significant correlation linked remodelling of the right and LVs though the regression of left over right wall thickness explained only about 60% of the overall data variability [42] (Fig. 5, right panel). The first documentation of RV diastolic dysfunction in hypertension was provided by Chakko et al. [43] in 1990 by documenting faster RV atrial filling, prolonged deceleration half-time, lower early/atrial filling velocity ratio and peak filling rate/stroke volume through pulsed wave Doppler echocardiography. That trend was confirmed by the other authors who subsequently addressed that issue [28,29,43–47] (see Table 1 for a synopsis of the available results). All studies reported a statistically significant association between RV and LV indices of diastolic filling (e.g. Fig. 6) without or, at its best, a poor relationship with anterior and posterior ventricular wall thickness as well as left ventricular mass. Galderisi et al. [46] and Cicala et al. [28] applied tissue Doppler analysis, a newer echocardiographic technique measuring intramyocardial velocities [48], to study right diastolic function in hypertensive patients. Both authors reported a prolonged RV relaxation time, an indirect measure of the active isometric relaxation phase, to indicate that the overall right ventricular diastolic interval is impaired during the course of systemic hypertension (Fig. 7, left panel and Table 1) through mechanisms independent of the degree of septal hypertrophy (Fig. 7, right panel). Because of its dependence upontransansvalvular pressor gradients [10,11], a delayed isometric relaxation time is consistent with an augmented pressor overload in the lesser circulation. In agreement with previous results [42], about one-third of the hypertensive group showed evidence of RVH (RV thickness> 5mm) [46].

II.d *Prehypertension: definition, epidemiology, cardiovascular subclinical disease and mortality*

The BP category "prehypertension" was first introduced by the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) in 2003, replacing former categories of "high normal" and "above-optimal" BP [49]. The rationale for redefining this category was to emphasize the excess risk associated with BP in this range and to focus increased clinical and public health attention on prevention. Regardless of terminology, this condition is a precursor of hypertension [50,51] and is associated with excess morbidity and deaths from cardiovascular causes [52,53]. Furthermore, an association of prehypertension with other cardiovascular risk factors has been established [54-57]. Prehypertension was defined as a systolic blood pressure of 120–139 mmHg and/or a diastolic blood pressure of 80–89 mmHg [49] (Table 2).

A rationale basis for creating the prehypertension blood pressure category came, at least in part, from a metaanalysis that included approximately 1 million individuals from 61 longterm epidemiological studies. The metaanalysis demonstrated that mortality from ischemic heart disease and stroke in individuals aged 40–89 years increases in a log–linear relationship together with increases in both systolic and diastolic blood pressure [58] (Figure 8). For each 20 mmHg increase in systolic blood pressure or 10 mmHg increase in diastolic blood pressure over 115/75 mmHg, there is a twofold increase in mortality associated with coronary artery disease and stroke. Furthermore, longitudinal data from the Framingham Heart study indicated that individuals formerly classified as having 'normal' and 'highnormal' blood pressure (120–139/80–89 mmHg) are at increased risk of developing fullblown hypertension and cardiovascular disease later in life than those who have an optimal blood pressure (<120/80 mmHg) [51,59].

In contrast with JNC-7, in 2007 the ESH-ESC Committee [60] has decided not to use the term ‘prehypertension’ for the following reasons: (1) even in the Framingham Heart study, the risk of developing hypertension was definitely higher in patients with high-normal blood pressure than in those with normal blood pressure; (2) because of the serious meaning of the word hypertension for general populations, the term ‘prehypertension’ might create anxiety and lead to unnecessary consultations with a doctor; (3) this category is a highly differentiated one in practice, with the extremes consisting of patients in no need of any intervention as well as of those with a very high-risk profile such as diabetes, chronic kidney disease, or hyperlipidemia for whom drug treatment is required, although lifestyle changes recommended by the JNC 7 for all prehypertensive individuals can be a valuable population strategy [60].

The publication of JNC-7 led to the initiation of population-based surveys to describe the prevalence of pre hypertension and increased awareness of the importance of the problem by doctors and health organizations. The Third National Health and Nutrition Examination Survey (NHANES III) 1999–2000 reported that the overall prevalence of prehypertension in the US was 31%, higher in men than in women, and was higher in obese than in normal weight persons [61]. On the basis of the NHANES 2005–2006 data, an estimated 25% of the us population aged 20 years or older has prehypertension, including over 32 million men and 21 million women [62]. Prehypertension is associated with the same traditional cardiovascular risk factors as fullblown hypertension, such as obesity, diabetes mellitus and dyslipidemia. NHANES 1999–2000 data showed that 64% of individuals with prehypertension had at least one other cardiovascular risk factor, and the percentage increased to 94% in those aged 60 years or older [61]. Prehypertension is associated with subclinical cardiovascular disease, including both microvascular and macrovascular pathology. Microalbuminuria, an organ-specific manifestation of generalized endothelial dysfunction that is associated

with increased risk of cardiovascular disease, is more common in individuals with prehypertension than in those with normal blood pressure [63-65]. Individuals with prehypertension often have subclinical atherosclerosis, manifested by increased common carotid artery intima-media thickness [66] and increased calcium deposition in the coronary arteries [67]. Prehypertension also accelerates the development of LVH and diastolic dysfunction. The population-based MONICA (Monitoring of trends and Determinations in Cardiovascular Disease) –Augsburg/KORA (Cooperative Research in the Region of Augsburg) study compared echocardiographic data from 119 individuals with prehypertension that persisted over the decade from 1994 or 1995 to 2004 or 2005 with data from 142 individuals in whom blood pressure remained normal over this time [68]. Over these 10 years, prehypertensive individuals had a significantly greater age-related increase in LV wall thickness (11.9% versus 4.7%, P <0.001) and LVM (15.7% versus 8.6%, p = 0.006) and an increased incidence of LV concentric remodeling (hazard ratio [HR] 10.7; 95% CI 2.82–40.4) and LVH (HR 5.3; 95% CI 1.58–17.9), compared with individuals with normal blood pressure. The ratio of peak early to late diastolic transmitral flow velocities decreased by 7.7% in patients with normal blood pressure compared with 15.7% in those with prehypertension (p = 0.003) and at follow-up the ratio of peak early diastolic transmitral flow to peak early diastolic myocardial relaxation velocities was higher (9.1 versus 8.5, p = 0.031) and left atrial size was larger (36.5mm versus 35.3mm, p = 0.024) in prehypertensive than in normotensive individuals. The adjusted odds ratio for incident diastolic dysfunction was 2.52 (95% CI 1.0–6.3) for the prehypertensive group. Thus, persistent prehypertension accelerates the development of LVH and diastolic dysfunction.

Prehypertension has been associated with a variety of cardio-vascular diseases and with cardiovascular-associated and all-cause mortality in a number of large cohort studies. The increment in cardiovascular risk associated with progression from normotension to

prehypertension is similar to that associated with the progression from prehypertension to hypertension. In the MONICA study, participants who transitioned from normotension to the upper levels of prehypertension had the same increase in risk of cardiovascular events (HR 1.57; 95% CI 1.06–2.33) as those who progressed from the lower level of prehypertension to the hypertensive range (HR 1.64; 95% CI 1.19–2.26) [69]. A major objective of JNC-7 in creating the prehypertensive classification of blood pressure was to provide a tool for the identification of individuals for whom early adoption of a healthy lifestyle could lower blood pressure and prevent progression to hypertension, with associated reductions in target organ damage and cardiovascular events. Lifestyle modifications, such as weight loss, dietary alterations and exercise, have been shown consistently in randomized, controlled trials to effectively lower blood pressure and are recommended for patients with prehypertension [70-72]. Dietary modification can lower blood pressure effectively independently of weight loss in individuals with prehypertension. Treatment of prehypertensive patients with antihypertensive agents in addition to non-pharmacological measures has been explored in clinical trials. The Trial of Preventing Hypertension (TROPHY) study tested whether pharmacological treatment with the angiotensin II receptor antagonist candesartan cilexetil can prevent or delay the transition from prehypertension to stage 1 hypertension [73]. Participants with prehypertension were randomly assigned to receive candesartan cilexetil or placebo for 2 years, followed by 2 years of placebo for all participants. In addition, all participants received instructions for lifestyle modification. During the first 2 years, the risk of developing hypertension was reduced by 66.3% in the participants who received candesartan cilexetil compared with the placebo group; the magnitude of risk reduction decreased to 16% by year 4, but was still statistically different from placebo. The treatment was also well tolerated. TROPHY provided the first demonstration that pharmacological treatment for patients with prehypertension is

safe and at least partially effective in reducing the risk of incident hypertension. However, no difference in the occurrence of cardiovascular events was observed between the treatment groups and the trial was not sufficiently powered to detect such a difference, had it occurred. Similarly to the TROPHY study, the Prevention of Hypertension with the ACE-inhibitor Ramipril in Patients with High Normal Blood Pressure (PHARAO) trial was a prospective, randomized, controlled study designed to analyze the effect of the angiotensin converting enzyme (ACE) inhibitor ramipril on preventing or delaying hypertension in 1,008 individuals with prehypertension [74]. Participants with pre hypertension were randomly assigned to receive ramipril or placebo and were followed for 3 years. Unlike TROPHY, PHARAO did not include a period of follow-up after withdrawal of active treatment. Hypertension developed in 31% of participants in the ramipril group and 43% of those in the placebo group, with a statistically significant 34% reduction in risk for the ramipril group. The incidence of cerebrovascular and cardiovascular events was low and not significantly different between groups.

In conclusion, individuals with prehypertension have an increased risk of fullblown hypertension, target organ damage and cardiovascular-related morbidity and mortality. Lifestyle modifications that lower blood pressure reduce morbidity and mortality associated with cardio-vascular events, and are recommended for all patients with prehypertension. Pharmacological treatment reduces progression from prehypertension to hypertension, but more studies are needed to determine the effects of pharmacological treatment on target organ damage and cardiovascular-related morbidity and mortality [75].

II.e *Tissue Doppler Imaging and Two-Dimensional Strain*

Tissue Doppler Imaging (TDI) is a relatively new echocardiographic technique originating from standard Doppler in order to obtain a quantitative analysis of myocardial function. Myocardial velocities and motions are tightly related to systolic and diastolic activity of the heart and are smaller (5-20 cm/sec) than blood velocities; TDI analysis is based on quantification of such parameters. While during standard echocardiographic examination low frequency myocardal tissue volocities are cutted out by default filters, in TDI examination blood flow high frequency are blocked by default filters or by color-based auto-correlation systems. Early reports by Isaaz *et al* showed the correspondance between TDI low myocardial velocities recorded at posterior side of mitral annulus and LV posterior wall alterated contractility [76]. Later on McDicken *et al* and Sutherland *et al* enhanced previous systems by adding a direct color-Doppler view of myocardial wall movements [77,78]. Pulsed-wave TDI (PW-TDI) is usually performed on apical view to assess longitudinal motion of LV both at mitral annulus and myocardial wall level. Sampling at mitral annulus level allows a quantification of global systo-diastolic LV longitudinal shift, while myocardial wall sampling allows a direct analysis only of the sampled section. In all cases, the selection of a small sample volume (< 5mm) allow the detection of myocardial peak velocities (cm/sec) and of time intervals (msec). Myocardial TDI velocities vary according to ventricle anatomy being higher at cardiac base and lower at apex; so, to quantify myocardial function a cardiac base level measurement is recommended. American Society of Ecocardiography (ASE) recommends to place the sample volume at the junction of LV lateral wall with mitral annulus. Tissue-Doppler Imaging pattern showed two distinct “myocardial phases”:

- A systolic phase including a forward systolic myocardial (S_m) velocity, an isovolumetric precontraction time (IPCT) and a contraction time (CT).

- A diastolic phase including an isovolumetric relaxation time (IVRT) and two backward myocardial diastolic velocities, early diastolic (E_m) and atrial (A_m).

Notably, E_m velocity demonstered to be a relatively pre-load independent index of myocardial relaxation.

Two-dimensional strain (2Dstrain) imaging is a new technique which uses standard B-mode images for speckle tracking analysis, in which the speckled pattern (acoustic backscatter generated by the reflected ultrasound beam) is followed frame by frame [79]. This speckle pattern is unique for each myocardial region and it is relatively stable throughout the cardiac cycle. The displacement of this speckled pattern is considered to follow myocardial movement and a change between speckles represents myocardial deformation. When tracking a defined region of speckles, a software algorithm follows the change in geometric position of this region, frame by frame, and extracts the displacement, velocity, strain and strain rate of a defined myocardial segment (Figure 9). In contrast to TDI derived parameters, speckle tracking is an angle independent technique as the movement of speckles can be followed in any direction. For the apical views this implies that not only longitudinal, but also transverse parameters can be calculated, which is not possible in TDI recordings. In short axis images both circumferential and radial parameters can be calculated for all myocardial segments. In addition to the circumferential deformation parameters, ventricular rotation

and twist (additional parameters for LV function) can also be calculated using this technique [80,81]. Since the deformation parameters can be calculated in two dimensions (while TDI derived parameters are one-dimensional), this technique is often referred as two-dimensional strain echocardiography (2DSE). Validation of early versions of 2DSE software in a tissue mimicking gelatin block revealed a good correlation compared to sonomicrometry, although values (both strain and strain-rate) were overestimated in the lower range of values [82]. These findings were also found in

an animal model (sonomicrometry in pigs with myocardial infarction), where 2DSE was found to slightly overestimate values compared to the reference test. A weaker correlation was found in the lower range of deformation values [82]. Tracking is affected by dyskinetic segments (e.g. ischemia), causing the fiber orientation to change, thus affecting acoustic properties and speckle integrity. Using a new (two-stage) tracking algorithm, a better correlation was found between the 2DSE values and those obtained using sonomicrometry over the entire broad range of tested clinical relevant values [83]. For radial and circumferential parameters, a good correlation was found using sonomicrometry in dogs [84]. The first study to determine the feasibility and accuracy of 2DSE in patients with myocardial infarction reported that of all segments, 98% in the control population and 80% in the patient group could be analyzed, findings which were reproduced in later studies [84]. Importantly, 2DSE data are highly reproducible and analysis is affected by only small intraobserver (mean 4.4 (SD 1.6)%) and interobserver variability (7.3 (SD 2.5)%) [85]. Values were significantly reduced in the infarcted segments, implying a reduction in systolic deformation. There was no significant difference between TDI and 2DSE parameters [86]. In a direct comparison of TDI and 2DSE with MRI-tagging as a reference, comparable values were found for 2DSE and TDI in both normal and dysfunctional segments. For radial measurements, 2DSE was more reliable than TDI [87]. At present, the optimal frame rate for speckle tracking seems to be 50–70 frames per second (FPS), which is lower compared to TDI (>180 FPS): this could result in undersampling, especially in patients with tachycardia.

STUDY AIMS

The right-sided cardiovascular system is not immune to the effect of systemic hypertension. Consistent echocardiographic evidence (see Table 1 for a synopsis of the available data) indicates that systemic hypertension associates with thickened wall of the RV, a central element of the low-pressure system. RV remodelling develops in parallel with a similar process at the left side, likely as a result of ventricular interdependence [12] driven by vasoactive and trophic factors, including sympathetic stimulation and locally released substances such as angiotensin II and endothelin(s) [2], targeting both myocardial walls. That explanation is not exclusive, though, and other pathophysiological mechanisms including primarily or secondarily increased pulmonary afterload maybe operative as well. Available evidences originate from studies carried out on hypertensive models or subjects but no data as so far been reported on the effects of a mild increase of BP on RV structure and function. On these grounds, we designed the present study to analyze the effect(s) of such a mild increase on RV.

PATIENTS AND METHODS

IV.a *Study population*

Ninety-eight never-treated asymptomatic patients (see Table 3 for demographics and clinical characteristics of the overall sample) without history of any disease, with normal physical examination and no abnormalities at routine biochemical tests participated in the study. The group included 30 controls with optimal BP (casual BP <120/80mmHg) and 68 patients referred for hypertension screening to our outpatient clinic. Inclusion criteria required fasting plasma glucose below 126 mg/dl, serum creatinine less than 1.2mg/dl, no proteinuria at the dipstick test, negative urinocolture, normal sediment, ejection fraction above 50%, no evidence or history of lung disease, congestive cardiac failure and/or left ventricular dysfunction, ischemic heart disease, atrial fibrillation and clinically significant valvular defect (<2 on a 1–4 ordinal scale) at Doppler recordings. Patients with office BP above 160/100mmHg and body mass index (BMI) above 30 kg/m^2 were excluded. In all, renal ultrasound scans showed normal-sized kidneys and no evidence of cortical scarring or obstructive uropathy, whereas routine clinical and biochemical evaluation excluded other secondary forms of hypertension.

IV.b *Experimental procedures*

Anthropometric measurements (height and weight) were made after each participant had removed his shoes and upper garments. Blood samples were obtained between 08:00 and 09:00 AM after overnight fasting and 15 minutes of supine rest. Twenty-four-hour BP was measured using a validated [88] oscillometric monitor (Diasys Integra, Novacor) on a regular work day. Recording began between 08:30 and 09:00 AM with readings every 15 min until midnight, and every 30 min from midnight to 08:00 AM

with at least 90% valid measurements. Office pressures were the mean of at least three recordings taken at the time of the echocardiographic study. Total, low-density lipoprotein (LDL), high-density lipoprotein (HDL)-cholesterol, triglycerides were assessed by enzymatic colorimetric techniques (Boehringer-Mannheim), fasting plasma glucose by the glucooxidase method using a Beckman Glucose Analyzer II (Beckman Instruments), and plasma insulin by immunoradiometric assay (Biosource; no cross-reactivity with human proinsulin, between-assay variation coefficient of 5%).

IV.c *Conventional echocardiograpy*

Monodimensional and bidimensional echocardiograms were obtained according to the recommendations of the Joint American and European Society of Echocardiography [89] using standard parasternal and apical views through a machine (Vivid 7; General Electric Healthcare) equipped with a harmonic 4.0-MHz variable-frequency phased-array transducer. The LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), end-diastolic thickness of ventricular septum (IVSThd), end-diastolic thickness of LV posterior wall (PWThd) and of RV free wall (RWThd) were measured by M-mode echocardiography. Using these parameters, we calculated LV mass and the relative LV wall thickness as follows: LV mass (g) = 1.04 × ((LVEDD + IVSThd + PWTh)^3 − LVEDD^3) − 13.6. Relative LV wall thickness (RWT) = 2 × PWThd/LVEDD. Left ventricular mass (LVM) index was determined by dividing the LV mass measurement by the body surface area (g/m^2) (LMVbs) or by height (LVMh) (h$^{2.7}$). LV end-diastolic volume (LVEDV) and end-systolic volume (ESV) were calculated from the apical 2- and 4-chamber views using a modified Simpson's method. LV ejection fraction was calculated as ejection fraction (LVEDV–LVESV)/LVEDV × 100. Endsystolic left atrial dimensions were measured in the parasternal axis view from the trailing edge of the posterior aortic–anterior left atrial complex [89]. TAPSE, an index

of RV systolic function [90] was measured as tricuspid annulus plane systolic excursion during the same cardiaa cycle (mm). Systolic pulmonary artery pressure (SPAP) was estimated through the modified Bernoulli equation adding a constant 5mmHg as a standard measure of right atrial pressure [91]. Tricuspid and mitral inflow velocities were obtained by pulsed-wave Doppler echocardiography positioning a sample volume between outflow tract and valve leaflet tips in the apical four-chamber view. Inflow measurements included peak velocity (cm/s) during early (E) and late (A) filling, their ratio (E/A ratio), E-wave deceleration time and isovolumic relaxation time (IVRT) (ms) [92].

IV.d *Tissue Doppler and Two-Dimensional Strain echocardiography*

Pulsed-wave TDI was performed with a variable frequency, phased-array transducer (2.5MHz), bypassing the high-pass filter to display tissue velocities. Gains were minimized to allow a clear tissue signal with minimal background noise aligning the echo image to the annular motion. From the apical four-chamber view, the Doppler sample volume (20-mm axial length) was placed at the lateral tricuspid annulus as well as at the septal and lateral mitral annulus. The Nyquist limit was adjusted to a velocity range of 1.5–15cm/s. The monitor sweep speed was set at 50–100mm/s to optimize the spectral display of myocardial velocities. For the assessment of global longitudinal LV systo-diastolic function we acquired and measured by PW-TDI the mitral annulus systolic (s′) and early (e′) and late (a′) diastolic velocities at septal and lateral sides. Outcome RV measures were peak systolic (Sm), early (Em) and late (Am, corresponding to the wall motion caused by atrial systole) later tricuspid annular diastolic velocities (cm/s) [93] averaged over five consecutive cardiac cycles at end-expiratory apnea with the patients in partial left decubitus. All tissue Doppler echocardiography measurements were recorded on site and read off-line by three skilled

operators blindly to clinical and echocardiographic data. The average within and between-observer percentage of error for velocity measurements was 3 and 9%, respectively [94].

For 2Dstrain analysis, RV and IVS longitudinal strain (ε, i.e. the per cent systolic deformation relative to the diastolic value) and strain rate (SR, i.e. deformation velocity, s^{-1}) were obtained by blinded sonographers from apical four-chamber views at the end of expiration and breath holding. Images were acquired at an $80s^{-1}$ frame rate and stored digitally on a hard disk for offline analysis by speckle-tracking methodology from 2D grey-scale images. Image analysis was performed offline on a PC workstation using custom analysis software (Echopac PC, Version 6.0.X; GE Healthcare, Fairfield, CT). ε values were generated according to the spatial and temporal shift of the corresponding acoustic markers rejecting segments of poor quality, despite manual correction.

For LV analysis, we acquired LV short-axis views at the apical, mid, and basal levels, and LV apical two- and four-chamber views using a high-frame rate (80 frames/s). The basal shortaxis view contained the mitral valve, the mid short-axis view contained the chordae tendineae, and the apical short-axis view was acquired distal to the papillary muscles. At each plane, three consecutive cardiac cycles were acquired at end expiration breath holding and stored digitally on a hard disk for offline analysis. The LV endocardial border of the end-systolic frame was manually traced. Once traced this line, the computer automatically created a region of interest including the entire transmutably wall for all patients, and the software selected natural acoustic markers moving with the tissue. Automatic frame-by-frame tracking of these markers during cardiac cycle (2D systolic time interval method) yielded a measure of rotation, rotational velocity, strain, and strain rate at any point of myocardium. The LV was divided into 16 segments, and each segment was individually analyzed [86]. 2D LV strain, strain rate, and rotation were measured using a dedicated software package. In the present study, longitudinal

strain and strain rate were assessed in the six LV walls on the apical 2-chamber view and in the six LV walls on the apical four-chamber view. Circumferential strain and strain rate were assessed in the six LV walls on the parasternal LV short-axis view at the level of the chordae tendineae, and their average values were used for comparison. Radial strain and strain rate were assessed in the six LV walls on the parasternal LV shortaxis view at the level of the chordae tendineae [95]. The sonographers were blinded from the subject belonging BP group. The intraclass correlation coefficient (*r*i) was calculated according to Bland and Altman's procedure [96]. Three values of 2D strain were sampled for each patient and for each septal and lateral mid segment: the correlation coefficient (*r*i) for septal was 0.87 and for lateral it was 0.88.

For RV analysis, region of interest was the lateral mid-RV segment and results were averaged over three consecutive cardiac cycles. Pulmonary valve closure delimited RV peak ε. No patient showed evidence of post-systolic peak. Evaluation variables were longitudinal peak ε and systolic SR (S_{SR}) (as measures of systolic function and contractility, respectively) and early (E_{SR}) and late (A_{SR}) diastolic SR (as indices of early myocardial relaxation and late ventricular filling, respectively) (Figure 10). Within-observer variability (n = 10 triplicates by the same observer) was 8.1, 10.3, 7.3, and 8.2% (mean variation coefficients) for RV peak ε, S_{SR}, E_{SR}, and A_{SR}, respectively. The corresponding values for between-observer variability (n = 5 replicates by each of the three sonographers) were 11.1, 12.9, 10.9, and 11% respectively.

IV.e *Data processing*

Mitral annular velocities were the average of septal and lateral mitral annular measurements, as recommended by recent consensus documents [97]. Mid-wall fractional shortening (MDFS) was the index of ventricular systolic function accounting for the epicardial migration of the LV midwall during systolic myocardial contraction

[89]. Left ventricular mass index (LVMI) was calculated according to the Penn Convention indexed by height$^{2.7}$, the power that linearizes the relation between LVM and body height. LVH was defined as LVMI above 51 g/m$^{2.7}$ and concentric LVH was diagnosed if relative wall thickness [RWT, calculated as 2*PWT/LVEDD] was greater than 0.42 [89]. Insulin sensitivity was assessed through the homeostasis model assessment (HOMA) [98].

IV.f *Statistical analysis*

Study variables were stratified by 24-h systolic BP tertiles (cut-offs: 117, 130mmHg) and between-group differences were tested by Bonferroni's method for multiple comparisons. The strength of association was tested through Spearman's ρ correlation coefficients and distribution of categorical parameters by χ^2 statistics. Descriptive statistics were arithmetic means±standard deviation (SD) or medians (interquartile range) for skewed data. Statistical significance was set at $p < 0.05$.

RESULTS

V.a *Right and left ventricle behaviour by ascending systolic blood pressure*

Age, sex distribution, BMI, lipids, fasting plasma glucose, insulin, HOMA (Table 3), SPAP, TAPSE, MDFS, EDD, left atrial dimensions (Table 4) and transvalvular Doppler indices of RV and LV diastolic function (Table 5) did not differ by 24-h SBP tertiles. IVS thickened gradedly, although still within normal limits, by increasing systemic 24-h SBP, whereas PW remodeled to a lesser extent poorly related to the systemic BP load; RV wall thickness did not change (Fig. 11). LVMI and RWT increased but the trend reached the formal limits of statistical significance only for the latter parameter (Table 4). LVH was present in nine patients (9%), only two (2%) of whom with RWT above 0.42, the cut-off for concentric LVH. RV thickness exceeds 5 mm in only three (3%) subjects.

As compared with the bottom normotensive third, tricuspid Em was reduced to a highly significant extent in the mid, high-normal 24-h SBP stratum and slowed further in the upper mildly hypertensive third in which also Sm was lower; Am did not change (Fig. 12, left panel). Data sampled at the mitral annulus showed similar trends (Fig. 12, right panel). On an intraindividual basis, peak systolic (Sm) and early diastolic tricuspid (Em) velocity values intercorrelated (rho = 0.60, $P<0.001$, n = 98) and both associated inversely with IVST (Fig. 13, left and right panel). The correlations with PWT (-0.19 and -0.25, respectively) and LVMI (-0.09 and -0.20, respectively) were either not significant or of definitely lower strength. Positive and statistically significant correlations existed between peak tricuspid velocities and the homologous mitral parameters (Em: rho = 0.48, Sm: rho = 041, $P<0.001$ for both, n = 98).

Mid-tertile RV and IVS peak ε and E_{SR} were lower than the referent group without further changes in the upper 24-h SBP third (Figure 14, top left and right panels). Right

ventricular S_{SR} and A_{SR} did not significantly change in contrast to significant trends to decrease and increase, respectively, at the mid-septum (Figure 14, bottom left and right panels). Right ventricular strain peak ε and E_{SR} were inverse correlates of IVS thickness (ρ = -0.36 and -0.40, respectively, $p < 0.001$, n = 89) and a similar intra-individual association existed for mid-septal samplings (peak ε: ρ = -0.32, p = 0.002; S_{SR} : -0.34, $p < 0.001$; E_{SR}: -0.40, $p < 0.001$; A_{SR}: 0.28, p = 0.007, n = 89).

At LV level, 2D longitudinal systolic strain appeared significantly lower both at mid septum and mid lateral level in relation to SBP increase, in comparison with lower tertile ($p < 0.002$). Also the analysis of longitudinal 2D strain rate, essentially at septum level, confirmed a progressive impairment both of systolic and diastolic parameters by ascending SBP. Instead the radial and circumferential 2D systolic strain functions were comparable in all three tertles and in all LV segments. Even considering only the patients with LVM within normal values (in both middle an upper tertile), we found that the same previously described structural and functional abnormalities were present, but in a milder expression. It was relevant that the demographic, clinic, and echo-Doppler conventional parameters of the subgroup with normal LVM were super imposable with those of lower BP group.

DISCUSSION

Some preliminary comments about the experimental design adopted in this study, which aimed at the evaluation of the functional inter-relationship between RV function and systemic BP levels in early uncomplicated hypertension, will facilitate the discussion of the results and their pathophysiological implications. First, we recruited healthy, never-treated, lean patients excluding patients with both moderate-to-severe hypertension to minimize the chance of hypertensive heart disease [99] and obesity because of its confounding noxious influence on RV and LV function [100,101]. Their metabolic profile was screened in the light of recent suggestions about a role for impaired insulin sensitivity in the genesis of increased pulmonary resistance [35] and ventricular systolic and diastolic dysfunction in early hypertension [102] and other normotensive phenotypes of the metabolic syndrome [103]. Second, ventricular function was assessed by TDI in apical views, a technique that, by extending Doppler applications to the measurement of myocardial wall motion, measures longitudinal diastolic and systolic function by and large independent of preload, afterload and heart rate [94,100,101]. Third, we reported only data about systolic myocardial deformation along the longitudinal axis because this is the only reliable determination allowed by the thin RV structure [104]. For the sake of clarity, analysis of IVS mechanics was limited to longitudinal shortening, although abnormalities of the radial and circumferential components [105] may co-exist in early hypertension [102]. Moreover, we restricted strain analysis to the mid-RV segment that, as reported for IVS [106], could not reflect the overall behaviour of the RV, an additional limitation to be taken in mind. Fourth, BP load was assessed by 24-h monitoring rather than office determinations because of its greater power in predicting hypertensive cardiac damage (e.g. [107]), focusing on SBP values because of their greater association with cardiac remodeling and myocardial

oxygen demands [108]. Finally, tertile stratification by 24-h SBP separated a lower optimal BP third (24-h SBP <117mmHg) from an intermediate highnormal (24-h SBP 117–30mmHg) partition and an upper (24-h SBP >130mmHg) stratum of patients with established, mildly elevated hypertension [60].

Within that specific experimental context, the reduced Em in the mid, high-normal BP tertile constitutes, at least to our knowledge, the first demonstration of an association between increments in systemic BP levels still below the conventional threshold of arterial hypertension and impaired RV relaxation. RV diastolic abnormalities might plausibly anticipate a weakening systolic contractility at least in those patients with high-normal BP bound to evolve towards established arterial hypertension [73], but this is only a speculative possibility since crosssectional studies cannot establish temporal sequences. On the contrary, the appearance of a delayed systolic velocity combined with a further deceleration of the diastolic component in the upper hypertensive tertile indicates the sensitivity of global RV function to varying peripheral afterload, somewhat discrepant from previous TDI studies of RV function in systemic hypertension showing no change in systolic velocity [28,29]. However, our results are consistent with data obtained by more refined echocardiographic techniques such as ultrasonic strain and strain rate [29]. Notably, RV abnormalities at TDI examination coexisted with unchanged TAPSE, a marker of RV systolic function [90], and trans-tricuspidal Doppler indices of diastolic function [92], in line with the known greater capability of TDI to detect subclinical diastolic and systolic functional changes [93,100,101].

2D-strain results confirm TDI data about the occurrence of subclinical systolic and diastolic RV dysfunction at the very early stages of arterial hypertension. However, abnormalities in RV mechanics did not overlap, though, with those of IVS characterized by changes in all strain parameters (peak ε, S_{SR}, E_{SR} , and A_{SR}) as a function of

increasing systemic afterload. Whether that difference originates from technical problems related, for example, to the peculiar anatomical pattern of the RV [9] or deeper pathophysiological determinants is unclear. Still, cross-sectional studies such as ours and statistical associations are not informative about cause– effect relationships and the reasons why increasing systemic BP influences RV function remain unknown.

An obvious question is why mild increments in systemic BP should affect the RV, a structure not directly exposed to the systemic BP load, even more in absence of evidence for secondary RV overload as a consequence of transmission to the pulmonary circuit of raised LV diastolic pressure [11]. In fact, the neutral behavior of both LA size and transmitral Doppler parameters, two well recognized indices of LV diastolic function [92,109], excluded clinically significant LV diastolic dysfunction, a negative inference corroborated by the absence of concentric LVH, a close associate of abnormalities of that kind [99]. Increased pulmonary pressure raising in parallel to heightened systemic resistance has been invoked as a pathogenic mechanism in some patients with essential hypertension [22,33], but we found neither increased SPAP nor RV wall hypertrophy to support that theory. Other investigators reported in the past similarly negative data [31], although an increased pulmonary reactivity to vasoconstrictor stimuli [32] cannot be excluded on the basis of resting determinations. Whether different results would be obtained in presence of an insulin-resistant status, as suggested by previous animal studies [35], is an interesting issue that our study cannot address since HOMA, a surrogate measure of insulin sensitivity [98], as well as the other phenotypic hallmarks of the insulin resistance syndrome [110], were in the normal range as expected in preselected lean, nondiabetic patients. If hemodynamic overload could not explain our findings, a viable alternative could be offered by the behavior of the interventricular septum, a structure involved in both RV ejection and filling [111] and ventricular interdependence, that is the transmission of forces from one to the other

ventricle independent of neural, humoral or circulatory influences [12]. In consonance with that view, RV systolic and diastolic velocities decreased by increasing septal thickness and both correlated with the homologous indices measured at the mitral level. 2D-strain analysis add confirmatory data. In fact, decreasing RV peak ε and E_{SR} associated quite strongly with BP-driven remodelling of IVS, a 'bilayered' structure sharing fibres with both ventricles [112] that contributes to RV ejection and filling and ventricular interdependence[111].

Importantly, septal remodeling did not exceed conventional limits for hypertrophy suggesting that thickness *per se* was not a critical determinant of impaired RV function in agreement with reports of preserved TDI velocity indices in patients with hypertrophic cardiomyopathy and extremely hypertrophied septa [113]. In turn, IVS acted as the afterload-transducing cardiac structure by thickening as a linear function of systemic BP, a divergent behavior from posterior wall and LVMI explained by the peculiar bending radius, the additive burden of RV load and, perhaps, higher sensitivity to humoral stimuli [106,114]. As a further extrapolation, one might also infer that the diastolic and systolic components of RV dysfunction shared probably some common pathophysiological background given their high statistical correlation. Still, cross-sectional studies such as ours and statistical associations are not informative about cause–effect relationships and the precise reasons by which increasing systemic BP influences RV function remain unknown. Additional mechanistic insight might theoretically derive from multiple linear regression analyses accounting for the several clinical and echocardiographic correlates of the RV function. However, reliable conclusions from that approach require the independence of predictor variables, a rare occurrence in observational studies such as ours in which multicollinearity introduces biases and makes conclusions uncertain [115].

An additional point worth of comment relates to the emerging differences between the observed 2D-strain imaging results and those obtained by TDI analyses of tricuspid annular motion. In fact, the impaired systolic function (reduced peak ε) in subjects with high-normal 24-h SBP contrasted with the preserved tricuspid peak systolic annular motion velocity by TDI. On the same line, the unchanged early myocardial relaxation (E_{SR}) in the transition from high-normal to hypertensive BP values is at odds with the further deceleration of peak early diastolic tricuspid annular motion evaluated by velocity echocardiography. Those discrepancies are not surprising given the intrinsic heterogeneity of the two methods [79] and the complexities of cardiac function. Whatever the case, it is important to note that abnormal strain imaging co-existed with unchanged global markers of systolic (TAPSE) [90] and diastolic (transvalvular diastolic Doppler indices) [92] function, confirming the potential of deformation imaging in the detection of subclinical RV dysfunction [116].

Our results could represent an initial rational basis for some future clinical applications of echocardiographic evaluation of the RV in pre- and/or hypertension. First, prehypertensive subjects showing RV impairment could progress to hypertension faster than those without RV involvement so taking advantage on a closer echocardiographic and clinical follow-up. Moreover, if this assumption will be confirmed, such patient category will probably benefit from early pharmacological treatment. Second, even in really hypertensive patients RV dysfunction could identify a sub-population with an higher incidence rate of heart failure and could benefit from more intensive BP lowering strategies. Lastly, RV functional and structural changes could be used to monitor the efficacy of any BP lowering intervention; it could be hypothesized that RV dysfunction could reverse with the return of BP level into the normal range.

However, any of these putative clinical implication warrants an appropriate prospective validation on a specific and larger population within a clinical trial.

Although focused primarily on RV abnormalities, our TDI data are of interest also in confirming previous data about the early appearance of hypertensive LV diastolic and systolic dysfunction in prehypertensive [117] and uncomplicated hypertensive individuals [118]. Moreover, subclinical LV dysfunction, both systolic and diastolic, coexisted with an unchanged insulin sensitivity, as indirectly assessed by HOMA index [98], a piece of evidence putting in less stringent perspectives the link between metabolic derangements and cardiac abnormalities reported by others in the early stage of hypertension [102] and other phenotypes of the insulin resistance syndrome [103]. Moreover, we found several structural and functional LV systolic and diastolic abnormalities by 2D strain echocardiography in relation to BP increase similar, even of a lesser extent, to hypertensive patients, whose abnormalities are nevertheless more severe. In fact, we observed a progressive significantly lower longitudinal 2D systolic deformation at septum and LV lateral wall level that parallels SBP increase and these abnormalities are present even considering patients in middle and upper tertiles with normal LVM.

In conclusion, high-normal and mildly increased systemic BP is accompanied by combined systolic and diastolic RV dysfunction, an abnormality to which interventricular septum remodeling may contribute in the light of its crucial role in the pathophysiology of that ventricular chamber. Further studies are needed to understand in full the determinants and the clinical relevance of that phenomenon, in particular the interaction between mildly increased BP and obesity as well as the effect of early antihypertensive interventions on RV function.

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