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CICLO 19°

LONG-TERM MODIFICATIONS IN LEFT VENTRICULAR STRUCTURE AND FUNCTION AFTER ADRENALECTOMY OR MEDICAL TREATMENT IN PATIENTS WITH PRIMARY ALDOSTERONISM

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INDICE

ACRONISMS

ACLF: atrial contribution to left ventricular filling

APA: aldosterone producing adenoma (Conn's adenoma)

ARR: aldosterone/active renin ratio

E_i/A_i (early/late diastolic LV filling wave integrals ratio)

IRT: isovolumetric relaxation time

LAD/ AoD: left atrial dimension/aortic root diameter

LVEDD: LV end-diastolic dimension

LVESD: LV end-systolic dimension

IVSd: end-diastolic interventricular septum thickness

LVMI: left ventricular mass index

PFVE: early diastolic peak flow velocity

PFVA: late diastolic peak flow velocity

PWd: end-diastolic LV posterior wall thickness

RWT: relative wall thickness.

VSn: left ventricle

SUMMARY (RIASSUNTO)

Background e scopo dello studio: diversi studi sperimentali condotti *in vitro* e *in vivo* hanno chiaramente dimostrato un ruolo dell'aldosterone nel promuovere, a livello cardiaco, la deposizione di collagene, la fibrosi miocardica ed il rimodellamento ventricolare, anche indipendentemente dagli effetti dell'ormone sulla pressione arteriosa. Ciò spiegherebbe, almeno in parte, le evidenze di una prognosi più sfavorevole nei pazienti ipertesi con iperaldosteronismo rispetto ai pazienti ipertesi essenziali, così come l'effetto benefico della terapia con anti-aldosteronici osservato in diversi studi di intervento. Purtroppo *in vivo* non è facile indagare singolarmente gli effetti cardiaci dell'aldosterone senza l'influenza anche del sistema renina-angiotensina, anch'esso di notevole rilievo nell'omeostasi cardiovascolare. L'iperaldosteronismo primario (IP) è una forma di ipertensione secondaria che permette di indagare in modo selettivo gli effetti cardiaci dell'aldosterone in quanto è una condizione in cui il sistema renina-angiotensina risulta soppresso. Nella letteratura medica esistono pochi studi prospettici che hanno indagato le modificazioni morfologico-funzionali del ventricolo sinistro (VSn) prima e dopo trattamento medico o chirurgico dell'IP. Poiché negli ultimi anni abbiamo raccolto un'ampia casistica di pazienti affetti da tale patologia, ci è stato possibile valutare tali modifiche in modo compiuto e in particolare di distinguere tra gli effetti del trattamento chirurgico rispetto al trattamento farmacologico, con le possibili ricadute dal punto di vista prognostico.

Metodi e Risultati: cinquantacinque pazienti con IP sono stati reclutati in uno studio prospettico durato in media 6.4 anni (intervallo: 4.5 - 8 anni) dopo adrenalectomia (n=41) o dopo terapia medica (n=14). La diagnosi di adenoma di Conn è stata posta in base a: prelievo selettivo nelle vene surrenaliche (per indagare un'eventuale lateralizzazione della secrezione dell'aldosterone), analisi istopatologica del tessuto e alle modifiche clinico bioumorali durante il follow-up. Al momento del reclutamento e durante il follow-up sono stati eseguiti

ecocardiogrammi seriati per la stima degli spessori parietali del VSn e per lo studio della funzione diastolica del VSn mediante misurazione della flussimetria Doppler transmitralica.

Al momento del reclutamento, rispetto ai pazienti successivamente trattati con terapia medica, i pazienti con IP che successivamente sono stati trattati chirurgicamente erano più giovani, con minore indice di massa corporea e con valori di pressione arteriosa diastolica più bassi. Inoltre presentavano un maggiore grado di ipertrofia del VSn e di rimodellamento concentrico del VSn, ma minore compromissione della funzione diastolica.

Dopo follow-up, nonostante i pazienti operati assumessero meno farmaci (numero farmaci assunti: 1.7±1.4 vs 2.6±0.8, p= 0.024), in entrambi i gruppi si è osservato un significativo calo pressorio ed una riduzione (p< 0.001) del diametro telediastolico del VSn, della massa indicizzata del VSn ma con un aumento dello spessore parietale relativo; questi ultimi due parametri variavano in modo significativo solo nei pazienti trattati chirurgicamente. La funzione diastolica non si modificava in modo rilevante nei pazienti trattati chirurgicamente, mentre nei pazienti in terapia medica (nei quali, peraltro, era già evidente una compromissione della funzione diastolica al momento del reclutamento rispetto ai pazienti successivamente sottoposti ad adrenalectomia) abbiamo osservato una significativa (p= 0.002) riduzione del contributo atriale al riempimento del VSn.

In entrambi i gruppi la riduzione della massa indicizzata del VSn è risultata indipendente dai valori pressori pre-trattamento, dall'indice di massa corporea, dall'età, dalla durata dell'ipertensione arteriosa e del follow-up, e dalla terapia farmacologica assunta.

Conclusioni: in pazienti con IP l'iperaldosteronismo si associa ad aumento degli spessori parietali e della massa del VSn. La terapia medica o chirurgica è in grado di ridurre i valori di pressione arteriosa, il diametro telediastolico e la massa indicizzata del VSn, aumentandone però lo spessore parietale relativo. A parità di riduzione pressoria al follow-up e nonostante una netta riduzione del numero di farmaci assunti, le suddette modifiche anatomiche sono

risultate più evidenti nei pazienti trattati chirurgicamente. A differenza di quanto osservato nei pazienti sottoposti ad adrenalectomia (i quali però presentavano una minore compromissione iniziale della funzione diastolica), la terapia medica è risultata in grado di migliorare la funzione diastolica del VSn inducendo una riduzione del contributo atriale al riempimento del VSn.

ABSTRACT

Background and aim: hyperaldosteronism has been related to collagen deposition, myocardial fibrosis, and ventricular remodeling in experimental studies. More recent evidence suggest that these detrimental effects can develop independently of blood pressure and a significant decrease in the mortality rate of patients with heart failure who were treated with aldosterone antagonists has been reported. Primary aldosteronism (PA) is a form of secondary arterial hypertension that offers an important clinical opportunity for assessing the effects of hyperaldosteronism on the left ventricular (LV) anatomy and function because, in this condition, its effects are isolated from those of the renin-angiotensin axis.

In the literature, only few longitudinal studies have evaluated cardiac changes after treatment of hyperaldosteronism with either surgical or medical treatment. Hence, in the present study we have explored the relationship between aldosterone and the heart by assessing cardiac anatomic and functional evolution of a large number of patients with PA surgically or medically-treated.

Methods and Results: fifty-five patients with PA were enrolled in a prospective study and were followed for a mean of 6.4 years (range: 4.5 to 8 years) after adrenalectomy (n=41) or medical treatment (n=14). The diagnosis of APA (aldosterone producing adenoma) was based on adrenal vein sampling and pathology results and on follow-up data. At baseline and at follow-up we performed Doppler echocardiography for estimation of LV wall thickness and dimensions and transmitral LV filling flow velocity indexes.

At baseline, PA patients who subsequently underwent adrenalectomy were younger and had lower body mass index and lower diastolic blood pressure than PA patients medically-treated. The former showed an excess LV hypertrophy and concentric remodeling, but with a less degree of diastolic dysfunction compared with the latter.

At follow-up, despite a greater reduction of antihypertensive drugs in surgically-treated patients (number of drugs: 1.7±1.4 vs 2.6±0.8 in surgically and medically-treated, respectively, p= 0.024) in both groups there was a significant reduction of blood pressure levels. A significant (p< 0.001) reduction in LV end-diastolic diameter, a reduction in LV mass index but with an increase in the relative wall thickness was observed in both groups. However, the last two parameters were significant only in the surgically-treated PA. As regards the diastolic function, no significant modification was observed in the surgically-treated PA. At variance, a significant (p= 0.002) reduction in the atrial contribution to LV filling was observed in medically-treated PA, possibly because they showed a higher degree of diastolic dysfunction at baseline.

In both groups LV mass decrease was independent from pre-treatment blood pressure, body mass index, age, known duration of hypertension, follow-up interval and medical treatment.

Conclusions: in PA patients, the excess aldosterone is associated with both increased LV wall thickness and mass. Treatment of hyperaldosteronism with either surgical or medical treatment induce a reduction in blood pressure levels, LV end-diastolic diameter, a reduction in LV mass index and an increase in the relative wall thickness, particularly in the surgically-treated PA. With a similar fall of blood pressure and despite a greater reduction of antihypertensive drugs, these changes were more prominent in the adrenalectomized patients. Treatment can improve the diastolic function, but this was observed only in the medically-treated PA patients, likely because they had a higher degree of diastolic dysfunction at baseline.

INTRODUCTION

Left ventricular hypertrophy (LVH), the most common cardiac consequence of hypertension, represents a maladaptive response to the increased afterload, since it is an important independent predictor of cardiovascular complications and death (1,2). The hemodynamic load is not the only determinant of LVH, because for similar elevations of blood pressure, a wide interval of severities and types of LVH has been observed in relation to genetic, demographic, and humoral factors (3-6). In particular, the renin angiotensin system (RAS) has emerged as an important player in the pathogenesis of myocardial hypertrophy (5,7). In fact, its active peptide, angiotensin II, may cause myocardial cell hypertrophy and/or hyperplasia through increased expression of the proto-oncogenes c-*fos*, c-*myc*, and c-*jun* and synthesis of the heat shock protein HSP 70 and other proteins (8).

Cardiac fibrosis

Myocardial cells are supported by a matrix consisting of a macromolecular network of fibers with intricate 3D organization (9) that largely determines the structural and functional integrity of the heart. Myocardial hypertrophy also involves extracellular matrix and collagen deposition and variable extents of fibrosis, which are particularly evident in the perivascular areas and correlate directly with the severity of LVH (10-12). In the heart, fibroblasts constitute the vast majority (>90%) of nonmyocyte cells, accounting for 90% to 95% of nonmyocyte cell mass (13). They produce most of the matrix macromolecules, including collagen, the principal structural protein. Of the many collagen types, the major fibrillar collagens are types I and III, which constitute the bulk of cardiac extracellular collagen matrix. About 85% of total collagen is type I, which is associated mainly with thick fibers that confer tensile strength and resistance to stretch and deformation, whereas ≈11% of total collagen is type III, which is associated with thin fibers that confer elasticity (13).

Extracellular matrix production can increase in response to a variety of injuries, including the pressure overload observed in high blood pressure, thus leading to the development of cardiac fibrosis (CF), which is a major cause of cardiac dysfunction because an excessive deposition of collagen may be responsible for abnormal tissue stiffness and diastolic dysfunction. The latter is considered an early marker of heart involvement in hypertension (for review, (14)), and is associated with CF more closely than with LVH (15,16).

Cardiovascular genomic and nongenomic effects of aldosterone

Both angiotensin II and aldosterone play important roles in the heart (17-20). Angiotensin II induces cardiomyocyte hypertrophy in both ventricles (8,21), stimulates collagen synthesis by fibroblasts, and regulates collagen degradation by blunting the activity of matrix metalloproteinase-1, the key enzyme of collagen degradation (19). Aldosterone is extracted through the human heart through a spironolactone-sensitive pathway and promotes CF by acting through different pathogenic mechanisms (19,22). It induces oxidative stress and impairs endothelial nitric oxide synthase through a mineralocorticoid receptor-dependent mechanism (23). It increases types I and III procollagen mRNA in both ventricles, although it does not seem to influence matrix metalloproteinase-1 activity in cultured cardiac fibroblast preparations (16). Aldosterone may also act on the cardiac angiotensin II receptor, because its administration, along with a high-salt diet, increased angiotensin II type 1 (AT-1) receptor density in the left ventricle of rats; this increase was prevented by both spironolactone and losartan (24). Thus, aldosterone causes extracellular matrix deposition by enhancing the transcription of collagen type I and III genes and by augmenting the effects of angiotensin II on AT-1 receptors (24,25). However, available evidences collectively indicate that the fibrogenetic effect of excess aldosterone is critically dependent upon sodium intake because it was shown to be markedly blunted in the presence of low or very low sodium diets (26).

Of interest, in a genetic model of hypertension, interstitial fibrosis and not LVH was found to be responsible for abnormal myocardial diastolic stiffness *in vitro* in the isolated heart (27), thus suggesting that excessive aldosterone secretion is a causative factor of both myocardial fibrosis and diastolic dysfunction.

Moreover, in addition to the above mentioned and well-documented genomic effects of aldosterone, evidence exists for nongenomic (i.e.: not due to mineralocorticoid receptor-dependent changes in gene expression) effects of aldosterone in the cardiovascular system (see for review (23,28)). In fact, aldosterone exerts direct rapid effects on the vasculature which are not blocked by inhibitors of transcription and may be either mineralocorticoid receptor independent or dependent. In both vascular smooth muscle cells and endothelial cells, aldosterone induces a rapid increase in intracellular calcium through inositol 1,4,5-triphosphate, diacylglycerol, and protein kinase C (23). Moreover, it seems to have a rapid, direct vasoconstrictor effect, in concert with catecholamines and angiotensin II, to maintain blood pressure and organ perfusion in the face of acute circulatory volume loss (haemorragia or diarrheal disease). Such direct vasoconstrictor actions of aldosterone might also play a role in the rapid accommodation of blood pressure to changes in posture. The nongenomic effects of aldosterone in the cardiovascular system are not well established, but it is possible that classical intracellular mineralocorticoid receptor mediates at least some of the rapid nongenomic effects seen *in vitro* with aldosterone (although others may be exerted independently) (28). Unfortunately, one of the main limitations of the studies investigating the *in vivo* and/or *in vitro* cardiovascular effects of aldosterone is due to the fact that, given that mineralocorticoid receptors are largely constitutively occupied but not activated by physiological glucocorticoids, the effects of aldosterone administered *in vitro* or *in vivo* may or may not equate with true physiological mineralocorticoid roles.

As regards the role of aldosterone in development of cardiac fibrosis, it has been reported that cardiomyocyte mineralocorticoid receptors are normally overwhelmingly occupied by glucocorticoids, in tonic inhibitory mode (29-31). In situations in which there is tissue damage, reactive oxygen species generation and change in intracellular redox status, such glucocorticoid-occupied mineralocorticoid receptor may become activated, as suggested experimentally by inference (32-34) or directly in preliminary studies on isolated cardiomyocytes (35). In the context of inappropriate salt status, or tissue damage, mineralocorticoid receptor activation in cardiomyocytes has clearly deleterious effects. Experimentally, cardiomyocyte-selective overexpression of 11ß-HSD2, allowing aldosterone to access mouse cardiomyocyte mineralocorticoid receptor *in vivo*, has been shown to be followed by cardiac hypertrophy and fibrosis (36).

However, it must be considered that in many systems (*e.g.* blood pressure regulation and cardiac fibrosis), the time course of effects is such that it is not possible to distinguish between rapid nongenomic and classical genomic effects in the context of homeostatic physiology.

Cardiovascular effects of aldosterone in humans

The detrimental cardiovascular effects of aldosterone reported in experimental studies are supported by clinical findings demonstrating that in patients with heart failure elevated serum aldosterone levels correlates with an adverse prognosis (37), and patients with primary aldosteronism present more cardiovascular (CV) events than patients with essential hypertension, independently of blood pressure levels (38,39). On the other hand, the RALES (40), EPHESUS (41), and 4E trials (42) showed conclusively that mineralocorticoid receptor blockade, on top of standard of care, was of major therapeutic benefit.

However, evidence is still limited in humans, most likely because of the lack of models in which the effects of the RAS and aldosterone can be dissociated.

Primary Aldosteronism

Humans Primary Aldosteronism (PA) is characterized by excess aldosterone secretion and suppression of RAS, and therefore offers an appealing opportunity to evaluate the detrimental effects of hyperaldosteronism on cardiac anatomy and function as well as the favourable effects due to surgical or medical treatment of PA.

More than ten years ago, Rossi and Coll. have reported that in a series of consecutive patients with PA due to different causes, LV wall thickness and mass were slightly increased and Doppler velocity indexes of early diastolic transmitral flow were decreased compared with similar patients with essential hypertension (EH) (43). However, only 60% of those patients with PA had an APA (aldosterone producing adenoma or Conn's adenoma), and therefore, the fact that their plasma renin and aldosterone levels showed some overlap with those of EH might have hampered the detection of more marked differences in the LV between groups (43). Since suppression of the RAS and aldosterone excess are generally more pronounced in PA patients with APA than in those with idiopathic hyperaldosteronism (IHA), it is conceivable that if the changes of LV anatomy and function are related to the excess aldosterone, they would also be more pronounced in the former patients. Therefore, to better define the effects of hypertension and excess aldosterone due to APAs on the heart, in a subsequent study Rossi and Coll. compared LV dimension, thickness and transmitral Doppler flow indexes in 26 consecutive patients with APAs and 26 patients with EH, individually matched for age, sex, race, body mass index, casual blood pressure, and known duration of hypertension (44). The main findings were the following:

1) a thicker interventricular septum (P=.015) and posterior wall (P=.009) and a higher LV mass index (118±5 versus 100±4 g/m^2, P=.009) were observed in APA compared with EH patients.

2) relative wall thickness (RWT), LVM, LVMI and LV concentric remodeling were more common in APA than in EH patients (Figure 1).

3) both septum and posterior wall thicknesses had a significant direct relationship with age, plasma aldosterone, and mean blood pressure.

4) the integral of the early diastolic filling wave (E_i) (*P*=.011) and the ratio E_i/A_i (A wave integral) (*P*=.038) were lower and the atrial contribution to LV filling was higher (52±2% versus 46±2%, *P*=.038) in APA than in EH patients.

5) the ratio E_i/A_i was significantly (*P*=.008) inversely related only to age and plasma aldosterone.

The Authors concluded that in APA patients the excess aldosterone was associated with both increased LV wall thickness and mass and blunted early diastolic LV filling indexes, compared with demographically similar EH with superimposable blood pressure values, profile, and variability (44).

To clarify the causal role of aldosterone in dermining CF, Rossi and Coll. performed a videodensitometric analysis of myocardial texture in 17 consecutive patients with PA and 10 patients with EH, matched for demographics, casual blood pressure, and known duration of hypertension (45). Compared with EH patients, PA patients showed a higher LV mass index (53.7±1.8 versus 45.5±2.0 $g/m^{2.7}$; *P*=0.008) and lower values of the cyclic variation index of the myocardial mean gray level of septum (CVI_s; -12.02±5.84% versus 6.06±3.08%; *P*=0.012) and posterior wall (-11.13±6.42% versus 8.63±9.62%; *P*=0.012) (Figure 2). A regression analysis showed that CVI_s was predicted by the PQ duration, supine plasma renin activity, plasma aldosterone, and age, which collectively accounted for ≃36% of CVI_s variance. In summary, the PA patients exhibited greater alterations of videodensitometric indexes of LV myocardial texture, compared with demographically and hemodynamically similar EH patients. The changes of myocardial texture (probably due to increased collagen deposition) involved

the interventricular septum and the LV posterior wall and were evident in PA patients with quite small Conn's adenoma, suggesting that these changes occur early in the course of the disease (45). Changes in myocardial extracellular matrix and collagen deposition can be also estimated noninvasively by analysis of the ultrasonic backscatter signal, which arises from tissue heterogeneity within the myocardium and describes myocardial texture (46,47). With this metod Kozakova M. et al investigated the relations between myocardial integrated backscatter (an index of myocardial fibrosis) and circulating aldosterone in healthy normotensive volunteers and 42 hypertensive patients (47). They found that myocardial integrated backscatter was directly related to plasma aldosterone ($p<0.01$) thus confirming that circulating aldosterone may induce alterations in LV myocardial texture, possibly related to increased myocardial collagen content (47).

Thus, in contrast with the popular notion that PA is a "benign" form of hypertension, compelling evidence for a detrimental effect of the excess aldosterone on the heart is accumulating, both experimentally and from cross-sectional and longitudinal studies (38,48-50).

In the last decade, a number of cross-sectional echocardiographic evaluations in patients with PA have reported an excess LVH and diastolic dysfunction compared with other forms of hypertension (43-45,50-56). However, these abnormalities were not uniformly detected (57-61) (Table 1).

As regards longitudinal studies, the few echocardiographic observations of cardiac changes after treatment of aldosteronism are confined to short-term follow-up studies, mostly after removal of an adrenal adenoma (43,44,52,59). In one of them, Rossi and Coll. observed a normalization of all indexes of LV filling at 1-year follow-up after surgical removal of APA in PA patients, but not in medically-treated essential hypertensive patients (44). However, only 6 patients were medically-treated and they had more severe LVH at baseline (44).

In the literature there is only one long-term follow-up study in a substantial cohort of patients with PA after either surgical or medical treatment (56). Catena and Coll., in their 11-year follow-up study demonstrate that: 1) patients treated with either adrenalectomy or spironolactone have significant decrease of LVMI, a response that occurs within the first year only after surgical treatment; 2) in both groups the LV diastolic filling pattern have only mild and nonsignificant improvement; 3) pre-treatment plasma aldosterone concentrations predict LVMI decrease during follow-up, independent of blood pressure changes (56). However, in this study the diagnosis of APA and IHA were questionable and medical treatment during follow-up was not adequately considered. Thus, further studies are necessary to assess the relationship between aldosterone and the heart.

In the present study we have explored, in patients with PA, the cardiac anatomic and functional evolution which could be induced by the removal of the excess of aldosterone with adrenalectomy or by the correction of hyperaldosteronism by medical treatment.

AIM OF THE STUDY

The aim of our study is to investigate the relationship between aldosterone and the heart by evaluating, in patients with PA due to APA and IHA, the cardiac anatomic and functional evolution which could be induced by the removal of the excess of aldosterone with adrenalectomy or by the correction of hyperaldosteronism by medical treatment.

METODS

Patients

We studied 55 Caucasian patients referred to the Hypertension Center of the Clinica Medica 4 of the University of Padua between 1992 and 2007. The vast majority (47 patients, APA group: 26 women and 21 men) had PA caused by an APA. The diagnosis was based on a demonstration of elevated plasma aldosterone/PRA ratio that was unresponsive to a captopril test (62-64), of unilateral nodular adrenal enlargement shown by CT and MRI in all cases (65), on the results of adrenal vein sampling and on follow-up data. It was confirmed at surgery and histology in 41 patients. Eight patients were judged by exclusion to have PA caused IHA. Blood pressure was measured with a mercury sphygmomanometer and the auscultatory method using Korotkoff phase V for diastole before and after echocardiography and the mean of three measurements taken in the supine position at least 3 minutes apart from one another.

Biochemical assessment

For plasma renin activity and aldosterone measurements, 10 mL venous blood was collected into prechilled tubes containing 200 µL Na_2EDTA after the subjects had been lying quietly in the supine position for at least 1 hour. Samples were centrifuged immediately at 3000*g* at 4°C for 15 minutes, and the supernatant was collected and frozen at -20°C until assayed. PRA was measured by a commercially available kit (Ares Serono; supine normal values with a daily sodium intake of 100 to 200 mmol, 0.51 to 2.64 ng angiotensin $I \cdot mL^{-1} \cdot h^{-1}$) as generation of

angiotensin I after incubation for 2 hours at 37°C, pH 6.0. Blood samples were taken after 1 hour in the supine position and again 45 minutes after administration of 50 mg captopril PO.

Plasma aldosterone (normal values with a daily sodium intake of 100 to 200 mmol, 1.2 to 12.0 ng/dL) was measured by radioimmunoassay with a commercially available kit (Ares Serono). All patients were in sinus rhythm at the time of the echocardiographic study, and none had any valvular or ischemic heart disease.

Echocardiography

All patients underwent standard M-mode and two-dimensional echocardiography (model SPR 8000, Esaote Biomedica at baseline and model Megas, Esaote Biomedica and model Cypress, Acuson during the follow-up) with a 3.5-MHz transducer. The measurement of LV diameters and posterior wall and septal thicknesses was performed at the levels of the tip of the mitral valve leaflets, according to the criteria of the American Society of Echocardiography (66) calculating the average of at least three cardiac cycles. LV mass was calculated with the method of Devereux et al (67) corrected with the appropriate regression equation and normalized for body surface area to obtain LVMI. RWT was calculated at end-diastole according to the following equation: RWT=(interventricular septum thickness+posterior wall thickness)/LV diameter. LVH, defined as an LVMI >110 g/m^2 in women and ≥125 g/m^2 in men (68), was classified as concentric in the presence of an RWT > 0.45 and as eccentric with an RWT <0.45. LV concentric remodeling was diagnosed in the presence of an RWT > 0.45 and of a normal LVMI (69,70).

Doppler Evaluation

Transmitral flow velocity with Doppler was measured in the apical four-chamber view, as reported (71,72). To obtain the highest velocities, the sample volume was positioned below the AV plane between the tips of the mitral leaflets, paying the utmost attention to maintaining the ultrasonic beam as parallel as possible to the direction of flow (71-73). With minimal

adjustments of the probe, the sampling was optimized to obtain the Doppler curve with the maximal velocity of flow and the minimal spectral dispersion. On the Doppler recording, obtained with the patient in apnea at the end of a normal expiration and with a paper speed of 50 mm/s, the following parameters were measured: early diastolic peak flow velocity (PFVE), late diastolic peak flow velocity (PFVA), their ratio PFVE/PFVA, early/late diastolic LV filling wave integrals (E_i/A_i) and ACLVF (74). All Doppler measurements were performed by two readers (A.S. and M.C.), who were kept unaware of the cause of hypertension. The measurements of all indexes were carried out on at least three different cardiac cycles, and the average value was used for the analysis.

Follow-up Study

All APA patients (n= 41) who underwent surgical removal of the tumor, the six APA patients who did not underwent surgical removal of the tumor and underwent medical treatment, and the eight patients with IHA were available for echocardiography and Doppler reassessment 6.4 years (range: 4.5 to 8 years) after surgery or the initial evaluation.

Follow-up data were collected by a committee (GPR, GP) that was unaware of the echocardiographic features, through direct contact with the patients by compilating a predefined form, which is reported in the next two pages. The form included information about: clinical and demographical features, biochemical assessments, medical treatment, cardiovascular events.

FORM FOR FOLLOW-UP DATA

Cognome ……Nome……n° paziente ……..
Altezza:…….Peso:…….
Data di nascita GG……..MM……..AAAA……..
Data Ecocardiogramma GG……..MM……..AAAA……..
Operato 1 SI 2 NO
Data eventuale surrenectomia GG….MM….AAAA…Laparoscopica …; Laparotomica…..
Sesso 1 =M 2 =F Altezza…….. Peso……..
Iperplasia bilat 1 SI 2 NO Adenoma 3 =DX 4 =SIN 5 =bilat
Incidentaloma 6 =DX 7 =SIN
Ipertensione primaria (essenziale) 8 9
Anno diagnosi Ipertensione: AAAA……

Terapia medica ATTUALE Molecola Dose Totale/die

Calcio antagonista	1	SI	2	NO…….
α-bloccante	1	SI	2	NO……..……..….
ACE inibitore	1	SI	2	NO..……..….
βα-bloccante	1	SI	2	NO……..……..….
Sartano	1	SI	2	NO…….....
Diuretico	1	SI	2	NO..…….…..
Statine	1	SI	2	NO……...…
Nitrato	1	SI	2	NO……..…
Digitalici	1	SI	2	NO……
Antiartmici	1	SI	2	NO…….
Anticoagulanti	1	SI	2	NO…….
Antidiab os. /Insulina	1	SI	2	NO……..…..
ASA	1	SI	2	NO…….

Valori di potassiemia: Data (GG/MM/AAAA)…… sK (mEq/L)……..

ECG: Data (GG/MM/AAAA)…… **Ritmo sinusale** 1 SI 2 NO **PQ**……..msec
Fibrillazione atriale Blocco AV 2° Blocco AV 3°

Ecocardiogramma: Data (GG/MM/AAAA)……
Registrazione VHS o DVD 1 SI 2 NO numero:……
Spessore setto IV diastole (mm)……. Spessore parete posteriore diastole (mm)…….
Diametro telediastolico (V. sinistro) …….
Ampiezza onda E al picco (mm) …… Ampiezza onda A al picco (mm) ……
Durata onda E (msec) ……. Durata onda A (msec) ……
Integrale onda E…….. Integrale onda A……

Microalbuminuria: (mg/die)…… **Creatininuria: (**g/die)……**; Diuresi** (mL):…….
Decesso 1 SI 2 NO Data (GG/MM/AAAA)……
Causa di exitus:
SCA 1 =SI 2 =NO GG……..MM……..AAAA……..
Ictus 1 =SI 2 =NO GG……..MM……..AAAA……..
Altre cause cardiovascolari 1 =SI 2 =NO GG……..MM……..AAAA…….
Altre cause non cardiovascolari 1 =SI 2 =NO GG……..MM……..AAAA…….

Malattie intercorrenti:

			Data
Ricoveri ospedalieri (Motivo)	1 =SI	2 =NO	GG……..MM……..AAAA……
Ha avuto SCA	1 =SI	2 =NO	GG……..MM……..AAAA……
Ha avuto angina stabile	1 =SI	2 =NO	GG……..MM……..AAAA……
Ictus	1 =SI	2 =NO	GG……..MM……..AAAA……
Rivascolarizzazione (Tipo)	1 =SI	2 =NO	GG……..MM……..AAAA……
Buona salute	1 =SI	2 =NO	GG……..MM……..AAAA……
Riscontro di diabete	1 =SI	2 =NO	GG……..MM……..AAAA……
Fibrillazione atriale	1 =SI	2 =NO	GG……..MM……..AAAA……

CONSIDERAZIONI e note eventuali:
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Statistical Analysis

The data are expressed as mean±SD (or SEM or range), and the comparison between groups was performed with Student's *t* test for unpaired data or the nonparametric Mann-Whitney test for data not normally distributed (75). The relationship between end-diastolic interventricular septum thickness and LV end-diastolic posterior wall thickness, RWT, and the ratio E_i/A_i as dependent variables and the other variables was investigated with a stepwise multiple regression, using the backward method and an F-to-remove criterion of 0.150. Statistical significance was defined as $P < 0.05$. SPSS 15.00 for Windows (SPSS Italy Inc., Bologna, Italy), licensed to our Department, was used for all analyses.

RESULTS

Clinical Features of the Patients

Demographic, clinical and biochemical features of the 41 PA patients who underwent surgical removal of the tumor and of the 14 PA patients who did not undergo surgical removal of the tumor and underwent medical treatment (including the eight patients with IHA) are shown in Table 2. Patients who underwent adrenalectomy were younger, mostly women, with a lower BMI, BSA and diastolic blood pressure compared with patients medically-treated.

No difference between groups was observed in terms of known duration of hypertension, plasma potassium, plasma aldosterone levels, plasma active renin and/or their ratio (Table 2).

Baseline (cross-sectional) Doppler echocardiography assessment of LV wall thickness and dimensions and transmitral LV filling flow velocity indexes

Echocardiographic LV Thickness and Dimension

The results of the measurements of LV wall thickness and dimensions at baseline in the two groups are shown in Table 3.

At baseline, interventricular septum and LV posterior wall thickness, the end-systolic and end-diastolic LV diameters, the RWT and LVMI were similar in the two groups. When evaluated in terms of LVH and concentric remodeling, an excess of LVH and rate of concentric remodeling was observed at baseline in both groups (Figure 3, panel A; Figure 4). The overall prevalence of LVH was 49%. Of interest, LVH and concentric remodeling were more common in PA surgically-treated patients compared to PA patients who received medical treatment (Figure 3, panel A; Figure 4).

Echocardiography Doppler Indexes and Diastolic Function

The results of the measurements of transmitral Doppler flow velocity at baseline in the two groups are shown in Table 3.

In both groups, early PFVE and PFVA were within the normal interval for age (72,73).

In medically-treated PA patients early PFVE and PFVA were significantly lower compared with surgically-treated patients, but their average ratio (PFVE/PFVA), as well as the IRT and the DT of the E wave were similar in the two groups.

Of interest, medically-treated PA patients showed a significantly lower E_i/A_i ratio (*P*=.008) and a significantly increased ACLVF (*P*=.016) compared with PA patients who underwent adrenalectomy, thus indicating a worst diastolic function at baseline in the former.

Follow-up Doppler echocardiography assessment of LV wall thickness and dimensions and transmitral LV filling flow velocity indexes

All the 55 PA patients were available at follow-up (mean 6.4 years; range 4.5 to 8 years) after surgery or the initial evaluation. Of them, 41 underwent surgical excision of an aldosterone-producing adenoma, resulting in cure of hypertension in 10, whereas 31 still require antihypertensive treatment although at a much smaller dosage and with a fewer number of

agents than before surgery. In 22 of them BP resulted normalized, whereas in 9 of them the BP control was inadequate.

Fourteen patients were treated with medical therapy either because of idiopathic hyperaldosteronism (n=8) or because they refused surgery (n=6). In all these patients, an acceptable control of the high BP was achieved with medical therapy, which required two or more drugs and included an aldosterone antagonist in twelve of them.

After follow-up, despite a greater reduction of antihypertensive drugs in patients surgically-treated (number of drugs: 1.7±1.4 vs 2.6±0.8 in surgically and medically-treated, respectively, p= 0.024) in both groups there was a significant reduction of blood pressure levels: average blood pressure was 139±14 and 135±7 mmHg in patients surgically and medically-treated, respectively (NS). The follow of blood pressure at follow-up from baseline was highly significant ($p<0.001$) for both groups. Of interest, in patients treated with adrenalectomy a significant (p=0.002) increase in BMI (25.2±4.1 at baseline vs 27.3±4.2 at follow-up) during follow-up, was observed. At variance, no difference of BMI was observed in medically-treated patients (29.3±4.2 at baseline vs 28.1±4.1 at follow-up).

Echocardiographic LV Thickness and Dimension at follow-up

The changes of LV dimensions, and LV thickness observed in these patients are shown in Tables 4 and in Figure 3 (panel B) and Figure 4.

In both groups a significant ($p< 0.001$) reduction in LV end-diastolic diameter, a reduction in LVM index and an increase in the relative wall thickness was observed. However, although baseline LVM index and relative wall thickness were similar, the reduction in LVM index and the increase in the relative wall thickness was significant only in the surgically-treated PA and not in the medically-treated patients (Table 4).

No differences were observed in terms of septum and posterior wall thickness, left atrial dimension, aortic root diameter and their ratio in both groups (Table 4).

Figure 4 shows the modifications of LVH and LV remodeling before and after follow-up. Prevalence of LVH significantly decreased in both treatment groups, whereas the LV remodeling as well as the normal LV geometry had only mild and non significant modifications, thus confirming a shift from LVH to LV remodeling mainly related to the decrease in LV end-diastolic diameter.

In a regression analysis, a model including pre-treatment blood pressure, body mass index, age, known duration of hypertension, follow-up interval and medical treatment was unable to explain the left ventricular mass decrease at follow-up.

Echocardiography Doppler Indexes and Diastolic Function at follow-up

As regards the diastolic function, no significant modification was observed in the surgically-treated PA. At variance, a significant (p= 0.002) reduction in the atrial contribution to LV filling (ACLF) and an increase in E*i*/A*i* integral ratio was observed in medically-treated PA, which presented a worst diastolic function at baseline (Table 4).

DISCUSSION

The present results provide an important novel piece of information, which is relevant for the understanding of the effects of aldosterone on LV mass and filling. Primary aldosteronism is the most common endocrine cause of secondary hypertension and is increasingly recognized in patients referred to specialized centers for hypertension (48). Although it was long regarded as a benign (ie, devoid of cardiovascular complications) form of hypertension, clinical data are available to challenge this view (38,39,48-50).

A growing body of evidence links aldosterone to development and/or progression of cardiovascular disease, seemingly separate from its effects on blood pressure. In fact, animal and human studies support the contention that cardiac damage in aldosteronism is not just the result of a pressure-volume overload, but might involve additional endocrine and paracrine

mechanisms (38,49,50,76-78). A number of cross-sectional echocardiographic evaluations have reported an excess increase of LV mass and diastolic dysfunction in patients with primary aldosteronism as compared with other types of hypertensive disease (43-45,50-56), although this finding has not been confirmed in other studies (57-61). Disparity of the findings could be ascribed to the limited sample size of some studies and (particularly) to the differences in the severity and duration of hypertension (44,49). In our study we investigated 55 PA patients, all of them available at follow-up. We found that LVH and concentric remodeling were especially exaggerated when compared with other cohorts of patients with essential hypertension (43).

Prospective studies

The few echocardiographic observations of cardiac changes after treatment of aldosteronism are confined to short-term follow-up studies, mostly after removal of an adrenal adenoma (43,52,59). Previously, Rossi and Coll. have reported an increase in LV concentric remodeling and LVM in patients with hypertension due to Conn's adenoma compared with demographically and hemodynamically similar patients with essential hypertension and with markedly lower plasma aldosterone levels. In the former, a significant decrease of LV early filling indexes and an increase of atrial contribution to LV filling, was found. Both the thickening of the LV walls and the changes of LV filling showed a relationship with plasma aldosterone levels and were corrected by adrenalectomy (43,44). In particular, a normalization of all indexes of LV filling was observed at 1-year follow-up after surgical removal of APA but not in medically-treated PA patients. All these data suggest that excess aldosterone affects LV anatomy and function both by increasing LV mass, possibly by promoting the deposition of extracellular matrix and/or collagen, and by changing LV filling, in part through a prolongation of the AV conduction time.

A more recent study has examined the long-term echocardiographic evolution in a large cohort of patients with PA after surgical or medical treatment (including spironolactone in all) (56).

Results demonstrate that adrenalectomy and spironolactone are both effective in decreasing the LV mass, although this effect occurs earlier after surgical treatment. In both treatment groups, the LV diastolic filling pattern had only mild and nonsignificant improvement. Pretreatment plasma aldosterone concentrations predict LVMI decrease during follow-up, independent of treatment-related blood pressure changes (56). However, in this study the diagnosis of APA and IHA were questionable and medical treatment during follow-up was not adequately considered.

Our study has been conducted in a large cohort of patients with PA who were diagnosed using standardized procedures that were homogeneously applied by the same physicians (48,79). This practice, together with the collection of data in a single database, should have limited any possible selection bias.

Echocardiographic features at baseline

Our results confirm the presence of greater LV mass and more prevalent LVH (49% of the patients) in PA patients, that is associated with evidence of an abnormal pattern of LV diastolic filling, such as that reported in previous studies (43,44,56).

The increased LV mass in PA patients might reflect the increased circulating volume resulting from the renal effects of the hormone. However, the cardiac hemodynamic overload is not the only determinant of LV hypertrophy, and various hormones can play specific roles in different subsets of hypertension. The renin-angiotensin-aldosterone system is an important contributor to the pathogenesis of LV hypertrophy (49,50) and PA permits evaluation of the cardiac effects of elevated aldosterone independent from those of angiotensin. Since LVH is an important independent predictor of major cardiovascular events in hypertension, an increased LV mass in patients with PA could explain the worse cardiovascular outcome in comparison with other hypertensive groups (38,39).

At the time of diagnosis, our PA patients more often had concentric LV remodeling or hypertrophy than eccentric hypertrophy (Figure 3, panel A), most likely because they were diagnosed at an early stage of their disease and therefore had no evidence of hypervolemia and/or congestive heart failure.

At baseline, medically-treated PA showed a worst diastolic function compared with PA patients who underwent adrenalectomy. This could be due to the fact that the former were older, with a higher prevalence of overweight and obesity and with higher DBP levels compared with the latter.

Echocardiographic features at follow-up

In our long-term echocardiographic follow-up, we observed a significant ($p<0.001$) reduction in average blood pressure in both patients surgically- and medically-treated, as well as a significant ($p< 0.001$) reduction in LV end-diastolic diameter.

In both groups a reduction in LVM index (from 115±22 to 106±18 in adrenalectomized patients and from 118±26 to 103±21 in medically-treated patients) but associated with an increase in the relative wall thickness (from 0.43±0.07 to 0.46±0.06 in adrenalectomized patients and from 0.41±0.06 to 0.45±0.05 in medically-treated patients) was observed. However, these modifications attained statistical significance only in the surgically-treated PA and not in the patients on medical therapy.

The modifications of the anatomic parameters after follow-up translated into a reduced prevalence of hypertrophy in both treatment groups, whereas the LV remodeling as well as the normal LV geometry had only mild and non significant modifications, thus confirming a shift from LVH to LV remodeling mainly related to the decrease in LV end-diastolic diameter.

A regression analysis showed that in both groups LV mass decrease was independent from pre-treatment blood pressure, body mass index, age, known duration of hypertension, follow-up interval and medical treatment.

Diastolic function at follow-up

A significant reduction in the atrial contribution to LV filling (ACLF) and an increase in E*i*/A*i* integral ratio, thus indicating an improvement of the diastolic function, was observed only in medically-treated PA, likely because they had a higher degree of diastolic dysfunction at baseline. Of interest, at baseline medically-treated PA were older, with a higher prevalence of overweight and obesity and with higher DBP levels compared with PA patients who underwent adrenalectomy. These features could account for their worst diastolic function at baseline. Thus, it is plausible that the improvement of the diastolic function after treatment of hyperaldosteronism resulted evident only in the patients who at baseline presented an impaired function.

Effects of treatments

This study presents evidence that PA is associated with LVH out of proportion to blood pressure levels thus confirming the hypothesis that excess aldosterone affects LV anatomy and function both by increasing LV mass, possibly by promoting the deposition of extracellular matrix and/or collagen, and by changing LV filling, in part through a prolongation of the AV conduction time (44). Treatment of hyperaldosteronism with either surgical or medical treatment induce a reduction in blood pressure levels, in LV end-diastolic diameter, a reduction in LV mass index but with an increase in the relative wall thickness. With a similar fall of blood pressure and despite a greater reduction of antihypertensive drugs, these changes were more prominent in adrenalectomized patients. We also observed an improvement of the diastolic function, which resulted evident only in medically-treated PA patients, because they presented a higher degree of diastolic dysfunction at baseline.

These findings underscore the importance of a timely identification of this endocrine disorder to obtain regression of cardiac abnormalities. In particular, they might be relevant for understanding the LV changes of patients with secondary aldosteronism, such as those with

congestive heart failure in whom blockade of the mineralocorticoid receptor with spironolactone strikingly improved outcome. Future studies will have to address the potential benefits of the newest mineralocorticoid receptor antagonists on cardiac structural and functional abnormalities of primary aldosteronism and to clarify whether these therapeutic interventions can effectively prevent late cardiovascular complications.

CONCLUSIONS

In PA patients, the excess aldosterone is associated with both increased LV wall thickness and mass. Treatment of hyperaldosteronism with either surgical or medical treatment induce a long-term reduction in blood pressure levels, in LV end-diastolic diameter, a reduction in LVM index and an increase in the relative wall thickness, particularly in the surgically-treated PA.

It must be noted that, with a similar fall of blood pressure and despite a greater reduction of antihypertensive drugs, these changes were more prominent in adrenalectomized patients. Of particular interest, treatment can improve the diastolic function, as observed in medically-treated PA patients. Probably, this effect was evident only in medically-treated PA patients because they presented a worst diastolic function at baseline compared with adrenalectomized patients.

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Table 1: Cross-sectional echocardiographic evaluation of LVH prevalence (%) in patients with PA and other forms of hypertension

Authors	**PA (%)**	**EH (%)**	**RVH (%)**	**Ph (%)**	**References**
Catena C. 2007	33	21			(56)
Fallo F. 2006	27	17	--	--	(55)
Matsumura K. 2006	88	44	--	--	(50)
Milliez P. 2005	34	24	--	--	(38)
Rossi G.P. 2002	30	0	--	--	(45)
Rizzoni D. 1998	29	39	68	36	(60)
Rossi G.P. 1997	35	15	--	--	(44)
Shigematsu Y. 1997	66	29			(53)
Yoshitomi Y. 1996	81	--	64	--	(59)
Denolle T. 1993	48	--	40	25	(52)
Yoshihara F. 1996	90	86	80	--	(58)

EH: essential hypertension; RVH: renovascular hypertension; PA: primary aldosteronism; Ph: Pheocromocytoma

Table 2: Clinical features of PA patients treated with surgery (41) and medically-treated (14), at baseline.

Variable	**Surgically-treated APA** (n°41)	P (2-tail)	**Medically-treated PA** (n°14)
Sex, F/M	25/16	0.002	2/13
Age (yrs)	54±13	0.005	64±8
Body mass index (Kg/m^2)	25±4	0.010	29±4
Body surface area (m^2)	1.8±0.2	0.007	1.9±0.1
Plasma potassium (mmol/L)	3.29±0.6	NS	3.36±0.6
Known duration of HT (yrs)	8.8±1.4	NS	9.4±2.6
Systolic BP (mmHg)	168±18	NS	174±23
Diastolic BP (mmHg)	100±11	0.01	109±10
Plasma aldosterone (ng/dl)	63.2±56.1	NS	73.4±70.6
Plasma active renin (??)	0.83±1.0	NS	0.77±0.4
ARR	207±253	NS	95±93

Values are mean±SD.; APA: aldosterone producing adenoma (Conn's adenoma), ARR: aldosterone/active rennin ratio,

BP: blood pressure

Table 3: LV dimension, thickness and transmitral flow indexes, assessed by echocardiography and Doppler, at baseline in patients with PA surgically-treated (41) and medically-treated (14).

Variable	**Surgically-treated APA** (n°41)	P (2-tail)	**Medically-treated PA** (n°14)
IVSd (cm)	1.11±0.16	NS	1.15±0.22
PWd (cm)	1.07±0.15	NS	1.04±0.09
LVESD (cm)	3.22±0.5	NS	3.26±0.3
LVEDD (cm)	5.06±0.5	NS	5.30±0.4
LVMI (g/m2)	115±22	NS	118±26
RWT	0.43±0.07	NS	0.41±0.06
LAD/AoD	1.13±0.13	NS	1.18±0.11
PFVE (mm/s)	70±15	0.006	59±10
PFVA (mm/s)	75±16	0.026	62±12
PFVE/PFVA	0.99±0.35	NS	0.98±0.24
IRT (ms)	103±22	NS	85±10
DT (ms)	192±60	NS	183±47
E*i*/A*i* integral ratio	1.39±0.5	0.008	0.97±0.2
ACLVF (%)	43.5±9.4	0.016	50.9±4.8

Values are mean±SD.; ACLF: atrial contribution to left ventricular filling; E_i/A_i (early/late diastolic LV filling wave integrals ratio); IRT: isovolumetric relaxation time; LAD/ AoD: left atrial dimension/aortic root diameter; LVEDD: LV end-diastolic dimension; LVESD: LV end-systolic dimension; IVSd: end-diastolic interventricular septum thickness; LVMI: left ventricular mass index; PFVE: early diastolic peak flow velocity; PFVA: late diastolic peak flow velocity; PWd: end-diastolic LV posterior wall thickness; RWT: relative wall thickness.

Table 4: Changes of LV dimension, thickness and transmitral flow indexes, assessed by echocardiography and Doppler, in patients with PA treated or with surgery (41) and medically-treated (14), before and after follow-up (FW).

Variable	**Surgically-treated APA** (n°41)		P (2-tail)	**Medically-treated PA** (n°14)		P (2-tail)
	Before	**After FW**		**Baseline**	**After FW**	
IVSd (cm)	1.11±0.16	1.13±0.14	NS	1.15±0.22	1.13±0.14	NS
PWd (cm)	1.07±0.15	1.07±0.13	NS	1.04±0.09	1.07±0.09	NS
LVESD (cm)	3.22±0.5	2.96±0.4	<0.001	3.26±0.3	3.01±0.2	NS
LVEDD (cm)	5.06±0.5	4.80±0.4	<0.001	5.30±0.4	4.82±0.2	<0.001
LVMI (g/m2)	115±22	106±18	0.21	118±26	103±21	NS
RWT	0.43±0.07	0.46±0.06	0.05	0.41±0.06	0.45±0.05	NS
LAD/AoD	1.13±0.13	1.09±0.13	NS	1.18±0.11	1.01±0.36	NS
PFVE (mm/s)	70±15	68±17	NS	59±10	68±17	NS
PFVA (mm/s)	75±16	73±16	NS	62±12	80±25	NS
PFVE/PFVA	0.99±0.35	1.00±0.38	NS	0.98±0.24	0.86±0.19	NS
IRT (ms)	103±22	98±22	NS	85±10	106±20	NS
DT (ms)	192±60	253±69	0.001	183±47	221±62	NS
E*i*/A*i* integral ratio	1.39±0.5	1.33±0.3	NS	0.97±0.2	1.41±0.2	0.002
ACLVF (%)	43.5±9.4	43.4±5.6	NS	50.9±4.8	41.7±3.9	0.002

Values are mean±SD.; ACLF: atrial contribution to left ventricular filling; E_i/A_i (early/late diastolic LV filling wave integrals); LAD/ AoD: left atrial dimension/aortic root diameter; LVEDD: LV end-diastolic dimension; LVESD: LV end-systolic dimension; IVSd: end-diastolic interventricular septum thickness; LVMI: left ventricular mass index; PFVE: early diastolic peak flow velocity; PFVA: late diastolic peak flow velocity; PWd: end-diastolic LV posterior wall thickness; RWT: relative wall thickness.

FIGURE LEGEND

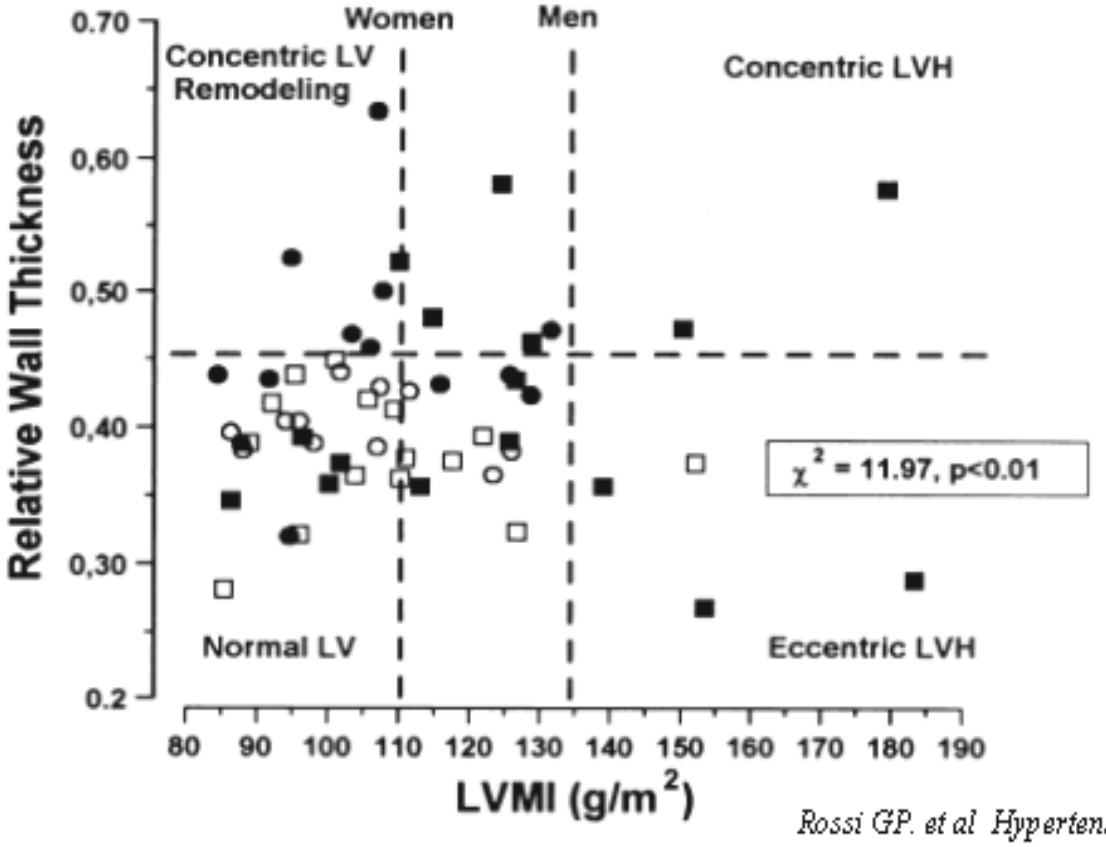
Figure 1: Individual values of LVMI and RWT in 34 PA patients (closed symbols) and 34 matched EH patients (open symbols). Vertical lines indicate the cutoff value for LVH in men (squares) and women (circles). Horizontal line divides patients with concentric LVH, or LV concentric remodeling, from those with eccentric LVH, or normal LV, respectively. A significantly higher proportion of patients with LVH and LV concentric remodeling was found in the PA patient groups. (*Rossi GP Hypertension 1996*).

Figure 2: The bar graph shows the mean values of CVI_s, CVI_{pw}, and CVI_m. in 17 consecutive patients with PA and 10 patients with primary (essential) hypertension who were matched for demographics, casual blood pressure, and known duration of hypertension. Patients with PA had significantly lower values for both indexes compared with EH patients, thus suggesting the presence of CF. (*Rossi GP Hypertension 2002*).

Figure 3: Individual values of LVMI and RWT in PA patients treated with surgery (open circles) and with medical treatment (closed triangles) at baseline (panel A) and after follow-up (panel B). Vertical lines indicate the cutoff value for LVH in men and women. Horizontal line divides patients with concentric LVH, or LV concentric remodeling, from those with eccentric LVH, or normal LV, respectively.

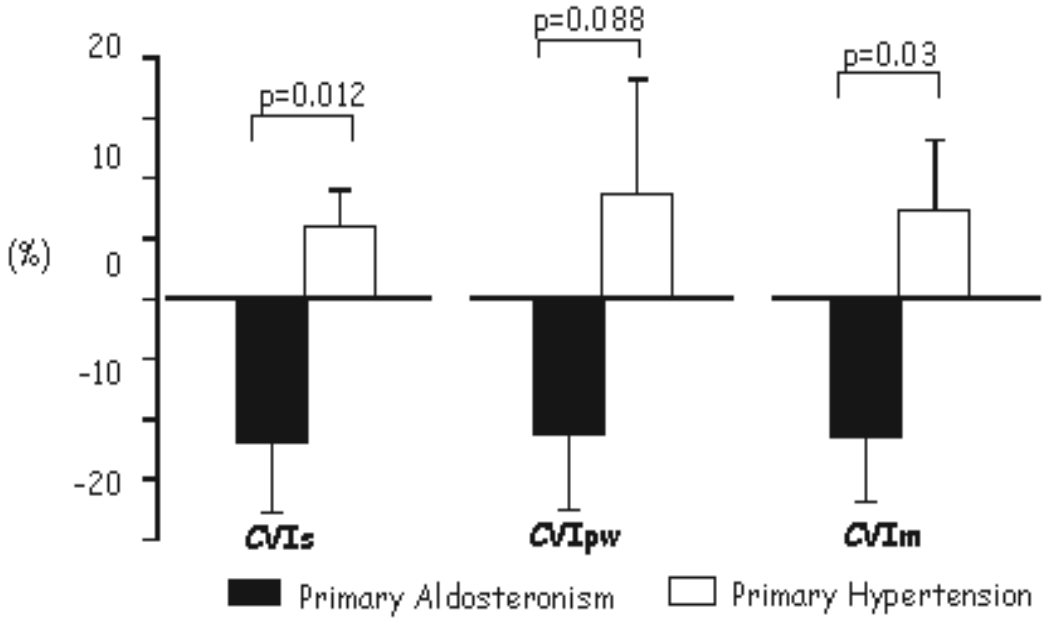
Figure 4: Modification of the geometric patterns of LV (normal, LVH and LV remodeling) before (white bars) and after follow-up (black bars). **Panel A**: PA patients surgically-treated (n 41). **Panel B**: PA patients medically-treated (n 14).

Fig. 1: LVMI and RWT individual values in 34 PA (closed symbols) and 34 EH patients (open symbols)



Rossi GP. et al Hypertension 1996

Fig.2: mean values of cyclic variation index in the interventricular septum (CVIs), LV posterior wall (CVIpw) and the average of CVIs and CVIpw (CVIm) in PA and PH patients



Rossi GP. et al Hypertension 2002

Fig. 3: Individual values of LVMI and RWT in PA patients treated with surgery (open circles) and with medical treatment (closed triangles) at baseline (panel A) and after follow-up (panel B).

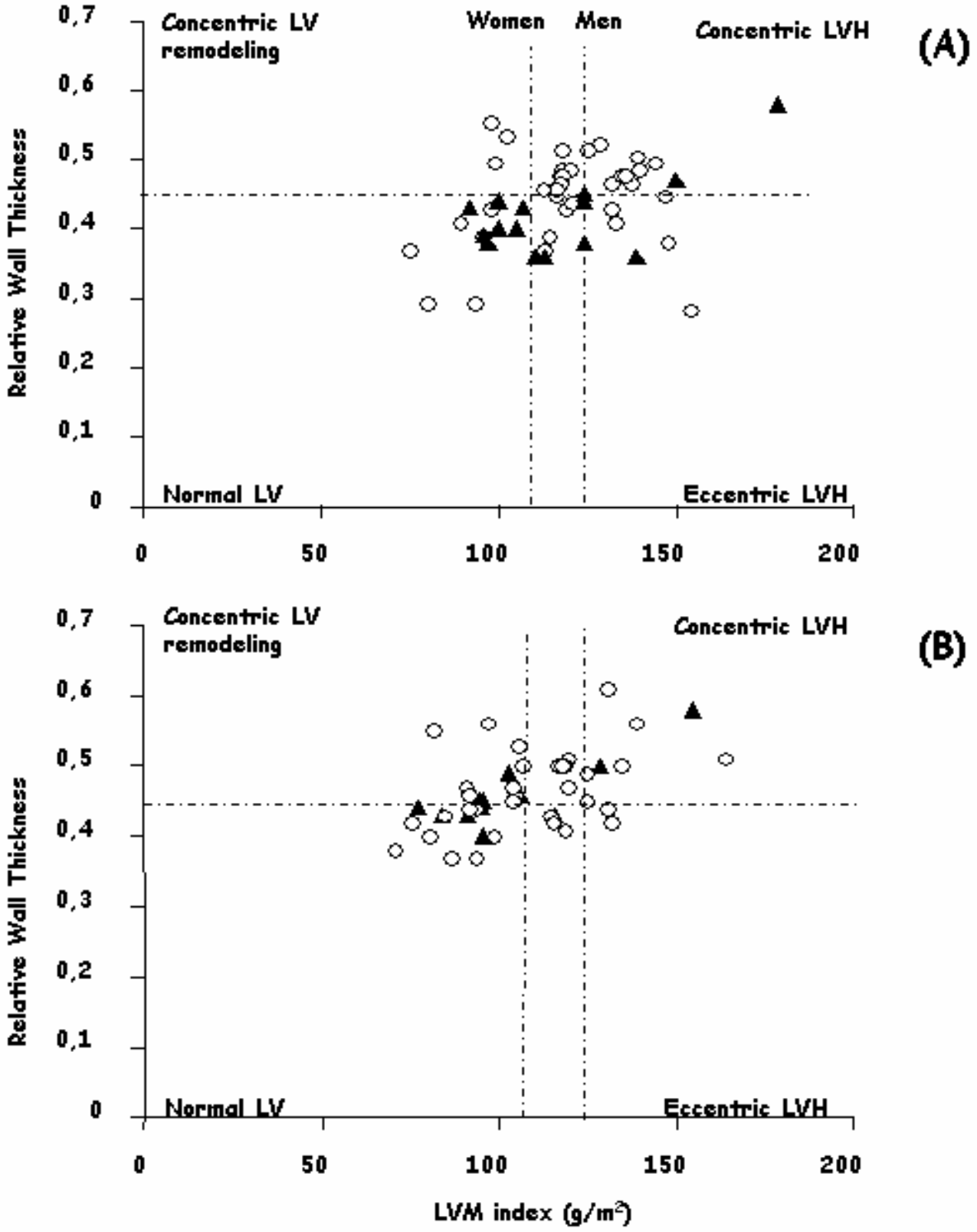


Fig. 4: modification of the geometric patterns of LV (normal, LVH and LV remodeling) before (white bars) and after follow-up (black bars). Panel A: PA patients surgicallt treated (n 41). Panel B: PA patients medically treated (n 14).