Effects of PDE type 5 inhibitors on Left Ventricular Diastolic Dysfunction in Resistant Hypertension

Ana Paula Cabral de Faria, Rodrigo Modolo, Beatriz Vaz Domingues Moreno, Heitor Moreno

Faculdade de Ciências Médicas – Universidade Estadual de Campinas (FCM-UNICAMP), São Paulo, SP – Brazil

Abstract

Resistant hypertension (RHTN) is a multifactorial disease characterized by blood pressure (BP) levels above goal (140/90 mmHg) in spite of the concurrent use of three or more antihypertensive drugs of different classes. Moreover, it is well known that RHTN subjects have high prevalence of left ventricular diastolic dysfunction (LVDD), which leads to increased risk of heart failure progression. This review gathers data from studies evaluating the effects of phosphodiesterase-5 (PDE-5) inhibitors (administration of acute sildenafil and short-term tadalafil) on diastolic function, biochemical and hemodynamic parameters in patients with RHTN. Acute study with sildenafil treatment found that inhibition of PDE-5 improved hemodynamic parameters and diastolic relaxation. In addition, short-term study with the use of tadalafil demonstrated improvement of LVDD, cGMP and BNP-32 levels, regardless of BP reduction. No endothelial function changes were observed in the studies. The findings of acute and short-term studies revealed potential therapeutic effects of IPDE-5 drugs on LVDD in RHTN patients.

Introduction

Resistant hypertension (RHTN) is a multifactorial condition characterized by blood pressure (BP) levels above goal (140/90 mmHg) in spite of the concurrent use of three or more antihypertensive drugs of different classes or controlled BP with the use of four or more agents[1]. The overall prevalence is estimated from 15% to 18% of all hypertensive individuals in population-based studies[2,3] and frequently the increasing number of antihypertensive drugs used in the course of disease[1,4] is associated with with overweight or obesity and diabetes type 2; however, those conditions are not enough to primarily explain the individuals' physical limitations and cardiovascular complaints. In an echocardiography study, it was observed that 95% of RHTN and 72% of controlled hypertensive subjects had left ventricular diastolic dysfunction (LVDD) with preserved systolic function[5].

Previous studies have demonstrated that hypertensive rat models produced by chronic treatment with nitric oxide (NO) inhibitor – NG-nitro-L-arginine methyl ester (L-NAME) – showed marked impairment of the first temporal derivative negative pressure of the LV diastolic pressure (-dP/dt, in mmHg/s), indicating LVDD in those animals [6,7]. Curiously, this effect was reversed by oral administration of sildenafil, a selective phosphodiesterase type 5 inhibitor (IPDE-5) after 8 weeks of treatment[8]. Indeed, immunohistochemistry revealed reduced L-NAME-related myocardial lesions, in addition to increased PDE-5 intensity in the intercalary discs between myocytes [9]. Hence, this finding was related to improvement in LVDD due to direct sildenafil effect on cardiac relaxation in L-NAME-treated rats.

Therefore, because of the high prevalence of LVDD (95%) observed in our Outpatient Clinic specialized in RHTN (Campinas, Brazil) [5] and the lack of standard treatment, which reduces mortality rates [10], our group recently sought to investigate LVDD condition by echocardiography – a non-invasive diagnostic method frequently used – in association with IPDE-5 in acute (sildenafil) and short-term (tadalafil) administration. Thus, this clinical update report two recently published findings that evaluated the effects of PDE-5 inhibitors on diastolic function in the specific group of resistant hypertensive subjects [11,12].

Keywords

Hypertension; Left Ventricular Dysfunction; Phosphodiesterase 5 Inhibitors / therapeutic use; Heart Failure; Vasodilator Agents / therapeutic use.

Mailing Address: Ana Paula Cabral de Faria •
Rua Tessália Vieira de Camargo 126, Barão Geraldo. Postal Code: 13093-970, Campinas, SP – Brazil.
E-mail: aninha_cfaria@hotmail.com; ana.cabralfaria@gmail.com
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LVDD TREATMENT in RHTN: primary clinical studies using IPDE-5 drugs

Acute study

The hypothesis for the first recently published study involved a selective IPDE-5 and LVDD in RHTN patients, considering that acutely administered sildenafil could improve hemodynamic parameters, endothelial and left ventricular diastolic functions [11]. This crossover, single-blind and placebo-controlled study included 26 subjects diagnosed with RHTN (Clinicaltrial.gov - Protocol ID: CAAE-0758.0.146.000-09). Endothelial function (assessed by flow-mediated dilation method-FMD) and echocardiogram were determined during pre and post-sildenafil treatment, as well as measures of nitrite and plasma cyclic guanosine monophosphate (cGMP) levels. Additionally, non-invasive hemodynamic parameters (Finometer - Finapres Medical Systems; Amsterdam, Netherlands) were evaluated prior to and during the entire period of sildenafil treatment, with increasing dose administration (37.5, 50 and 100 mg) at 30-minute intervals.

No differences were found in nitrite and cGMP levels, as well as in endothelial function after sildenafil use. Conversely, hemodynamic evaluation revealed that sildenafil administration contributed to the decrease in mean blood pressure (MAP) at increasing doses, when compared to baseline levels (84.17±21.04 to 75±17.21 mmHg, $p<0.05$). Total peripheral resistance (TPR) was markedly reduced after the first dose of 37.5 mg (1149±459.7 to 1037±340 dyn.s/cm−5, $p<0.05$), but heart rate increased progressively with cumulative doses of this short-acting IPDE-5. Finally, improvement in diastolic function with reduction of: (1) left atrial volume (25.4±1.1 to 20.9±0.9 mL, $p<0.05$), (2) isovolumetric relaxation time (104.4±3.8 to 88.3±3.0 ms, $p<0.05$), (3) E/e' lateral and E/e' septal ratios (7.7±0.7 to 6.4±0.6 and 9.8±0.8 to 7.9±0.6, respectively, $p<0.05$) was found, when compared to pre-sildenafil echocardiogram.

The findings suggested that acute inhibition of PDE-5 improves hemodynamic parameters – reducing MAP levels through TPR reduction – as well as diastolic relaxation, although endothelial function changes were not observed [11] .

Short-term study

In a second recently published study, our group investigated whether tadalafil use, a long-acting IPDE-5 drug, improved LVDD in RHTN patients, regardless of BP reduction [12]. A total of 19 patients were included in this crossover, single-blind and placebo-controlled study (ClinicalTrials.gov - Protocol ID: CAAE-0044.0.146.000-09). All subjects received oral tadalafil (20 mg/day) for 2 weeks. Endothelial (FMD method) and LV diastolic (echocardiography) functions, nitrite, plasma cGMP and B-type natriuretic peptide (BNP-32) levels were determined at baseline and post-tadalafil treatment.

No changes in endothelial function or nitrite levels were observed. On the other hand, cGMP increased and BNP-32 reduced after the use of tadalafil (62.4±32.2 to 112.6±75.3 pmol/mL and143.3±33.3 to 119.3±31.3 pg/mL, respectively, $p<0.05$). Echocardiography revealed improvement of the LVDD variables: (1) peak E-wave velocity (67.8±18.3 to 77.8±16.0 cm/s, $p<0.05$); (2) E/A ratio (0.9±0.3 to 1.08±0.3, $p<0.05$); (3) E-wave deceleration time (234.1±46.0 to 194.4±43.3 ms, $p<0.05$); (4) lateral E'-wave velocity (7.7±2.1 to 8.8±2.8 cm/s, $p<0.05$); (5) isovolumetric relaxation time (128.7±17.6 to 96.8±26.9 ms, $p<0.05$); and (6) both septal and lateral S'-wave velocities (6.3±1.4 to 7.7±1.7 and 7.5±2.3 to 8.3±2.2 cm/s, respectively, $p<0.05$) post-tadalafil treatment. Moreover, the study showed reductions in dyspnea, palpitations, and fatigue reported by the patients.

In summary, this short-term study demonstrated clinical relevance with the use of tadalafil for 2 weeks on LVDD treatment and diastolic function-related biomarkers in RHTN subjects, and this effect was independent of BP reduction [12].

Mechanism discussion

The findings of the acute study with increasing doses of sildenafil (37.5, 50 and 100 mg at 30-minute intervals) showed improvement in the hemodynamic profile and LVDD in RHTN patients.

Previously, studies have evaluated the administration of IPDE-5 inhibitor in hypertensive groups. Firstly, it was demonstrated that sildenafil use during 16 days reduced ambulatory BP levels in untreated hypertensive subjects [13]. A second study has demonstrated BP reduction with acute sildenafil administration in a single dose (50 mg) in RHTN [14]. This study also found that the combination of sildenafil and organic nitrate (isosorbide mononitrate) was well tolerated and resulted in a greater decrease in brachial and central BP levels, raising the idea that this new therapeutic approach might be effective to RHTN patients. Despite these important findings, the mechanism of BP reduction was not reported.

The proposal to investigate hemodynamic parameters continuously contributed to detect that BP reduction was due to TPR reduction, since cardiac output remained unaltered. Curiously, the marked decrease in MAP levels and TPR occurred after the first sildenafil dose (37.5 mg), which was not sustained with consecutive administration of increasing doses (50 mg and 100 mg). In accordance with previous studies [15,16], those findings indicated that sildenafil did not have a dose-dependent effect [11].

The proposed causal mechanism for LVDD improvement in the acute study was also due to TPR reduction [11]. Taken together, those findings suggest that LVDD is characterized by increased afterload – resulting from increased TPR – with myocardial relaxation impairment of the left ventricle. Hence, it contributes to resistance in ventricular filling and alterations of diastolic pressure/volume ratio[17,18] (figure 1).

The short-term study assessed the effects of long-acting IPDE-5 (tadalafil 20 mg/day for 2 weeks) and resulted in LVDD improvement, regardless of BP reduction, and in cGMP and BNP-32 alterations after drug use in RHTN subjects. However, no nitrite and endothelial function changes were observed [12]. Those findings reinforced the hypothesis of the direct tadalafil effects on cardiomyocytes, as we could exclude the potential influence of NO-mediated vasodilation, and consequently, reduction of ventricular afterload (TPR was not altered).

Previous studies have demonstrated that PDE-5, through cGMP signaling pathway, leads to adverse cardiac remodeling [19-22] and its inhibition – with increased levels of cGMP – results in positive effects, such as the blocking of adrenergic, hypertrophic and apoptotic signaling pathways [23]. In accordance with these clinical findings, a study demonstrated the increase in plasma cGMP levels and left ventricular diastolic and systolic capacitance and decrease in measurements of cardiomyocyte passive stiffness during serial treatment with sildenafil and with BNP [24]. The PDE-5 enzyme was found in the intercalary discs between myocytes and IPDE-5 may have a potential relevance for diastolic relaxation by preventing the L-NAME–induced impairment in -dP/dt measurement. Thus, attenuation of deleterious hemodynamic and morphological alterations observed with L-NAME treatment might be modulated by PDE5 inhibition in cardiac myocytes [9]. In addition, IPDE-

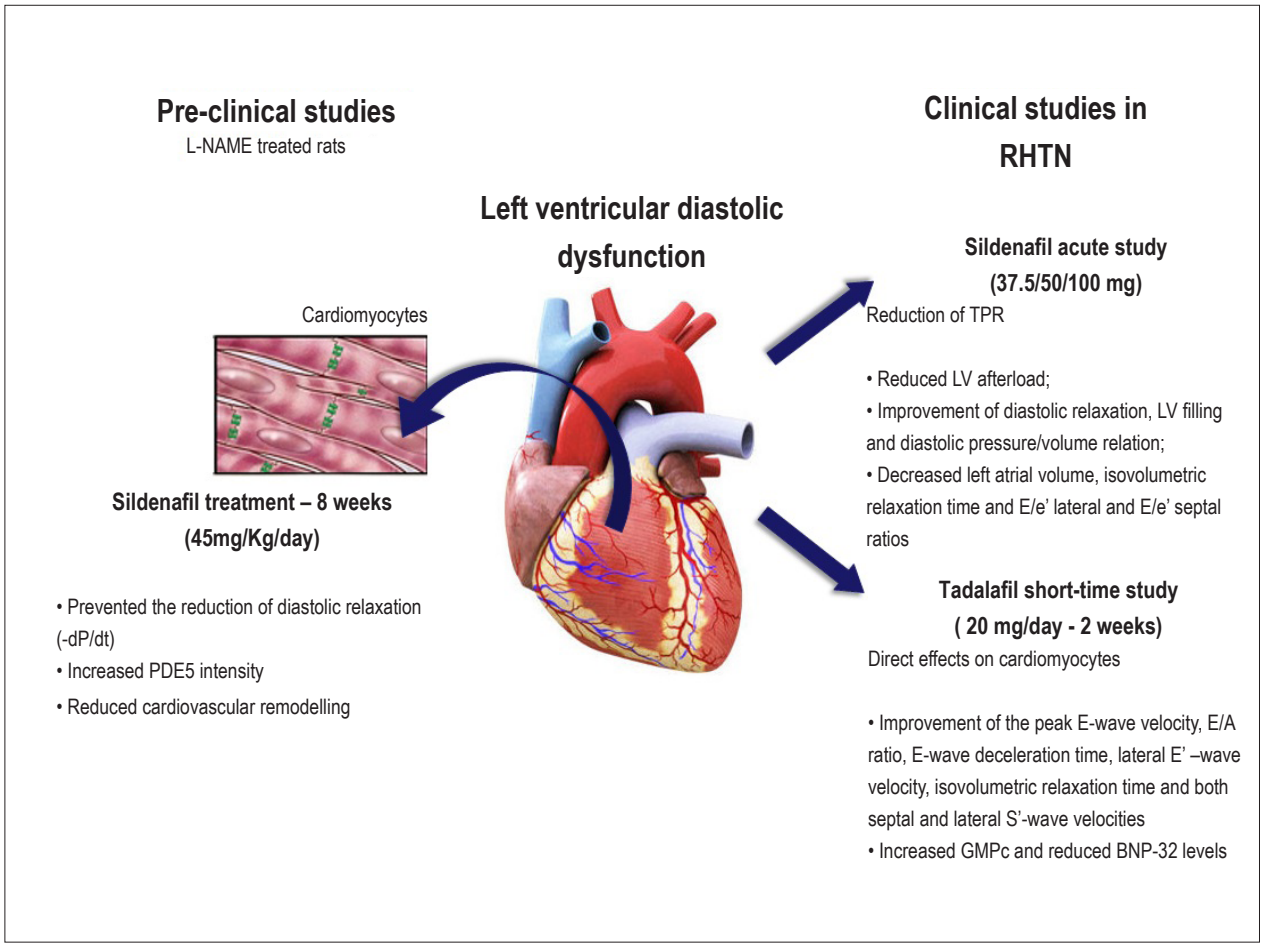

Figure 1 – *Potential mechanisms for the improvement of left ventricular diastolic dysfunction in preclinical and clinical studies.*

5 treatment may reduce cardiac inflammation followed by an improved remodeling process, as well as cardiac apoptosis, resulting in improved LV function in experimental models of angiotensin II-induced heart failure [25]. These mechanisms highlight the importance of PDE-5 as a strategic pharmacological target for cardiomyocytes relaxation and, consequently, for LVDD improvement by increasing cGMP levels after treatment with IPDE-5 drugs.

Finally, the reduction of BNP-32 levels – a clinical biomarker widely used for diagnosis, prognosis, and treatment of heart failure [26] – in the short-term study revealed a close association with LVDD [12]. Similarly to previous studies, which demonstrated that natriuretic peptides were strong predictors of diastolic dysfunction [27-29], the short-term study suggested the potential diagnostic role in measuring BNP-32 levels to evaluate cardiovascular alterations related to LVDD (Figure 1).

Clinical Implications

Resistant hypertension is a chronic disease and several factors that contribute to a complex pathophysiology might differ among the subjects, which compromise the efficacy of therapeutic regimens. Hence, those many different mechanisms may result in greater difficulties to achieve BP control, even despite the use of multiple drugs with confirmed adherence, leading to resistance to antihypertensive treatment [30, 31]. The challenge of RHTN treatment points out that the inclusion of new drugs is necessary to the therapeutic scheme of resistant hypertensive patients. In this context, recently IPDE-5 drugs were tested as antihypertensive treatment [13, 14]. Moreover, due to the high prevalence of LVDD in RHTN subjects [5] – which is associated with worse outcomes [32] – and evidence from preclinical studies that have demonstrated diastolic function improvement [6, 24], IPDE-5 emerges as a highly promising candidate for the treatment of clinical conditions, such as LVDD, associated with resistance to antihypertensive therapy.

Some studies have sustained the hypothesis that IPDE-5 drug use is a viable pharmacological strategy for improvement in LV relaxation due to (1) shortening in both lateral and septal T E-E´(a Doppler-derived index of LV relaxation performance) [33]; (2) the reverse cardiac remodeling effect; and (3) the reduced levels of BNP precursor over time [34]. LVDD treatment in RHTN population is important because LVDD does not have a standard treatment, therefore the use of therapeutic candidates could reduce mortality, especially in resistant hypertensive subjects, who have high cardiovascular risk[35].

Recent studies, including the acute study from our group[11], have shown BP reduction after sildenafil administration[14,26]. This effect must be carefully interpreted. Although those studies may point out to a meaningful clinical effect on BP, we must consider that they were conducted in a short period of time, not allowing us to conclude that a chronic treatment would have the same impact on BP levels.

Finally, both acute and short period administration of IPDE-5 drugs (sildenafil and tadalafil, respectively) were well tolerated according to patient self-reports. This may represent a great clinical advantage, especially when treating RHTN subjects, since those patients are taking multiple drugs and the adverse effects are relevant for treatment adherence [36].

The results of the abovementioned acute and short-term studies contributed to advance our knowledge about potential therapeutic effects of IPDE-5 drugs on LVDD in RHTN patients. As we did not investigate drug action in the long term, those findings reinforce that future prospective clinical studies must be conducted to evaluate efficacy and safety of IPDE-5 candidates in treatment of LVDD using a larger RHTN population in a long-term trial.

Author contributions

Conception and design of the research: Moreno H; Acquisition of data: Faria APC; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Faria APC, Modolo R, Domingues-Moreno BV, Moreno H; Statistical analysis and Writing of the manuscript: Faria APC, Modolo R, Moreno H.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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