International Journal of Cardiology 275 (2019) 145–151

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Left ventricular dysfunction in ADPKD and effects of octreotide-LAR: A cross-sectional and longitudinal substudy of the ALADIN trial☆

Letizia Spinelli [a,*,1], Antonio Pisani [b,1], Giuseppe Giugliano [a], Bruno Trimarco [a], Eleonora Riccio [b], Bianca Visciano [b,c], Giuseppe Remuzzi [c,d,e,**], Piero Ruggenenti [d,e], On behalf of the ALADIN-Cardiovascular Study Group [2]

[a] Department of Advanced Medical Sciences, Federico II University, Naples, Italy
[b] Department of Public Health, Nephrology Unit, Federico II University, Naples, Italy
[c] Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy
[d] IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", Clinical Research Centre for Rare Diseases "Aldo e Cele Daccò", Bergamo, Italy
[e] Unit of Nephrology and Dialysis, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

ARTICLE INFO

Article history:
Received 31 July 2018
Received in revised form 12 October 2018
Accepted 18 October 2018
Available online 22 October 2018

Keywords:
Speckle-tracking echocardiography
Left ventricular dysfunction
Renal disease
Somatostatin analogues

ABSTRACT

Background and aim: In autosomal dominant polycystic kidney disease (ADPKD) cardiac abnormalities have been observed before the onset of hypertension or renal dysfunction. We sought to characterize, in ADPKD patients, left ventricular (LV) function and its changes after somatostatin-analogue octreotide-LAR treatment.
Methods: In a 1:1:1 cross-sectional study, we evaluated LV function by speckle-tracking echocardiography in 34 ADPKD patients from one ALADIN-trial center and in 34 age- and gender-matched healthy controls and 34 equally-matched renal controls with non-cystic chronic kidney disease. Changes in LV function were compared in the 16 and 18 ADPKD patients originally randomized to 3 year-treatment with octreotide-LAR or placebo, respectively.
Results: LV twist and untwisting rates were lower in ADPKD patients that in healthy or renal controls ($6.1 \pm 2.6°$ vs. $11.1 \pm 2.1°$ and $10.2 \pm 3.7°$; $-49.5 \pm 18.1°$/s vs. $-79.8 \pm 12.2°$/s and $-84.3 \pm 25.9°$/s, respectively, all $p < 0.001$). The correlation between LV mass or diastolic BP and untwisting rate was positive in ADPKD patients ($r = 0.38$, $p = 0.025$ and $r = 0.44$, $p = 0.011$, respectively), not significant in healthy controls and negative in renal controls ($r = -0.38$; $p = 0.023$ and $r = -0.40$, $p = 0.012$, respectively. LV untwisting rate improved from $-49.9 \pm 18.6°$/s to $-70.3 \pm 27.5°$/s with octreotide-LAR, but did not change with placebo ($p = 0.027$ for treatment effect). At adjusted linear regression analysis, octreotide-LAR therapy emerged as the only independent predictor of untwisting rate improvement at final visit [beta coefficient −0.504 (95% CI −46.905–−6.367), $p = 0.014$].
Conclusions: In ADPKD patients LV function is early impaired. Somatostatin-analogue therapy might help in preventing or ameliorating LV dysfunction in this population.
Clinical Trial Registration http://www.clinicaltrials.gov, NCT0030928.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Correspondence to: L. Spinelli, Department of Advanced Biomedical Sciences, Federico II University, Via Pansini, 5, 80131 Naples, Italy.
** Correspondence to: G. Remuzzi, IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Via Stezzano, 87, 24126 Bergamo, Italy.
E-mail addresses: letspine@unina.it (L. Spinelli), giuseppe.remuzzi@marionegri.it (G. Remuzzi).

[1] These authors contributed equally to the work.

[2] Members of the ALADIN-Cardiovascular Study Organization were as follows (all in Italy): Principal investigator: L. Spinelli (Naples); Study coordinator: A. Pisani (Naples); Coordinating center: P. Ruggenenti, G. Remuzzi — IRCCS-Istituto di Ricerche farmacologiche Mario Negri, Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Villa Camozzi, Ranica (Bergamo); Participating center: A. Pisani, E. Riccio, B. Visciano, M. Amicone, C. Marchitiello, L. Spinelli, Echocardiographic evaluations: L. Spinelli (Naples); Monitoring of the ALADIN trial, drug distribution and pharmacovigilance (Mario Negri Institute): N. Rubis, O. Diadei, W. Calini, A. Villa, M. Sabatella (Ranica); Database and laboratory data validation (Mario Negri Institute): B. Ene-Iordache, S. Carminati, D. Martinetti (Ranica); Randomization (Mario Negri Institute): G. A. Giuliano (Ranica); Data analysis: G. Giugliano, L. Spinelli (Naples); Regulatory affairs (Mario Negri Institute): P. Boccardo, S. Peracchi (Ranica).

https://doi.org/10.1016/j.ijcard.2018.10.063
0167-5273/

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD), the most common monogenic renal disorder, affects 12.5 million people worldwide. Mutations in the Polycystic Kidney Disease 1 and 2 (PKD-1 and PKD-2, respectively) genes have a well-defined role in uncontrolled cystogenesis in both kidneys, the hall-mark of the disease, as well as in liver, and less frequently in pancreas, seminal vesicles and arachnoid membrane [1]. PKD-1 [2] and PKD-2 [3] encode for two membrane proteins, Polycystin 1 and 2 (PC-1 and PC-2, respectively). PC-2 is a non-selective calcium ion channel that is modulated by PC-1 in response to still poorly understood mechanisms, including flow-induced movements in tubular primary cilium [1]. Genetically determined PC-1 or PC-2 dysfunction may result in decreased intracellular calcium inflow with increased cAMP production and activation of cAMP-mediated mechanisms which contribute to cyst cell growth and fluid secretion in kidneys and other target organs [4]. Both proteins are expressed in cardiomyocytes and appear to elicit a direct effect on cardiac cells performance [5–8]. Impaired ventricular ejection fraction has been demonstrated in mice lacking PC1 in hearts [7]. PC2 is a modulator of the cardiac ryanodine receptor, a calcium release channel, found on the sarcolemma reticulum membrane [8]. PC-2-deficient zebrafishes had heart with altered calcium signal and developed a systolic and diastolic dysfunction [9]. Thus, the alteration of polycystin levels in the heart could directly contribute to cardiac remodeling in patients with ADPKD in the absence of renal failure or high blood pressure (BP). In experimental polycystic kidney disease [10,11] and also in humans with ADPKD and/or polycystic liver disease, the somatostatin analogue octreotide-Long-Acting-Release (LAR) exerts an inhibitory effect on hepato-renal cystogenesis, most likely mediated by cAMP inhibition [12–14]. Somatostatin receptor subtypes are expressed on the surface of both myocytes and myocardial fibroblasts, along with tubular cells and cholangiocytes [15]. Conceivably, binding of these receptors by octreotide-LAR could limit or prevent early myocardial dysfunction in patients with ADPKD through mechanisms similar to those that modulate cysts generation and growth.

Speckle-tracking echocardiography, a reproducible advanced ultrasound technique, is able to provide comprehensive information on cardiac mechanics. This technique allows analysis of myocardial tissue deformation by quantifying tissue strain and strain rate. Left ventricular (LV) longitudinal strain is a sensitive marker of very early myocardial dysfunction in many clinical conditions [16–18]. The assessment of LV rotational dynamics, throughout the whole cardiac cycle, by speckle tracking echocardiography has been validated versus magnetic resonance imaging [19–21]. Impaired diastolic untwisting motion of the LV along its longitudinal axis, resulting from opposite rotation of the LV apex compared with the base, can detect early LV diastolic dysfunction [22].

Thus, we used speckle-tracking echocardiography to assess whether and to what extent LV function is impaired in patients with ADPKD and can be improved by octreotide-LAR.

2. Methods

The present single-center study included 34 ADPKD patients clinically monitored by serial echocardiographic evaluations in the context of the multicenter, prospective, randomized, placebo controlled trial designed to assess the effect of "A Long-Acting somatostatin on DIsease progression in Nephropathy due to ADPKD" (ALADIN) [13]. Specifically, the present study was organized into a cross-sectional matched-cohort phase followed by a longitudinal phase. In the cross-sectional phase we compared echocardiographic parameters of 34 ADPKD patients enrolled at the Federico II ALADIN center with those of 34 age- and gender-matched subjects with normal BP and no evidence of renal disease (healthy controls) or with 34 age- and gender-matched patients with non-cystic chronic renal disease (renal controls) and renal function similar to that of the ADPKD patients. Chronic renal disease of renal controls was due to: focal and segmental proliferative glomerulonephritis (5 patients), membranoproliferative glomerulonephritis (4 patients), IgA nephropathy (4 patients), primary glomerulonephritis (3 patients), rheumatoid arthritis (2 patients), systemic lupus erythematosus (8 patients), xanthinuria (2 patients) and diabetes mellitus (6 patients).

In the ALADIN trial, central randomization was used to allocate study participants to 3 year octreotide-LAR or placebo, in a 1:1 ratio [13]. In the longitudinal phase of the present study (Fig. 1 of [23]), we evaluated cardiac functional changes in the ADPKD patients who had been randomized to three-year treatment with octreotide-LAR or placebo in the context of the ALADIN trial [13]. The study was approved by the Ethical Committee of the University of Naples Federico II. ADPKD patients provided written informed consent to both phases of the study, renal and healthy controls to the cross-sectional phase. The study conformed to the principles of the Declaration of Helsinki.

2.1. Cross-sectional, matched-cohort phase

All ADPKD patients consecutively included in the ALADIN trial at the Outpatient Clinic of the Federico II University of Naples were evaluated for study participation. Selection criteria are reported in Ref. [23]. In the context of a 1:1:1 controlled design, for each ADPKD patient we identified one healthy and one renal control with adequate echocardiographic imaging (Fig. 1 of Ref. [23]). After history recording and clinical evaluation including BP measurement, venous blood was sampled from ADPKD patients and controls after an overnight fast for routine laboratory evaluations including serum creatinine measurement for glomerular filtration rate (GFR) estimation. Urine was also sampled from 24-hour collection to measure creatinine and protein excretion. ADPKD patients and their matched renal and healthy controls underwent baseline speckle-tracking echocardiography.

2.2. Prospective, randomized phase

This was a post-hoc analysis of ALADIN trial aimed to evaluate treatment effect in a subset of patients enrolled in the trial [13]. All baseline evaluations including speckle-tracking echocardiography were repeated at the final visit after three-year follow-up, as shown in Fig. 1 of Ref. [23]. No systematic change in diet and pharmacological treatment was introduced throughout the study. However, adjustments in the posology of antihypertensive medications (if any) were allowed to target systolic/diastolic BP <130/80 mm Hg.

2.3. Measurements and definitions

BP was measured at the dominant arm after 5-min rest in the sitting position. The mean of three measurements, taken 2-min apart, was recorded for statistical analyses. GFR was estimated by the Chronic Kidney Disease Epidemiology (CKD-EPi) equation. Arterial hypertension was defined as BP >140/90 mm Hg or need for antihypertensive therapy [24] and diabetes as fasting blood glucose concentration >126 mg/dl or treatment with insulin or oral hypoglycemic agents [25].

2.4. Echocardiography

All echocardiographic evaluations were performed by a single observer (L.S.), who was blinded to patient treatment, using a digital ultrasonic device system (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). The details are described in Ref. [23]. Speckle-tracking echocardiography analysis was performed offline by using dedicated software (EchoPac PC version 110.0.0; GE Vingmed Ultrasound). For all measurements three consecutive cardiac cycles were analyzed and averaged for each variable in every segment. Basal and apical short-axis views were used for the measurement of rotation and twist. On each short-axis plane the endocardial border was traced at end-systole. A region of interest was manually adjusted to include the entire myocardial thickness and the tracking quality for each segment was automatically evaluated. Rotation and rotation rate profiles for each segment in both short-axis planes were measured. By convention, clockwise rotation as viewed from the apex was expressed as a negative angle, whereas counterclockwise rotation was expressed as a positive angle. Instantaneous global LV twist and twist rate were then calculated by subtracting global basal rotation from global apical rotation and global basal rotation rate from global apical rotation rate, respectively, at corresponding time points in the cardiac cycle. LV untwisting rate was calculated as the early diastolic negative peak on LV twist rate curve. Peak systolic longitudinal strain was measured utilizing 4-chamber, 2-chamber and long axis apical views and dividing each LV wall in 3 segments. The peak negative systolic strain values obtained from the resulting 18 segments were averaged to calculate global longitudinal strain. Intra- and inter-observer reproducibility data for speckle-tracking measurements are reported in Ref. [23].

2.5. Statistical analysis

Continuous variables were expressed as mean ± SD or median with interquartile range, and categorical data as absolute numbers and percentages. Comparisons were made by one-way ANOVA with Bonferroni's post hoc test for continuous variables and by χ^2 test or Mann-Whitney U test for categorical variables, as appropriate. Pearson's correlation coefficients were calculated to assess the relationships between continuous variables.

In ADPKD group, univariate and multivariate (entry criteria $p < 0.1$ at univariate analysis) linear regression analysis was performed to evaluate the relationships between baseline peak untwisting rate and the following clinical and echocardiographic variables: age, body surface area, GFR, systolic BP, diastolic BP, LV end-diastolic volume index, LV end-systolic volume index, LVM index, global longitudinal strain and twist. According to the entry criteria only LVM index and diastolic BP entered the multivariate model.

A general linear model for repeated measures with correction for treatment was performed to evaluate the treatment effect in ADPKD patients. Finally, an adjusted linear regression model was created to evaluate the independent association of octreotide-LAR treatment with final untwisting rate. Age, body surface area, GFR, heart rate, systolic BP, diastolic BP and octreotide-LAR treatment were the covariates included in the adjusted model.

A p value <0.05 was considered as statistically significant for all tests. Data were analyzed using SPSS (version 20.0; Chicago, Illinois, USA).

3. Results

Three patients denied consent and two had no adequate echocardiography. Thus, 34 of the 39 Federico II ALADIN patients entered this study (Fig. 1 of Ref. [23]).

3.1. Cross-sectional, matched-cohort phase

Demography, anthropometric and main clinical and laboratory parameters were similar in ADPKD patients and healthy and renal controls, with the exception of higher fasting serum glucose levels and urinary protein excretion in renal controls (Tables 1 and 2 of Ref. [23]). All participants had grade 1 functional capacity according to New York Heart Association (NYHA) classification. The distribution of patients with arterial hypertension was similar in ADPKD patients and renal controls, while 6 out of 34 renal controls (17.6%) had type 2 diabetes as compared to none in the ADPKD group (Table 1 of Ref. [23]). As per selection criteria, renal function was similarly impaired in ADPKD patients and renal controls, whereas kidney function was normal in healthy controls.

3.2. Echocardiographic findings

LV ejection fraction was normal in all groups. LVM index, relative wall thickness and left atrium volume were similar in ADPKD patients as compared with healthy controls. Conversely, all these parameters were higher in renal controls than in either APKD patients or healthy controls. The mitral E to Ea ratio was higher in ADPKD patients and renal controls than in healthy controls, while the other Doppler parameters were similar among all study groups (Table 1). At speckle-tracking analysis, ADPKD patients had lower global systolic longitudinal strain, peak systolic apical rotation and LV twist and slower early diastolic apical rotation rate and untwisting rate as compared to both healthy and renal controls. No significant difference was observed between renal and healthy controls in the above parameters, with exception of global longitudinal strain (Table 1).

3.3. Correlation analyses

In ADPKD patients, LV untwisting rate was significantly associated at univariate analysis only with LVM index and diastolic BP, and these associations did not change at multivariate analysis (Table 3 of Ref. [23]). We found a significant but opposite correlation between LVM index or diastolic BP and untwisting rate. Indeed, the correlation was positive in ADPKD patients ($r = 0.38$, $p = 0.025$ and $r = 0.44$; $p = 0.011$, respectively, Fig. 1, Left panels) and negative in renal controls ($r = -0.38$; $p = 0.023$ and $r = -0.40$, $p = 0.012$, respectively, Fig. 1, Right panels). As observed in renal controls, higher LVM index ($r = -0.31$, $p = 0.071$) or diastolic BP ($r = -0.32$, $p = 0.060$) tended to be associated with faster untwisting rate also in healthy controls, but the correlation failed to achieve the statistical significance.

3.4. Prospective, randomized phase

Main anthropometric, clinical and laboratory characteristics were very much the same between the 16 ADPKD patients randomized to octreotide-LAR therapy and the 18 randomized to placebo (Tables 1 and 2 of Ref. [23]). Consistent with the results of the ALADIN trial [13], blood glucose and BP were not appreciably affected by treatment. Table 2 summarizes baseline and final echocardiographic parameters according to treatment group. No appreciable change was observed in LVM index at final visit as compared to baseline in both treatment arms (Table 2). LV twist and untwisting rate significantly increased at the end of the octreotide-LAR treatment period as compared to baseline, but did not change appreciably with placebo (Fig. 2). The general linear model with correction for treatment showed a treatment effect only on LV untwisting rate that improved from $-49.9 \pm 18.6°/s$ to $-70.3 \pm 27.51°/s$ with octreotide-LAR, but did not change with placebo ($p = 0.014$) and on ejection fraction that significantly declined in the placebo group from $64.78 \pm 3.57\%$ to $61.78 \pm 2.12\%$ while did not change in the active treatment group ($p = 0.027$). At adjusted linear regression analysis, octreotide-LAR therapy emerged as the only independent predictor of untwisting rate improvement at final visit [beta coefficient −0.504 (95% CI −46.905–−6.367), $p = 0.014$] (Table 4 of Ref. [23]).

4. Discussion

In the cross-sectional, matched-cohort phase of the study we found that LV function was significantly impaired in ADPKD patients as compared to healthy and renal controls, whereas it did not differ appreciably between the two control groups. Although all study participants were in functional NYHA class 1 and had normal LV ejection fraction, ADPKD patients showed subclinical systolic dysfunction with reduced LV global longitudinal strain and twist in association with LV diastolic dysfunction. In the 3-year longitudinal, randomized phase, however, both LV systolic and diastolic function improved significantly in ADPKD patients on octreotide-LAR. Thus, at study end no statistically significant difference in LV function could be observed between octreotide-LAR-treated ADPKD patients and healthy controls. Conversely, the large difference observed between placebo-treated ADPKD patients and both control groups at baseline was still evident at study end. Moreover, placebo treatment was associated to a slight but significant decrease in LV ejection fraction. Baseline characteristics as well BP and blood glucose control and distribution of concomitant medications on follow-up were similar between ADPKD patients allocated to octreotide-LAR or placebo. An effect of changes in load conditions could be also ruled out as no changes in hematocrit values were observed between the baseline and the final evaluation in both treatment groups. Thus, the striking amelioration of LV function parameters in octreotide-LAR-treated patients most likely reflected a genuine, direct effect of treatment.

Altogether, these findings indicate that early LV dysfunction in ADPKD patients is mediated by disease-specific mechanisms that appear to be directly affected by somatostatin analogues. Whether the improvement in cardiac function was mediated by an inhibitory effect of octreotide-LAR on cAMP production in myocardial cells similar to the inhibitory effect observed in renal tubular cells [10] and cholangiocytes [11], is an intriguing hypothesis that merits further investigation.

4.1. Cross-sectional analyses

In renal controls, higher diastolic BP and LVM index both correlated with faster LV untwisting rate. A similar but not statistically significant effect was observed also in healthy controls. These findings were consistent with evidence that the increase in LV mass is associated with an increase in untwisting rate in hypertensive patients [26], sustained by a prevalent action of obliquely oriented epicardial fibers over mid wall circumferential fibers [27]. Conversely, higher diastolic BP or LVM index correlated with slower LV untwisting in ADPKD patients. Conceivably, data could not be explained by severity of hypertension or renal insufficiency since BP and kidney function were similar in ADPKD patients and renal controls. These findings provided additional, convincing evidence that in ADPKD LV diastolic dysfunction is mediated by disease-specific mechanisms different from, or additional to, hemodynamic changes associated with arterial hypertension. This hypothesis is consistent with evidence that altered intracellular calcium handling underlies LV diastolic

Table 1
Echocardiography parameters of healthy controls, renal controls and ADPKD patients.

	Healthy controls (n = 34)	Renal controls (n = 34)	ADPKD Patients (n = 34)	*p* value ADPKD patients vs. healthy controls	*p* value ADPKD patients vs. renal controls	*p* value renal vs. healthy controls
LVM index (g/m^2)	89.5 ± 7.1	111.2 ± 21.2	95.6 ± 16.4	0.354	<0.001	<0.001
Relative wall thickness	0.34 ± 0.02	0.41 ± 0.08	0.37 ± 0.05	0.073	0.004	<0.001
LV end-diastolic volume (ml)	92.0 ± 14.8	85.6 ± 19.7	95.5 ± 19.8	1.00	0.082	0.457
LV end-systolic volume (ml)	32.6 ± 6.4	32.0 ± 8.6	34.0 ± 7.6	1.00	0.796	1.00
LV ejection fraction (%)	63.1 ± 4.1	62.9 ± 4.2	64.3 ± 2.9	0.512	0.357	1.00
LA volume (ml/m^2)	25.8 ± 2.9	30.0 ± 4.3	27.8 ± 3.9	0.097	0.042	<0.001
E/A ratio	1.3 ± 0.3	1.1 ± 0.4	1.2 ± 0.3	0.897	0.789	0.576
E deceleration time (ms)	166 ± 19	146 ± 16	147 ± 35	0.725	1.00	0.345
Isovolumic relaxation time (ms)	76 ± 9	82 ± 8	83 ± 12	0.085	1.00	0.097
E/Ea ratio	6.6 ± 1.2	8.1 ± 2.4	8.2 ± 1.9	0.002	1.00	0.006
Global longitudinal strain (%)	−20.5 ± 2.1	−19.3 ± 2.1	−17.7 ± 1.8	<0.001	0.004	0.038
Peak systolic apical rotation (°)	6.2 ± 1.9	6.7 ± 4.4	2.3 ± 1.6	<0.001	<0.001	1.00
Peak systolic basal rotation (°)	−4.9 ± 2.8	−2.9 ± 4.5	−3.8 ± 2.4	0.477	0.760	0.035
LV twist (°)	11.1 ± 2.1	10.2 ± 3.7	6.1 ± 2.6	<0.001	<0.001	0.542
Early diastolic apical rotation rate (°/s)	−31.8 ± 8.2	−46.2 ± 22.1	−17.9 ± 10.8	0.001	<0.001	<0.001
Early diastolic basal rotation rate (°/s)	41.7 ± 10.9	38.9 ± 25.1	29.8 ± 21.3	0.048	0.191	1.00
LV untwisting rate (°/s)	−79.8 ± 12.2	−84.3 ± 25.9	−49.5 ± 18.1	<0.001	<0.001	1.00

Values are means ± SD.
ADPKD = autosomal dominant polycystic kidney disease; LVM = left ventricular mass; LV = left ventricular; LA = left atrium; E/A ratio = the ratio of the early (E) to late (A) mitral flow velocities; E/Ea ratio = the ratio of mitral E to mitral annulus early diastolic peak velocity (Ea).

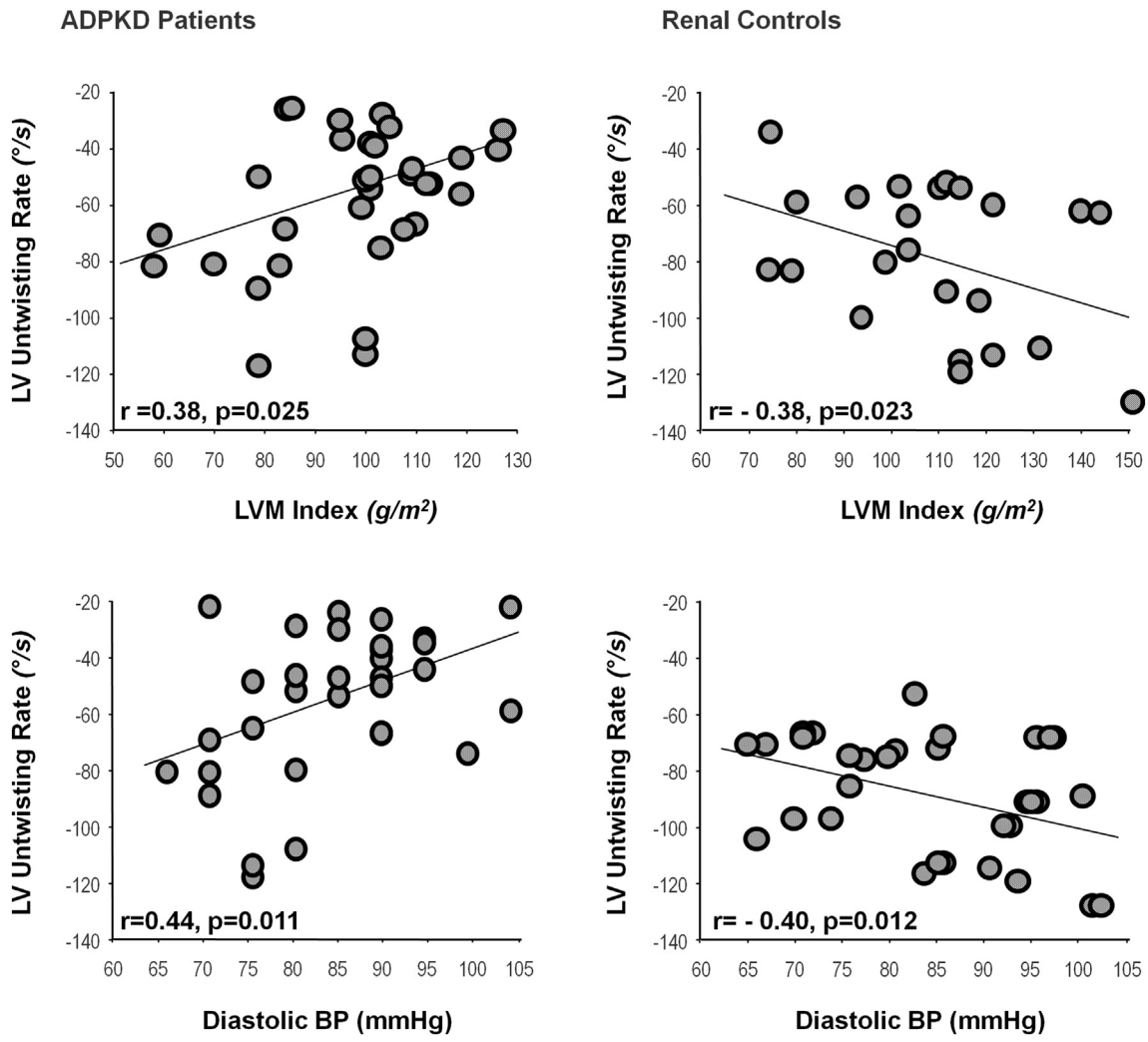

Fig. 1. Relationships between LV untwisting rate and LVM index (upper panels) and diastolic BP (lower panels), as assessed by Pearson's correlation coefficients in ADPKD patients (left panels), and renal controls (right panels). The coefficients of both correlations measured in ADPKD patients and renal controls had an opposite sign.

Table 2
Echocardiography parameters of ADPKD patients (categorized according to treatment with octreotide-LAR or Placebo).

	ADPKD patients				Treatment effect
	Octreotide-LAR (n = 16)		Placebo (n = 18)		
	Baseline	Final visit	Baseline	Final visit	
LVM index (g/m^2)	91.4 ± 17.4	95.4 ± 16.1	99.5 ± 14.9	100.3 ± 12.9	0.154
Relative wall thickness	0.36 ± 0.05	0.37 ± 0.04	0.37 ± 0.05	0.36 ± 0.03	0.198
LV end-diastolic volume (ml)	101.7 ± 22.5	92.2 ± 25.4	90.0 ± 15.8	95.3 ± 21.3	0.160
LV end-systolic volume (ml)	36.7 ± 8.4	33.6 ± 10.6	31.6 ± 6.0	36.3 ± 7.8	0.059
LV ejection fraction (%)	63.8 ± 2.0	63.8 ± 2.8	64.8 ± 3.6	61.8 ± 2.1	0.027
LA volume (ml/m^2)	26.7 ± 2.7	24.4 ± 2.8	28.7 ± 4.6	27.2 ± 2.5	0.537
E/A ratio	1.27 ± 0.28	1.25 ± 0.26	1.25 ± 0.26	1.12 ± 0.30	0.370
E deceleration time (ms)	150.4 ± 38.4	181.6 ± 29.2	148.2 ± 42.3	175.8 ± 33.4	0.845
Isovolumic relaxation time (ms)	82.5 ± 12.4	92.6 ± 9.7	87.9 ± 10.8	93.8 ± 10.6	0.481
E/Ea ratio	8.1 ± 2.5	8.2 ± 2.4	8.4 ± 1.3	9.6 ± 1.4	0.072
Global systolic longitudinal strain (%)	−17.8 ± 1.5	−18.5 ± 2.1	−17.6 ± 2.2	−18.0 ± 3.4	0.688
Peak systolic apical rotation (°)	2.6 ± 1.9	2.9 ± 1.8	2.1 ± 1.3	2.2 ± 1.5	0.678
Peak systolic basal rotation (°)	−3.7 ± 2.0	−5.9 ± 3.7	−3.9 ± 2.7	−4.6 ± 2.6	0.180
LV twist (°)	6.3 ± 2.2	8.7 ± 3.7	5.9 ± 3.0	6.8 ± 2.5	0.262
Early diastolic apical rotation rate (°/s)	−19.6 ± 10.3	−27.7 ± 22.2	−16.4 ± 11.2	−15.4 ± 10.5	0.184
Early diastolic basal rotation rate (°/s)	27.9 ± 20.7	42.6 ± 27.7	31.6 ± 22.3	32.2 ± 17.0	0.105
LV untwisting rate (°/s)	−49.9 ± 18.6	−70.3 ± 27.5	−49.2 ± 18.2	−47.6 ± 21.7	0.014

Values are means ± SD.
ADPKD = autosomal dominant polycystic kidney disease; LAR = long-acting-release; LVM = left ventricular mass; LV = left ventricular; LA = left atrium; E/A ratio = the ratio of the early (E) to late (A) mitral flow velocities; E/Ea ratio = the ratio of mitral E to mitral annulus early diastolic peak velocity (Ea).
Treatment effect: active treatment vs. placebo, general linear model analysis.

dysfunction [28]. Similarly, the subclinical changes in LV systolic function, most likely explained by a dysfunction of longitudinal subendocardial fibers, appear to reflect a myocardial cell dysfunction directly related to the disease rather than to confounding factors such as hypertension or renal insufficiency. Since either PC-1 or PC-2 are expressed on the surface of cardiomyocytes [5–8] probably to form a complex involved in the modulation of calcium ion inflow [1], it is conceivable that genetically determined changes in one of these two proteins might result, as observed in tubular cells and cholangiocytes [11], in impaired calcium inflow, with secondary activation of cAMP production, and myocardiocyte dysfunction. The hypothesis that impaired calcium handling might, at least in part, explain the early systolic and diastolic dysfunction we observed in our patients is supported by studies in animal models. PC-1 regulates L-type Ca2+ channel activity and plays a key role in the cardiomyocyte response to mechanical stress [7]. PC-2-deficient zebrafishes develop a systolic and diastolic dysfunction that is associated with a significant prolongation of both rise and decay time of calcium transients [8]. Cardiomyocytes from PC-2 deficient mice have altered calcium signaling, desensitized calcium-contraction coupling and altered response to adrenergic stimulus [29]. In addition to defective calcium cycling/influx in cardiomyocytes, increased cardiac apoptosis may also be a relevant determinant of the PC-1-deficient heart dysfunction [30]. Moreover, PC-2 may be involved in cardiomyocyte autophagic control [31]. Findings from clinical studies demonstrate that LV hypertrophy and diastolic dysfunction may ensue earlier and more frequently in hypertensive patients with ADPKD than in those without the disease and are also observed in normotensive patients with ADPKD [32,33]. Bi-ventricular diastolic dysfunction has been found even in young ADPKD patients with still normal BP [33].

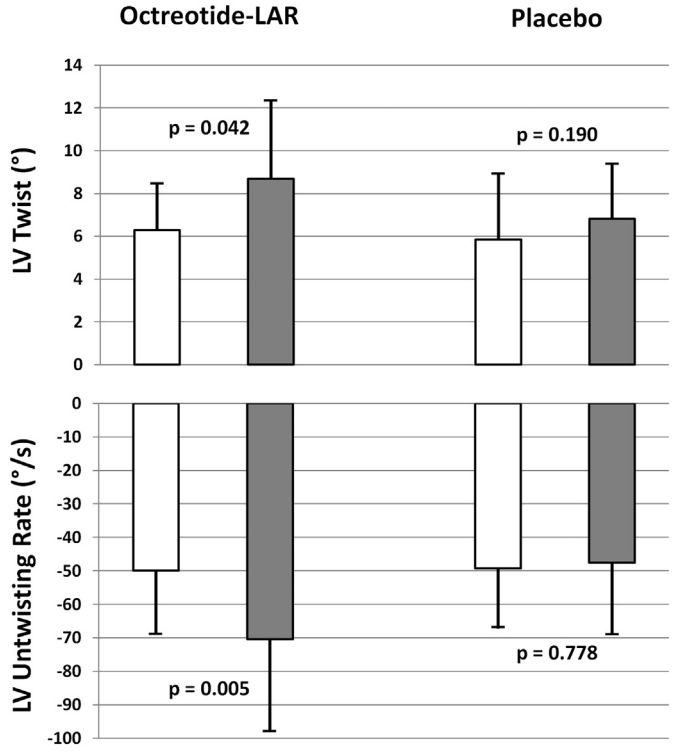

Fig. 2. Left ventricular twist (upper panel) and untwisting rate (lower panel) in ADPKD patients at baseline (white bars) and after 3-year treatment (gray bars) with octreotide-LAR or placebo. Both parameters significantly improved with octreotide-LAR as compared to baseline, but did not change appreciably with placebo.

4.2. Longitudinal analyses

The working hypothesis that early LV dysfunction in patients with ADPKD is mediated, at least in part, by disease-specific mechanisms that can be prevented or limited by binding of octreotide-LAR to somatostatin receptors expressed in the myocardium was corroborated by finding that active treatment ameliorated both systolic and diastolic LV function, independent of BP control. Somatostatin receptor subtypes sstr 1, sstr 2, sstr 4 and sstr 5 are uniformly expressed in human atrial and ventricular tissue [15]. Sstr1 and sstr 2 are expressed on the cellular surface of both cardiac myocytes and fibroblasts, whereas sstr 4 and sstr 5 are found only in cardiac fibroblasts. In cultured human cardiac fibroblasts, somatostatin induces a rapid and significant mobilization of intracellular calcium [15]. In rat fetal cardiomyocytes sstr 2 activation negatively regulates Ca^{++}-associated signaling pathways which are triggered by β 1 and β 2 adrenergic receptors [34]. Thereby, somatostatin elicits a positive inotropic effect in ventricular muscle, at least partly, due to an increase in the slow inward Ca^{++} current [35].Thus, it is conceivable that the effects of octreotide-LAR

on LV dysfunction we observed in our ADPKD patients could be at least in part explained by inhibition of calcium-mediated mechanisms, upon binding of the drug to one or more of the four different somatostatin receptor subtypes expressed in the human heart. Interestingly, the persistence of reduced longitudinal and rotational function in ADPKD patients treated with placebo was associated to decline in LV ejection fraction, indicating the progressive nature of cardiac involvement. Hence, cardiovascular manifestations of disease are the major contributor to mortality in ADPKD [36].

4.3. Limitations and strengths

This was a post-hoc, observational study in a subgroup of patients included in a clinical trial designed for other purposes [13]. The relatively small sample size reflects the rarity of the disease and the monocentric nature of the study that, because of resource constraints characteristic of academic, internally funded studies, could not be extended to all the centers involved in the original ALADIN trial [13]. However, evidence that baseline characteristics of patients included in the present study were similar to those of patients included in the ALADIN trial, reasonably excludes that major selection bias were introduced because of the monocentric design. The matching of renal and healthy controls with ADPKD patients, allowed achieving three well comparable groups, which limited the role of potential confounders of cross-sectional comparative analyses. The per-center balanced randomization allowed achieving a well-balanced distribution of patients with similar characteristics in the two treatment arms. Moreover, LV morpho-functional parameters were evaluated by precise and validated echocardiographic procedures [19–21]. Always, it has to be acknowledged that magnetic resonance imaging would represent a more accurate and reproducible technique for detecting changes in LV mass [37]. Finally, the study included patients with normal or marginally reduced GFR who account for the large majority of ADPKD patients worldwide. Altogether, the aforementioned considerations confirm the robustness and wide generalizability of our study findings.

5. Conclusions

LV function is impaired in ADPKD patients with normal or moderately reduced kidney function and is ameliorated by octreotide-LAR. Thus, somatostatin analogues in addition to prevent hepatorenal cystogenesis [12–14], and limit long-term GFR decline [13], can also help improving or preventing LV dysfunction in this population. Because, also on the basis of familial history, ADPKD patients can be easily identified even before the onset of symptoms related to renal and/or liver cyst growth, treatment could be started early enough to prevent irreversible myocardial dysfunction, an effect that could be cardioprotective in the long-run. Two-dimensional speckle-tracking echocardiography is a reliable and easily available tool to monitor cardiac function in ADPKD patients and their response to therapy.

Sources of funding

Novartis Italia (Origgio, Varese, Italy) freely supplied octreotide-LAR, but did not fund the study. The cross sectional and longitudinal studies including the echocardiography studies were internally funded.

Conflict of interest statement

The authors report no relationships that could be construed as a conflict of interest.

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