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## STATE-OF-THE-ART PAPERS

# Erectile Dysfunction in Heart Failure Patients

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Chronic heart failure (HF) and erectile dysfunction (ED) are 2 highly prevalent disorders that frequently occur concomitantly. Coronary artery disease, HF, and ED share several common risk factors, including diabetes mellitus, hypertension, smoking, and dyslipidemia. Additionally, the distinct physiologic sequelae of HF create unique organic and psychologic factors contributing to ED in this patient population. Standard HF therapy with beta-receptor blockers, digoxin and thiazide diuretics may worsen sexual dysfunction owing to medication side effects. This may, in turn, lead to noncompliance in misguided efforts to retain satisfactory sexual activity, with secondary worsening of cardiac capacity. This review describes the unique aspects of ED in the HF population. (J Am Coll Cardiol 2006;48:1111-9) © 2006 by the American College of Cardiology Foundation

Erectile dysfunction (ED) is the inability to achieve and/or maintain a penile erection sufficient enough to participate in satisfactory sexual activity (1). The 1998 FDA approval of sildenafil citrate (Viagra) as oral therapy for ED brought this once "private" disease into the public eye, with increasing interest by patients and physicians alike. Although quantifying the incidence of ED is inherently difficult, the Massachusetts Male Aging study demonstrated that among men 40 to 70 years of age, 52% experience some degree of ED (2). As the links between ED and cardiac disease are unveiled, clinicians are increasingly recognizing ED as an important harbinger of cardiac disease.

Heart failure (HF), also a highly prevalent condition, shares several risk factors with ED and frequently occurs concomitantly. Heart failure patients experience a decreased libido and frequency of coitus, negative changes in sexual performance, and a general dissatisfaction related to their sexual function (3). Although the coexistence of ED and coronary atherosclerotic disease (CAD) is well described, prevalence in the HF population is less delineated. In one small cohort of 62 HF clinic patients, approximately three-quarters reported compromised libido and ED (3). In a cohort of more than 300 HF patients, more than 90% reported reduced libido and erectile problems, which was independent of the New York Heart Association (NYHA) functional class (our data, unpublished). In our own chronic HF population, at least 75% of patients admitted to experiencing ED, regardless of the etiology of their HF (i.e., whether ischemic or nonischemic in origin). This suggests that HF itself, rather than simply atherosclerosis, contributes to the development of sexual dysfunction.

Because atherosclerosis is a leading cause of HF, many shared characteristics of these diseases have been linked to ED. Additionally, physiologic alterations specific to HF have been identified as important contributors to ED. Physicians are increasingly faced with the challenge of managing CAD, HF, and ED simultaneously. As such, it is imperative that we understand the common mechanisms of these disease processes and implications of their treatments. The causes of ED in this population, as well as treatment options, will be discussed in detail.

## PATHOPHYSIOLOGY OF ERECTILE FUNCTION AND DYSFUNCTION

Normal sexual function occurs via a symphony of simultaneous interplay between psychologic, hormonal, vascular, and neurologic factors. Ultimately, erection is a vascular phenomenon, beginning with increased arterial flow into the corpora cavernosa and spongiosum. Engorgement of these chambers eventually compresses venous outflow channels, thereby enlarging and hardening the penis (1). Maximal penile engorgement requires smooth muscle relaxation within the vascular chambers (4). Nitric oxide (NO), produced by cavernosal nerves and vascular endothelium, is a key contributor to the decreased penile vascular tone essential to normal erectile function (4,5). Nitric oxide stimulates adenylate cyclase, which increases intracellular cyclic guanosine monophosphate (cGMP) production (4). Cyclic GMP and cyclic adenosine monophosphate (cAMP) are the principal mediators of erectile smooth muscle relaxation (6). Neurogenic NO results in acute vasodilation of the corpus cavernosum, and is therefore crucial to achieving erection, whereas endothelially released NO plays a greater role in maintaining an erection (7). Cyclic GMP metabolism, mediated primarily by intracavernosal type 5 cGMP phosphodiesterase, revokes these vasodilatory effects, resulting in detumescence (8).

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**Abbreviations and Acronyms**

ACE	=	angiotensin-converting enzyme
ARB	=	angiotensin-receptor blocker
CAD	=	coronary atherosclerotic disease
cGMP	=	cyclic guanosine monophosphate
ED	=	erectile dysfunction
HF	=	heart failure
NO	=	nitric oxide
NYHA	=	New York Heart Association
PDE-5	=	phosphodiesterase-5

Alterations in any of the systems described can hinder the ability to achieve and maintain an erection. Inadequate vascular smooth muscle relaxation is the common final pathway leading to ED, and can be impaired by a number of organic and psychogenic conditions that alter the NO-cGMP pathway (7,9). Psychogenic factors such as stress, in addition to the treatment of certain psychologic conditions, may interfere with erectile function (10). Architectural abnormalities such as a structural imbalance of trabecular smooth muscle and connective tissue may hinder penile engorgement (11). An imbalance of vascular contractile (norepinephrine, endothelin, and prostanoids) and relaxation (vasointestinal polypeptide and NO) mediators can also disturb normal erectile function (12).

**ERECTILE DYSFUNCTION AS  
A MARKER OF CARDIAC DISEASE**

Atherosclerosis is a systemic vascular disease and is the most common cause of vasculogenic ED in older men (13,14). Erectile dysfunction shares several modifiable risk factors with cardiovascular disease, including atherosclerosis (15), hypertension, hyperlipidemia, diabetes mellitus (16), smoking (17), obesity, and sedentary lifestyle (18). Recent data suggest that ED may be an indicator of underlying CAD, and vice versa.

Men with ED appear to be at higher risk of myocardial infarction and peripheral vascular disease (19,20). Among patients with coronary artery disease, prevalence reports of ED have ranged from 42% to 75% (21-28). Montorsi et al. reported the rate of ED in patients with CAD to be as high as 42% to 57%. Conversely, the incidence of positive exercise stress testing in patients with ED ranged from 5% to 56% (14). Erectile function has also been correlated with coronary plaque burden and number of diseased coronary arteries (21,29).

The overlap between ED and CAD has developed some enthusiasm for considering ED as penile angina, as well as a stimulus to initiate cardiac screening. Shamloul et al. (30) reported penile peak systolic velocities less than 35 cm/s to have 100% specificity for predicting ischemic heart disease. In patients with angiographically proven CAD and clinical ED, a study reported that 67% experienced symptoms of ED before coronary symptoms, with sexual symptoms occurring a mean of 38.8 months earlier. This incidence

increased to 100% in type I diabetes patients (22). More recently, analysis of generally healthy and active men comprising the placebo arm of the Prostate Cancer Prevention Trial found that the development of ED frequently preceded development of coronary events, with an adjusted hazard ratio of 1.25 (confidence interval 1.02 to 1.53;  $p = 0.04$ ) for developing angina. Although atherosclerosis is a common cause of HF, the development of ED did not confer similar predictive values for developing HF (31).

Endothelial dysfunction appears to be a common link between ED and CAD. Because endothelial dysfunction is a hallmark of chronic HF, the overlap between ED and HF is not surprising. Whether endothelial dysfunction plays a role in ED in nonischemic cardiomyopathy without atherosclerosis, however, is unknown. Alterations in the endothelial L-arginine-NO-mediated smooth muscle relaxation pathway have been demonstrated in atherosclerotic coronary arteries of humans and animals (32-35). These findings are similar to those seen in the penile L-arginine-NO pathway and would support the concept that vasculogenic changes in the penile vascular bed mirror those in the coronary arteries. In fact, systemic endothelial-dependent vasodilation is decreased in men with ED (36,37). Because ED is associated with a high incidence of occult cardiovascular disease (28), this might be even more pronounced in diabetic patients with coronary artery disease but without any cardiovascular symptoms.

**FACTORS IN HEART FAILURE  
CONTRIBUTING TO ERECTILE DYSFUNCTION**

Heart failure patients may experience ED for a variety of reasons, similarly to the general population. These include underlying atherosclerosis, traumatic injury, neurologic pathology, hormonal deficiencies, medication side effects, and psychogenic contributions. Additionally, HF is a disease state with unique social, psychologic, physiologic, and drug-related consequences that may contribute to the high incidence of ED. The various causes and potential mechanisms of ED in this patient population have been summarized in Table 1.

**Psychologic influences.** Depression and anxiety are common comorbid conditions in HF. In fact, cardiovascular disease, ED, and depression have been described as a mutually reinforcing triad (38). It is unknown whether HF and/or ED causes depression or if these conditions develop independently. Depressive symptoms may fluctuate with the natural course of HF and may be due to the physical limitations affecting daily activities as well as the poor prognosis of many of these patients (39-41). Performance anxiety and fear of death also play a role in sexual dysfunction (42). Further complicating matters, depression, and anxiety are frequently treated with selective serotonin-reuptake inhibitors (SSRIs), which are well known to adversely affect sexual function. Additionally, the condition of ED may play a role in the genesis of depression and

**Table 1.** Causes of Erectile Dysfunction in Patients With Heart Failure

Cause	Mechanism
Psychogenic	
• Depression	• Decreased libido
• Performance Anxiety	• Increased sympathetic tone
• Treatment	• Medications (i.e., SSRIs)
• Fear	
Atherosclerosis	• Decreased penile arterial inflow • Endothelial dysfunction
Impaired cardiovascular exercise tolerance	• Blunted heart rate response • Blunted stroke volume
Impaired vasomotion	• Impaired endothelial-independent vasodilation • Endothelial dysfunction • Increased endothelin 1 • Increased noradrenalin • Decreased prostacyclin
Medications	
• Beta-adrenergic receptor blockers (some)	• Unknown mechanism
• Digoxin	• Corporal smooth muscle sodium-pump inhibition
• Spironolactone	• Androgen suppression
• Diuretics	• Unknown mechanism

SSRIs = selective serotonin reuptake inhibitors.

anxiety, and successful ED treatment may also improve these psychological conditions.

**Cardiovascular exercise tolerance.** Although difficult to standardize, the “average” coitus appears to expend approximately 5 metabolic equivalents or is roughly comparable to a brisk walk up to two flights of stairs (43). Level of sexual function appears to have a significant link with the 6-min walk test. Conversely, there is only a weak correlation with NYHA functional class and no relationship between sexual performance and ejection fraction (3). On the other hand, patients in NYHA class IV may be unlikely to express sexual desire owing to overwhelming symptoms of dyspnea. In HF, exercise capacity is limited by the inability to increase heart rate and stroke volume beyond a submaximal stage of exercise (44). Patients with chronic HF maintain increased vasoconstriction with decreased exercise-induced vasodilation (45). Neurohormonal activation leads to lack of preload response, impaired autonomic regulation, and increased vascular resistance, all of which appear to contribute to the blunted hemodynamic response to exercise seen in HF. Additionally, severely reduced left ventricular function reduces cardiac capacity, which may further limit physical exertion, including that required for satisfactory sexual intercourse.

**Atherosclerosis.** Atherosclerosis is a systemic disease, and is the most common cause of cardiomyopathy in the U.S. It also accounts for approximately 40% of ED in men over 50 years of age (15). Intimal hyperplasia and plaque deposition can create focal stenosis of the common iliac, hypogastric, or pudendal arteries, thereby decreasing arterial inflow into the penile corpora cavernosa (46). Additionally, atherosclerosis

is associated with endothelial dysfunction, which has also been implicated in ED (as discussed in detail subsequently).

**Altered vasomotion.** Endothelial dysfunction has emerged as a common link between coronary atherosclerosis and ED. Studies evaluating whether or not NO production is altered in HF are conflicting (46–52). It has been postulated that endothelial damage leads to decreased bioavailability of endothelium-derived NO, possibly via mRNA down-regulation of endothelial NO synthase and cyclooxygenase. Such a deficiency appears to be specific to the physiologic state of HF (53). Other theories link decreased NO bioavailability to underlying atherosclerosis, including alterations in the L-arginine–NO pathway (32–35), consequences of oxygen-derived free radicals (54), and cell surface receptor abnormalities at the G protein level (55).

Heart failure is also associated with an imbalance of several other circulating vasomodulators that work at the endothelial level. Increased levels of potent vasoconstrictors, such as endothelin, have been demonstrated in HF (56,57). Endothelin 1 is thought to play a major role in maintaining smooth muscle tone of the corpus cavernosa by inducing sustained contractions in the corpus cavernosa and penile vessels (4,58). Endothelin may also modulate other contractile agents such as noradrenalin (59–61), cellular proliferation, and/or phenotypic expression (62). These changes are accompanied by a reduction in circulating vasodilators such as prostacyclin (63). This imbalance of vasomodulators favors vasoconstriction, thereby prohibiting the vascular events necessary to achieve and maintain adequate erection.

Heart failure patients also develop dysfunctional endothelium-independent vasodilatation (52,64). This may result from decreased arterial compliance, impaired responsiveness due to cGMP dysfunction, or altered NO diffusion through the arterial wall (65–67). Coupled with endothelial dysfunction, the effects of these changes may be amplified clinically.

## DRUG THERAPY IN HEART FAILURE AND ERECTILE DYSFUNCTION

Several of the medications used as cornerstone HF therapy have been implicated in causing or worsening ED. In general, most of the studies are small and limited by the inability to excise medication effects from the consequences of underlying diseases such as HF, hypertension, and atherosclerosis. Treating HF may attenuate some of these adverse physiologic adaptations, and it is expected that improving cardiac function would improve cardiac capacity. However, there are no data establishing whether or not effective HF treatment has beneficial, deleterious, or any net effect on sexual function.

**Digoxin.** In an analysis of multiple cardiovascular medications, digoxin has had the highest association with complete ED (68), although the mechanism is not understood. Early studies described high serum estrogen, as well as lower testosterone and luteinizing hormone with digoxin use

(69,70). More recent studies did not confirm these results (71-73). Other studies point to digoxin-associated corporeal smooth muscle sodium-pump inhibition, which leads to corporeal contraction and impaired NO-induced relaxation (68,74).

**Diuretics.** Several diuretics have been associated with sexual dysfunction, although the mechanism again remains ill defined (75). Specifically, the thiazides chlorthalidone and hydrochlorothiazide have been associated with impaired sexual function (76,77). In one study, 10% to 20% of patients taking thiazide diuretics experienced decreased sexual function (78). In another study, total sexual symptom distress score worsened when hydrochlorothiazide was added to propranolol therapy. Conversely, patients taking captopril did not experience a change in sexual symptoms with the addition of hydrochlorothiazide (79). Spironolactone, the aldosterone antagonist currently used as standard HF therapy, has antiandrogen effects and thereby may cause erectile failure, gynecomastia, and decreased libido (1). Whether or not these effects will be seen with the newer more selective mineralocorticoid receptor eplerenone remains to be seen (80).

**Beta-adrenergic receptor blockers.** Historically, beta-blockers have been linked to depressed erectile function (75). Initial theories blamed decreased perfusion pressure and/or direct effects on smooth muscle, although the same adverse sexual effects are not seen with alpha-adrenergic receptor blockers. In fact, alpha-blockers may actually improve sexual dysfunction (81). Beta-blockers may also potentiate alpha-1 adrenoceptor-mediated corporal smooth muscle contraction, thereby interfering with erectile function (1). Propranolol use appears to be associated with significant sexual dysfunction (79). More recently, carvedilol, the now preferred agent for beta-blocker therapy in HF patients, has also been implicated in sexual dysfunction. A recent study comparing carvedilol with the angiotensin-receptor blocker (ARB) valsartan demonstrated a decline in sexual activity within the carvedilol-treated group. However, this was in a hypertensive (not HF) population, and patients with comorbidities such as diabetes mellitus and coronary atherosclerosis were excluded. Additionally, it is unknown if these data represent deleterious effects of carvedilol or beneficial effects of valsartan (82).

Curiously, sexual side effects are not experienced by the majority of patients taking beta-blockers. Studies with both metoprolol and atenolol have demonstrated neutral effects on sexual function (76,83). In a study of 96 cardiovascular patients, 31% reported ED after beginning atenolol and being informed of its possible adverse sexual side effects. However, only 3% of men who were similarly treated reported ED when they were blinded to the study drug, suggesting that ED with beta-blockers is related to patient knowledge of these potential side effects (84). The disparate results of these varied beta-blockers and dosages may be related, at least in part, to separate actions on peripheral structures and the central nervous system (85).

In our own experience, however, several HF patients who experienced reduced libido, ED, and even depression while being treated with metoprolol (as, in the past, with atenolol) showed improved erections after being switched to carvedilol. This may be due to improved contractile function in addition to the alpha-blocking properties and the resultant improved perfusion.

**Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers.** The impact of angiotensin-converting enzyme (ACE) inhibitors and ARBs on ED is equally elusive. Angiotensin-converting enzyme inhibitors, particularly captopril, have been associated with improved sexual function (86,87). Although some supporters attribute these benefits to improved cardiac function, there are insufficient data to support this. There is an even greater paucity of data regarding the effects of the newer ARBs on sexual function. A Japanese study reported that hypertensive patients <65 years of age experienced improved sexual function when switched from a calcium-channel blocker to candesartan (88). When the ARB valsartan was compared with the beta-blocker carvedilol, long-term therapy with valsartan was associated with improved sexual activity (82). Dusing (89) confirmed these results when he reported improved orgasmic function, intercourse, and overall sexual satisfaction in hypertensive patients treated for 6 months with valsartan. Once again, data specific to the HF population are lacking. In our own patients, we have frequently replaced ACE inhibitors with ARBs and have achieved mixed results.

## TREATING ERECTILE DYSFUNCTION IN THE HEART FAILURE PATIENT

**Safe sex in heart failure.** In general, the metabolic demands of sexual activity are modest. The safety of engaging in sex, similarly to other physical activities, depends on the cardiovascular reserve of the patient. The Second Princeton Consensus Conference offers guidelines to assessing the risk of sexual activity in all cardiac patients, including the HF patient. Patients whose symptoms are NYHA class I are not considered to be at increased risk of coitus-induced cardiovascular events. Those patients with NYHA class II symptoms are classified as "intermediate/indeterminate" risk of exacerbating symptoms during sexual activity and should be properly assessed and rehabilitated so that they can be restratified into the "low- or high-risk" category before sexual activity. Although the exact risk is not known, HF patients with NYHA class III or IV symptoms are considered to be at "high-risk" for further decompensation with sexual activity. Under these guidelines, high-risk patients should be treated and stabilized before engaging in coitus (90). Even more in diabetic patients with HF and CAD, it is recommended not only to stabilize the cardiac condition but also to exclude silent myocardial ischemia before resuming sexual activity or starting treatment for ED.

Importantly, the aforementioned guidelines are based on current knowledge of pathophysiologic demands of sexual activity and physiologic alterations of HF but not on randomized controlled trials. In our own experience with patients with stable NYHA class III symptoms, we have recommended ED therapy, if warranted, and have seen satisfactory results, whether patients were treated with phosphodiesterase-5 (PDE-5) inhibitors or even with implantable devices (as described subsequently).

**Managing heart failure.** Intuitively, the first goal for treating patients with HF and ED is to optimize HF therapy, as endorsed by the newly updated American College of Cardiology/American Heart Association guidelines (91). Improved cardiac status may reduce symptoms, improve exercise capacity, and decrease depression, thereby secondarily improving sexual activity. Several studies have demonstrated improved endothelial function in HF patients receiving various medical therapies, including ACE inhibitors, ARBs, statins, and dobutamine therapy (92-96). This may be due to the medications themselves and/or physiologic shifts from cardiac compensation. One would expect that improvement in such endothelial function would improve erectile function.

Next, cardiologists should inquire about sexual function and its role in the individual patient's life, because this is unfortunately not standard care in the primary care (or most cardiologists') practice. If clinically feasible, drugs with potential adverse sexual side effects should be discontinued or replaced. The practices we have included in our own multidisciplinary sexual health clinic (for high-risk cardiac patients) include avoiding digoxin and thiazide diuretics as well as replacing beta-blockers such as propranolol with carvedilol (owing to its additional alpha-blocking effects). Additionally, we would recommend replacing spironolactone with eplerenone, because one would expect the more selective agent to have less antiandrogen effects. After the preceding adjustments have been made, we would then recommend a more specific approach to ED.

**Phosphodiesterase-5 inhibitors in heart failure.** Sildenafil citrate (Viagra) was the first oral drug approved for ED in the U.S. The newer PDE-5 inhibitors vardenafil (Levitra) and tadalafil (Cialis) appear to be as effective as sildenafil (65-69). By inhibiting type 5 phosphodiesterase, the PDE-5 inhibitors enhance cGMP-NO-mediated vasodilatation by preventing PDE-5 catabolism of cGMP and thereby delaying detumescence. The PDE-5 inhibitors increase the number and duration of erections as well as the percentage of successful sexual intercourse (97,98).

The American College of Cardiology and the American Heart Association expressed concerns in their 1999 consensus document regarding the lack of cardiovascular safety data from controlled clinical trials of sildenafil in men who had ED and congestive HF. Initially, HF was listed as a relative contraindication for the use of sildenafil, owing to concerns of concomitant use of other vasodilators that could result in significant hypotension, but perhaps more owing

to lack of data in the HF population (99). Subsequently, a multicenter, prospective, randomized, double-blind, placebo-controlled, flexible-dose trial demonstrated that flexible dosing of sildenafil from 25 to 100 mg was well tolerated, improved erectile function, and increased sexual satisfaction in ambulatory subjects with mild to moderate (congestive) HF (100). These findings echoed the results of 2 earlier smaller investigations (101,102).

Also of interest are potential hemodynamic benefits of sildenafil in the HF patient. Despite initial concerns that sildenafil-induced vasodilation may provoke a reflex tachycardia, this has not been substantiated in clinical trials. Bocchi et al. (101) studied several hemodynamic parameters in HF patients treated with sildenafil during the 6-min walk test and maximal exercise testing. Sildenafil decreased heart rate response throughout the 6-min walk test and increased the total exercise time. Basal blood pressure was slightly lower before either test, but there was no difference during exercise. In their study of sildenafil use in HF patients, Webster et al. (102) found no significant change in blood pressure or heart rate from baseline. More recently, a small study by Hirata et al. (103) further confirmed that sildenafil use decreased heart rate acutely. Additionally, they reported a significant increase in cardiac index (by  $0.37 \text{ l/min} \times \text{m}^2$ ), which is likely due to the observed reduction in total systemic resistance. Another potential hemodynamic benefit of sildenafil in HF is that at low doses, it has been shown to increase endothelium-dependent flow-mediated vasodilation (104).

There are, however, some remaining concerns that have been raised regarding the long-term effects of sildenafil use in HF. Chronic use of milrinone, a PDE-3 inhibitor, has been associated with increased mortality in patients with moderate to severe CHF (105). There is a theoretical risk that long-term use of PDE-5 inhibitors, because they cause some degree of PDE-3 inhibition as well, also may prove to be harmful. However, because sildenafil is highly selective for PDE-5 inhibition, it would seem unlikely to significantly alter myocellular cAMP levels as is seen with long-term milrinone use. Previous experiments evaluating the effects of PDE-5 inhibition on levels of cyclic nucleotides and cardiac contractility have been inconsistent, likely owing to differing species, pharmacologic agents, and doses. Available clinical data in patients with ischemic heart disease, HF, and primary pulmonary hypertension demonstrate systemic vasodilation without clear chronotropic and inotropic effects (106).

Although the newer PDE inhibitors vardenafil and tadalafil may not pose additional cardiac risks, no clinical safety data on their use is available in the HF patient population. As of now, we preferably recommend sildenafil, and sometimes vardenafil, for safe use in chronic stable HF patients. In general, tadalafil should be avoided owing to its longer half-life. We usually start low-dose sildenafil at 25 to 50 mg, with repeated use on separate days, and eventual dose increments up to 100 mg. All of the PDE-5 inhibitors

potentiate the hypotensive effects of nitrates and are contraindicated with concomitant nitrate or other NO donor use (nitroprusside, molsidomine) (6).

In general, most HF patients are initially successfully treated with PDE-5 inhibitors, whereby success in clinical studies is measured as improvement of erections or other markers, such as the International Index of Erectile Function score. In follow-up of our own patients, however, only 30% to 40% of patients remain on PDE-5 inhibitors long term and might seek further ED treatment (such as surgical alternatives) in the future.

**Other oral therapy.** Currently, there are no data supporting the efficacy of nutritional supplements, herbal therapy, or vitamins in the treatment of ED in the general or HF population (107). Other commonly seen oral drugs for the treatment of ED are apomorphine (Apokyn, Uprima) and yohimbine (Yocon). Apomorphine is centrally acting and has shown mild clinical efficacy in treatment of ED (108); however, it is currently unavailable in the U.S. Yohimbine is an alpha-2 receptor blocker with limited efficacy in the treatment of ED (109). Its use is not recommended in the HF patient owing to its cardiovascular side effects, including tachycardia and hypertension.

**Other traditional ED therapy.** In the HF population, there are currently no known adverse cardiovascular effects to androgen replacement therapy when indicated, intraurethral suppositories, penile prosthesis, or vacuum-assist erection devices. However, penile injection therapies (and sometimes vacuum device therapy) have some risks in HF patients who are on chronic anticoagulation. Although no large-scale data have reported severe bleeding episodes in patients taking aspirin and clopidogrel, patients treated with warfarin would not be ideal candidates for these therapies owing to increased bleeding risks. In general, these therapies are best guided by the expertise of a urologist in close collaboration with the patient's cardiologist (110).

**Surgical management of ED.** Penile revascularization surgery is another treatment alternative for ED resulting from discrete localized arterial lesions. However, only a minority of ED patients have suitable vascular anatomy, and finding a vascular surgeon experienced in this uncommon procedure can prove to be difficult. Unfortunately, many urologists are reluctant to perform such elective surgeries in the HF patient, and long-term results are not very convincing. Surgical implants of penile prostheses are usually a last resort for men who have failed all other medical and semi-invasive treatments (111,112). These may, however, represent a viable alternative in otherwise untreatable ED in the HF population, as long as these patients are in optimized and stable cardiac condition. In our own HF patients, we are referring increasing number of patients for device implantation with good and satisfactory success rates. Even though it is an invasive surgical procedure, penile implant therapy as a last resort of ED treatment has been shown to have the highest success and satisfaction rates (113), even in our own HF population.

Finally, percutaneous transluminal angioplasty (PTA), is emerging as a potential treatment modality for patients with focal atherosclerotic lesions of the hypogastric (internal iliac), common iliac, or pudendal arteries. Few and small studies have reported success rates of 57% to 84% with resolution of ED after PTA of the common and external/internal iliac arteries as well as of the internal pudendal arteries (114-116). Randomized controlled studies are required to establish the definitive role of PTA in the treatment of arteriogenic impotence. At this time, it is a potential future treatment option for a select group of patients. This may become a suitable alternative for HF patients, because it would avoid the cardiovascular risks of general anesthesia.

## TREATING DEPRESSION

Psychologic counseling aids symptoms of depression and may thereby improve sexual function. However, as mentioned, many of the newer and more effective antidepressants, such as the selective serotonin reuptake inhibitors, can decrease libido and/or worsen erectile function (117). Conversely, trazodone, clomipramine, and other tricyclic antidepressants may cause delayed or retarded ejaculation, which would benefit men suffering from premature ejaculation (41,118). A small study demonstrated that HF patients with ED who were treated with sildenafil had improvement in depression scores during the treatment period (102). This finding further emphasizes the importance of the HF-ED-depression triad. The net effect of treating depression with potentially sexually deleterious medications remains unknown. An ethically reasonable approach is to adequately treat depression and then to counteract medication side effects with the use of PDE-5 inhibitors if necessary.

## SEXUAL COUNSELING

Patients may become noncompliant with their HF medical regimen, fearing that such medications cause or worsen sexual function. Many cardiac patients are uncomfortable discussing sexual function (119), despite their informational needs and desire to discuss their sexual health (119,120). To dispel fear and anxiety, couples should receive information about the physiologic requirements of sexual activity, the pathophysiology of HF (including its treatment) relative to sexual function, and the psychologic sequelae of HF. Although the literature describes HF patients as reluctant to discuss sexual function, it has been our own experience that when approached by their physician, patients are welcoming and appreciative of the opportunity to discuss this topic and explore treatment options.

## FUTURE TREATMENTS

The Rho A/Rho kinase pathway is emerging as a novel player in the regulation of penile erection, and future

investigations may further define its role in ED and HF (121). Neovascularization is another emerging therapy for the treatment of arteriogenic ED. Intracavernosal injection of vascular growth factors has been demonstrated in animal models and may eventually become another therapeutic option (122). Further clinical studies with selective endothelin antagonists should be considered, given their established elevation in HF and causative role in ED. Gene therapy may also play a future role; studies are currently being conducted in animals with gene transfer of endothelial NO synthase to the penises of aged rats (123).

## CONCLUSIONS

Erectile dysfunction is highly prevalent among HF patients, and can significantly and adversely affect quality of life. Erectile dysfunction, CAD, and HF share risk factors as well as underlying disease mechanisms, such as atherosclerosis and endothelial dysfunction. Additionally, there are unique sequelae to HF that may also contribute to ED, including depression, neurohormonal changes, an imbalance of circulating vasomodulators, reduced cardiac capacity, and potential adverse effects of HF medical therapy. Treatment with sildenafil is a safe option, but safety data on the newer PDE-5 inhibitors are lacking in the HF population. Despite the unique issues of sexual dysfunction in the setting of HF, most patients are not receiving adequate counseling in this matter. By raising physician and patient awareness of this common and important issue, we create the opportunity to further impact our patients' lives in a meaningful and positive way.

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## Erectile Dysfunction in Heart Failure Patients

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