

# Sexual Dysfunction in Essential Hypertension: Myth or Reality?

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*Erectile dysfunction is currently considered a condition with high prevalence in the general population, exerting a major impact on patients' and their sexual partners' quality of life. Available data indicate that hypertension represents a risk factor for erectile dysfunction, which is more frequent in hypertensive compared with normotensive subjects. The pathophysiologic basis of erectile dysfunction in hypertension is under thorough investigation, and several mechanisms have been proposed. Erectile dysfunction has also been related to cardiovascular risk factors and might be used as a marker of cardiovascular disease in the future. Although male sexuality has been studied rather extensively, female sexual dysfunction in hypertension is underexplored. Recently published hypertension guidelines either ignore or superficially address sexual dysfunction, underlining the need for more attention and better education of health care professionals on this issue. (J Clin Hypertens. 2006;8:269–274) ©2006 Le Jacq Ltd.*

The history of erectile dysfunction comprises myths, misperceptions, and misadventures. Around 400 BC, Hippocrates was the first to describe erectile pathophysiology incorrectly. He suggested

that erection was caused by air (in ancient Greek, “pneuma”) and vital spirits that flow in the penis. It took almost 2000 years to define erection correctly, when Leonardo da Vinci observed the reflex erections in men hanging from the gallows and described that they were caused by blood entrapment in the penis. It was not until the end of the 19th century that the neurovascular mechanism of erection was proposed by Eckhard, when he observed that pelvic nerve stimulation in dogs results in erection.

Erectile dysfunction is defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse. It is estimated that approximately 20–30 million American men and more than 150 million men worldwide have some degree of erectile dysfunction.

Sexuality represents an important quality-of-life issue that is frequently overlooked by general practitioners and specialists in the hypertension field. Historically, erectile dysfunction has been considered the province of urologists and mental health professionals, since it was believed that it was mainly psychogenic. But today, most patients who seek help go to their family doctors or internists. Physicians skilled in the treatment of medical disorders often feel unqualified to treat patients with sexual dysfunction; the vast majority of physicians are not given adequate training in human sexuality. However, a better understanding of sexual function and the application of general medical rules in the management of sexual dysfunction is important in handling this problem.

This article briefly reviews the prevalence and pathophysiology of erectile dysfunction in men with essential hypertension compared with normotensive subjects, outlines the evidence for the relationship between cardiovascular disease and erectile dysfunction, and addresses female sexual dysfunction.

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**Table I.** Erectile Dysfunction Risk in Patients with Essential Hypertension

STUDY	COUNTRY	NO. OF SUBJECTS		AGE (YR)	ERECTILE DYSFUNCTION PREVALENCE (%)	AGE-ADJUSTED RISK
		STUDIED				
Johannes et al., 2000 <sup>2</sup>	United States	847		40–69	52	1.13 untreated 1.52 treated
Braun et al., 2000 <sup>3</sup>	Germany	4489		30–80	19.2	1.58
Martin-Morales et al., 2001 <sup>4</sup>	Spain	2476		25–70	18.9	1.72
Marumo et al., 2001 <sup>5</sup>	Japan	1014		40–79	27	2.79
Mak et al., 2002 <sup>6</sup>	Belgium	799		40–70	61	1.67
Akkus et al., 2002 <sup>7</sup>	Turkey	1982		≥40	69.2	2.81
Bacon et al., 2003 <sup>8</sup>	United States	31,742		53–90	33	1.3
Nicolosi et al., 2003 <sup>9</sup>	Japan	600		40–70	34	1.45
	Malaysia	600			22	
	Italy	600			17	
	Brazil	600			15	
Mirone et al., 2004 <sup>10</sup>	Italy	12,558		17–98	19.9	1.3
Shiri et al., 2004 <sup>11</sup>	Finland	1846		55–75	Previous study 5 years ago: 74	6.9
Ponholzer et al., 2005 <sup>12</sup>	Austria	2869		20–80	32.2	2.05

### ERECTILE DYSFUNCTION PREVALENCE

The Massachusetts Male Aging Study (MMAS)<sup>1</sup> in 1994 reported an unexpectedly high rate (52%) of erectile dysfunction prevalence in the general population. Since then, many studies have reported the prevalence of erectile dysfunction, ranging from 15% in Brazil to 74% in Finland.<sup>2–12</sup> A recent study of 22,839 men in eight countries (Men's Attitudes to Life Events and Sexuality [MALES] study<sup>13</sup>) reported an overall prevalence of 16%, ranging from 10% in Spain to 22% in the United States. The large variation in difference may reflect different sample populations, different assessment methods, and cultural differences in the willingness of individuals to discuss such issues and accept the social stigma of erectile dysfunction.

Although essential hypertension is widely accepted as a risk factor for erectile dysfunction, available data are controversial and indicate that this relationship is not definitely established. In a study of 440 impotent men, arterial hypertension was not an independent predictor of vasculogenic erectile dysfunction.<sup>14</sup> Similar results were obtained in several other studies where hypertension alone was not an independent risk factor for vasculogenic erectile dysfunction.<sup>15,16</sup> Some epidemiologic studies have found only marginal effects of hypertension on erectile function.<sup>17,18</sup> In the majority of epidemiologic studies, however, it is reported that hypertension increases the risk of erectile dysfunction; the relative risk ranges from 1.3 to 6.9 (Table I).<sup>2–12</sup> Available data indicate that

erectile dysfunction is more frequent in patients with essential hypertension when compared with normotensive subjects (Table II).<sup>19–24</sup>

A major limitation in the majority of these studies, however, is that hypertension recognition relies on self-reporting, while no attempt has been made to validate responses with medical records or physician or partner reports.

The Treatment of Mild Hypertension Study (TOMHS)<sup>25</sup> was the first large hypertension investigation to report the prevalence of erectile dysfunction in hypertensive patients. The prevalence of erectile dysfunction at baseline was low (14.4% in men and 4.9% in women); however, this could be due to several factors: 1) the study included only mildly hypertensive patients since diabetic and severely hypertensive individuals were excluded; 2) there was only one question assessing sexual dysfunction; 3) patients' age ranged from 45 to 69 years, excluding older patients; and 4) the study was old and patients were not at that time familiar with the issue or willing to discuss it.

In a recent open, prospective study of 2130 Spanish men with essential hypertension, erectile dysfunction was present in 45.8% of hypertensive men,<sup>26</sup> a percentage that is significantly higher than the 18.9% found in the general Spanish population.<sup>4</sup>

We have studied 358 patients with essential hypertension without any additional factors that affect erectile function and compared them with 276 normotensive individuals with similar baseline characteristics.<sup>24</sup> Erectile dysfunction was detected

**Table II.** Prevalence of Erectile Dysfunction in Hypertensive (Treated and Untreated) and Normotensive Subjects

STUDY	TREATED	UNTREATED	NORMOTENSIVES	COMMENTS
	HYPERTENSIVES	HYPERTENSIVES		
Riley et al., 1987 <sup>19</sup>	55	26	–	Impotence (%)
Bulpitt et al., 1976 <sup>20</sup>	25	17	7	Impotence (%)
Bauer et al., 1981 <sup>21</sup>	19	20	10	Impotence (%), 99, 78, and 477 patients, respectively
Croog et al., 1988 <sup>22</sup>	58	44	–	Sexual dysfunction (%), 626 patients
Johannes et al., 2000 <sup>2</sup>	42.5	26.5	23	Incidence 1000 annually
Dusing 2003 <sup>23</sup>	79	65	–	Probably select population (%)
Rosen et al., 2004 <sup>13</sup>	26	–	13	One question only (%)
Doumas et al., 2005 <sup>24</sup>	40.4	19.8	14.1	267, 91, and 276 patients, respectively (%)

in 35.2% of hypertensive men compared with 14.1% of normotensive subjects. However, this study sample is not large enough to permit definite conclusions regarding erectile dysfunction prevalence in essential hypertension.

### Factors Affecting Erectile Dysfunction in Hypertension

It is well recognized that erectile function declines with age. The prevalence of erectile dysfunction in the MMAS<sup>1</sup> increased from 52% in men aged 40–70 years to more than 95% in men older than 70 with diabetes. Aging is accompanied by several diseases that affect erectile function, such as hypertension and diabetes. Thus, it is not unexpected that hypertension and erectile dysfunction coexist in older individuals.

Studies in hypertensive patients have reported that erectile dysfunction is more frequent and more severe in patients with long-standing hypertension (>5–6 years) compared with patients with recent-onset hypertension.<sup>24,27</sup>

Hypertension severity is associated with erectile dysfunction as well; erectile dysfunction is more prevalent in patients with severe hypertension.<sup>24,28</sup> Patients with severe hypertension tend not only to have erectile dysfunction, but to have its severe form.<sup>24</sup> Erectile dysfunction may also be increased in people with prehypertension.<sup>24</sup>

Treatment of hypertension has also been associated with erectile dysfunction, and treated hypertensives may be more likely to have erectile dysfunction than untreated hypertensives. An overview of available data regarding the effects of various antihypertensive drugs on erectile function is beyond the scope of this article, but there is some evidence that  $\beta$  blockers and diuretics may adversely affect sexual function more than other antihypertensive medications. In placebo-controlled studies, however, this has not been proven.<sup>25</sup> It should be remembered that: 1) hypertensives have more

erectile dysfunction than normotensives; 2) most people who begin therapy for hypertension are usually older than 50, a time when sexual function is beginning to worsen; and 3) decreasing blood pressure by any means may affect penile blood flow, especially in people older than 60.

No definite data exist regarding the role of smoking, alcohol intake, and the level of physical activity on erectile function in patients with essential hypertension.

### PHYSIOLOGY AND PATHOPHYSIOLOGY OF ERECTION

#### Physiology of Normal Erection

A successful erection and satisfactory sexual intercourse is a complex process, implicating neurosensory and neuromotor pathways, hormonal and vascular changes, interpersonal and psychosocial relationships, and cultural and personal beliefs.

The penis is kept in a flaccid state in the absence of sexual stimulation via a baseline sympathetic tone that results in tonic contraction of cavernosal smooth muscle. Erection starts with central brain stimulation of arousal centers, resulting in an increase of parasympathetic activity that overrides the basal sympathetic tone. Subsequently, nitric oxide (NO) synthase activity increases, resulting in NO release from non-adrenergic, noncholinergic neurons and endothelial cells which, in turn, stimulates guanylate cyclase, leading to elevated intracellular levels of cyclic guanosine monophosphate. Increased cyclic guanosine monophosphate levels result in the decrease of intracellular calcium, thus causing dilation of penile vessels, relaxation of the corporeal smooth muscle, and increased arterial inflow and passive restriction of penile venous outflow. When ejaculation occurs or sexual stimulation is withdrawn, there is a massive sympathetic discharge that results in vasoconstriction and detumescence.

The ability to attain and maintain a firm erection requires sufficient arterial inflow and efficient trap-

ping of venous outflow. Thus, clinical conditions that negatively affect vascular function are expected to exert deleterious effects on erectile function. Essential hypertension and atherosclerotic cardiovascular disease represent such clinical entities.

### Erectile Dysfunction Pathogenesis in Essential Hypertension

Several lines of evidence indicate that the pathophysiologic (structural and functional) abnormalities induced by hypertension per se may be implicated in the occurrence of erectile dysfunction.

Animal data indicate that hypertension results in structural changes in penile vasculature. Cavernous vessels are affected by high blood pressure in the same way as vessels throughout the vascular tree. Recent data show that apart from vascular smooth muscle hypertrophy of the cavernous arteries, the smooth muscle layer in the cavernous space and collagen type III fibers in the extracellular matrix are increased in hypertensive compared with normotensive rats.<sup>29,30</sup>

Angiotensin II is known to induce contraction of the corporal smooth muscle in vitro and in vivo via angiotensin type 1 receptors. Angiotensin II levels increase during the detumescence phase of erection in humans, underlining the role of angiotensin II in the termination of penile erection. The intracavernosal injection of angiotensin II terminates spontaneous erection in dogs; in contrast, the intracavernous injection of an angiotensin receptor blocker dose-dependently increases the intracavernosal pressure.<sup>31</sup> Angiotensin II induces vascular hypertrophy in hypertension and induces endothelial dysfunction through NO reduction and may be responsible for the structural and functional changes in penile vasculature observed in hypertension. Recent animal data suggest that angiotensin receptor blockers may exert beneficial effects on the penile structural effects caused by hypertension.<sup>29</sup>

Other mechanisms implicated in erectile dysfunction in hypertension include enhanced chymase activity,<sup>32</sup> reduced testosterone<sup>33</sup> and bradykinin levels,<sup>34</sup> increased endothelin-1,<sup>35</sup> and polymorphisms of NO and angiotensin-converting enzyme genes.<sup>36,37</sup> Ongoing research should help clarify their contribution in erectile dysfunction.

### ERECTILE DYSFUNCTION AND CARDIOVASCULAR RISK FACTORS

One of the most important advances in studies of erectile dysfunction is establishing its relationship to cardiovascular disease. The structure of erectile tissue and the vascular system are essentially

similar; thus, factors affecting erectile function might also affect other vascular beds. Since erectile function regulation seems more complex than regional blood flow modulation in most of the extracavernosal sites of the vasculature, erectile dysfunction may be an early marker of an impaired vasoactive regulatory environment.

Several lines of data indicate that coronary heart disease and erectile dysfunction share common risk factors.<sup>1</sup> In MMAS, erectile dysfunction in subjects with cardiovascular risk factors was higher than in controls (31% vs. 19.6%)<sup>1</sup>; the probability of undiagnosed coronary heart disease in people with erectile dysfunction is about 40%.<sup>38</sup> Erectile dysfunction correlates with the number of coronary vessels occluded.<sup>39</sup> Thus, physicians who treat patients with erectile dysfunction should be aware of the possibility of underlying cardiovascular disease.

In conditions such as hypertension and diabetes, the underlying pathophysiologic process may result in erectile dysfunction. On the other hand, erectile dysfunction may actually be a risk marker of cardiovascular complications in hypertensive patients.<sup>40</sup> Recent animal data suggest that erectile dysfunction may be an early marker for hypertension since the onset of erectile dysfunction is detectable before the onset of hypertension.<sup>41</sup>

### FEMALE SEXUAL DYSFUNCTION

Female sexual dysfunction has probably been prevalent in society since ancient times; however, it has not received much attention until recently. Improvements in medical care have allowed our approach to broaden from treatment of life-threatening diseases to disorders that detract from the quality of life.

Female sexual dysfunction can be divided in four broad categories: 1) disorders of sexual desire; 2) sexual arousal; 3) orgasm; and 4) sexual pain. It may be more frequent than male sexual dysfunction (43% vs. 31%) according to a 1999 report, based on the US National Health and Social Life Survey.<sup>42</sup> Recent studies have confirmed the high prevalence of female dysfunction in the general population.<sup>43,44</sup>

It is generally accepted that the prevalence of sexual dysfunction in individuals with a disease is higher than the prevalence in the healthy population; however, data in hypertensive women are not conclusive. Existing data include the TOMHS study (which, although a large double-blind, controlled randomized trial, has several limitations)<sup>25</sup> and a rather small case-control study that addressed female sexual dysfunction in 104 women with mild hypertension (67 on treatment) in comparison with 107 healthy controls.<sup>45</sup> It was reported that hyper-



tensive women exhibited decreased vaginal lubrication, less frequent orgasm, and more frequent pain compared with normotensive women.

The relative lack of data regarding female sexual dysfunction in hypertension does not imply that hypertensive women are free of sexual problems; rather, it suggests that adequate studies have not been performed and appropriate questions have not been asked. In a sensitive manner, sexual dysfunction must be routinely addressed in hypertensive women.

#### INCLUSION OF ERECTILE DYSFUNCTION DATA IN HYPERTENSION GUIDELINES

Despite the fact that available data indicate that erectile dysfunction represents a significant associated medical condition in patients with essential hypertension (if not a consequence), recently published guidelines either do not comment on the issue or address it rather superficially.

The European Society of Hypertension/European Society of Cardiology guidelines (2003) completely ignore this topic.<sup>46</sup> The British guidelines (2004) mention erectile dysfunction only as an adverse effect of diuretics and  $\beta$  blockers.<sup>47</sup> The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) summarizes erectile dysfunction<sup>48</sup>; however, it mostly deals with the effects of antihypertensive therapy. Although we do not argue with the JNC 7, we believe that this issue deserves further analyses so that erectile dysfunction will be properly recognized and managed in hypertensive patients.

#### MANAGEMENT OF ERECTILE DYSFUNCTION IN HYPERTENSIVE PATIENTS

Although several therapeutic options are available, phosphodiesterase-5 inhibitors represent the first choice in treatment. Phosphodiesterase-5 inhibitors are effective in patients with essential hypertension and may be safely coadministered with all classes of antihypertensive drugs (caution with  $\alpha$  blockers), even in patients taking multiple antihypertensive agents.<sup>49,50</sup>

Patients should be stable on  $\alpha$  blockers prior to initiating a phosphodiesterase-5 inhibitor at the lowest dose. Three phosphodiesterase-5 inhibitors (sildenafil, vardenafil, and tadalafil) have been currently approved by the FDA, with differences in pharmacokinetic characteristics (mainly onset or duration of action, and food effect on absorption). A more extensive review regarding antihypertensive agents and erectile dysfunction will be published in a forthcoming issue.

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