

# Chronic Treatment with Tadalafil Improves Endothelial Function in Men with Increased Cardiovascular Risk

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## Abstract

**Objective:** Erectile dysfunction (ED) is often associated with a cluster of risk factors for coronary artery disease and reduced endothelial function. Acute and chronic administration of oral sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, improves endothelial function in patients with ED. Tadalafil (TAD) is a new PDE5 inhibitor with a long half life that allows alternate day administration. Aim of the study was to evaluate whether chronic therapy (4 weeks) with TAD improves endothelial function in patients with increased cardiovascular risk and whether this effect is sustained after discontinuation of therapy.

**Methods:** We randomized 32 patients with increased cardiovascular risk to receive either TAD 20 mg on alternate days or matching placebo (PLB) for 4 weeks. Patients underwent evaluation of brachial artery flow-mediated dilation (FMD), nitrite/nitrate and endothelin-1 plasma levels at baseline, at the end of treatment period and after two-weeks follow-up.

**Results:** At 4 weeks, FMD was significantly improved by TAD (from  $4.2 \pm 3.2$  to  $9.3 \pm 3.7\%$ ,  $p < 0.01$  vs. baseline), but was not modified by PLB (from  $4.1 \pm 2.8$  to  $4.0 \pm 3.4\%$ ,  $p = \text{NS}$ ). At 6 weeks the benefit in FMD was sustained in patients that received TAD ( $9.1 \pm 3.9\%$  vs.  $4.2 \pm 3.2\%$ ,  $p = 0.01$  vs. baseline;  $9.1 \pm 3.9\%$  vs.  $9.3 \pm 3.7\%$ , vs. 4 weeks,  $p = \text{NS}$ ) while no changes in FMD were observed in patients randomized to PLB. Also, compared to baseline, a net increase in nitrite/nitrate levels ( $38.2 \pm 12.3$  vs.  $52.6 \pm 11.7$  and  $51.1 \pm 3.1$ ,  $p < 0.05$ ) and a decrease in endothelin-1 levels ( $3.3 \pm 0.9$  vs.  $2.9 \pm 0.7$  and  $2.9 \pm 0.9$ ,  $p < 0.05$ ) was found both at four and six-weeks after TAD; these changes were inversely correlated as shown by regression analysis (adjusted  $R^2 = 0.81$ ,  $p < 0.0001$ ).

**Conclusions:** Chronic therapy with TAD improves endothelial function in patients with increased cardiovascular risk regardless their degree of ED. The benefit of this therapy is sustained for at least two weeks after the discontinuation of therapy. Larger studies are needed in order to assess the possible clinical implications of chronic therapy with TAD.

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**Keywords:** Phosphodiesterase type 5; Endothelial dysfunction; Erectile dysfunction; Rehabilitation; Arterial dilatation

## 1. Introduction

A large body of evidence has accumulated to suggest that the impairment of vascular endothelial function is an initial step towards the development of

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atherosclerosis and that endothelial function is impaired in patients with overt atherosclerotic disease as well as in those at increased cardiovascular risk [1–4]. Flow mediated dilatation (FMD) induced by reactive hyperemia has been shown to be endothelium-dependent and can be assessed by high-resolution ultrasound in superficial arteries for the non invasive assessment of endothelial function in vivo [5].

Erectile dysfunction (ED) is common in men with vascular disease and cardiovascular risk factors [6–9], and in these patients endothelial dysfunction is an important abnormality that contributes to a decrease in penile vascular responses to sexual stimuli. After sexual stimulation, nitric oxide (NO) is released by vascular endothelial cells of cavernous arteries and induces smooth muscle cell relaxation. NO exerts many of its effects by activation of soluble guanylate cyclase, resulting in increased production of cyclic guanosine monophosphate (cGMP), which leads to lower intracellular calcium levels and, therefore, vasodilatation [10]. cGMP is, in turn, broken down by intracellular phosphodiesterases (PDEs) that are a family of enzymes, present in different tissues, responsible for the breakdown of cyclic nucleotides. PDE type-5 (PDE5) is the most important isoenzyme isolated from human corpus cavernosum smooth muscle and endothelium, and is responsible for the breakdown of cGMP in the corpora cavernosa.

PDE5 inhibitors have been shown to be effective for the oral treatment of various forms of ED [10,11]. tadalafil is a newer PDE5 inhibitor with a different chemical moiety than its precursor, sildenafil, from which differs having a pharmacokinetic profile with a mean 17.5 hours half-life. Previous studies have shown that acute sildenafil treatment has favorable effects on brachial artery flow-mediated dilatation up to 24 h post-dose in men with and without erectile dysfunction [12,13]. The longer half-life of tadalafil compared to

that of sildenafil (i.e.  $\sim 4.5$  h) makes it useful for long term use and chronic, not on demand, therapy with PDE5 inhibitors has been envisaged for patients with erectile dysfunction.

In the present study we sought to determine whether chronic therapy with tadalafil improves endothelial function in patients with increased cardiovascular risk and whether these effects are sustained in the long term.

## 2. Methods

### 2.1. Patient population

The study population included 49 consecutive men with increased cardiovascular risk attending the cardiovascular prevention clinic over one month period and reporting some degree of ED. Included in the study were those aged between 59–71 years, presence of more than 2 risk factors for coronary artery disease (CAD) causing a 10-year cardiovascular risk  $>20\%$  [14,15] regardless to the degree of their ED. At the end of the study each patient was asked if the treatment assumed during the last four weeks had improved his erections (Global Assessment Question; GAQ). Patients with clinically significant findings on physical exam or presence of known clinically significant diseases that would prejudice the completion of the study or contraindicate TAD assumption as well as those currently using medications (or products) that interfere with forearm blood flow were excluded from the study. Patients with heart conditions, such as unstable angina and/or arrhythmia (Lown class  $>3$ ), recent acute MI ( $<3$  months), primary valvular, congenital heart disease, myocardial, pericardial or endocardial disease, congestive heart failure, were also excluded. Men presenting with contraindications to tadalafil administration such as presence of recent myocardial infarction, concomitant use of nitrates, and those unable to comply with the protocol or refusing the exam related to the end-point were excluded. After evaluation of inclusion and exclusion criteria and after having given informed written consent 32 men with increased cardiovascular risk, were included in the study, 16 of whom complaining from ED. Patients assuming angiotensin receptor blockers ( $N = 2$ ), calcium channel blockers ( $N = 2$ ) or statins ( $N = 8$ ) were similar in the different groups and a list of those who were assuming medication is given in Table 1. Most of patients with a smoking and family history were

**Table 1**

Clinical features of study patients at baseline

	N = 32	Tryglicerides	LDL-Chol	HDL-Chol	HBA1c	Glucose
Mean age (years)	65.4 $\pm$ 6.3					
BMI (kg/m <sup>2</sup> )	25.4 $\pm$ 3.2					
Risk factors for CAD						
Total cholesterol $> 5.20$ mmol/l	16 (16)	1.64 $\pm$ 0.14	3.13 $\pm$ 0.21	1.31 $\pm$ 0.20	–	5.59 $\pm$ 0.16
Diabetes type 2	8 (8)	1.51 $\pm$ 0.35	3.06 $\pm$ 0.45	1.33 $\pm$ 0.24	6.85 $\pm$ 0.47	7.92 $\pm$ 0.21
Hypertension ( $>135/85$ )	9 (9)	1.21 $\pm$ 0.49	2.99 $\pm$ 0.31	1.79 $\pm$ 0.38	–	5.38 $\pm$ 0.61
Cigarette smoking	10 (4)	1.37 $\pm$ 0.22	3.04 $\pm$ 0.25	1.41 $\pm$ 0.13	–	5.24 $\pm$ 0.29
Family history	16 (12)	1.38 $\pm$ 0.14	3.11 $\pm$ 0.20	1.50 $\pm$ 0.21	–	5.25 $\pm$ 0.30
Presence of ED	16 (16)	1.77 $\pm$ 0.11	3.21 $\pm$ 0.14	1.10 $\pm$ 0.17	–	5.87 $\pm$ 0.11

Normal values: Tryglicerides  $<1.80$  mmol/l; LDL-Chol  $<3.36$  mmol/l; HDL-Chol  $>1.55$  mmol/l; HBA1c  $<6\%$ ; Glucose  $<6.99$  mmol/l; Parentheses indicate the number of subjects under active drug treatments.

under salicylate therapy in conventional doses for secondary prevention. All patients were exposed to such risk factors for a period longer than 24 months and were on optimal therapy for their disease.

## 2.2. Study protocol

The study design was parallel double-blinded, placebo controlled. After a 4-weeks run-in period, men underwent baseline evaluation and were then randomized to receive either tadalafil 20 mg (TAD; Cialis™, Lilly Icos, Indianapolis, IN, USA) or matching placebo (PLB) every other day during a 4 weeks period; drugs were provided by the pharmacy of our Institution. Patients were studied three times: at baseline, at the end of each treatment period and two-weeks after the last treatment dose. At each study visit patients underwent study of FMD, and samplings for the evaluation of nitrite (NO<sub>2</sub>), nitrate (NO<sub>3</sub>) and endothelin-1 levels.

## 2.3. Evaluation of brachial artery reactivity

Flow-mediated vasodilatation (FMD) and nitroglycerine-induced (endothelium-independent) vasodilatation of brachial artery were measured by an experienced investigator, unaware of the clinical data. The same investigator performed the 3 studies in each patient in order to avoid inter-observer variability. Patients were asked to avoid caffeine-containing drinks and to refrain from smoking for the 6 hours as well as from tadalafil assumption for the 48 hours preceding the study since it is known that the latter is the time-course of interaction between tadalafil and nitrates [16]. Imaging studies of the right brachial artery were performed using an Acuson Sequoia ultrasound machine equipped with a 7.5 MHz linear-array transducer. Studies were conducted in quiet and temperature controlled rooms (22–23 °C) according to a previously reported protocol [17].

In brief, patients were studied in the supine position and after 15 minutes rest, the right brachial artery was scanned over a longitudinal section 3 to 5 cm above the right elbow, at the site where the clearest image was obtained. A pneumatic tourniquet was placed around the forearm distal to the target artery and was inflated to a pressure of 220 mmHg for 3 minutes. Reactive hyperemia was induced by sudden cuff deflation. The changes in diameter of the right brachial artery were measured at rest, during reactive hyperemia, after 10 min recovery and after 5 minutes of sublingual nitroglycerine (spray). A scan was performed continuously for 30 sec before and for 90 sec after cuff deflation. Fifteen minutes later, a third scan was recorded to confirm vessel recovery. A fourth scan was performed for the 2 minutes proceeding and 180 sec following sublingual nitroglycerine (GTN 0.4 mg).

All measurements were performed off line by an experienced operator unaware of the clinical data. The diameter change was expressed as the percent change compared to baseline. Flow velocity profile was also recorded at 15 sec intervals. Mean flow velocity was calculated by measurement of the area under the velocity profile curve. Blood flow (ml/min) was calculated from vessel cross-sectional area and brachial artery blood flow velocity. In our hands the methodology has an interobserver variability in diameter measurements of  $0.38\% \pm 0.26\%$  (range 0.1%–1.2%) yielding a coefficient of variation of 1.26% and a coefficient of repeatability of 0.5%.

## 2.4. Laboratory analysis

At each visit 10 ml of blood were withdrawn at the end of each test and were assayed plasma nitrite and nitrate levels and endothelin-1. Blood was collected in 5 ml tubes with 2% EDTA and 500 IU Aprotinin. Endothelin-1 was extracted through absorption column

cartridge (Sep-pack C18, Waters, MA, USA) and measured by RIA; intra and inter-assay coefficient of variation were 3% and 6% respectively. Serum NO<sub>2</sub> + NO<sub>3</sub> levels were measured with the use of the Greiss reagent as described elsewhere [11]. Briefly, aliquots (250 µl) of serum were diluted with ultrapure water incubated at room temperature with 250 µl substrate buffer in the presence of nitrate-reductase for 45 minutes to convert NO<sub>3</sub> to NO<sub>2</sub>. Total NO<sub>2</sub> (NO<sub>2</sub> + NO<sub>3</sub>) was then analyzed by reacting the samples with Greiss reagent. Amounts of NO<sub>2</sub> in serum were estimated from a standard curve of NaNO<sub>2</sub> obtained by enzymatic conversion of NaNO<sub>3</sub>. Since very little or no NO<sub>2</sub> is found in serum we did not attempt to differentiate between NO<sub>2</sub> and NO<sub>3</sub> but rather enzymatically converted all NO<sub>3</sub> to NO<sub>2</sub>; results are expressed as NO<sub>2</sub> + NO<sub>3</sub>.

## 2.5. Statistical analysis

Data are presented as mean  $\pm$  S.D. or percentages when appropriate. After testing data for normality, Wilcoxon Signed Rank test was used to compare values before and after each therapy and the relative changes in values in response to each therapy. The effects of tadalafil administration on vascular function, plasma levels of endothelin-1 and plasma nitrite and nitrate levels were analyzed by one way repeated measures analysis of variance (ANOVA) or Friedman Repeated ANOVA on Ranks. A *p* value <0.05 was considered statistically significant. In addition, linear regression analysis with least square method was performed to evaluate the relation of the FMD with endothelin levels.

## 3. Results

The clinical characteristics of study patients and their biochemical status at baseline are shown in Table 1. Thirty-two patients met the inclusion criteria, entered into and completed the study. Safety analyses included all enrolled subjects. The most frequent adverse events in Tadalafil treated subjects were dyspepsia, headache, back pain, pain and myalgia, spontaneous erection, nasal congestion, infection and were present in overall 2 out of 16 patients (12%). These adverse events are typically reported with PDE5 inhibitors. There were no reports of abnormal vision or priapism in either group, and no clinically significant changes attributable to TAD in vital signs, i.e. orthostatic hypotension, mean blood pressure or laboratory tests. No subject discontinued the medication due to adverse events. Amongst the 16 patients complaining of ED at baseline, 9 received TAD and 7 placebo; as expected, in this group of patients a positive response to GAQ was reported in 8 out 9 (88%) and 1 out 7 (14%), respectively. No difference in endothelial function was detected between patients with or without ED (mean difference  $-0.1$  range  $-0.6$  to  $0.5$ ; patients with vs. patients without ED).

Baseline brachial artery diameter remained unchanged either after TAD or PLB at both 4 and 6 weeks (Table 2). Hyperemic diameters increased significantly after 4 week therapy with TAD but not after

**Table 2**

Effect of tadalafil and placebo on endothelial function

	Tadalafil		Placebo	
	Baseline	Therapy	Baseline	Therapy
<b>Endothelial markers</b>				
Serum nitrogen oxides, $\mu\text{mol/l}$	$38.2 \pm 12.3$	$52.6 \pm 11.7^*$	$36.5 \pm 12.3$	$39.1 \pm 8.2$
Endothelin-1, pg/ml	$3.3 \pm 0.9$	$2.9 \pm 0.7^*$	$3 \pm 0.8$	$3.6 \pm 0.7$
<b>Brachial artery diameter</b>				
Basal-1 (mm)	$4.46 \pm 0.52$	$4.47 \pm 0.46$	$4.41 \pm 0.74$	$4.39 \pm 0.53$
Hyperemia (mm)	$4.65 \pm 0.61$	$4.89 \pm 0.45^\dagger$	$4.64 \pm 0.65$	$4.57 \pm 0.59$
FMD (%)	$4.2 \pm 0.6$	$9.3 \pm 0.3^\dagger$	$4.3 \pm 0.6$	$4.1 \pm 0.9$
Basal-2 (mm)	$4.45 \pm 0.69$	$4.47 \pm 0.57$	$4.42 \pm 0.63$	$4.4 \pm 0.57$
Nitroglycerin (mm)	$5.23 \pm 0.71$	$5.26 \pm 0.69$	$5.19 \pm 0.49$	$5.18 \pm 0.61$

Data are expressed as means  $\pm$  S.D. FMD = flow-mediated dilatation. \* $p < 0.05$  and  $^\dagger p < 0.01$  vs. respective baseline value.

PLB (Table 2). Therefore, flow mediated dilatation increased significantly after chronic TAD but not after PLB (Table 2). After 2 weeks of treatment withdrawal, FMD remained significantly higher in patients initially randomized to TAD compared to both baseline and PLB (Fig. 1). These changes were comparable with those obtained after 4 weeks of therapy.

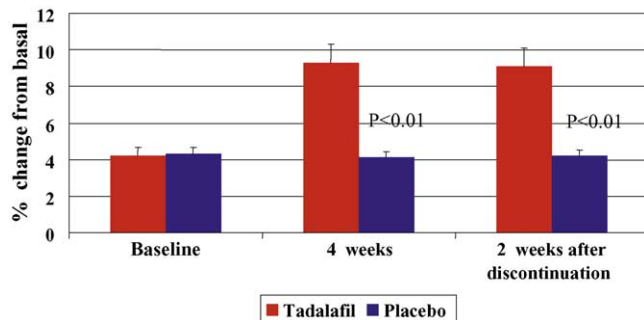


Fig. 1. Percent change compared to baseline in endothelial function (FMD) in patients treated with tadalafil and placebo after 4 weeks of therapy with Tadalafil 20 mg on alternate days and after 2 weeks of discontinuation of therapy.  $p$  values refer to comparison between tadalafil vs. placebo.

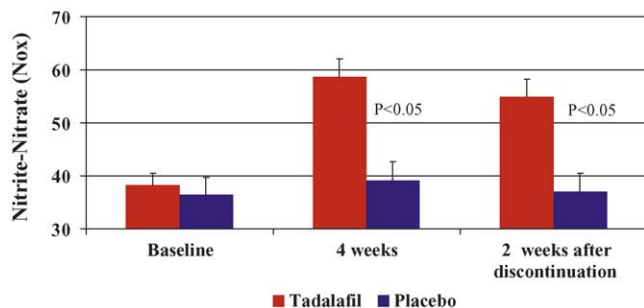


Fig. 2. Plasma levels of nitrite-nitrate in patients treated with tadalafil or placebo after 4 weeks of treatment and 2 weeks of discontinuation of therapy.

Significant increase from baseline in nitrite and nitrate levels were found in patients allocated to TAD compared to those receiving PLB (37.7% vs. 7.1%,  $p < 0.01$ ). These changes were maintained also at 2 weeks after discontinuation of therapy (Fig. 2). Finally, endothelin-1 levels decreased after TAD vs. PLB ( $-12\%$  vs.  $20\%$ ,  $p < 0.01$ ), and this improvement

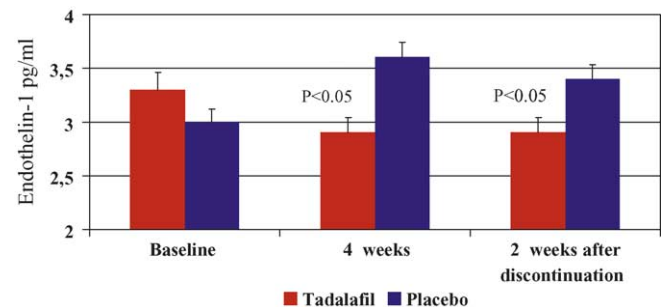


Fig. 3. Plasma levels of endothelin-1 in patients treated with tadalafil or placebo after 4 weeks of treatment and 2 weeks of discontinuation of therapy.

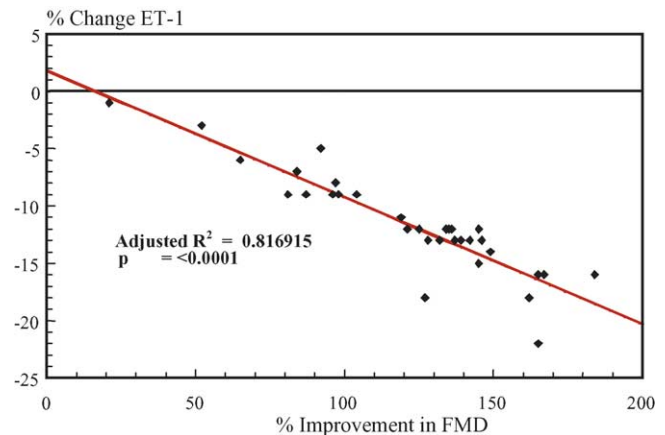


Fig. 4. Regression analysis between the percentages of improvement in FMD and changes in ET-1 levels in each single patient studied ( $N = 32$ ).

was maintained also at 2 weeks from discontinuation of therapy (Fig. 3). Regression analysis showed that the percentage of changes in FMD was inversely correlated with variations in ET-1 levels ( $r = -0.91$ ; adjusted  $R^2 = 0.81$ ,  $p < 0.0001$ ; Fig. 4).

#### 4. Discussion

The present study demonstrates for the first time that chronic therapy with tadalafil improves endothelial function in men with increased cardiovascular risk and that these effects are sustained after discontinuation of therapy. The improvement of endothelial function observed with chronic not on demand tadalafil administration was also associated with an increase in nitrite/nitrate levels and a concurrent decrease in endothelin-1.

It is likely that the results of the present study are dependent on the inhibitory effect of tadalafil on cGMP degradation at the endothelial level and are consistent with previous reports showing that PDE5 inhibition improves endothelial function in men [18]. The effect of tadalafil on endothelial function is likely to be a class effect; however, this study is novel in that it shows that the effects are sustained in the long term after discontinuation of chronic tadalafil therapy. Kukreja et al. demonstrated that in mice sildenafil administration stimulates the synthesis and transcription of iNOS and eNOS mRNA in cardiac myocytes. This action appears to be mediated by a sildenafil-induced direct stimulation of NOS via PKC and/or ERK pathways resulting in increased NO generation, guanylate cyclase activation and enhanced formation of cGMP leading to a robust cardioprotective effect [19]. Also, recent findings showed that in diabetic patients the effects of sildenafil on endothelial function are sustained for at least 24 hours [12,13].

The endothelium is involved in numerous physiologic functions, such as the regulation of vascular tone and permeability, the maintenance of equilibrium between coagulation and fibrinolysis, and the proliferation of smooth muscle cells [20]. Vascular endothelium produces a variety of regulatory mediators, among which endothelin-1 [21,22]. In the present study we have shown that Tadalafil reduces plasma levels of endothelin-1 and increases nitrite/nitrate levels suggesting a beneficial effect of tadalafil on endothelial function. The sustained improvement of endothelial function after discontinuation of chronic tadalafil therapy is not related to a reduced breakdown of cGMP since, according to the drug half-life, tadalafil should have been completely washed out

after 4 days and therefore have produced little or no relevance to TAD/GTN interaction [16]. The persistence of TAD effect is more likely to be related to an induction of NO production as suggested by the fact that the long lasting effect was of a similar magnitude of that observed during chronic therapy and by the fact that nitrite/nitrate levels were still elevated after two weeks of withdrawal. It is possible that the chronic effect of tadalafil on the endothelium leads to a stimulation of NO release as a result of an increased shear stress, leading to an upregulation of the NO system. Furthermore, alternative mechanisms involved in the persistence of effects after tadalafil withdrawal may be related to structural changes of the vessel wall that have not been investigated in this study.

The results of this study have important clinical implications for patients with impaired endothelial function regardless by the presence of ED even if also in the small cohort of our impotent patients ( $N = 16$ ), tadalafil treatment markedly improved the GAQ. It is known that men with increased cardiovascular risk show a higher incidence of ED. Epidemiological studies have also demonstrated a strict correlation between ED and cardiovascular disease and suggested the hypothesis that vascular ED may be an early marker of cardiovascular disease [23]. Montorsi et al. have reported that in 70% of men undergoing coronary angiography ED preceded the clinical manifestations of coronary artery disease [24]. Kim et al. have reported a 56% incidence of positive exercise tests in men with vascular ED and without any cardiovascular symptom and have found significant atherosclerosis at angiography in all those patients that underwent coronary angiography [25]. Similar findings were reported in men with ED and low peak flow velocities at penile Duplex ultrasound [26]. Altogether, these findings suggest that the alteration of endothelial function, which is a marker of early stages of atherosclerosis, has an earlier symptomatic impact on erectile function being the penile circulation mainly dependent upon endothelial function and less on metabolic induced vasodilation. Restoring endothelial function in patients with dysfunctional endothelium may help to prevent or slow the development of atherosclerosis, may protect from the development of ED and may represent an innovative therapeutic strategy for patients with known ED. Indeed, recent studies are expanding the role of PDE5 inhibition to the chronic treatment of pulmonary hypertension, primary hypertension and heart failure, conditions in which sildenafil has been shown to improve pulmonary pressures as well as functional

capacity [27–31]. Our data on the sustained reduction of endothelin-1 after chronic tadalafil therapy may suggest an efficacy of the drug on pulmonary hypertension since endothelin-1 is involved in the pathogenesis of this condition.

In men with vasculogenic ED the possibility of a long-term challenge with tadalafil has the potential to restore spontaneous erections through a steady improvement of penile flow (unpublished data). Since reduced penile flow is of critical importance in the development and progression of ED and penile fibrosis, chronic therapy will represent an important therapeutic strategy. The pathophysiological role of endothelin-1 in modulating penile flaccidity and tumescence is not well understood in humans yet, and different concentrations have been found in systemic and cavernous blood of healthy and impotent patients [32]. It is generally recognized that endothelin-1 systemic and cavernous plasma levels are increased in impotent patients when compared to controls [33] so that endothelin-receptor antagonism has been hypothesized to be beneficial for erectile mechanism in men with some degree of ED [34]. Because it has been hypothesized a synergism between endothelin-1, phenylephrine and RhoA/Rho-kinase-mediated vasoconstriction in the corpus cavernosum [35–37], it is conceivable that tadalafil-induced stimulation of NOS activity and long-term increases in the nitrite/nitrate levels may have determined overlapping mechanism leading to reduced vasoconstrictory effects on arterial wall that cannot have been detected by our ultrasound imaging technique. If chronic tadalafil therapy will be proven effective for the sustained improvement of ED, in the future it will be important to assess the scheme of

treatment that may lead to a sustained improvement of endothelial function and, more importantly, the time interval between cycles of therapies. To this end further studies are required to elucidate the putative cardioprotective effects of chronic therapy with tadalafil and to assess its role in the improvement of sexual function in men with ED.

In conclusion chronic, not on demand therapy with PDE5 inhibitor tadalafil improves endothelial function in men with increased cardiovascular risk. We do not know whether tadalafil is as effective as other drugs in further reducing cardiovascular events in patients with endothelial dysfunction. The present study population was composed of a small cohort of patients with diabetes, hypertension and hypercholesterolemia which are frequently associated with endothelial dysfunction. Treatment with statins, antihypertensive or antidiabetes medications have been shown to improve endothelial dysfunction over the time and we hypothesize that tadalafil may have added to the effects of these drugs to prevent or slow the development of atherosclerosis as well as of ED. These beneficial effects on endothelial function appear to be long-term and sustained after discontinuation of therapy supporting the use of tadalafil for rehabilitation in patients with ED.

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## References

- [1] Flavahan NA. Atherosclerosis or lipoprotein-induced endothelial dysfunction. Potential mechanisms underlying reduction in EDRF/nitric oxide activity. *Circulation* 1992;85(5):1927–38.
- [2] Ross R. The pathogenesis of atherosclerosis: a perspective for 1990s. *Nature* 1993;362:801–9.
- [3] Panza JA, Quyyumi AA, Brush JE, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Engl J Med* 1990;323:22–7.
- [4] Schächinger V, Britten MB, Zeiher AM. Prognostic Impact of Coronary Vasodilator Dysfunction on Adverse Long-Term Outcome of Coronary Heart Disease. *Circulation* 2000;101:1899.
- [5] Sorensen E, Celermajer S, Spiegelhalter D, Georgakopoulos D, Robinson J, Thomas O, et al. Non-invasive measurement of human endothelium dependent arterial responses: accuracy and reproducibility. *Br Heart J* 1995;74:247–53.
- [6] Kloner RA, Speakman M. Erectile Dysfunction and Atherosclerosis Current Atherosclerosis reports 2002;4:397–401.
- [7] Soloman H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. *Heart* 2003;89:251–4.
- [8] Rosen MP, Greenfield AJ, Walker TG, et al. Cigarette smoking: an independent risk factor for atherosclerosis in the hypogastric-cavernous arterial bed of men with atherogenic impotence. *J Urol* 1991;145:759–63.
- [9] Feldman HA, Goldstein I, Hatzichristou D, et al. Impotence and its medical and psychological correlates: results of the Massachusetts Male Ageing Study. *J Urol* 1994;151:54–61.
- [10] Aversa A, Pili M, Fabbri A, Spera E, Spera G. Erectile dysfunction: expectations beyond phosphodiesterase type-5 inhibition. *J Endocrinol Invest* 2004;27:192–206.
- [11] Brock GB, McMahon CG, Chen KK, Costigan T, Shen W, Watkins V, et al. Efficacy and safety of tadalafil in the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002; 168:1332–8.

- [12] Desouza C, Parulkar A, Lumpkin D, Akers D, Fonseca VA. Acute and prolonged effects of sildenafil on brachial artery flow-mediated dilatation in type 2 diabetes. *Diabetes Care* 2002;25(8):1336–9.
- [13] Gillies HC, Roblin D, Jackson G. Coronary and systemic hemodynamic effects of Sildenafil citrate: from basic science to clinical studies in patients with cardiovascular disease. *Int J Cardiol* 2002;86:131–41.
- [14] Task Force Report: Prevention of coronary heart disease in clinical practice. *Eur Heart J* 1998;19:1434–1503.
- [15] De Backer G, Ambrosioni E, Kort-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Cardiovasc Prevent Rehabil* 2003;10(Suppl 1):S1–S78.
- [16] Kloner RA, Hutter AM, Emmick JT, Mitchell MI, Denne J, Jackson G. Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol* 2003;42(10):1855–60.
- [17] Vitale C, Fini M, Leonardo F, Rossini P, Cerquetani E, Onorati D, et al. Effect of estradiol valerate alone or in association with cyproterone acetate upon vascular function of postmenopausal women at increased risk for cardiovascular disease. *Maturitas* 2001;40(3):239–45.
- [18] Kukreja RC, Ockaili R, Salloum F, Yin C, Hawkins J, Das A, et al. Cardioprotection with phosphodiesterase-5 inhibition a novel preconditioning strategy. *J Mol Cell Cardiol* 2004;36:165–73.
- [19] Kukreja RC, Ockaili R, Salloum F, Xi L. Sildenafil-induced cardioprotection in rabbits. *Circ Res* 2003;60:700–1.
- [20] Bhagat K, Vallance P. Inflammatory cytokines impair endothelium-dependent dilatation in human veins in vivo. *circulation* 1997;96:3042–7.
- [21] Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999;340:115–26.
- [22] Kaiser DR, Billups K, Mason C, Wetterling R, Lundberg JR, Bank AJ. Impaired brachial artery, endothelium dependent and independent vasodilatation in men with erectile dysfunction and no other clinical cardiovascular disease. *J Am Coll Cardiol* 2004;43:179–84.
- [23] Shamloul R, Ghanem HM, Salem A, Elnashaar A, Elnaggar W, Darwish H, et al. Correlation between penile Duplex findings and and stress electrocardiography in men with erectile dysfunction. *Int J Impotence Res* 2004;16:235–7.
- [24] Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. *Eur Urol* 2003;44:360–5.
- [25] Kim SW, Paick J, Park DW, Chae I, Oh B. Potential predictors of asymptomatic ischemic heart disease in patients with vasculogenic erectile dysfunction. *Urology* 2001;58(3):441–5.
- [26] Kawanishi Y, Sogou T. Screening of ischemic heart disease with cavernous artery blood flow in erectile dysfunction patients. *Int J Impot Res* 2001;13(2):100–3.
- [27] Weimann J, Ullrich R, Hromi J, Fujino Y, Clark MW, Bloch KD, et al. Sildenafil is a pulmonary vasodilator in awake lambs with acute pulmonary hypertension. *Anesthesiology* 2000;92(6):1702–12.
- [28] Abrams D, Schulze-Neick I, Magee AG. Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. *Heart* 2000;84(2):E4.
- [29] Zhao L, Mason NA, Morrell NW, Kojonazarov B, Sadykov A, Maripov A, et al. Sildenafil inhibits hypoxia-induced pulmonary hypertension. *Circulation* 2001;104:424–8.
- [30] Wilkens H, Guth A, Konig J, Forestier N, Cremers B, Hennen B, et al. Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. *Circulation* 2001;104:1218–22.
- [31] Wagner FD, Buz S, Knosalla C, Hetzer R, Hoher B. Modulation of circulating endothelin-1 and big endothelin by nitric oxide inhalation following left ventricular assist device implantation. *Circulation* 2003;108(Suppl 1):II278–84.
- [32] Becker AJ, Uckert S, Stief CG, Truss MC, Hartmann U, Jonas U. Systemic and cavernous plasma levels of endothelin (1–21) during different penile conditions in healthy males and patients with erectile dysfunction. *World J Urol* 2001;19(4):267–71.
- [33] Francavilla S, Properzi G, Bellini C, Marino G, Ferri C, Santucci A. Endothelin-1 in diabetic and nondiabetic men with erectile dysfunction. *J Urol* 1997;158(5):1770–4.
- [34] Kim NN, Dhir V, Azadzi KM, Traish AM, Flaherty E, Goldstein I. Pilot study of the endothelin-A receptor selective antagonist BMS-193884 for the treatment of erectile dysfunction. *J Androl* 2002;23(1):76–83.
- [35] Wingard CJ, Husain S, Williams J, James S. RhoA-Rho kinase mediates synergistic ET-1 and phenylephrine contraction of rat corpus cavernosum. *Am J Physiol Regul Integr Comp Physiol* 2003;285(5):R1145–52 Epub 2003 Jul 31.
- [36] Matsumura Y, Kita S, Okui T. Mechanisms of endothelin-1-induced potentiation of noradrenergic response in rat mesenteric artery. *Clin Exp Pharmacol Physiol* 2001;28(7):540–4.
- [37] Bivalacqua TJ, Usta MF, Champion HC, Kadowitz PJ, Hellstrom WJG. Endothelial dysfunction in erectile dysfunction: role of the endothelium in erectile physiology and disease. *J Androl* 2003;24(Suppl N° 6):S17–37.

## Editorial Comment

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Rosano, Aversa, Vitale, Fabbri, Fini and Spera in their paper “Chronic Treatment with Tadalafil Improves Endothelial Function in Men with Increased Cardiovascular Risk” have focused on an increasingly important overlap of vascular and urological concepts [1]. There are three striking things about this paper the have significant resonance and are interdependent [1]. The measurement of systemic vascular improvement from a phosphodiesterase type 5 inhibitor in men with cardiovascular risk [2], the persistence of these changes after serum presence of the drug has disappeared and

[3] the fact that this deserves a place in urological literature.

This study is about endothelial dysfunction in general and new prospects for moderating diseases of the endothelium using, what is now, a common urological tool—a phosphodiesterase inhibitor (PDEI). It takes men at risk for general CV disease and makes standard assessments of systemic endothelial function (flow-mediated arterial reactivity [2] and serum endothelin and nitrate levels) comparing tadalafil and placebo treatments. A vital premise is that CV disease is systemic and erectile dysfunction is only one (important) local manifestation. This premise is further evident in the action of the PDEI—as a systemic treatment producing systemic results (as well as the expected high level of local penile benefit). Furthermore, the premise is evident in the

biochemical results—only systemic (rather than just penile) vascular abnormalities and their remediation would produce the significant changes in serum measurements of endothelin and nitrate.

The persistence of the changes observed in functional and biochemical status after the pharmacological trigger has disappeared indicate that fundamental changes have been made to the CV system here postulated as due to an upregulation of the NO system or structural changes. There are limited ways in which a system can be persistently changed and genomic effects predominate in achieving structural and functional adaptation [3].

There is some suggestion that certain types of endothelial impairment may not respond to acute PDEI therapy [4]. It is too early to say that PDEI treatment of the dysfunctional, or at risk, endothelium is a specific treatment. The vasodilator effect should moderate the functional and long term degradative effect of overactive or unopposed vasoconstrictor pathways or possibly specifically inhibit them. A true intermediate or long term genomic effect that remediates the dysfunctional endothelium would have broad implications for certain CV disease states. And to find that intermediate duration (4 weeks) tadalafil therapy could achieve this would possibly allow for pulsed therapy or lower dose continuous therapy.

Urologists are uniquely situated to be the unintended purveyors of general endothelial therapy to men with CV disease.

## References

- [1] Soloman H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. *Heart* 2003;89:251–4.
- [2] Kaiser DR, Billupski, et al. Impaired brachial artery, endothelium dependent and independent vasodilatation in men with erectile dysfunction and no other clinical cardiovascular disease. *J Am Coll Cardiol* 2004;43:179–84.
- [3] Hale TM, Shoichet MJ, Bushfield TL, Adams MA. Time course of vascular structural changes during and after short-term antihypertensive treatment. *Hypertension* 2003;42(2):171–6.
- [4] Dishy V, Harris PA, Pierce R, Prasad HC, Sofowora G, Bonar HL, et al. Sildenafil does not improve nitric oxide-mediated endothelium-dependent vascular responses in smokers. *Br J Clin Pharmacol* 2004;57(2):209–12.

## Editorial Comment

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Endothelial dysfunction is a key point in patients with erectile dysfunction (ED). The restoring of sexual function by PDE-5 inhibitors is likely due to

a multilevel effect of these drugs on endothelial function. Tadalafil (Cialis<sup>TM</sup>, Lilly-Icos, Indianapolis, IN, USA) is the last PDE-5 compound released on the market to treat ED. It has been proved to be as effective as sildenafil and vardenafil in different categories of patients and diseases. However, its peculiar long half-life (17.5 vs. 4 hours of both sildenafil and vardenafil) made this drug appealing for a not *on demand* use. In other words, chronic administration of Tadalafil (2–3 times per week), while curing ED, would exert a sort of continuous “endothelial rehabilitation” of penile circulation during sexual intercourse-free periods. Given the high prevalence of ED in common vascular diseases, included coronary artery disease, and the beneficial systemic effects of PDE-5 inhibitors on vascular districts other than penile, a systemic “endothelial rehabilitation” might be postulated. If true, one would expect a sustained improvement and/or normalization of sexual function even after drug discontinuation. So far, no clinical data are yet available to support this hypothesis.

In this study, Rosano et al. found tadalafil to improve endothelial function in a small cohort of patients with  $\geq 2$  coronary risk factors and calculated 10-year cardiovascular risk  $>20\%$ . ED was present only in half of patients ( $n = 16$ ). The hyperemic vasodilation of the brachial artery after transient occlusion (a largely shear-mediated NO release phenomenon) was taken as test for endothelium integrity and was evaluated by standard two-dimensional images. As compared to placebo, percent flow-mediated dilation was significantly augmented by tadalafil both acutely and, more intriguing, after two weeks of active treatment discontinuation. Endothelial improvement nicely coupled with decrease in ET-1 plasma levels suggesting a shift towards endothelium-mediated vasodilating substances.

The study major limitation is not having purposely included only patients with ED, those who have been benefited most from this therapy. Although a beneficial effect on sexual function was reported by the majority of ED patients during tadalafil administration, no data was given while drug was discontinued. Also, it is unknown whether changes in sexual function were somehow related to changes in endothelial function.

Similarly to Rosano’s study, Desouza et al. previously showed normalization of % flow dilation response up to 24 hours following 100 mg daily dose of Sildenafil taken for two weeks [1]. Although all pts had ED, no data on concomitant change in sexual function parameters was reported in that study. Available data on sexual function in ED patients, showed a 50–60% rate of responders at 36 hrs after Tadalafil

withdrawal [2]. No data are available at a longer time interval from active drug. Reasons for the apparent discrepancy between sexual effect and endothelial effect are not easily understood. However, endothelial dysfunction is one of many pathophysiological mechanisms at work in ED. Impaired arterial flow due to occlusion or stenosis of hypogastric/pudendal arterial beds with diffuse distal vascular obstruction has been frequently found in patients with vasculogenic ED and is likely to be the leading cause ED. The organic vascular changes may in turn induce cavernosal fibrosis, hypoxemia and impaired relaxation of cavernosal smooth muscle cells [3,4].

Thus, before readers of *European Urology* “paste and copy” these data into their every day clinical

practice, we definitely need more scientific data on the “endothelial rehabilitation” concept.

## References

- [1] Desouza C, Parulkar A, Lumpkin D, et al. Acute and prolonged effects of sildenafil on brachial artery flow-mediated dilatation in type 2 diabetes. *Diabetes care* 2002;25:1336–9.
- [2] Prost H, Padma-Nathan H, Giuliano F, et al. Efficacy of Tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomised trial. *Urol* 2003;62:121–5.
- [3] Siroky MB, Azadzo KM. Vasculogenic erectile dysfunction: newer therapeutic strategies. *J Urology* 2003;170:S24–30.
- [4] Siroky MB, Master TA, Azadzo KM. Effect of chronic ischemia on constitutive and inducible nitric oxide synthase expression in erectile tissue. *J Androl* 2004;25:382.