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New Possibilities in Heart Failure: The Effects of Tadalafil on Diastolic Function in Patients Undergoing Robot-Assisted Radical Prostatectomy

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Abstract: Inhibitors of phosphodiesterase type 5 (PDE5i) are the first-line treatment for erectile dysfunction and are also used to treat pulmonary hypertension. PDE5i impedes the breakdown of nitric oxide (NO)-driven cyclic guanosine monophosphate (cGMP) in smooth muscle cells of the vascular bed, acting as a potent vasodilator. In heart failure, cGMP signaling is altered. The modulation of cGMP has therefore emerged as a potential therapeutic option for heart failure. In this prospective observational study, we aim to investigate whether tadalafil, a long-acting PDE5i used for erectile dysfunction, could also improve diastolic function assessed by cardiac ultrasound. A total of 23 patients were enrolled, undergoing nerve-sparing robot-assisted radical prostatectomy for prostate cancer and treated with 20 mg tadalafil on alternate days to recover erectile function. All patients underwent tadalafil treatment for at least 6 months. Participants underwent a clinical and cardiac ultrasound with color Doppler assessment at baseline, after 3 months, and after 6 months. At 6 months, no significant difference was found apart from lower E/e' ratio (7.4 $\pm$ 2.7 vs. 6.3 $\pm$ 1.3; $p < 0.03$), peak velocity of TR jet (2.4 $\pm$ 0.2 vs. 2.1 $\pm$ 0.2; $p < 0.001$), and PAPs (27.3 $\pm$ 3.6 vs. 22.9 $\pm$ 5.7; $p < 0.005$). Our prospective study shows that 6 months of erectile dysfunction therapy for secondary to radical prostatectomy is associated with a favorable effect on diastolic function, improving the E/e' ratio and peak velocity of the TR jet.

Keywords: diastolic disfunction; echocardiography; erectile dysfunction; nitric oxide signaling

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1. Introduction

Inhibitors of phosphodiesterase type 5 (PDE5is) are a class of drugs that suppresses the degradation of cyclic guanosine monophosphate (cGMP) and were initially studied for the treatment of angina pectoris [1] before being considered and employed as first-line therapy for erectile dysfunction and pulmonary hypertension. The most commonly used PDE5is are sildenafil, vardenafil, tadalafil, and avanafil [2]. The enhancement of cGMP, derived from nitric oxide, leads to the distension of vascular smooth muscle and vasodilatation, which justifies the therapeutic efficacy in erectile dysfunction and pulmonary hypertension [3]. In addition to the therapeutic role of PDE5is in erectile dysfunction and pulmonary hypertension, preclinical studies showed that PDE5i could likely play a role in mediating cardioprotection through complex mechanisms, suggesting a possible clinical role of PDE5i for the treatment of cardiovascular diseases [4–8]. Patients affected by

prostate cancer very frequently need cardiovascular assessment based on the increased risk of cardiovascular side effects during hormonal treatment [9]. Cross links between urologic treatment and cardiovascular disease are well recognized. It is indeed well established that cGMP signaling is abnormal in heart failure [10]; therefore, the modulation of cGMP has emerged as a potential therapeutic strategy for heart failure. However, no clear evidence supports PDE5i therapy for heart failure due to the controversial results obtained by trials investigating the role of a cGMP-augmenting therapy with PDE5i in the treatment of heart failure [8,10]. Due to these premises, further research is urgently needed to clarify the role of cGMP-augmenting therapies across the entire spectrum of heart failure, possibly even in the preclinical phase.

In the current prospective study, we aimed to investigate whether tadalafil, a long-acting PDE5i, improves the diastolic function. This was assessed using cardiac ultrasound in patients with no cardiovascular diseases, taking PDE5i for the prevention of erectile dysfunction after nerve-sparing robot-assisted radical prostatectomy (RARP) for prostate cancer.

2. Materials and Methods

2.1. Study Population

We conducted a prospective observational study involving patients who underwent nerve-sparing robot-assisted radical prostatectomy for prostate cancer at Federico II University Hospital, Naples, Italy (Research Ethics Board of "Federico II" University of Naples, n.316/20), from November 2018 to December 2019. Patients in treatment with tadalafil for erectile function recovery, i.e., penile rehabilitation, for at least 6 months after prostatectomy were included in the study [11]. Exclusion criteria were considered: diabetes mellitus, left ventricular (LV) ejection fraction <53%, more than mild valvular disease, atrial fibrillation, history of dyspnea, and inadequate echocardiographic imaging. All the patients underwent thorough cardiac clinical assessment before starting tadalafil therapy and were assessed again at 3- and 6-month follow-up visits. These visits included medical history, clinical examination, heart rate measurement, blood pressure, body mass index, and color Doppler cardiac ultrasound, performed at the Interdepartmental Laboratory of Echocardiography at the same University. All patients were treated with tadalafil 20 mg every other day for at least 6 months. All patients provided written informed consent.

2.2. Transthoracic Echocardiography

An experienced echocardiologist (L.F.) performed all image acquisitions using a GE Vivid E95 ultrasound machine (GE Healthcare, Horten, Norway) provided by a 3.5 MHz transducer. LV quantitative analysis was conducted in accordance with guidelines [12]. LV mass and relative wall thickness were calculated using a two-dimensional parasternal long-axis view. LV mass was indexed to the patient's height elevated to 2.7, while the left atrial (LA) volume was indexed to the body surface area. LV ejection fraction (LVEF) was determined using the biplane method computing the LV end-diastolic and end-systolic volumes in apical four- and two-chamber views. LV diastolic function was measured according to current recommendations [13]. Global Longitudinal Strain (GLS) was assessed offline using a workstation (EchoPAC only software version 113, GE Healthcare, Horten, Norway), with images taken in the apical views (three-chamber, four-chamber, and two-chamber). An automated 2D strain software with manual adjustment capability was used to trace endocardial and epicardial borders. Peak longitudinal strain was measured for the basal, mid, and apical segments for each wall, obtaining a 16-segment bullseye. GLS was obtained as a mean of all peak strain before the aortic valve closure. The reproducibility of GLS was previously published [14,15]. The day-to-day variability in the measurements of parameters investigating LV diastolic function was previously assessed in our laboratory by calculating intraclass correlation coefficients [16]. Our results indicated excellent reliability of the estimates of LV diastolic function.

RV Systolic Function

Tricuspid annular plane systolic excursion (TAPSE) was measured to assess RV systolic function. Pulmonary arterial systolic pressure (PASP) was estimated in accordance with current guidelines; tricuspid regurgitation peak velocity was added to an estimate of right atrial pressure (RAP). RAP was estimated from the measurement of the size and the respiratory reactivity of the inferior vena cava (IVC): (a) RAP = 5 mmHg when IVC diameter is <2.1 cm and has normal inspiratory collapse; (b) RAP = 10 mmHg when IVC diameter is >2.1 cm or when it collapses <50%; (c) RAP = 15 mmHg when IVC is both dilated and collapses <50%; (d) RAP = 20 mmHg when IVC is dilated and has no visible collapse [17].

2.3. Statistical Analysis

Continuous variables are expressed as mean ± standard deviation. Statistical differences between continuous variables were tested using the unpaired Student's *t*-test or the equivalent nonparametric procedure (Mann–Whitney U test) for variables not normally distributed. A comparison of echocardiographic variables before and after the use of tadalafil was performed using the paired *t*-test. A *p*-value of <0.05 was considered statistically significant. The day-to-day variability in chosen variables was assessed by calculating intraclass correlation coefficients (ICCs) and their 95% CIs. Statistical analysis was performed using SPSS package, release 12 (SPSS Inc., Chicago, IL, USA).

3. Results

Of a total of 49 subjects, we excluded 19 because of: LVEF < 53% (*n* = 4), more than mild valvular disease (*n* = 4), atrial fibrillation (*n* = 2), inadequate echocardiographic imaging (*n* = 3), and drop-out at follow-up (*n* = 10). The remaining 30 patients were included in this analysis (Figure 1).

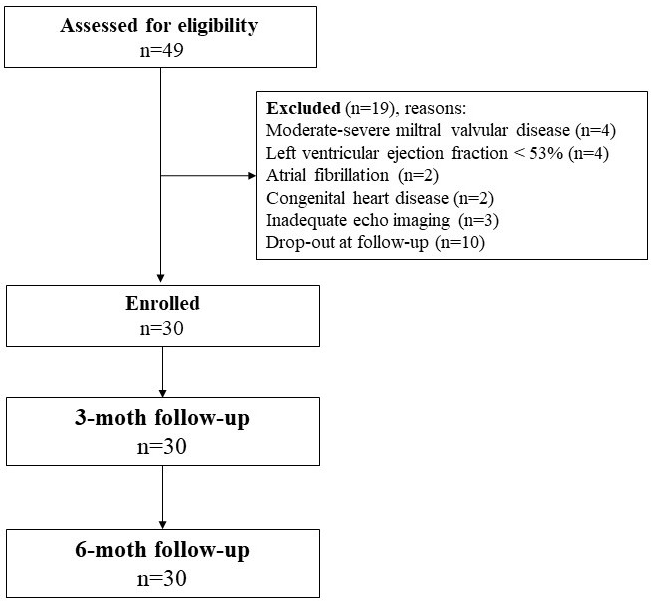

Figure 1. Patient flow and study design.

The mean age was 64 + 7.6 years. At baseline, 11 patients had arterial hypertension, 7 were dyslipidemic, 8 were smokers, none were diagnosed with chronic obstructive pulmonary disease (COPD) and diabetes mellitus, and only 1 patient presented with peripheral arterial disease. Patient characteristics at enrollment and after 6 months of treatment with tadalafil are reported in Table 1.

Table 1. Characteristics of the patients at baseline and after 6 months of treatment with tadalafil.

	Baseline	At 6 Months	*p*-Value
SBP (mm Hg)	127 ± 13	129 ± 16	0.71
DBP (mm Hg)	73.6 ± 7.9	75.7 ± 8.7	0.33
HR (bpm)	72.0 ± 10.7	69.2 ± 10.5	0.45
BW (kilograms)	78.6 ± 8.5	77.3 ± 9.7	0.49

BW = body weight; DBP = diastolic blood pressure; SBP = systolic blood pressure; HR = heart rate.

Echocardiographic data were collected at 3 and 6 months for all patients. After 3 months of treatment with tadalafil, no difference was found between echocardiographic parameters, as reported in Table 2.

Table 2. Echocardiographic findings at 3 months of treatment with tadalafil.

	Baseline	At 3 Months	*p*-Value
LVM/ht$^{2.7}$ (g/m$^{2.7}$)	35.0 ± 7.0	36.1 ± 10.1	0.54
RWT	0.37 ± 0.6	0.35 ± 0.5	0.53
E/e' ratio	7.4 ± 2.7	6.9 ± 1.4	0.2
TAPSE (mm)	23.9 ± 3.5	23.2 ± 4.0	0.56
TR vel (m/s)	2.4 ± 0.2	2.3 ± 0.2	0.8
LAVi (mL/m^2)	28.4 ± 6.8	37.8 ± 5.2	0.3
EF (%)	60.4 ±4.9	60.7 ± 3.3	0.9
GLS (%)	21.0 ± 1.6	20.8 ± 1.6	0.7
PAPs (mmHg)	27.3 ± 3.6	26.0 ± 6.0	0.36

LVM/ht$^{2.7}$ = LV mass was indexed to patients' height elevated to 2.7; RWT = relative wall thickness; TAPSE = tricuspid annulus pulsed systolic excursion; TR vel = tricuspid jet velocity; LAVi = left atrial volume index; FE = ejection fraction, GLS = global longitudinal strain; PAPs = pulmonary arterial peak systolic pressure.

At 6 months, there was no significant variation in standard echocardiographic parameters, but E/e' ratio, peak velocity of TR jet, and PAPs were significantly lower, as reported in Table 3 (Figure 2).

Table 3. Echocardiographic findings at 6 months of treatment with tadalafil.

	Baseline	At 6 Months	*p*-Value
LVM/height$^{2.7}$(g/m$^{2.7}$)	35.0 ± 7.0	37.4 ± 11	0.27
RWT	0.37 ± 0.6	0.36 ± 0.6	0.62
E/e'ratio	7.4 ± 2.7	6.3 ± 1.3	*0.03*
TAPSE (mm)	23.9 ± 3.5	23.0 ± 3.0	0.34
TR vel (m/s)	2.4 ± 0.2	2.1 ± 0.2	*0.001*
LAVi (mL/m^2)	28.4 ± 6.8	27.3 ± 5.6	0.51
EF (%)	60.4 ±4.9	61.0 ± 3.3	0.60
GLS (%)	21.0 ± 1.6	20.8 ± 1.5	0.44
PAPs (mmHg)	27.3 ± 3.6	22.9 ± 5.7	*0.005*

See Table 2 for the legend.

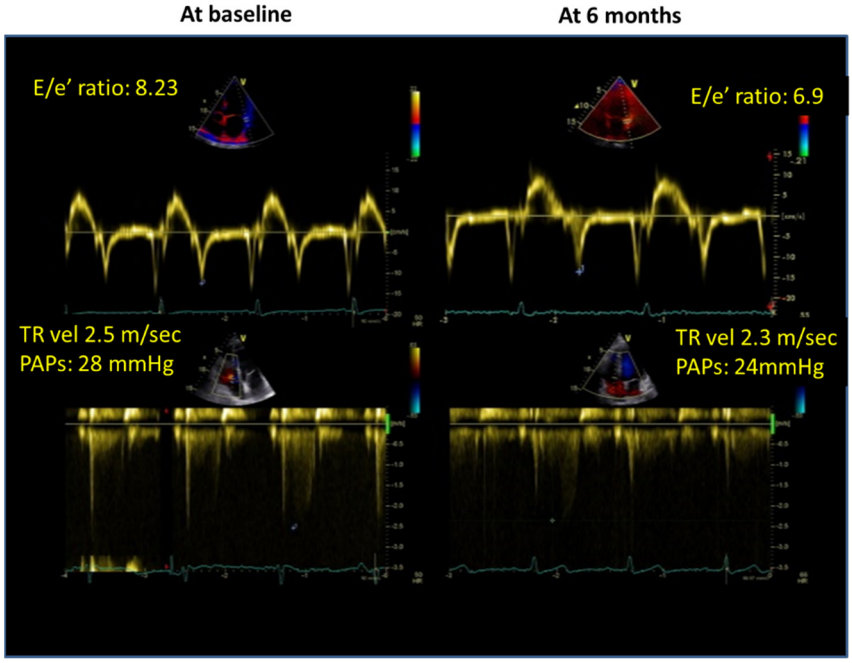

Figure 2. Clinical case of patient undergoing 6 months of tadalafil treatment. Patient's diastolic function at baseline (**left**) panel and after 6 months of treatment (**right**) panel; from top to bottom: pulsed Doppler velocity on mitral valve, tissue Doppler velocity of the lateral mitral annulus, peak systolic tricuspid jet velocity.

4. Discussion

Our prospective study shows that PDE5 inhibition with tadalafil for 6 months, in patients who underwent penile rehabilitation for erectile function secondary to radical prostatectomy, is associated with favorable effects on left ventricular diastolic function, improving the E/e' ratio and the tricuspid jet (TR). Although over 20 parameters have been suggested to noninvasively assess left ventricular diastolic function, not all these parameters are currently utilized in routine clinical practice [13]. In 2016, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) proposed a simple algorithm for the noninvasive evaluation of left ventricular diastolic function based on the evaluation of the E/e' ratio and peak TR velocity [13]. The ESC 2021 guidelines on heart failure confirmed that both the E/e' ratio and peak TR velocity should be used as echocardiographic markers of left ventricular diastolic dysfunction/raised left ventricular filling pressures [18]. It remains to be proven that the improvement in E/e' ratio and peak TR velocity observed in our patients after tadalafil therapy may have clinical importance. Indeed, the patients enrolled in our study showed no signs of left ventricular diastolic dysfunction. However, the finding that a drug can improve left ventricular diastolic function may be of interest, although additional investigations dedicated to this issue are needed. Pre-emptive intervention with drugs capable of improving left ventricular diastolic function could prevent the onset of left ventricular diastolic dysfunction in subjects at greater risk or attenuate its progression to heart failure. Data on the beneficial effect of drugs acting on the guanylate cyclase stimulator on patients with chronic HF with reduced ejection fraction have recently been published. Increased levels of cyclic GMP caused by inducing nitric oxide soluble guanylate cyclase (cGM) pathway appear to have a positive impact on hospitalization for heart failure and mortality [19]. Even if no data on nitric oxide pathways induction in patients with HF with preserved systolic function have been provided, a beneficial analogous effect could be supposed for both cGM and PDE drugs that act by increasing nitric oxide levels with a beneficial impact on cardiovascular function. It is known that asymptomatic left ventricular diastolic dysfunction can evolve into overt heart failure. In a randomly selected cohort of

2042 subjects ≥45 years old that were followed for 4 years, Kane et al. demonstrated that diastolic dysfunction was an independent risk factor for heart failure in the elderly, even in apparently healthy subjects [20]. A subsequent meta-analysis of 13 reports based on 11 distinct studies assessing a total of 25,369 participants followed for 7.9 years on average, including asymptomatic subjects with diastolic dysfunction, revealed a 70% increased risk of progressing to heart failure in subjects with asymptomatic diastolic dysfunction in comparison with subjects without asymptomatic diastolic dysfunction [21]. To date, no treatment has been shown to convincingly reduce mortality and morbidity in a population of patients with heart failure with preserved ejection fraction [21]. Therefore, the development of new therapies remains a challenging and unresolved task. The observed improvements in diastolic function indices after 6 months of tadalafil therapy could be tested in a prospective and randomized trial to assess whether tadalafil provides clinical benefit in patients with heart failure and preserved ejection fraction. Previous studies have investigated the effects of PDE5i on cardiac function, reporting controversial results. In 44 patients with stable systolic heart failure randomly assigned to placebo or sildenafil, Guazzi et al. demonstrated that PDE5 inhibition with sildenafil significantly improves left ventricular diastolic function properties [22]. In contrast, in the subsequent Relax trial by Redfield et al., including 216 patients with heart failure with preserved ejection fraction, sildenafil showed no beneficial effects on exercise capacity and left ventricular diastolic function [23]. Similarly, Andersen et al. reported that sildenafil treatment for 9 weeks did not show any significant improvements in the predetermined primary endpoints (LV filling pressure at rest or during exercise) in 70 patients with diastolic dysfunction and preserved ejection fraction after acute myocardial infarction. In addition, Andersen and coworkers did not detect any significant improvement in diastolic function, as assessed by Doppler echocardiography, following the treatment with sildenafil [24]. Differently, in a 12-week, randomized, double-blind, placebo-controlled trial, Kim et al. reported that PDE 5 inhibition with udenafil ameliorates systolic and diastolic function of the left ventricle along with exercise capacity in patients with chronic heart failure with reduced ejection fraction [25]. A subsequent meta-analysis performed by De Vecchis et al. found that PDE5 inhibitors improved clinical outcomes, exercise capacity, and pulmonary hemodynamics in the RCTs of patients (n = 555) with heart failure and reduced left ventricular ejection fraction [26]. In contrast, in the RCTs of patients with heart failure with preserved left ventricular ejection fraction (n = 373), no benefit was shown from PDE5i use regarding all of the investigated endpoints. Again, in a randomized placebo-controlled study, Liu et al. found that treatment with sildenafil for 12 weeks in 52 patients with heart failure with preserved ejection fraction and predominantly isolated post-capillary pulmonary hypertension did not affect the cardiac structure, cardiac function, exercise response, or quality of life [27]. More recently, Belyavskiy et al. investigated 50 patients with heart failure with preserved ejection fraction and combined pre- and post-capillary pulmonary hypertension [28]. In the 30 patients treated with sildenafil for 6 months, the authors observed improvements in exercise capacity, pulmonary hemodynamic parameters, and right ventricular function. No changes occurred in the control group [29].

One explanation for the seemingly contradictory findings in the above studies may be due to the differences in the assessment methods of the effects of the drugs. It is also possible that a lack of homogeneity in the characteristics of the study populations in terms of etiology, comorbidities, and therapies associated with PDE5 inhibitors may have contributed. The efficacy of PDE5 inhibitors might differ according to the pathological process under study. A single class of drugs cannot prove effective in all clinical scenarios. PDE5 inhibitors demonstrated clinical benefit in patients with heart failure with reduced ejection fraction. In the preserved ejection fraction setting, PDE5 inhibitors may only benefit select patients with reversible pulmonary hypertension and right ventricular systolic dysfunction. Additionally, further differences in cardiovascular response to treatment could be found in the different genetic backgrounds. Indeed, Manca P. et al. demonstrated that the impact of heart failure treatment on the right heart chamber could be influenced by different genetic backgrounds,

determining heterogenic results [30]. Given the small numbers of patients enrolled in the various studies, we cannot exclude a play of chance. The PASSION trial evaluating the impact of tadalafil on clinical endpoints in patients with combined pre- and post-capillary pulmonary hypertension due to heart failure with preserved ejection fraction is ongoing, under the direction of Dr. M. Hoeper, Hanover, and Dr. S. Rosenkranz, Cologne, and will provide relevant information with potential implications for the clinical use of PDE5 inhibition in patients with heart failure and preserved ejection fraction [31].

Several study limitations should be acknowledged. Because of the small sample size, this study should be interpreted as a preliminary investigation; the precision for estimation of the magnitude of effects of tadalafil is far too low. Given the observational nature of the study, no sample size estimation was calculated. The probands were in control of themselves after 6 months of treatment; thus, a randomized control design of the study was not conceivable. Therefore, the possible evidence of causality between tadalafil therapy and improvement in diastolic function should be considered. The enrolled population was limited to prostate cancer patients undergoing robot-assisted radical prostatectomy at our tertiary urologic center; thus, no information about the impact of more invasive, conventional surgical treatment was explored. Possible additional beneficial effects on the cardiovascular system could be assumed secondary to a less invasive treatment.

5. Conclusions

In conclusion, the efficacy of tadalafil in improving some echocardiographic parameters of left ventricular diastolic function observed in our study must be interpreted as hypothesis-generating. We recommend that the role of tadalafil in the prevention and treatment of diastolic dysfunction should be considered for future studies.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ghofrani, H.A.; Osterloh, I.H.; Grimminger, F. Sildenafil: From angina to erectile dysfunction to pulmonary hypertension and beyond. *Nat. Rev. Drug Discov.* **2006**, *5*, 689–702. [CrossRef] [PubMed]
2. Huang, S.A.; Lie, J.D. Phosphodiesterase-5 (PDE5) Inhibitors in the Management of Erectile Dysfunction. *J. Formul. Manag.* **2013**, *38*, 407–419.
3. Burnett, A.L. The Role of Nitric Oxide in Erectile Dysfunction: Implications for Medical Therapy. *J. Clin. Hypertens.* **2006**, *8*, 53–62. [CrossRef] [PubMed]
4. Salloum, F.N.; Takenoshita, Y.; Ockaili, R.A.; Daoud, V.P.; Chou, E.; Yoshida, K.; Kukreja, R.C. Sildenafil and vardenafil but not nitroglycerin limit myocardial infarction through opening of mitochondrial K(ATP) channels when administered at reperfusion following ischemia in rabbits. *J. Mol. Cell Cardiol.* **2007**, *42*, 453–458. [CrossRef] [PubMed]
5. Lee, K.H.; Kwon, S.J.; Woo, J.S.; Lee, G.J.; Lee, S.R.; Jang, H.H.; Kim, H.S.; Kim, J.W.; Park, H.K.; Cho, K.S.; et al. Effects of sildenafil on nanostructural and nanomechanical changes in mitochondria in an ischaemia-reperfusion rat model. *Clin. Exp. Pharmacol. Physiol.* **2014**, *41*, 763–768. [CrossRef]
6. Mátyás, C.; Németh, B.T.; Oláh, A.; Török, M.; Ruppert, M.; Kellermayer, D.; Barta, B.A.; Szabó, G.; Kökény, G.; Horváth, E.M.; et al. Prevention of the development of heart failure with preserved ejection fraction by the phosphodiesterase-5A inhibitor vardenafil in rats with type 2 diabetes. *Eur. J. Heart Fail.* **2017**, *19*, 326–336. [CrossRef]

7. Frankenreiter, S.; Bednarczyk, P.; Kniess, A.; Bork, N.I.; Straubinger, J.; Koprowski, P.; Wrzosek, A.; Mohr, E.; Logan, A.; Murphy, M.P.; et al. cGMP-Elevating Compounds and Ischemic Conditioning Provide Cardioprotection Against Ischemia and Reperfusion Injury via Cardiomyocyte-Specific BK Channels. *Circulation* **2017**, *136*, 2337–2355. [CrossRef]
8. Imai, Y.; Kariya, T.; Iwakiri, M.; Yamada, Y.; Takimoto, E. Sildenafil ameliorates right ventricular early molecular derangement during left ventricular pressure overload. *PLoS ONE* **2018**, *13*, e0195528. [CrossRef]
9. Noale, M.; The Pros-IT CNR study group; Maggi, S.; Artibani, W.; Bassi, P.F.; Bertoni, F.; Bracarda, S.; Conti, G.N.; Corvò, R.; Gacci, M.; et al. Pros-IT CNR: An Italian prostate cancer monitoring project. *Aging Clin. Exp. Res.* **2017**, *29*, 165–172. [CrossRef]
10. Kong, Q.; Blanton, R.M. Protein kinase G I and heart failure: Shifting focus from vascular unloading to direct myocardial antiremodeling effects. *Circ. Heart Fail.* **2013**, *6*, 1268–1283. [CrossRef]
11. Aydogdu, O.; Gokce, M.I.; Burgu, B.; Baltaci, S.; Yaman, O. Tadalafil rehabilitation therapy preserves penile size after bilateral nerve sparing radical retropubic prostatectomy. *Int. Braz J. Urol.* **2011**, *37*, 336–346. [CrossRef] [PubMed]
12. Lang, R.M.; Badano, L.P.; Mor-Avi, V.; Afilalo, J.; Armstrong, A.; Ernande, L.; Lachskampf, F.A.; Foster, E.; Goldstein, S.A.; Kuznestova, T.; et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J. Am. Soc. Echocardiogr.* **2015**, *28*, 1–39. [CrossRef] [PubMed]
13. Nagueh, S.F.; Smiseth, O.A.; Appleton, C.P.; Byrd, B.F., 3rd; Dokainish, H.; Edvardsen, T.; Flachskampf, F.A.; Gillebert, T.C.; Klein, A.L.; Lancellotti, P.; et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J. Am. Soc. Echocardiogr.* **2016**, *29*, 277–314. [CrossRef] [PubMed]
14. Santoro, C.; Esposito, R.; Lembo, M.; Sorrentino, R.; De Santo, I.; Luciano, F.; Casciano, O.; Giuliano, M.; De Placido, S.; Trimarco, B.; et al. Strain-oriented strategy for guiding cardioprotection initiation of breast cancer patients experiencing cardiac dysfunction. *Eur. Heart J. Cardiovasc. Imaging* **2019**, *20*, 1345–1352. [CrossRef]
15. Alcidi, G.M.; Esposito, R.; Evola, V.; Santoro, C.; Lembo, M.; Sorrentino, R.; Lo Iudice, F.; Borgia, F.; Novo, G.; Trimarco, B.; et al. Normal reference values of multilayer longitudinal strain according to age decades in a healthy population: A single-centre experience. *Eur. Heart J. Cardiovasc. Imaging* **2017**, *19*, 1390–1396. [CrossRef]
16. Sorrentino, R.; Esposito, R.; Santoro, C.; Vaccaro, A.; Cocozza, S.; Scalamogna, M.; Lembo, M.; Luciano, F.; Santoro, A.; Trimarco, B.; et al. Practical Impact of New Diastolic Recommendations on Noninvasive Estimation of Left Ventricular Diastolic Function and Filling Pressures. *J. Am. Soc. Echocardiogr.* **2020**, *33*, 171–181. [CrossRef]
17. Rudski, L.G.; Lai, W.W.; Afilalo, J.; Hua, L.; Handschumacher, M.D.; Chandrasekaran, K.; Solomon, S.D.; Louie, E.K.; Schiller, N.B. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J. Am. Soc. Echocardiogr.* **2010**, *23*, 685–713.
18. Armstrong, P.W.; Pieske, B.; Anstrom, K.J.; Ezekowitz, J.; Hernandez, A.F.; Butler, J.; Lam, C.S.P.; Ponikowski, P.; Voors, A.A.; Jia, G.; et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **2020**, *382*, 1883–1893. [CrossRef]
19. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) With the Special Contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef]
20. Kane, G.C.; Karon, B.L.; Mahoney, D.W.; Redfield, M.M.; Roger, V.L.; Burnett, J.C.; Jacobsen, S.; Rodeheffer, R.J. Progression of Left Ventricular Diastolic Dysfunction and Risk of Heart Failure. *J. Am. Med. Assoc.* **2011**, *306*, 856–863. [CrossRef]
21. Echouffo-Tcheugui, J.B.; Erqou, S.; Butler, J.; Yancy, C.W.; Fonarow, G.C. Assessing the Risk of Progression from Asymptomatic Left Ventricular Dysfunction to Overt Heart Failure: A Systematic Overview and Meta-Analysis. *JACC Heart Fail.* **2016**, *4*, 237–248. [CrossRef] [PubMed]
22. Guazzi, M.; Vicenzi, M.; Arena, R.; Guazzi, M.D. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: Results of a 1-year, prospective, randomized, placebo-controlled study. *Circ. Heart Fail.* **2011**, *4*, 8–17. [CrossRef] [PubMed]
23. Redfield, M.M.; Chen, H.H.; Borlaug, B.A.; Semigran, M.J.; Lee, K.L.; Lewis, G.; LeWinter, M.M.; Rouleau, J.L.; Bull, D.A.; Mann, D.L.; et al. RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: A randomized clinical trial. *J. Am. Med. Assoc.* **2013**, *309*, 1268–1277. [CrossRef]
24. Andersen, M.J.; Ersbøll, M.; Axelsson, A.; Gustafsson, F.; Hassager, C.; Køber, L.; Borlaug, B.A.; Boesgaard, S.; Skovgaard, L.T.; Møller, J.E. Sildenafil and diastolic dysfunction after acute myocardial infarction in patients with preserved ejection fraction: The Sildenafil and Diastolic Dysfunction After Acute Myocardial Infarction (SIDAMI) trial. *Circulation* **2013**, *127*, 1200–1208. [CrossRef] [PubMed]
25. Kim, K.-H.; Kim, H.-K.; Hwang, I.-C.; Cho, H.-J.; Je, N.; Kwon, O.-M.; Choi, S.-J.; Lee, S.-P.; Kim, Y.-J.; Sohn, D.-W. PDE 5 inhibition with udenafil improves left ventricular systolic/diastolic functions and exercise capacity in patients with chronic heart failure with reduced ejection fraction; A 12-week, randomized, double-blind, placebo-controlled trial. *Am. Heart J.* **2015**, *169*, 813–822.e3. [CrossRef] [PubMed]

26. De Vecchis, R.; Cesaro, A.; Ariano, C.; Giasi, A.; Cioppa, C. Phosphodiesterase-5 Inhibitors Improve Clinical Outcomes, Exercise Capacity and Pulmonary Hemodynamics in Patients with Heart Failure with Reduced Left Ventricular Ejection Fraction: A Meta-Analysis. *J. Clin. Med. Res.* **2017**, *9*, 488–498. [CrossRef]
27. Liu, L.C.; Hummel, Y.M.; van der Meer, P.; Berger, R.M.; Damman, K.; van Veldhuisen, D.J.; Voors, A.A.; Hoendermis, E.S. Effects of sildenafil on cardiac structure and function, cardiopulmonary exercise testing and health-related quality of life measures in heart failure patients with preserved ejection fraction and pulmonary hypertension. *Eur. J. Heart Fail.* **2017**, *19*, 116–125. [CrossRef]
28. Belyavskiy, E.; Ovchinnikov, A.; Potekhina, A.; Ageev, F.; Edelmann, F. Phosphodiesterase 5 inhibitor sildenafil in patients with heart failure with preserved ejection fraction and combined pre- and postcapillary pulmonary hypertension: A randomized open-label pilot study. *BMC Cardiovasc. Disord.* **2020**, *20*, 1–15. [CrossRef]
29. *Phosphodiesterase-5 Inhibition in Patients with Heart Failure with Preserved Ejection Fraction and Combined Post- and Pre-Capillary Pulmonary Hypertension (PASSION), A Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Multi-Center, Phase III Trial; EudraCT number 2017-003688-37*; European Medicines Agency: Amsterdam, The Netherlands, 2018.
30. Manca, P.; Cannatà, A.; Nuzzi, V.; Bromage, D.I.; Varrà, G.G.; Rossi, M.; Ferro, M.D.; Paldino, A.; Gigli, M.; Barbati, G.; et al. Prevalence and Evolution of Right Ventricular Dysfunction Among Different Genetic Backgrounds in Dilated Cardiomyopathy. *Can. J. Cardiol.* **2021**, *37*, 1743–1750. [CrossRef]
31. Cameli, M.; Miglioranza, M.H.; Magne, J.; Mandoli, G.E.; Benfari, G.; Ancona, R.; Sibilio, G.; Luksic, V.R.; Dejan, D.; Griseli, L.; et al. Multicentric Atrial Strain COmparison between Two Different Modalities: MASCOT HIT Study. *Diagnostics* **2020**, *10*, 946. [CrossRef]