Editorial Commentary

Novel non-pharmacological therapy to modulate the autonomic tone in patients with heart failure with pulmonary hypertension

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Autonomic nervous system (ANS) in heart failure (HF)

In chronic HF, it has been recognized that complex ANS imbalances including loss of parasympathetic nervous system (PNS) inhibition of sympathetic nervous system (SNS) reflex arcs exist and ANS balance can be deteriorated during heart failure exacerbation (1-3). Whereas SNS activation maintains cardiac output acutely by positive inotropic and chronotropic effects, however, chronic autonomic dysregulation with increased SNS activity and reduced PNS lead to progressive myocardial dysfunction, neurohormonal activation and increased risk of malignant arrhythmias and sudden cardiac death in patients with HF (4,5). Over-activation of SNS and attenuation of PNS input have long been known to be a cardinal feature in the pathophysiology of cardiac remodeling and systolic HF. In the study by Cohn *et al.*, in fact, the authors reported that plasma norepinephrine levels were independently predictive of mortality in patients with systolic HF (6).

ANS in pulmonary hypertension

In recent years, clinical relevance of ANS disturbances in pulmonary arterial hypertension (PAH) has attracted attention as a new therapeutic target irrespective of the existence of HF (7,8). PAH is a chronic pulmonary vascular disease characterized by increased pulmonary vascular resistance (PVR) leading to right ventricular (RV) failure with associated ANS disturbances (9). In the study by Chen *et al.*, pulmonary artery denervation (PADN) using catheter ablation improved hemodynamic function, exercise capacity and reduced PAH-related events and death in patients with PAH (mean PA pressure ≥25 mmHg at rest) of different causes (7). Given the fact that right HF in PAH is the consequence of increased arterial afterload, a full description of the cardiopulmonary unit is required (10). The cardiopulmonary unit is composed of two functional subsystems: the RV (contractility and chamber stiffness) and the pulmonary circulation (resistance and compliance). An adapted RV in PAH characterized by a slightly dilated RV with preserved systolic function and normal filling pressures usually have preserved RV to PA coupling described by systolic and arterial elastance (11). RV to PA coupling is maintained at resting conditions for as long as the RV can adapt but not a sensitive parameter to identify an early disease state.

Non-pharmacological modulation of ANS in HF with pulmonary hypertension

The salutary effects of established pharmacotherapies for HF, including renin-angiotensin-aldosterone system inhibitors and beta-blockers, are demonstrated to be related to modulation of ANS tone and related reductions in arrhythmia and favorable ventricular remodeling, especially in systolic HF. Nowadays, there has been expanding interest in the non-pharmacological strategies to modulate ANS tone in patients with HF and pulmonary hypertension. In the study by Zhang *et al.*, authors shown that PADN improved exercise capacity and reduced clinical events in left HF patients with combined pre- and post-capillary pulmonary hypertension (CpcPH) accompanied with reduced left atrial pressure and dosage reduction of diuretics (12). Compared to sham PADN with sildenafil treatment, PADN improved echocardiographic, hemodynamic and biological (NT-pro BNP) parameters at rest, leading to relief of symptoms and improved functional capacity at 6-month follow-up although 2 fatal pulmonary embolisms were occurred during the follow-up period. In patients with group 1 PAH sildenafil, an orally administered a selective inhibitor of 5-phosphodiesterase, targets the nitric oxide pathway and has been shown to increase pulmonary hemodynamics, functional capacity and survival. On the contrary, recent clinical trials have reported that there was no significant therapeutic effect of sildenafil on hemodynamics and functional capacity in HF (13). In the study by Wang *et al.*, interestingly, the authors showed that the neutral effects of sildenafilo in HF could possibly be related to a negative impact on mitochondrial function and endoplasmic reticulum stress (14).

Vagal nerve stimulation (VNS) in patients with systolic HF

Because autonomic imbalance with increased adrenergic and reduced parasympathetic activity (via the vagus nerve) may affect cardiac contractility and sinoatrial function, modulation of the ANS via VNS has been identified as a potential therapeutic target in HF. Stimulation of the vagal nerve is obtained through an implantable stimulator system that delivers electrical impulses via a bipolar cuff electrode around the vagus nerve in the neck (3). In the INOVATE-HF study by Gold *et al.*, authors shown that, in chronic HF patients, VNS improved exercise capacity (6-minute walk distance), quality-of-life and NYHA functional class as pre-specified secondary endpoint at the 12-month visit, however, did not reduce the rate of death or HF events (15). Comparison of recent randomized controlled trials of sildenafil and non-pharmacological modulation of ANS in HF is summarized in *Table 1* (12,13,15-17). Although PADN was shown to improve exercise capacity (6-minute walk distance) as primary end point in HF with CpcPH, further study is needed to determine the long-term survival benefit of PADN in the same patient cohort.

Potential mechanism of PADN in pulmonary hypertension

In most recent preclinical study using a rat model with PAH by Yoshida *et al.*, the authors reported that VNS restored autonomic balance, decreased mean PA pressure, attenuated pulmonary vascular remodeling, and preserved RV function and also that VNS improved the survival rate in both the prevention and treatment protocols (8). Furthermore, in this study, acute VNS did not change nitric oxide synthesis or pulmonary vascular mechanics, despite acute as well as chronic VNS exhibiting significant inflammatory suppression in rats with PAH. Potential mechanism of PADN with radiofrequency catheter ablation of the PA nerve plexuses in PA trunk in PAH might be similar to mechanism of VNS because both PADN and VNS has reported having little acute hemodynamic effect but improving hemodynamics, exercise capacity and symptoms at the 6-month follow-up after intervention (12,15,18). What is more, favorable therapeutic effect of PADN in HF patients with CpcPH was observed in left atrial pressure (reduction of PCWP and mitral E/e') leading to decreased PA pressure and PVR. In other words, PADN might have therapeutic effect in group 2 PAH. Of course, pathophysiological mechanism of elevating left atrial pressure is different between valvular heart disease and HF, and indeed between HF preserved and reduced ejection fraction. After all, because the precise underlying mechanisms of treatment effect of PADN has still reminded unclear, further study is needed to determine the salutary hemodynamic effects of PADN to improve clinical status in PAH patients irrespective of PAH phenotype.

Table 1 Comparison of randomized controlled trials of sildenafil and non-pharmacological modulation of ANS in HF

Study	n	NYHA	EF	RHC	Intervention	Control	Study duration	Primary efficacy endpoints	Primary efficacy endpoint met
PADN-5 (12)	98	II–IV	–	mPAP ≥25 mmHg; PCWP >15 mmHg; PVR >3.0 WU	PADN	Sildenafil and sham	6 months	Change in 6MWD from baseline	Yes
RELAX (14)	216	II–III	≥50%	–	Sildenafil	Placebo	6 months	Change in peak VO_2 from baseline	No
Hoendermis ES (16)	52	II–IV	≥45%	mPAP >25 mmHg; PCWP >15 mmHg	Sildenafil	Placebo	3 months	Change in mPAP from baseline	No
INOVATE-HF (15)	707	III	≤40%	–	VNS	Optimal medical treatment	16 months (mean)	Death or HF hospitalization	No
NECTAR-HF (17)	96	II–IV	≤35%	–	VNS	Stimulation off	6 months	Change in LVESD from baseline	No

MWD, minute wall distance; mPAP, mean pulmonary arterial pressure; PADN, pulmonary artery denervation; ANS, autonomic nervous system; HF, heart failure; VNS, vagal nerve stimulation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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