World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v6.i11.1175

World J Cardiol 2014 November 26; 6(11): 1175-1191
ISSN 1949-8462 (online)
© 2014 Baishideng Publishing Group Inc. All rights reserved.

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (4): Congestive heart failure

Positive airway pressure therapy for heart failure

Takao Kato, Shoko Suda, Takatoshi Kasai

Takao Kato, Department of Cardiology, Juntendo University School of Medicine, Tokyo 113-8421, Japan
Shoko Suda, Takatoshi Kasai, Department of Cardiology, Juntendo University School of Medicine and Cardio-Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine, Tokyo 113-8421, Japan
Author contributions: Kato T, Suda S and Kasai T drafted the article; Kasai T revised it critically.
Supported by Grant-in-Aid for Scientific Research (C) Grant, Japan, No. 26507010; Grant to the Respiratory Failure Research Group from Ministry of Health, Labor and Welfare, Japan
Correspondence to: Takatoshi Kasai, MD, PhD, Department of Cardiology, Juntendo University School of Medicine and Cardio-Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. kasai-t@mx6.nisiq.net
Telephone: +81-3-38133111 Fax: +81-3-56890627
Received: May 30, 2014 Revised: July 16, 2014
Accepted: September 18, 2014
Published online: November 26, 2014

Abstract

Heart failure (HF) is a life-threatening disease and is a growing public health concern. Despite recent advances in pharmacological management for HF, the morbidity and mortality from HF remain high. Therefore, non-pharmacological approaches for HF are being developed. However, most non-pharmacological approaches are invasive, have limited indication and are considered only for advanced HF. Accordingly, the development of less invasive, non-pharmacological approaches that improve outcomes for patients with HF is important. One such approach may include positive airway pressure (PAP) therapy. In this review, the role of PAP therapy applied through mask interfaces in the wide spectrum of HF care is discussed.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

Key words: Acute decompensated heart failure; Congestion; Continuous positive airway pressure; Non-invasive positive airway pressure ventilation; Sleep disordered breathing

Core tip: Less-invasive, non-pharmacological approaches may improve outcomes for patients with heart failure, and the role of positive airway pressure therapy is discussed in this review.

Kato T, Suda S, Kasai T. Positive airway pressure therapy for heart failure. *World J Cardiol* 2014; 6(11): 1175-1191 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1175.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1175

INTRODUCTION

Heart failure (HF) is a life-threatening disease and is a growing public health concern[1,2]. The prevalence of HF has increased along with the aging of the general population[3] and because of improved survival after acute myocardial infarction[4,5]. Indeed, a better understanding of the pathophysiology and medical management of myocardial infarction means that such patients are living longer with damaged hearts, and many of them go on to develop HF[5,6]. Despite recent advances in pharmacological management of HF, the morbidity and mortality from HF remain high[4,5]. Therefore, non-pharmacological approaches to HF, including cardiac resynchronization therapy, and left ventricular (LV) assist devices, are increasingly utilized. However, most non-pharmacological approaches are invasive, have limited indication and are considered only for advanced HF. Accordingly, the development of less invasive, non-pharmacological approaches that may improve outcomes for patients with HF is important.

Positive airway pressure (PAP) therapy represents a potentially beneficial non-pharmacological approach to the management of HF. PAP therapy involves the maintenance of positive airway pressure through invasive

(applied with endotracheal intubation or tracheostomy) or non-invasive (applied without endotracheal intubation or tracheostomy) means. Because we focused on less invasive approaches to the management of HF, we confined our discussion to non-invasive positive pressure ventilation, including continuous positive airway pressure (CPAP), in which PAP is applied through nasal masks, oro-nasal masks and face masks[7]. In the wide spectrum of HF care, PAP therapy can be used to improve oxygenation, decrease right ventricular (RV) afterload, alleviate hypoventilation and hypercapnia, improve lung and respiratory muscle functions, and normalize abnormal respiratory patterns. In this review, we discuss various types or modes, devices and equipment for PAP therapy, its effect on hemodynamics and respiration, and conditions for which PAP therapy should be considered in the care of HF patients. We also review the indications and evidence supporting the efficacy of PAP therapy in patients with HF.

EFFECT OF PAP ON HEMODYNAMICS AND RESPIRATION

All PAP therapies, which are considered for HF and mentioned later, adjunctively provide positive end-expiratory pressure. Therefore, the effect of PAP therapy, including positive end-expiratory pressure, on hemodynamics and respiration are described herein.

Effect on hemodynamics

PAP has several effects on hemodynamics. First, PAP diminishes systemic venous return and RV preload by increasing intrathoracic pressure[8-10]. Second, PAP alters pulmonary total vascular resistance (PVR), which is the major determinant of RV afterload, *via* an alternation in lung volume[11]. In the lungs, there are two types of vessels: the intra-alveolar vessels, which are compressed as lung volume increases, and the extra-alveolar vessels, which are exposed to dilating forces as lung volume increases. Thus, a change in total PVR is characterized by a U-shaped curve according to the alteration in lung volume (the lowest PVR can be observed in the lung volume around functional residual capacity)[12]. For example, when lung volume increases from residual volume to functional residual capacity, the effects of this increased volume on extra-alveolar vessels will predominate, and thus, vascular capacitance will increase. Consequently, total PVR will decrease. When the lung volume continues to increase from functional residual capacity to total lung capacity, the effects of this further increased volume on intra-alveolar vessels will predominate; vascular capacitance will therefore decrease, and total PVR will increase[12,13]. Although PAP without an excessive shift in lung volume does not cause a clinically important increase in RV afterload[12], it is possible that RV afterload can be increased by PAP[14]. Third, a decrease in RV preload (decrease in systemic venous return to RV) and an increase in RV afterload (increase in PVR) lead to a reduction in pulmonary venous return and limitations in LV inflow and filling. In addition, in cases with increased RV afterload, RV dilatation with a septal shift toward the LV can occur. This further limits the LV filling and causes reductions in cardiac output and overall organ perfusion[8,10,14-16]. Fourth, increased intrathoracic pressure relative to atmospheric pressure causes a pressure difference between the extrathoracic and intrathoracic cavities because most of the systemic circulation is at atmospheric pressure, which is lower than that of the LV and thoracic aorta[17]. Therefore, PAP therapy can reduce RV preload and increase RV afterload, whereas PAP therapy reduces LV preload and afterload (Figure 1). In general, subjects without HF are predominantly preload-dependent[18]. Therefore, in subjects without HF or in patients who manifest preload-dependent LV function, such as those with RV infarction or hypovolemia, a reduction in cardiac preload with PAP therapy may decrease cardiac output to a greater degree than decreasing afterload and its related increase in cardiac output[14].

Conversely, a failing heart is more sensitive to decreased afterload, and patients with HF are usually hypervolemic and thus insensitive to decreased preload. Therefore, patients with HF are predominantly afterload-dependent, and cardiac output can be increased by PAP therapy in those patients. Nevertheless, in HF patients, the preload- and afterload-dependent status will determine the cardiac output responses (increase or decrease) (Figure 1).

Effect on respiration

PAP also has several effects on respiration in HF. First, PAP maintains alveolar pressure and prevents the alveoli from collapsing at the end of expiration and thus improves gas exchange and oxygenation through the recruitment of alveolar units, counterbalance of hydrostatic forces leading to pulmonary edema, and maintenance of airway patency[19-22]. Particularly in HF patients with pulmonary congestion in whom lung compliance is impaired, PAP induces recruitment of collapsed alveoli, reversal of atelectasis, and induces a fluid shift from the alveoli and the interstitial space to the pulmonary circulation, consequently decreasing the amount of intrapulmonary shunting and improving oxygenation[21,23]. Second, PAP can reduce respiratory muscle load and the work of breathing[24-26] and can improve lung function through lung inflation and maintenance of functional residual capacity[27]. Third, PAP prevents upper airway narrowing and collapse and thereby functions as a "pneumatic splint"[28-30]. This is highly effective in the treatment of sleep-disordered breathing (SDB)[31], which is frequently observed in patients with HF[32]. Fourth, some PAP therapy provides pressure support during inspiration to maintain ventilation. This is particularly important in HF patients with hypoventilation. Fifth, if hypoxic pulmonary vasoconstriction occurs due to hypoxia in association with acute decompensated HF (ADHF) or HF accompanied by chronic obstructive lung disease (COPD)

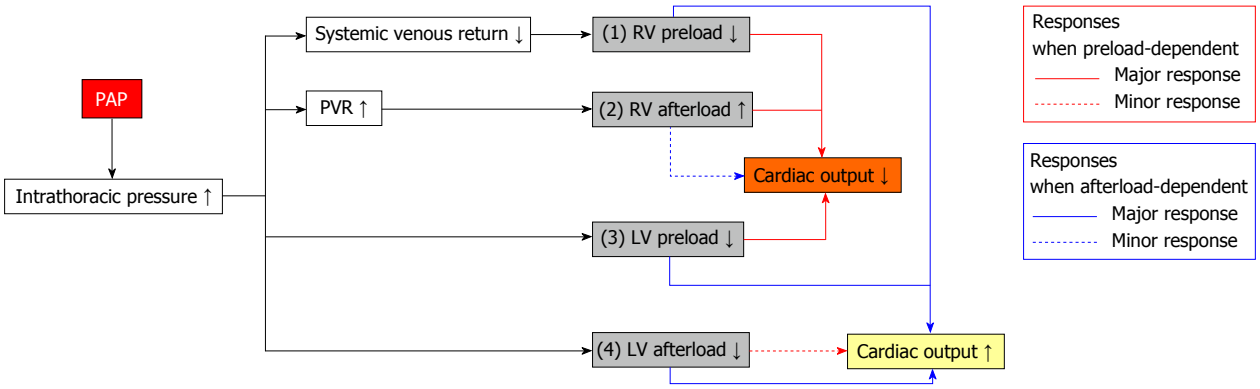

Figure 1 Effects of positive airway pressure on hemodynamics. First, PAP decreases systemic venous return and RV preload by increasing intrathoracic pressure; Second, PAP increases PVR by increasing lung volume. Thus, it is possible that RV afterload can be increased by PAP; Third, a decrease in RV preload and an increase in RV afterload lead to reductions in pulmonary venous return and limitations of LV inflow, filling and preload; Fourth, increased intrathoracic pressure relative to atmospheric pressure causes a pressure difference between the intrathoracic and extrathoracic cavities. Therefore, PAP may decrease LV afterload. In subjects without HF who are generally preload-dependent or in HF patients who manifest preload-dependent reduction, decreased RV and LV preload in addition to the increase in RV afterload may cause a net decrease in cardiac output, whereas a decrease in LV afterload may cause a minor response toward increasing cardiac output. Conversely, patients with HF are more sensitive to decreased afterload and are thus predominantly afterload-dependent. PAP therapy causes a net increase in cardiac output through decreases in RV preload, LV preload and afterload, whereas an increase in RV afterload may cause a minor response toward decreasing cardiac output. LV: Left ventricular; PAP: Positive airway pressure; PVR: Pulmonary vascular resistance; RV: Right ventricular; HF: Heart failure.

Table 1 Summary of equipped functions of each type/mode of positive airway pressure

	CPAP	Bi-level PAP	VAPS	ASV
Positive end-expiratory pressure	+	+	+	+
Pressure support during inspiration	-	+	+	+
Guarantee of tidal volume or minute ventilation	-	-	+	-
Servo-control of ventilation	-	-	-	+
Automated control of pressure level during expiration	+	-	-	+
Backup ventilation	-	±[1]	+[2]	+[2]

[1]Bi-level PAP devices that are only capable of spontaneous mode cannot provide back-up ventilation; [2]Most devices automatically provide a set backup ventilation rate based on their VAPS or ASV algorithm. ASV: Adaptive servo-ventilation; Bi-level PAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; VAPS: Volume assured pressure support.

and SDB, PAP can attenuate the increase in PVR by improving oxygenation through the abovementioned effect and by alleviating vasoconstriction. Consequently, such attenuation of increased PVR can be associated with improving hemodynamics. Finally, considering that the short-term servo-control of ventilation using adaptive servo ventilation (ASV) during wakefulness reduced muscle sympathetic nervous system activity in patients with chronic HF[33,34], keeping ventilation consistent with ASV may provide further beneficial effects on hemodynamics that are independent of the effects of PAP[35].

TYPES/MODES OF PAP IN HF TREATMENT

Several types or modes of PAP therapy can be considered for HF. Although each type or mode has different purposes, all of them apply positive pressure to the airway. In particular, all of them provide positive end-expiratory pressure. Thus, the benefits from the individual modes overlap. In this section, the types and modes of PAP generally applied for HF are described (Table 1).

CPAP

CPAP is the most widely used type/mode of PAP therapy in patients with HF. It provides a constant level of positive pressure to maintain airway patency during spontaneous breathing (Figure 2A). Because CPAP only provides a constant level of pressure during the entire respiratory cycle and because CPAP does not separately increase pressure during inspiration and thus does not directly support ventilation, sometimes CPAP is not classified as a form of non-invasive positive pressure ventilation. However, the International Consensus Conference in Intensive Care Medicine[7] defined non-invasive positive pressure ventilation as any form of PAP support applied without endotracheal intubation, in which the pressure is generated by the respiratory muscles only with a spontaneous support modality, such as CPAP, or by the ventilator only or by the ventilator and the respiratory muscles. Thus, we classify CPAP as non-invasive positive pressure ventilation unless otherwise indicated.

In general practice, CPAP is most commonly used for the management of SDB *via* specifically manufactured CPAP devices for home care. Some of these CPAP devices are designed to detect various degrees of upper airway obstruction and then adjust the pressure level to keep the airway open. Some of these systems can also provide information about the residual apneas or hypopneas while patients are on CPAP (*i.e.*, automated CPAP) (Figure 1B)[36,37]. Although treatment with automated CPAP improves patient satisfaction and compliance in a subset of patients with obstructive sleep apnea (OSA), the routine use of automated CPAP for OSA treatment provides limited benefit[38-40]. Furthermore, although

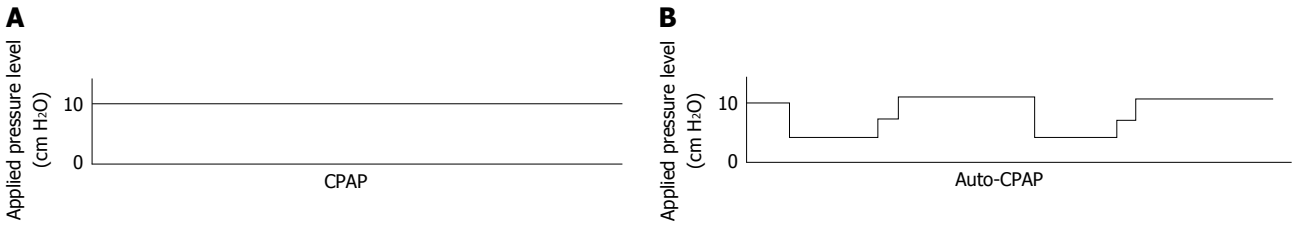

Figure 2 Differences between continuous positive airway pressure and automated continuous positive airway pressure. A: CPAP provides a constant level of positive pressure to the airway during spontaneous breathing; B: Automated CPAP devices are designed to detect various degrees of upper airway obstruction and consequently adjust the pressure level to keep the airway open. CPAP: Continuous positive airway pressure.

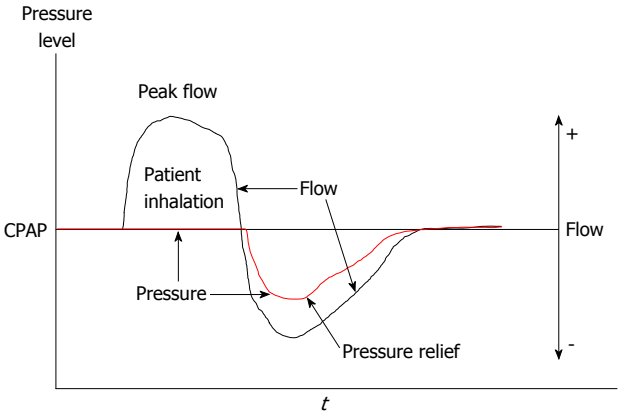

Figure 3 Algorithm of early expiratory phase pressure relief. The pressure is lowered in the early phase of expiration to enhance comfort, but the pressure returns to the critical pressure needed to keep the airway open before the next inspiration. CPAP: Continuous positive airway pressure.

more recent automated CPAP devices have an algorithm to detect central respiratory events, the accuracy of this algorithm remains to be elucidated. Thus, current guidelines do not recommend automated CPAP devices for the diagnosis of SDB or for the treatment of patients with HF, in which central respiratory events frequently coexist with OSA[41].

Some patients who cannot tolerate CPAP complain of difficulty while exhaling against the airway pressure generated by the CPAP device[42,43] especially in patients whose therapeutic pressure needed to eliminate OSA is fairly high (*e.g.*, > 10 cm H_2O). To resolve this issue, some CPAP devices use specific algorithms, such as early expiratory phase pressure-relief (Figure 2). Using these algorithms, the pressure is lowered in the early phase of expiration to enhance comfort, but the pressure returns to the critical pressure needed for keeping airway open before the next inspiration. Early expiratory pressure relief can be applied in combination with other modes of PAP therapy. Because patients with HF do not require such high pressures, even those with OSA, and because high-pressure CPAP might reduce cardiac output in some cases of HF, a pressure-relief algorithm is rarely used when treating HF patients.

Bi-level PAP

Bi-level PAP provides two fixed levels of PAP: a higher level of pressure during inspiration (inspiratory positive airway pressure (IPAP) and a lower level of pressure during expiration [expiratory positive airway pressure (EPAP)]. Its major difference from CPAP is that it provides pressure support during inspiration (Figure 3). The level of pressure support is determined as a difference between IPAP and EPAP, and the level of IPAP plays an important role in unloading respiratory muscles, reducing the work of breathing, controlling obstructive hypopnea or flow limitation, maintaining alveolar ventilation, and reducing the partial pressure of carbon dioxide ($PaCO_2$). EPAP produces respiration and hemodynamic effects that are similar to those provided by CPAP. In addition, most bi-level PAP devices have several modes for back-up ventilation, such as spontaneous breathing (S-mode), timed back-up ventilation, and spontaneous breathing with timed back-up ventilation (ST-mode). Bi-level PAP with S-mode can be used for patients who require high-pressure CPAP to control OSA or for those who cannot tolerate exhaling against high pressure CPAP[44]. However, patients with HF generally do not require high pressure, even those with OSA. Thus, the indication for bi-level PAP with S-mode in patients with HF is quite limited. When using CPAP, the airway pressure is increased at end-expiration but decreased during inspiration (Figure 4); because the net cardiac unloading effects during the respiration cycle are greater in bi-level PAP than in CPAP in association with an increased pressure level during inspiration and its unloading effects, bi-level PAP may be a better option for the treatment of HF[14,45]. In the care of HF, the purposes of treatment with bi-level PAP include the following: (1) reducing hypercapnia in some patients with acute decompensated HF or those with co-existing COPD and HF or those with obesity hypoventilation syndrome (OHS) and its related HF; (2) keeping ventilation consistent with a constant pressure support; and (3) back-up ventilation in patients with central sleep apnea (CSA). In patients with CSA, hypocapnia related to hyperventilation due to pulmonary congestion plays an important role in the development and maintenance of CSA[46]. Bi-level PAP sufficiently promotes ventilation and can reduce the carbon dioxide levels to below the apneic threshold during sleep.

Volume-assured pressure support

Volume-assured pressure support (VAPS) is an advanced mode of bi-level PAP developed for the treatment of pa-

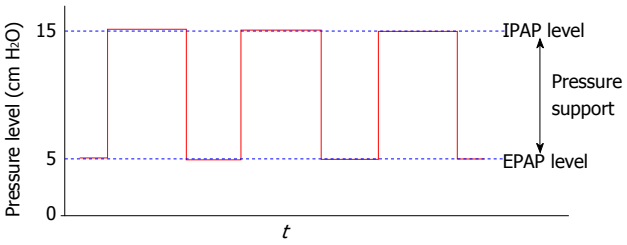

Figure 4 Bi-level positive airway pressure. Bi-level PAP provides two fixed levels of PAP, a higher level of pressure during inspiration (*i.e.*, IPAP) and a lower level of pressure during expiration (*i.e.*, EPAP), and thus provides pressure support during inspiration. EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PAP: Positive airway pressure.

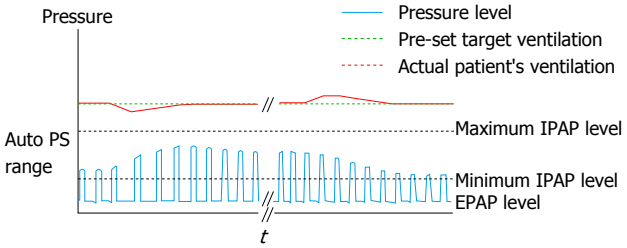

Figure 6 Volume assured pressure support. Using the volume assured pressure support mode, the device alters the level of pressure support from the minimum to maximum levels to maintain the pre-set ventilation or pre-set target tidal volume. This figure shows algorithm based on ventilation. EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PS: Pressure support.

tients with hypoventilation and hypercapnia[47-51]. In VAPS mode, the device alters the level of pressure support (*i.e.*, IPAP level) to maintain a pre-set target tidal volume. Devices with newer VAPS modes alter the respiratory rate in addition to the level of pressure support to maintain a pre-set minute ventilation. Nevertheless, VAPS mode guarantees a delivered tidal volume or minute ventilation despite patients' variable breathing effort, airway resistance, and lung or chest wall compliance (Figure 5).

ASV

ASV is an advanced mode of bi-level PAP developed for the treatment of Cheyne-Stokes respiration with CSA in patients with HF[52]. It is also used in the treatment of other forms of CSA, such as idiopathic CSA, CPAP-emerged CSA and opioid-induced CSA[53,54]. ASV devices automatically provide altering pressure support for each inspiration, ranging from a pre-set minimum level to a pre-set maximum level, to maintain moving target ventilation (determined based on volume or flow) determined by the patient's current breathing in addition to the back-up ventilation with variable respiratory rates (*i.e.*, servo-control of ventilation) (Figure 6). In addition, more recent devices provide altering EPAP levels that are sufficient for the control of upper airway narrowing or collapse, using an algorithm that is similar to that used by automated CPAP. The goals of ASV are to stabilize abnormal breathing patterns (*i.e.*, CSA with Cheyne-Stokes respiration) and to maintain the $PaCO_2$ level to prevent

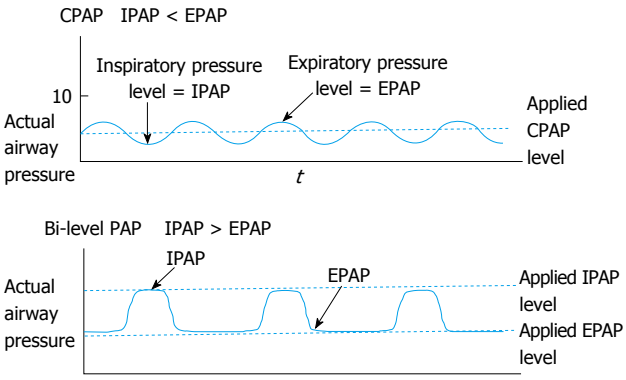

Figure 5 Differences in actual airway pressure between continuous positive airway pressure and bi-level positive airway pressure. While on CPAP, although a constant CPAP level is applied, actual airway pressure is not constant and oscillates. During inspiration, actual airway pressure decreases below the applied CPAP level, whereas during expiration, actual airway pressure increases above the applied CPAP level. Thus, the inspiratory pressure level in the airway (*i.e.*, IPAP) is lower than the expiratory pressure level in the airway (*i.e.*, EPAP). Conversely, while on bi-level PAP, the actual airway pressure increases during inspiration due to pressure support. Thus, IPAP is greater than EPAP according to the level of pressure support. CPAP: Continuous positive airway pressure; EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PAP: Positive airway pressure.

hypocapnia, which can trigger apnea reentry cycles[52] in addition to keeping the upper airway open (Figure 7).

There are two major ASV devices. In both products, pressure support is dynamically adjusted breath-to-breath as necessary to ensure that the patients' actual ventilation matches the target value in addition to the auto-titration of EPAP to maintain airway patency. The main points of difference are the mechanics used to assess the breathing status and to determine the target level. One type of device uses volume-targeted ASV, which sets a minute-ventilation target that is 90% of the recent average minute volume from a 3-min collection period and tries to maintain ventilation at the target level[52]. The other device uses flow-targeted ASV, which monitors the peak inspiratory flow of the patient over a recent moving 4-min window, calculating an average peak flow at every point within this window to set a target peak flow. It compares these data to an internal target and maintains a target peak inspiratory flow[55]. The other minor differences between volume-triggered and flow-triggered ASV devices are summarized in Table 2.

DEVICES, INTERFACE AND ADDITIONAL EQUIPMENT

In general, the equipment necessary for PAP therapy includes devices that provide PAP, tubing and several types of patient interfaces[56]. Ventilators that are used in standard critical care for invasive ventilation can also be used for non-invasive PAP therapy with specific patient interfaces. However, a few types of ventilators have specifically been designed to provide PAP noninvasively and are generally used during the acute phase of HF. Most of these non-invasive ventilators employ several of the

Table 2 Adaptive servo-ventilation devices

	Volume-triggered ASV	Flow-triggered ASV
Manufacturer	ResMed	Philips-Respironics
Target	90% of previous average ventilation (moving time window)	90% of average peak flow (moving time window)
EPAP/EEP	EEP automatically adjusted between min and max (4-20 cm H_2O) Cannot select auto EEP without PS	EPAP automatically adjusted between min and max (4-25 cm H_2O)
IPAP	Max pressure up to 30 cm H_2O IPAP changes within pre-set PS range from min (can be 0) to max Max PS can be limited by maximum pressure and current EEP	Max pressure up to 25 cm H_2O IPAP changes within pre-set PS range from min (can be 0) to max (21 cm H_2O) Max PS can be limited by pre-set maximum pressure and current EPAP level
Backup rate	Automatic 15 ± α breaths/min	Auto rate Fixed rate
Pressure wave form	Saw-tooth	Square shape
Inspiratory time	Automatic	Automatic in auto rate mode Set in manual rate mode

ASV: Adaptive servo-ventilation; EEP: End-expiratory pressure (*i.e.*, = EPAP); EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PS: Pressure support.

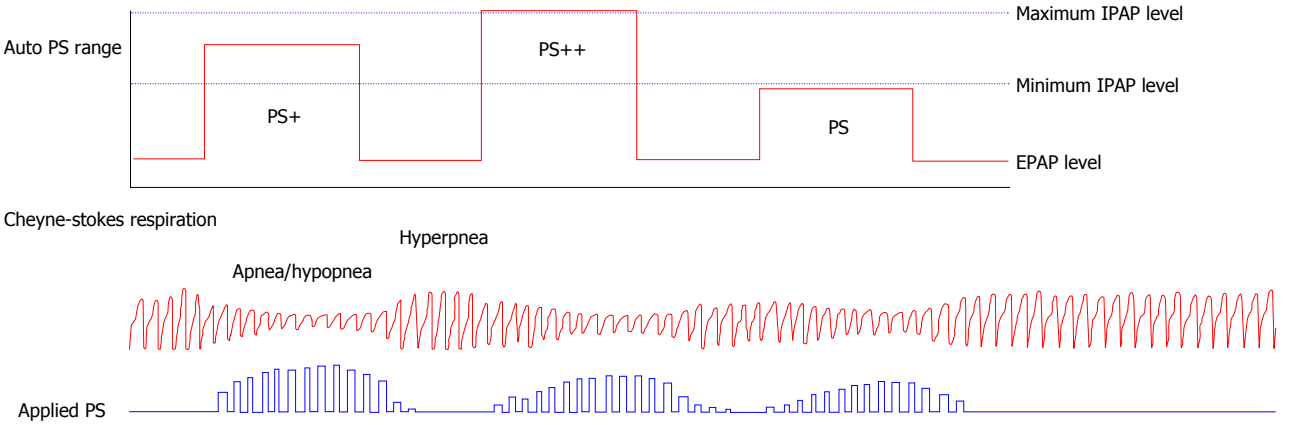

Figure 7 Adaptive servo-ventilation. Adaptive servo-ventilation devices automatically provide altering pressure support for each inspiration, ranging from a pre-set minimum level to a pre-set maximum level, to maintain moving target ventilation (determined based on volume or flow) determined by the patient's current breathing in addition to the back-up ventilation with variable respiratory rates. This stabilizes the abnormal breathing pattern (*i.e.*, cheyne-stokes respiration) and maintains the $PaCO_2$ levels to prevent hypocapnia, which can otherwise trigger apnea reentry cycles. EPAP: Expiratory positive airway pressure; IPAP: inspiratory positive airway pressure; $PaCO_2$: Arterial partial pressure of carbon dioxide; PS: Pressure support.

modes of PAP therapy mentioned earlier and can be used in many situations and conditions during the acute phase of HF. In addition, there are several smaller and more simplified devices that can provide only one or two modes for less intensive care in the general cardiology wards or for home care in patients with sub-acute or chronic phases of HF.

In terms of interface, various masks have been used for PAP therapy for HF; these include nasal masks, nasal pillows, oro-nasal (full-face) masks that cover the nose and mouth, and face (total-face) masks that cover the entire face[57], all of whose actual attachment portions to the face are made of silicone or other soft rubber-like materials to achieve a tighter air seal[58]. In acute HF, a disposable oro-nasal mask or face mask is usually used. In the home care setting, the choice of mask is the most important issue for patient comfort and tolerance to PAP therapy. Poorly fitted masks decrease the efficacy, compliance and adherence to PAP therapy. In addition to the mask itself, headgear or straps are used as a harness. Overly tight headgear may worsen the air leak and interfere with patient comfort and compliance.

Some patients receiving long-term PAP therapy complain of nasal oro-nasal dryness while on PAP devices[59]. For such patients, a heated humidifier can be used to maintain compliance with therapy[60]. One possible disadvantage of the use of heated humidifier includes the accumulation of condensate inside the tube, which can cause a decrease in inspiratory pressure and a delay of triggering when bi-level PAP is used. Condensation inside the tube is also frequently observed during the winter in the home care setting[61]. To resolve such condensate issues, heated tubing systems containing copper wire are now available for clinical use.

CONTRAINDICATION TO PAP THERAPY

There are several absolute contraindications to PAP therapy, such as the presence or absence of anatomic abnormalities for attaching the interface and recent

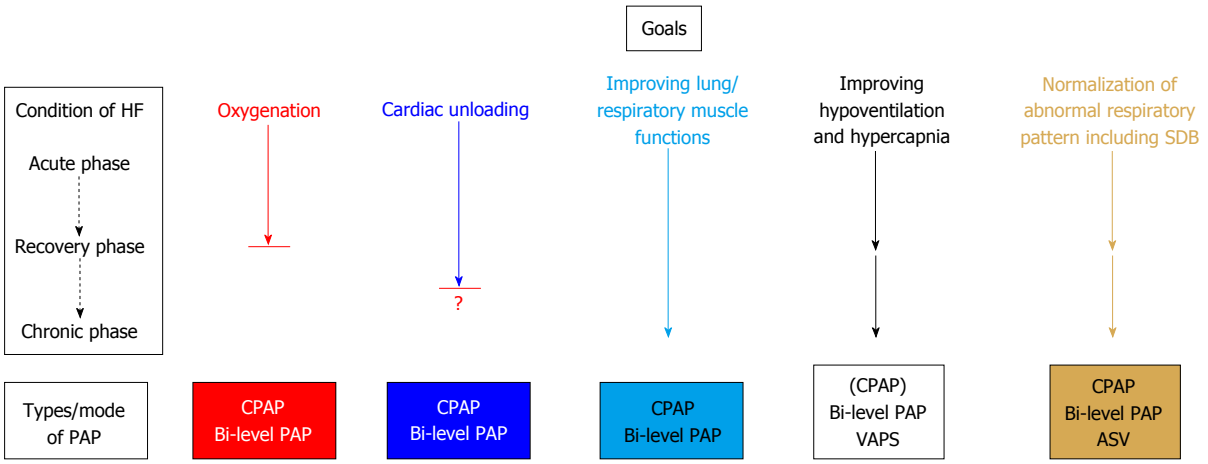

Figure 8 Importance of each goal of positive airway pressure therapy according to different heart failure conditions. In the wide spectrum of HF care, PAP therapy is used to help oxygenation, provide relief from cardiac load, improve lung and respiratory muscle function, reduce hypoventilation and hypercapnia, and normalize abnormal respiratory patterns, including SDB. The importance of each goal can differ according to the condition of HF. Improving oxygen is one of the most important goals in the acute phase. However, after recovery from acute decompensation, this goal becomes less important or is no longer considered. Providing cardiac unloading is another important goal in the acute phase to the recovery phase. However, the importance of this goal remains to be elucidated after recovery from acute decompensation. Improving lung and respiratory muscle function is sometimes important in the acute phase and after recovery. Improving hypoventilation is important in cases with hypercapnia in the acute phase. In addition, HF patients with hypoventilation and daytime hypercapnia can be treated by PAP therapy in the recovery or chronic phase. Normalization of abnormal respiratory patterns, particularly SDB suppression, is sometimes important in the recovery phase and is most important in the chronic phase. The specific types/modes of PAP that should be used differ according to each therapeutic purpose. ASV: Adaptive servo-ventilation; CPAP: Continuous positive airway pressure; HF: Heart failure; PAP: Positive airway pressure; SDB: Sleep disordered breathing; VAPS: Volume assured pressure support.

airway or gastrointestinal surgery. Relative contraindications include the need for the patient to be capable of airway protection, an increased risk of aspiration, swallowing impairment, excessive secretions, frequent coughing, severe hypoxemia (*i.e.*, $PaO_2/FiO_2 < 75$), acidemia, multiorgan failure, respiratory arrest, inability to fit the mask, or poorly motivated patient or family[62,63]. There is controversy regarding use of PAP therapy for patients with cardiogenic shock and hemodynamic instability[18]. In the care of HF, PAP therapy should be administered with caution in patients with severe right-side HF accompanied by severe liver congestion or cirrhosis, patients with hypertrophic obstructive cardiomyopathy and patients with severe aortic valvular heart disease because reductions in venous return to the heart may worsen liver congestion, ascites and edema, and because reductions in LV preload and afterload may cause further reduction in cardiac output unless these patients also have severe pulmonary congestion.

COMPLICATIONS

PAP therapy is generally safe, and only a few major complications can occur, including aspiration pneumonia[64,65], hypotension as a consequence of reduction of preload and afterload (see "Effect of positive airway pressure on hemodynamics"), and rarely, pulmonary barotraumas in association with excessive pressures. Because excessive pressures are not applied for patients with HF due to the risk of adverse reduction in cardiac output, actual applied pressures are much lower than such excessive pressure levels.

However, minor complications related to masks or pressures and air flows can occur. Fitting the mask too tightly for long periods of time may result in skin damage and ulceration, particularly around the nasal bridge[66]. Once established, such wounds may require artificial skin grafts, and of course, mask re-fitting should be considered. Furthermore, patients undergoing long-term PAP therapy with masks might have global facial flattening[67]. However, this may be a specific complication for children. Discomfort associated with pressures and air flows are common and can include dryness, pain in the nose or mouth and pneumophagia, all of which are usually resolved *via* the use of a humidifier or by a decrease in pressure levels.

CONDITIONS IN WHICH PAP THERAPY IS CONSIDERED FOR HF

In the wide spectrum of HF care, PAP therapy is used to improve oxygenation, reduce cardiac load, improve lung and respiratory muscle function, alleviate hypoventilation and hypercapnia, and normalize abnormal respiratory patterns, including SDB (Figure 8). In this section, specific conditions in which PAP therapy is frequently considered in the care of HF are described (Table 3).

Acute decompensated HF

Guidelines for ADHF generally recommend the use of PAP therapy if patients have breathing difficulty, signs of pulmonary edema, or hypoxia despite supplemental oxygen (Table 4)[5,68-71]. For patients with ADHF, the purposes of PAP therapy include augmentation of oxygenation through recruitment of collapsed alveoli, reversal of atelectasis, and induction of fluid shifts back from the alveoli

Table 3 Possible indication of each type/mode of positive airway pressure for each condition

	CPAP	Bi-level PAP	VAPS	ASV
Acute decompensated heart failure	o[1]	o	?[2]	?
Chronic HF with OSA	o	o	Δ[3]	Δ[4]
Chronic HF with CSA	Δ[5]	o	?	o
HF following acute decompensation	Δ[6]	o	?	Δ[7]
Chronic HF without SDB	×	?	?	Δ[8]
HF with hypoventilation (acute)	Δ[9]	o	o	×
HF with hypoventilation (chronic)	Δ[9]	o	o	?

[1]Bi-level PAP with S-mode for accompanying OSA; [2]Indicates that no clear data are available; [3]Can be used if accompanied by hypoventilation; [4]Can be used if Cheyne-Stokes respiration coexists; [5]Can be used if CSA is alleviated; [6]Can be used if OSA exists; [7]Can be used if CSA exists; [8]ASV may be useful for chronic HF patients with apnea-hypopnea index < 20 including those without SDB; [9]Can be used if hypoventilation is associated with OSA. ASV: Adaptive servo-ventilation; Bi-level PAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; CSA: Central sleep apnea; HF: Heart failure; OSA: Obstructive sleep apnea; SDB: Sleep disordered breathing; VAPS: Volume assured pressure support.

and the interstitial space to the pulmonary circulation, reducing respiratory muscle load and the work of breathing, and stabilizing hemodynamics *via* cardiac unloading.

In patients with ADHF, PAP therapy is usually administered by specifically designed ventilators for non-invasive PAP for acute or intensive care. The selection of modes (usually, CPAP or bi-level PAP) is dependent on whether patients require pressure support to ventilate appropriately. For example, patients with hypercapnia or respiratory muscle fatigue may require bi-level PAP. Otherwise, CPAP is used because most data suggest that there are no obvious clinical benefits to the use of bi-level PAP over CPAP[72,73]. In Japan, ASV is sometimes used for patients with ADHF, especially in institutions where specifically designed ventilators for non-invasive PAP for acute or intensive care are not available. The merits of using ASV for patients with ADHF may include the fact that devices for ASV are small, handy and mobile; ASV can be started in the emergency room, which allows PAP to be applied quite immediately upon presentation to the hospital; and ASV may synchronize patients' respiration more easily than typical bi-level PAP. However, these potential merits of ASV remain to be confirmed. It should be noted that ASV devices do not provide raw wave forms of parameters related to respiration, whereas specifically designed ventilators for non-invasive PAP for acute or intensive care do provide these data.

PAP therapy improves hemodynamics, respiratory function and oxygenation in patients with pulmonary edema in association with ADHF when compared with oxygen therapy alone[74-79]. Moreover, the use of PAP therapy in randomized prospective trials was associated with lower rates of intubation and improved 30-d mortality compared with oxygen therapy alone[74,76,77,79]. Thus, PAP therapy for ADHF is the universal standard.

SDB

SDB is frequently observed in patients with HF. In general, two types of SDB, OSA and CSA, can be observed in HF patients. Typically, CSA in HF patients is usually observed as Cheyne-Stokes respiration, which is a form of periodic breathing characterized by a crescendo-decrescendo pattern of breathing followed by central apnea or hypopnea[80].

OSA results from upper airway collapse and predisposes patients to the development and progression of HF *via* several mechanisms. For example, in patients with OSA, the blood pressure is frequently elevated as a result of overactivation of the sympathetic nervous system. Such high blood pressure may contribute to the development of HF in association with the direct deleterious effects of sympathetic overactivity. In addition, the generation of exaggerated negative intrathoracic pressure during obstructive apneas increases cardiac loads. Conversely, CSA appears to arise secondary to HF. In general, HF patients are likely to have chronic hyperventilation due to stimulation of the pulmonary vagal irritant receptors by pulmonary congestion and to increased chemosensitivity, which is characteristic of HF patients with CSA[46,81] and consequently results in hypocapnia. When $PaCO_2$ falls below the apneic threshold because of an increase in the apneic threshold during transition from wakefulness to sleep, CSA ensues[46,81]. Apnea persists until $PaCO_2$ rises above the apneic threshold; then, ventilation will resume; ventilatory overshoot occurs, and $PaCO_2$ will decrease below the apneic threshold in association with arousal during the ventilatory phase and increased chemosensitivity. This could also contribute to the pathogenesis of CSA with a Cheyne-Stokes respiration pattern by facilitating ventilatory overshoot and undershoot. Once triggered, the pattern of Cheyne-Stokes respiration will be sustained by the combination of increased respiratory chemoreceptor drive, pulmonary congestion, arousals, and apnea-induced hypoxia, which cause oscillations in $PaCO_2$ above and below the apnea threshold[46,81]. Nevertheless, CSA is also characterized by apnea, hypoxia, and increased sympathetic nervous activity and, when present in HF, is associated with an increased risk of death[46,81,82].

In patients with chronic HF, treatment of SDB alleviates underlying cardiac dysfunction. The standard treatment for OSA in patients with HF is CPAP. CPAP prevents upper airway narrowing and collapse and works as a "pneumatic splint"[28-30], thereby preventing obstructive apneas and hypopneas. It was reported that one night of CPAP resolved negative intrathoracic pressure swings in association with obstructive respiratory events and reductions in nocturnal blood pressure and heart rate[46,83]. Thus, HF patients with OSA may benefit from cardiac unloading by suppressing OSA *via* CPAP. Independent of OSA suppression, CPAP promotes reductions in LV preload and afterload in patients with HF. In fact, many studies regarding CPAP therapy for chronic HF patients demonstrated an improvement in LV systolic function in association with reductions in sympathetic nervous system activity and associated reductions in systemic arterial blood pressure and heart rate[46,84-87]. In terms of long-term clinical outcomes, two observational studies

Table 4 Recommendations for oxygen and bi-level positive airway pressure therapy for acute decompensated heart failure

Guidelines	Oxygen	PAP therapy
ACC/AHA (2009 updated)	To relieve symptoms related to hypoxemia: Class Ⅰ, level C	NA
ACCF/AHA (2013)	NA	NA
HFSA (2010)	Hypoxia+: Class Ⅰ, level C Hypoxia-: Class Ⅲ, level C	Dyspnea+ or pulmonary edema+: Class Ⅰ, level A
ESC (2012)	Hypoxemia+ (SaO_2 < 90% or PaO_2 < 60 mmHg): Class Ⅰ, level C	Dyspnea+ or pulmonary edema+ or RR > 20/min: Class Ⅱa, level B SBP < 85 mmHg: Class Ⅲ
JCS (2011)	Hypoxia+ (to keep SaO_2 > 95%, PaO_2 > 80 mmHg): Class Ⅰ, level C	Not responding to oxygen: Class Ⅰ, level A

ACC: American college of cardiology; ACCF: American college of Cardiology foundation; AHA: American heart association; ESC: European Society of Cardiology; HFSA: Heart failure society of America; JCS: Japanese Cardiology Society; NA: Not available; PaO_2: Arterial partial pressure of oxygen; RR: Respiratory rate; SaO_2: Oxyhemoglobin saturation; SBP: Systolic blood pressure; PAP: Positive airway pressure.

in chronic HF patients indicated that CPAP therapy for OSA results in a trend towards reduced mortality or a significant reduction in the composite endpoint of mortality and rehospitalization[88,89]. In addition, in one of those studies, the hospitalization-free survival rate in patients administered CPAP therapy was significantly higher in the more compliant group than in the less compliant group[89]. Therefore, good compliance with long-term CPAP therapy may provide better clinical outcomes in chronic HF patients with OSA.

Because HF patients with CSA have associated pulmonary congestion and increased LV filling pressures, CPAP has been applied to improve pulmonary congestion and increased LV filling through the cardiac unloading. However, studies regarding the effects of CPAP on the suppression of CSA in chronic HF patients produced inconsistent results, most likely due to the differences the application of CPAP. If CPAP was applied for a short period of time (*e.g.*, 1 night) at low pressure (*e.g.*, 5 cm and 7.5 cm H_2O), CSA was not alleviated[90,91]. However, if CPAP was applied for longer periods (*e.g.*, 7 d) at high pressure (8-12.5 cm H_2O), the severity of CSA decreased by > 50%[92-96]. In addition, CPAP with gradual titration alleviated CSA and was accompanied by an increase in $PaCO_2$[46,95,97,98]. reduction in sympathetic nervous system activity[99], and improvements in respiratory muscle function[100] and LV systolic function for 1-3 mo[46,95-98]. In terms of long-term clinical outcome, one small-randomized trial[97] showed that in chronic HF patients with CSA, CPAP produced a trend[90] toward a better outcome, and a sub-group of patients compliant with CPAP had significantly better outcomes. However, a large-scale randomized controlled study in chronic HF patients with CSA failed to demonstrate the benefits of CPAP in terms of long-term clinical outcomes (mean follow-up duration, 2-years)[101]. A post hoc analysis of this study suggested that patients whose apnea-hypopnea index (AHI) decreased below 15 in response to CPAP at 3 mo (*i.e.*, CPAP responder) had significantly better long-term clinical outcomes compared with the control groups. This implied that in approximately 50% of chronic HF patients, CPAP therapy suppressed CSA, but PAP therapy, which may suppress CSA more effectively and constantly, should be the focus.

One such PAP therapy is bi-level PAP[52]. A small randomized controlled trial comparing 10 HF patients with CSA on bi-level PAP without backup ventilation (*i.e.*, S-mode) and standard medical therapy versus 11 HF patients with CSA on standard medical therapy alone showed significant reduction in the AHI from 28.3 ± 12.3/h to 5.2 ± 3.8/h with one night of bi-level PAP with S-mode and significant improvement in LV ejection fraction at 3 mo with bi-level PAP with S-mode (20.3% ± 8.2% *vs* 3.2% ± 10.1% with standard medical therapy alone)[102]. Considering that bi-level PAP with S-mode may aggravate central apnea through hyperventilation, this is not a good option for all HF patients with CSA. Conversely, studies using bi-level PAP with spontaneous and timed backup ventilation mode (*i.e.*, ST-mode) in chronic HF patients showed sufficient reduction in the AHI with one night of bi-level PAP and significant improvement in LV ejection fraction at 3 mo with bi-level PAP with ST-mode[103-105]. In particular, in a study regarding the effects of bi-level PAP with ST-mode on the suppression of AHI and improvements in cardiac function in chronic HF patients with CSA that was not sufficiently suppressed by CPAP (*i.e.*, AHI ⩾ 15, non-responders), CSA sufficiently decreased in response to bi-level PAP with ST-mode (AHI, from 54.4 ± 7.8 at baseline to 30.3 ± 11.7 on CPAP to 8.4 ± 4.7 on bi-level PAP with ST-mode)[105]. Further, left ventricular ejection fraction (LVEF) and the plasma levels of B-type natriuretic peptide improved in chronic HF patients with CSA, even in patients deemed CPAP non-responders at 6 mo[105]. Another PAP therapy that is more effective at suppressing AHI in chronic HF patients with CSA is ASV[52]. Randomized and observational studies in which the effects of ASV on cardiac function were assessed showed that suppression of CSA *via* ASV reduced the levels of neurohumoral factors and improved LV systolic function and outcomes in chronic HF patients with CSA[106-109]. Furthermore, in studies on the effects of ASV on suppression of AHI and improvements of cardiac function in CPAP non-responders, CSA was sufficiently decreased in response to ASV, and cardiac functions and neurohumoral state were improved at 3 mo[110]. The effects of

ASV on long-term clinical outcomes in chronic HF patients with CSA will be clarified in an ongoing large-scale randomized controlled trial[111,112].

Both OSA and CSA can be observed in patients with chronic HF, and ASV can suppress OSA by modifying the EPAP levels in addition to suppressing CSA. Thus, ASV, particularly ASV with auto-titrating EPAP, may be a therapeutic option for SDB without the need to distinguish between OSA and CSA. Three randomized controlled trials assessed the effects of ASV on cardiac function in chronic HF patients with coexisting OSA and CSA[55,113,114]. These studies reported significant improvements in cardiac functions, especially reductions in neurohumoral factors. The effects of ASV for both types of SDB will be elucidated in an ongoing large-scale randomized controlled trial including chronic HF patients with either OSA or CSA[115].

HF patients following acute decompensation

Although patients with ADHF are frequently treated with PAP therapy, whether HF patients following recovery from acute decompensation remains unclear. In HF patients following recovery from acute decompensation, the presence or absence of SDB may play key roles in determining whether PAP therapy should be considered. Although most previous data regarding SDB in HF and its treatment with PAP mentioned earlier involve HF patients in the chronic phase, it was recently reported that hospitalized HF patients following ADHF frequently develop SDB and that the presence of SDB during hospitalization following ADHF is a predictor of readmission and mortality[116-118]. Thus, PAP therapy should be considered even for hospitalized HF patients, especially in the setting of symptomatic SDB. One study suggests a beneficial effect of in-hospital bi-level PAP (with S-mode) therapy for OSA on improvement of cardiac function following ADHF[117]. An ongoing study may elucidate whether PAP therapy improve outcomes in these patients[119]. However, there are no specific data regarding the effect of PAP therapy on hospitalized patients following ADHF who do not have SDB.

Chronic HF patients without SDB

Chronic HF patients even without SDB may also benefit from PAP therapy through its cardiac unloading effects. In fact, the short-term application of CPAP (*i.e.*, 5-10 cm H_2O) can increase cardiac output in stable HF patients with pulmonary congestion[120,121]. This possibility has been further assessed in a subgroup analysis of a small randomized trial regarding the effects of CPAP on cardiac function and clinical outcomes in HF patients with and without CSA[97]. In a subgroup analysis of patients without CSA, CPAP had no effect on either LVEF or the composite endpoint of mortality and cardiac transplantation rate. Bi-level PAP may be a better option for improving hemodynamics in HF patients with pulmonary congestion because net cardiac unloading effects during a respiration cycle may be greater in bi-level PAP than in CPAP (refer to the section regarding "Bi-level positive airway pressure")[14,45]. Furthermore, based on data showing the acute beneficial effects of short-term ASV application on sympathetic nervous system activity[33,34] and hemodynamics[35], ASV may be a more promising therapeutic option for chronic HF patients without SDB. In fact, Koyama *et al*[122] reported that ASV was associated with better clinical outcomes, regardless of the presence or absence of moderate CSA (*i.e.*, AHI < 20 or $\geqslant 20$). The possible benefits of ASV on cardiac function are being assessed in an ongoing randomized clinical trial in which HF patients with and without SDB are being randomized to either ASV treatment or medical therapy to assess the changes in LV ejection fraction at 6 mo[123].

Most acute hemodynamic effects of PAP therapy are more prominent in HF patients with pulmonary congestion or increased LV filling pressure *(i.e.*, pulmonary capillary wedge pressure $\geqslant 12$ mmHg)[45,121]. Patients with HF are more sensitive to decreased afterload and are usually hypervolemic and are thus insensitive to decreased preload. However, preload reduction may play a more prominent role in HF patients without hypervolemia. Therefore, chronic HF patients with low filling pressure and those without hypervolemia should not be treated with PAP therapy or at least should be treated with caution.

HF with hypoventilation and hypercapnia

Among patients with HF, there is a subset of patients who have hypoventilation and hypercapnia acutely or chronically. In the acute phase, it was reported that 35 of 80 patients with acute cardiogenic pulmonary edema had hypercapnia that was not associated with a previous history of COPD[124]. On the other hand, it was also reported that 25% of patients with ADHF had COPD[125]. Thus, PAP therapy can be considered in such HF patients with hypoventilation and hypercapnia in the acute phase. In general, specifically designed ventilators for non-invasive PAP for acute or intensive care are used, although small home-care devices can also be used. In terms of modes, bi-level PAP or VPAS, both of which can provide sufficient minute ventilation or tidal volume to reduce $PaCO_2$, should be used. ASV may also be considered. However, because ASV is designed to keep $PaCO_2$ consistent in patients with hypocapnia and $PaCO_2$ oscillation, its effects for the reduction in $PaCO_2$ will be insufficient.

In the chronic phase, hypoventilation and daytime hypercapnia are observed in some elderly HF patients with COPD or in obese HF patients with OHS. Some patients with COPD can suffer from hypoventilation and daytime hypercapnia in association with individual variations in chemoreceptor sensitivity to CO_2 and inspiratory muscle strength[126]. In addition, sleep-related hypoventilation and the initiation of long-term oxygen therapy can contribute to the development of hypoventilation and daytime hypercapnia in COPD patients. Mild physiologic hypoventilation during sleep, especially during rapid eye movement (REM) sleep, is exaggerated in patients with COPD. Hypoventilation and daytime hy-

percapnia can also be precipitated by supplemental oxygen therapy for hypoxia. Because both HF and COPD are more likely observed in elderly patients, the coexistence of HF and COPD has become more prevalent as the general population ages[127]. Although the use of PAP therapy in COPD patients with chronic hypoventilation has not been established, the potential benefits of PAP therapy in these patients generally include improvement in daytime and nighttime arterial blood gas parameters, increase in sleep duration, improvements in quality-of-life[128] and decreases in hospitalization rate[129,130]. For patients with HF and COPD, PAP therapy can be used for cardiac unloading. Furthermore, it was reported that OSA occurs in 10% to 15% of patients who have COPD (*i.e.*, overlap syndrome)[131]. In addition, HF patients frequently have OSA[32]. Hypoventilation and hypercapnia in patients with HF and COPD can be attributed to coexisting OSA. Another means of PAP therapy in patients with HF and hypoventilation and hypercapnia is to suppress coexisting OSA.

In patients with chronic HF with hypoventilation and hypocapnia, the selection of the mode of PAP therapy is dependent on the volume of ventilation required to reduce the $PaCO_2$ levels. In patients who only require alleviation of coexisting OSA to reduce $PaCO_2$, CPAP can be used during sleep. If patients require pressure support to reduce $PaCO_2$, bi-level PAP can be used. If patients require a guarantee on delivered tidal volume or minute ventilation to reduce $PaCO_2$, VAPS can be used. ASV may also be considered. However, it should be noted that the effects of ASV for the reduction of $PaCO_2$ will be insufficient.

In obese HF patients with hypoventilation and hypercapnia, the coexistence of OHS [defined as obesity (body mass index > 30 kg/m^2) and daytime hypoventilation with awake $PaCO_2$ > 45 mmHg in the absence of other causes of hypoventilation[29]] should be considered. Patients with OHS frequently have multiple risk factors for cardiovascular disease in association with comorbid obesity. OHS can cause LV hypertrophy and diastolic dysfunction, and longstanding OHS may promote LV systolic dysfunction[132]. In addition, OHS with severe hypoxia can cause pulmonary hypertension and subsequent right-sided HF. Therefore, OHS can induce the development and worsening of HF. Furthermore, approximately 90% of patients with OHS have OSA with and without REM sleep hypoventilation[133]. In OHS, hypercapnia is due to increased work of breathing, OSA, respiratory muscle impairment, decreased central ventilatory drive, and decreased response to leptin. Obesity *per se* can increase the work of breathing through the increased efforts required to move the rib cage and the diaphragm and through decreased lung compliance. In addition to mild physiologic hypoventilation during sleep, OSA contributes to hypoventilation during each obstructive respiratory event, especially for REM sleep during which apneas and hypopneas become more severe in both frequency and duration. Post-apnea (post-hypopnea) hyperpneas may not sufficiently compensate for hypoventilation to maintain eucapnia[134] and reduced pH level and bicarbonate excretion at night as well as progressive elevation in the serum bicarbonate level and subsequent depression of ventilation during the day[134,135]. Muscle impairment and decreased central ventilatory drive may play only a limited role in the pathogenesis of OHS[131]. Although it was reported that alterations in leptin levels and leptin resistance can cause hypoventilation[136], detailed mechanisms regarding these alternations in patients with OHS remain to be elucidated.

To treat HF patients with OHS, in addition to weight reduction, PAP should be considered to normalize ventilation and cardiac unloading. CPAP may be beneficial by preventing upper airway narrowing and hence improving alveolar hypoventilation, hypercapnia and oxygenation, and quality of life[28,137,138] in some patients with OHS. However, some OHS patients still have significant nocturnal oxygen desaturation, even on CPAP[139]. Providing pressure support with bi-level PAP should be considered for such patients and for those without OSA. Long-term bi-level PAP therapy improves hypercapnia, oxygenation, and increases lung volumes in patients with OHS[140]. In an observational study, the use of bi-level PAP in OHS patients was associated with reduced mortality compared with patients who were not treated with bi-level PAP[141]. Recent data suggest that VAPS may improve ventilation when compared with conventional bi-level PAP. However, the use of VAPS was associated with lower patient tolerance due to high pressure[47,48]. Therefore, VAPS can be considered in patients who do not tolerate CPAP or bi-level PAP.

CONCLUSION

PAP is a non-invasive and non-pharmacological therapy for HF in the acute setting and is now globally used. In addition, in chronic HF patients with SDB, PAP therapy should be used to alleviate SDB and to improve short-term cardiovascular outcomes. Similarly, in HF patients with hypoventilation and hypercapnia in association with COPD and OHS, PAP therapy should be used to improve hypoventilation and hypercapnia. However, it remains to be elucidated whether PAP therapy can improve cardiovascular outcomes in patients following ADHF, in chronic HF patients without SDB, and in those with hypoventilation and hypercapnia. In particular, whether PAP therapy can alter long-term outcomes is of great interest. Therefore, further research regarding these topics is needed.

Nevertheless, cardiologists and other clinicians should understand the benefits of PAP therapy, including the improvements in the control of respiration and cardiac unloading, as well as the indications, contraindications and complications of this therapy, as discussed in this review.

REFERENCES

1 **Ho KK**, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993; **22**: 6A-13A [PMID: 8376698 DOI: 10.1016/0735-1097(93)90455-A]

2 **Santulli G**. Epidemiology of cardiovascular disease in the 21st century: updated numbers and updated facts. *J Cardiovasc Dis* 2013; **1**: 1-2

3 **Santulli G**, Ciccarelli M, Trimarco B, Iaccarino G. Physical activity ameliorates cardiovascular health in elderly subjects: the functional role of the β adrenergic system. *Front Physiol* 2013; **4**: 209 [PMID: 23964243 DOI: 10.3389/fphys.2013.00209]

4 **Lloyd-Jones D**, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; **119**: e21-181 [PMID: 19075105 DOI: 10.1161/CIRCULATIONAHA.108.191261]

5 **Hunt SA**, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;**119**: e391-e479 [PMID: 19324966 DOI: 10.1161/CIRCULATIONAHA.109.192065]

6 **Krumholz HM**, Wang Y, Chen J, Drye EE, Spertus JA, Ross JS, Curtis JP, Nallamothu BK, Lichtman JH, Havranek EP, Masoudi FA, Radford MJ, Han LF, Rapp MT, Straube BM, Normand SL. Reduction in acute myocardial infarction mortality in the United States: risk-standardized mortality rates from 1995-2006. *JAMA* 2009; **302**: 767-773 [PMID: 19690309]

7 **Organized jointly by the American Thoracic Society**, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Société de Réanimation de Langue Française, and approved by ATS Board of Directors, December 2000. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute Respiratory failure. *Am J Respir Crit Care Med* 2001; **163**: 283-291 [PMID: 11208659 DOI: 10.1164/ajrccm.163.1.ats1000]

8 **Guyton AC**, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 1957; **189**: 609-615 [PMID: 13458395]

9 **Pinsky MR**. Determinants of pulmonary arterial flow variation during respiration. *J Appl Physiol Respir Environ Exerc Physiol* 1984; **56**: 1237-1245 [PMID: 6373691]

10 **Pinsky MR**. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol Respir Environ Exerc Physiol* 1984; **56**: 765-771 [PMID: 6368503]

11 **Whittenberger JL**, Mcgregor M, Berglund E, Borst HG. Influence of state of inflation of the lung on pulmonary vascular resistance. *J Appl Physiol* 1960; **15**: 878-882 [PMID: 13784949]

12 **Guarracino F**, Ambrosino N. Non invasive ventilation in cardio-surgical patients. *Minerva Anestesiol* 2011; **77**: 734-741 [PMID: 21709660]

13 **Burton AC**, Patel DJ. Effect on pulmonary vascular resistance of inflation of the rabbit lungs. *J Appl Physiol* 1958; **12**: 239-246 [PMID: 13525269]

14 **Luecke T**, Pelosi P. Clinical review: Positive end-expiratory pressure and cardiac output. *Crit Care* 2005; **9**: 607-621 [PMID: 16356246 DOI: 10.1186/cc3877]

15 **Guyton AC**. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev* 1955; **35**: 123-129 [PMID: 14356924]

16 **Goldberg HS**, Rabson J. Control of cardiac output by systemic vessels. Circulatory adjustments to acute and chronic respiratory failure and the effect of therapeutic interventions. *Am J Cardiol* 1981; **47**: 696-702 [PMID: 7008571 DOI: 10.1016/0002-9149(81)90557-9]

17 **Klinger JR**. Hemodynamics and positive end-expiratory pressure in critically ill patients. *Crit Care Clin* 1996; **12**: 841-864 [PMID: 8902374 DOI: 10.1016/S0749-0704(05)70282-7]

18 **Wiesen J**, Ornstein M, Tonelli AR, Menon V, Ashton RW. State of the evidence: mechanical ventilation with PEEP in patients with cardiogenic shock. *Heart* 2013; **99**: 1812-1817 [PMID: 23539555 DOI: 10.1136/heartjnl-2013-303642]

19 **Tobin MJ**. Mechanical ventilation. *N Engl J Med* 1994; **330**: 1056-1061 [PMID: 8080509 DOI: 10.1056/NEJM199404143301507]

20 **Manzano F**, Fernández-Mondéjar E, Colmenero M, Poyatos ME, Rivera R, Machado J, Catalán I, Artigas A. Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. *Crit Care Med* 2008; **36**: 2225-2231 [PMID: 18664777 DOI: 10.1097/CCM.0b013e31817b8a92]

21 **Smith TC**, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. *J Appl Physiol* (1985) 1988; **65**: 1488-1499 [PMID: 3053583]

22 **Esteban A**, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguía C, Nightingale P, Arroliga AC, Tobin MJ. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002; **287**: 345-355 [PMID: 11790214 DOI: 10.1001/jama.287.3.345]

23 **Malo J**, Ali J, Wood LD. How does positive end-expiratory pressure reduce intrapulmonary shunt in canine pulmonary edema? *J Appl Physiol Respir Environ Exerc Physiol* 1984; **57**: 1002-1010 [PMID: 6389451]

24 **de Miguel J**, Cabello J, Sánchez-Alarcos JM, Alvarez-Sala R, Espinós D, Alvarez-Sala JL. Long-term effects of treatment with nasal continuous positive airway pressure on lung function in patients with overlap syndrome. *Sleep Breath* 2002; **6**: 3-10 [PMID: 11917258 DOI: 10.1007/s11325-002-0003-6]

25 **Mezzanotte WS**, Tangel DJ, Fox AM, Ballard RD, White DP. Nocturnal nasal continuous positive airway pressure in patients with chronic obstructive pulmonary disease. Influence on waking respiratory muscle function. *Chest* 1994; **106**: 1100-1108 [PMID: 7924480 DOI: 10.1378/chest.106.4.1100]

26 **Petrof BJ**, Legaré M, Goldberg P, Milic-Emili J, Gottfried SB. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1990; **141**: 281-289 [PMID: 2405757 DOI: 10.1164/ajrccm/141.2.281]

27 **Verbraecken J**, Willemen M, De Cock W, Van de Heyning P, De Backer WA. Continuous positive airway pressure and lung inflation in sleep apnea patients. *Respiration* 2001; **68**: 357-364 [PMID: 11464081 DOI: 10.1159/000050527]

28 **Sullivan CE**, Berthon-Jones M, Issa FG. Remission of severe obesity-hypoventilation syndrome after short-term treatment during sleep with nasal continuous positive airway pressure. *Am Rev Respir Dis* 1983; **128**: 177-181 [PMID: 6346978]

29 **Berger KI**, Ayappa I, Chatr-Amontri B, Marfatia A, Sorkin IB, Rapoport DM, Goldring RM. Obesity hypoventilation syndrome as a spectrum of respiratory disturbances during sleep. *Chest* 2001; **120**: 1231-1238 [PMID: 11591566 DOI: 10.1378/chest.120.4.1231]

30 **Olson AL**, Zwillich C. The obesity hypoventilation syn-

drome. *Am J Med* 2005; **118**: 948-956 [PMID: 16164877 DOI: 10.1016/j.amjmed.2005.03.042]
31 **Sullivan CE**, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981; **1**: 862-865 [PMID: 6112294 DOI: 10.1016/S0140-6736(81)91118-1]
32 **Yumino D**, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, Parker JD, Bradley TD. Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. *J Card Fail* 2009; **15**: 279-285 [PMID: 19398074 DOI: 10.1016/j.cardfail.2008.11.015]
33 **Harada D**, Joho S, Oda Y, Hirai T, Asanoi H, Inoue H. Short term effect of adaptive servo-ventilation on muscle sympathetic nerve activity in patients with heart failure. *Auton Neurosci* 2011; **161**: 95-102 [PMID: 21195678 DOI: 10.1016/j.autneu.2010.12.001]
34 **Ushijima R**, Joho S, Akabane T, Oda Y, Inoue H. Differing effects of adaptive servoventilation and continuous positive airway pressure on muscle sympathetic nerve activity in patients with heart failure. *Circ J* 2014; **78**: 1387-1395 [PMID: 24705391 DOI: 10.1253/circj.CJ-13-1468]
35 **Haruki N**, Takeuchi M, Kaku K, Yoshitani H, Kuwaki H, Tamura M, Abe H, Okazaki M, Tsutsumi A, Otsuji Y. Comparison of acute and chronic impact of adaptive servo-ventilation on left chamber geometry and function in patients with chronic heart failure. *Eur J Heart Fail* 2011; **13**: 1140-1146 [PMID: 21831914 DOI: 10.1093/eurjhf/hfr103]
36 **Ueno K**, Kasai T, Brewer G, Takaya H, Maeno K, Kasagi S, Kawana F, Ishiwata S, Narui K. Evaluation of the apnea-hypopnea index determined by the S8 auto-CPAP, a continuous positive airway pressure device, in patients with obstructive sleep apnea-hypopnea syndrome. *J Clin Sleep Med* 2010; **6**: 146-151 [PMID: 20411691]
37 **Ikeda Y**, Kasai T, Kawana F, Kasagi S, Takaya H, Ishiwata S, Narui K. Comparison between the apnea-hypopnea indices determined by the REMstar Auto M series and those determined by standard in-laboratory polysomnography in patients with obstructive sleep apnea. *Intern Med* 2012; **51**: 2877-2885 [PMID: 23064561 DOI: 10.2169/internalmedicine.51.8249]
38 **Ayas NT**, Patel SR, Malhotra A, Schulzer M, Malhotra M, Jung D, Fleetham J, White DP. Auto-titrating versus standard continuous positive airway pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. *Sleep* 2004; **27**: 249-253 [PMID: 15124718]
39 **Nolan GM**, Ryan S, O'connor TM, McNicholas WT. Comparison of three auto-adjusting positive pressure devices in patients with sleep apnoea. *Eur Respir J* 2006; **28**: 159-164 [PMID: 16571610 DOI: 10.1183/09031936.06.00127205]
40 **Meurice JC**, Cornette A, Philip-Joet F, Pepin JL, Escourrou P, Ingrand P, Veale D. Evaluation of autoCPAP devices in home treatment of sleep apnea/hypopnea syndrome. *Sleep Med* 2007; **8**: 695-703 [PMID: 17638595 DOI: 10.1016/j.sleep.2007.03.019]
41 **Morgenthaler TI**, Aurora RN, Brown T, Zak R, Alessi C, Boehlecke B, Chesson AL, Friedman L, Kapur V, Maganti R, Owens J, Pancer J, Swick TJ. Practice parameters for the use of autotitrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome: an update for 2007. An American Academy of Sleep Medicine report. *Sleep* 2008; **31**: 141-147 [PMID: 18220088]
42 **Engleman HM**, Asgari-Jirhandeh N, McLeod AL, Ramsay CF, Deary IJ, Douglas NJ. Self-reported use of CPAP and benefits of CPAP therapy: a patient survey. *Chest* 1996; **109**: 1470-1476 [PMID: 8769496 DOI: 10.1378/chest.109.6.1470]
43 **Gay P**, Weaver T, Loube D, Iber C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep* 2006; **29**: 381-401 [PMID: 16553025]
44 **Kushida CA**, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, Boehlecke B, Brown TM, Coleman J, Friedman L, Kapen S, Kapur VK, Kramer M, Lee-Chiong T, Owens J, Pancer JP, Swick TJ, Wise MS. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep* 2006; **29**: 375-380 [PMID: 16553024]
45 **Yoshida M**, Kadokami T, Momii H, Hayashi A, Urashi T, Narita S, Kawamura N, Ando S. Enhancement of cardiac performance by bilevel positive airway pressure ventilation in heart failure. *J Card Fail* 2012; **18**: 912-918 [PMID: 23207079 DOI: 10.1016/j.cardfail.2012.10.009]
46 **Kasai T**. Sleep apnea and heart failure. *J Cardiol* 2012; **60**: 78-85 [PMID: 22824295 DOI: 10.1016/j.jjcc.2012.05.013]
47 **Janssens JP**, Metzger M, Sforza E. Impact of volume targeting on efficacy of bi-level non-invasive ventilation and sleep in obesity-hypoventilation. *Respir Med* 2009; **103**: 165-172 [PMID: 18579368 DOI: 10.1016/j.rmed.2008.03.013]
48 **Storre JH**, Seuthe B, Fiechter R, Milioglou S, Dreher M, Sorichter S, Windisch W. Average volume-assured pressure support in obesity hypoventilation: A randomized crossover trial. *Chest* 2006; **130**: 815-821 [PMID: 16963680 DOI: 10.1378/chest.130.3.815]
49 **Kelly JL**, Jaye J, Pickersgill RE, Chatwin M, Morrell MJ, Simonds AK. Randomized trial of 'intelligent' autotitrating ventilation versus standard pressure support non-invasive ventilation: impact on adherence and physiological outcomes. *Respirology* 2014; **19**: 596-603 [PMID: 24661390 DOI: 10.1111/resp.12269]
50 **Briones Claudett KH**, Briones Claudett M, Chung Sang Wong M, Nuques Martinez A, Soto Espinoza R, Montalvo M, Esquinas Rodriguez A, Gonzalez Diaz G, Grunauer Andrade M. Noninvasive mechanical ventilation with average volume assured pressure support (AVAPS) in patients with chronic obstructive pulmonary disease and hypercapnic encephalopathy. *BMC Pulm Med* 2013; **13**: 12 [PMID: 23497021 DOI: 10.1186/1471-2466-13-12]
51 **Ekkernkamp E**, Kabitz HJ, Walker DJ, Schmoor C, Storre JH, Windisch W, Dreher M. Minute ventilation during spontaneous breathing, high-intensity noninvasive positive pressure ventilation and intelligent volume assured pressure support in hypercapnic COPD. *COPD* 2014; **11**: 52-58 [PMID: 24111578 DOI: 10.3109/15412555.2013.829437]
52 **Teschler H**, Döhring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001; **164**: 614-619 [PMID: 11520725 DOI: 10.1164/ajrccm.164.4.9908114]
53 **Carnevale C**, Georges M, Rabec C, Tamisier R, Levy P, Pépin JL. Effectiveness of Adaptive Servo Ventilation in the treatment of hypocapnic central sleep apnea of various etiologies. *Sleep Med* 2011; **12**: 952-958 [PMID: 22030207 DOI: 10.1016/j.sleep.2011.07.008]
54 **Troitino A**, Labedi N, Kufel T, El-Solh AA. Positive airway pressure therapy in patients with opioid-related central sleep apnea. *Sleep Breath* 2014; **18**: 367-373 [PMID: 24062011 DOI: 10.1007/s11325-013-0894-4]
55 **Kasai T**, Usui Y, Yoshioka T, Yanagisawa N, Takata Y, Narui K, Yamaguchi T, Yamashina A, Momomura SI. Effect of flow-triggered adaptive servo-ventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and Cheyne-Stokes respiration. *Circ Heart Fail* 2010; **3**: 140-148 [PMID: 19933407 DOI: 10.1161/CIRCHEARTFAILURE.109.868786]
56 **Wysocki M**, Richard JC, Meshaka P. Noninvasive proportional assist ventilation compared with noninvasive pressure support ventilation in hypercapnic acute respiratory failure. *Crit Care Med* 2002; **30**: 323-329 [PMID: 11889302 DOI: 10.1097/00003246-200202000-00010]
57 **Kwok H**, McCormack J, Cece R, Houtchens J, Hill NS.

Controlled trial of oronasal versus nasal mask ventilation in the treatment of acute respiratory failure. *Crit Care Med* 2003; **31**: 468-473 [PMID: 12576953 DOI: 10.1097/01.CCM.0000045563.64187.20]
58 **Smaldone GC**. Assessing new technologies: patient-device interactions and deposition. *Respir Care* 2005; **50**: 1151-1160 [PMID: 16122399]
59 **Massie CA**, Hart RW, Peralez K, Richards GN. Effects of humidification on nasal symptoms and compliance in sleep apnea patients using continuous positive airway pressure. *Chest* 1999; **116**: 403-408 [PMID: 10453869 DOI: 10.1378/chest.116.2.403]
60 **Nishida T**, Nishimura M, Fujino Y, Mashimo T. Performance of heated humidifiers with a heated wire according to ventilatory settings. *J Aerosol Med* 2001; **14**: 43-51 [PMID: 11495484 DOI: 10.1089/08942680152007882]
61 **Hart DE**, Forman M, Veale AG. Effect of tubing condensate on non-invasive positive pressure ventilators tested under simulated clinical conditions. *Sleep Breath* 2011; **15**: 535-541 [PMID: 20669050 DOI: 10.1007/s11325-010-0397-5]
62 **Ozsancak A**, D'Ambrosio C, Hill NS. Nocturnal noninvasive ventilation. *Chest* 2008; **133**: 1275-1286 [PMID: 18460530 DOI: 10.1378/chest.07-1527]
63 **Aboussouan LS**, Ricaurte B. Noninvasive positive pressure ventilation: Increasing use in acute care. *Cleve Clin J Med* 2010; **77**: 307-316 [PMID: 20439563 DOI: 10.3949/ccjm.77a.09145]
64 **Girou E**, Schortgen F, Delclaux C, Brun-Buisson C, Blot F, Lefort Y, Lemaire F, Brochard L. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA* 2000; **284**: 2361-2367 [PMID: 11066187 DOI: 10.1001/jama.284.18.2361]
65 **Meduri GU**, Abou-Shala N, Fox RC, Jones CB, Leeper KV, Wunderink RG. Noninvasive face mask mechanical ventilation in patients with acute hypercapnic respiratory failure. *Chest* 1991; **100**: 445-454 [PMID: 1864119 DOI: 10.1378/chest.100.2.445]
66 **Gregoretti C**, Confalonieri M, Navalesi P, Squadrone V, Frigerio P, Beltrame F, Carbone G, Conti G, Gamna F, Nava S, Calderini E, Skrobik Y, Antonelli M. Evaluation of patient skin breakdown and comfort with a new face mask for noninvasive ventilation: a multi-center study. *Intensive Care Med* 2002; **28**: 278-284 [PMID: 11904656 DOI: 10.1007/s00134-002-1208-7]
67 **Fauroux B**, Lavis JF, Nicot F, Picard A, Boelle PY, Clément A, Vazquez MP. Facial side effects during noninvasive positive pressure ventilation in children. *Intensive Care Med* 2005; **31**: 965-969 [PMID: 15924228 DOI: 10.1007/s00134-005-2669-2]
68 **JCS Joint Working Group**. Guidelines for treatment of acute heart failure (JCS 2011). *Circ J* 2013; **77**: 2157-2201 [PMID: 23759659 DOI: 10.1253/circj.CJ-66-0068]
69 **Lindenfeld J**, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klapholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WH, Teerlink JR, Walsh MN. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2010; **16**: e1-194 [PMID: 20610207 DOI: 10.1016/j.cardfail.2010.04.004]
70 **McMurray JJ**, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33**: 1787-1847 [PMID: 22611136 DOI: 10.1093/eurheartj/ehs104]
71 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128**: e240-e327 [PMID: 23741058 DOI: 10.1161/CIR.0b013e31829e8776]
72 **Ho KM**, Wong K. A comparison of continuous and bi-level positive airway pressure non-invasive ventilation in patients with acute cardiogenic pulmonary oedema: a meta-analysis. *Crit Care* 2006; **10**: R49 [PMID: 16569254 DOI: 10.1186/cc4861]
73 **Gray A**, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008; **359**: 142-151 [PMID: 18614781 DOI: 10.1056/NEJMoa0707992]
74 **Park M**, Sangean MC, Volpe Mde S, Feltrim MI, Nozawa E, Leite PF, Passos Amato MB, Lorenzi-Filho G. Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Crit Care Med* 2004; **32**: 2407-2415 [PMID: 15599144 DOI: 10.1097/01.CCM.0000147770.20400.10]
75 **Takeda S**, Nejima J, Takano T, Nakanishi K, Takayama M, Sakamoto A, Ogawa R. Effect of nasal continuous positive airway pressure on pulmonary edema complicating acute myocardial infarction. *Jpn Circ J* 1998; **62**: 553-558 [PMID: 9741730 DOI: 10.1253/jcj.62.553]
76 **Pang D**, Keenan SP, Cook DJ, Sibbald WJ. The effect of positive pressure airway support on mortality and the need for intubation in cardiogenic pulmonary edema: a systematic review. *Chest* 1998; **114**: 1185-1192 [PMID: 9792593 DOI: 10.1378/chest.114.4.1185]
77 **Mehta S**. Continuous versus bilevel positive airway pressure in acute cardiogenic pulmonary edema? A good question! *Crit Care Med* 2004; **32**: 2546-2548 [PMID: 15599167 DOI: 10.1097/01.CCM.0000142946.76136.5C]
78 **Räsänen J**, Väisänen IT, Heikkilä J, Nikki P. Acute myocardial infarction complicated by left ventricular dysfunction and respiratory failure. The effects of continuous positive airway pressure. *Chest* 1985; **87**: 158-162 [PMID: 3881227 DOI: 10.1378/chest.87.2.158]
79 **Masip J**. Noninvasive ventilation in acute cardiogenic pulmonary edema. *Curr Opin Crit Care* 2008; **14**: 531-535 [PMID: 18787445 DOI: 10.1097/MCC.0b013e32830c4862]
80 **Schaffernocker T**, Morrison J and Khayat RN. Central sleep apnea: from pathophysiology to clinical management. *J Cardiovasc Dis* 2014; **2**: 32-38
81 **Yumino D**, Bradley TD. Central sleep apnea and Cheyne-Stokes respiration. *Proc Am Thorac Soc* 2008; **5**: 226-236 [PMID: 18250216 DOI: 10.1513/pats.200708-129MG]
82 **Javaheri S**, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007; **49**: 2028-2034 [PMID: 17512359 DOI: 10.1016/j.jacc.2007.01.084]
83 **Tkacova R**, Rankin F, Fitzgerald FS, Floras JS, Bradley TD. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. *Circulation* 1998; **98**: 2269-2275 [PMID: 9826313 DOI: 10.1161/01.CIR.98.21.2269]
84 **Kaneko Y**, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003; **348**: 1233-1241 [PMID: 12660387 DOI: 10.1056/NEJMoa022479]
85 **Mansfield DR**, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure.

Am J Respir Crit Care Med 2004; **169**: 361-366 [PMID: 14597482 DOI: 10.1164/rccm.200306-752OC]
86 **Usui K**, Bradley TD, Spaak J, Ryan CM, Kubo T, Kaneko Y, Floras JS. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. *J Am Coll Cardiol* 2005; **45**: 2008-2011 [PMID: 15963401 DOI: 10.1016/j.jacc.2004.12.080]
87 **Aggarwal S**, Nadeem R, Loomba RS, Nida M, Vieira D. The effects of continuous positive airways pressure therapy on cardiovascular end points in patients with sleep-disordered breathing and heart failure: a meta-analysis of randomized controlled trials. *Clin Cardiol* 2014; **37**: 57-65 [PMID: 24567977 DOI: 10.1002/clc.22201]
88 **Wang H**, Parker JD, Newton GE, Floras JS, Mak S, Chiu KL, Ruttanaumpawan P, Tomlinson G, Bradley TD. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol* 2007; **49**: 1625-1631 [PMID: 17433953 DOI: 10.1016/j.jacc.2006.12.046]
89 **Kasai T**, Narui K, Dohi T, Yanagisawa N, Ishiwata S, Ohno M, Yamaguchi T, Momomura S. Prognosis of patients with heart failure and obstructive sleep apnea treated with continuous positive airway pressure. *Chest* 2008; **133**: 690-696 [PMID: 18198253 DOI: 10.1378/chest.07-1901]
90 **Buckle P**, Millar T, Kryger M. The effect of short-term nasal CPAP on Cheyne-Stokes respiration in congestive heart failure. *Chest* 1992; **102**: 31-35 [PMID: 1623779 DOI: 10.1378/chest.102.1.31]
91 **Davies RJ**, Harrington KJ, Ormerod OJ, Stradling JR. Nasal continuous positive airway pressure in chronic heart failure with sleep-disordered breathing. *Am Rev Respir Dis* 1993; **147**: 630-634 [PMID: 8442598 DOI: 10.1164/ajrccm/147.3.630]
92 **Naughton MT**, Rahman MA, Hara K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. *Circulation* 1995; **91**: 1725-1731 [PMID: 7882480 DOI: 10.1161/01.CIR.91.6.1725]
93 **Krachman SL**, D'Alonzo GE, Berger TJ, Eisen HJ. Comparison of oxygen therapy with nasal continuous positive airway pressure on Cheyne-Stokes respiration during sleep in congestive heart failure. *Chest* 1999; **116**: 1550-1557 [PMID: 10593775 DOI: 10.1378/chest.116.6.1550]
94 **Köhnlein T**, Welte T, Tan LB, Elliott MW. Assisted ventilation for heart failure patients with Cheyne-Stokes respiration. *Eur Respir J* 2002; **20**: 934-941 [PMID: 12412686 DOI: 10.1183/09031936.00.02622001]
95 **Naughton MT**, Liu PP, Bernard DC, Goldstein RS, Bradley TD. Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. *Am J Respir Crit Care Med* 1995; **151**: 92-97 [PMID: 7812579 DOI: 10.1164/ajrccm.151.1.7812579]
96 **Tkacova R**, Liu PP, Naughton MT, Bradley TD. Effect of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 1997; **30**: 739-745 [PMID: 9283534 DOI: 10.1016/S0735-1097(97)00199-X]
97 **Sin DD**, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation* 2000; **102**: 61-66 [PMID: 10880416 DOI: 10.1161/01.CIR.102.1.61]
98 **Takasaki Y**, Orr D, Popkin J, Rutherford R, Liu P, Bradley TD. Effect of nasal continuous positive airway pressure on sleep apnea in congestive heart failure. *Am Rev Respir Dis* 1989; **140**: 1578-1584 [PMID: 2690705 DOI: 10.1164/ajrccm/140.6.1578]
99 **Naughton MT**, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med* 1995; **152**: 473-479 [PMID: 7633695 DOI: 10.1164/ajrccm.152.2.7633695]
100 **Granton JT**, Naughton MT, Benard DC, Liu PP, Goldstein RS, Bradley TD. CPAP improves inspiratory muscle strength in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med* 1996; **153**: 277-282 [PMID: 8542129 DOI: 10.1164/ajrccm.153.1.8542129]
101 **Bradley TD**, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005; **353**: 2025-2033 [PMID: 16282177 DOI: 10.1056/NEJMoa051001]
102 **Noda A**, Izawa H, Asano H, Nakata S, Hirashiki A, Murase Y, Iino S, Nagata K, Murohara T, Koike Y, Yokota M. Beneficial effect of bilevel positive airway pressure on left ventricular function in ambulatory patients with idiopathic dilated cardiomyopathy and central sleep apnea-hypopnea: a preliminary study. *Chest* 2007; **131**: 1694-1701 [PMID: 17400681 DOI: 10.1378/chest.06-2271]
103 **Willson GN**, Wilcox I, Piper AJ, Flynn WE, Norman M, Grunstein RR, Sullivan CE. Noninvasive pressure preset ventilation for the treatment of Cheyne-Stokes respiration during sleep. *Eur Respir J* 2001; **17**: 1250-1257 [PMID: 11491173 DOI: 10.1183/09031936.01.99086101]
104 **Kasai T**, Narui K, Dohi T, Ishiwata S, Yoshimura K, Nishiyama S, Yamaguchi T, Momomura S. Efficacy of nasal bi-level positive airway pressure in congestive heart failure patients with cheyne-stokes respiration and central sleep apnea. *Circ J* 2005; **69**: 913-921 [PMID: 16041159 DOI: 10.1253/circj.69.913]
105 **Dohi T**, Kasai T, Narui K, Ishiwata S, Ohno M, Yamaguchi T, Momomura S. Bi-level positive airway pressure ventilation for treating heart failure with central sleep apnea that is unresponsive to continuous positive airway pressure. *Circ J* 2008; **72**: 1100-1105 [PMID: 18577818 DOI: 10.1253/circj.72.1100]
106 **Pepperell JC**, Maskell NA, Jones DR, Langford-Wiley BA, Crosthwaite N, Stradling JR, Davies RJ. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. *Am J Respir Crit Care Med* 2003; **168**: 1109-1114 [PMID: 12928310 DOI: 10.1164/rccm.200212-1476OC]
107 **Philippe C**, Stoïca-Herman M, Drouot X, Raffestin B, Escourrou P, Hittinger L, Michel PL, Rouault S, d'Ortho MP. Compliance with and effectiveness of adaptive servoventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period. *Heart* 2006; **92**: 337-342 [PMID: 15964943 DOI: 10.1136/hrt.2005.060038]
108 **Oldenburg O**, Schmidt A, Lamp B, Bitter T, Muntean BG, Langer C, Horstkotte D. Adaptive servoventilation improves cardiac function in patients with chronic heart failure and Cheyne-Stokes respiration. *Eur J Heart Fail* 2008; **10**: 581-586 [PMID: 18486550 DOI: 10.1016/j.ejheart.2008.04.007]
109 **Yoshihisa A**, Shimizu T, Owada T, Nakamura Y, Iwaya S, Yamauchi H, Miyata M, Hoshino Y, Sato T, Suzuki S, Sugimoto K, Yamaki T, Kunii H, Nakazato K, Suzuki H, Saitoh S, Takeishi Y. Adaptive servo ventilation improves cardiac dysfunction and prognosis in chronic heart failure patients with Cheyne-Stokes respiration. *Int Heart J* 2011; **52**: 218-223 [PMID: 21828947 DOI: 10.1536/ihj.52.218]
110 **Kasai T**, Kasagi S, Maeno K, Dohi T, Kawana F, Kato M, Naito R, Ishiwata S, Ohno M, Yamaguchi T, Narui K, Momomura S. Adaptive servo-ventilation in cardiac function and neurohormonal status in patients with heart failure and central sleep apnea nonresponsive to continuous positive airway pressure. *JACC Heart Fail* 2013; **1**: 58-63 [PMID: 24621799 DOI: 10.1016/j.jchf.2012.11.002]
111 **Cowie MR**, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds A, Somers VK, Zannad F, Teschler H. Rationale and design of the SERVE-HF

study: treatment of sleep-disordered breathing with predominant central sleep apnoea with adaptive servo-ventilation in patients with chronic heart failure. *Eur J Heart Fail* 2013; **15**: 937-943 [PMID: 23535165 DOI: 10.1093/eurjhf/hft051]

112 Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure (SERVE-HF). ClinicalTrials.gov Identifier, NCT00733343. [accessed May 00733328, 00732014]. Available from: URL: http: //clinicaltrials.gov/ct2/show/NCT00733343?term=SERVE733343DHF&rank=00733341

113 **Randerath WJ**, Nothofer G, Priegnitz C, Anduleit N, Treml M, Kehl V, Galetke W. Long-term auto-servoventilation or constant positive pressure in heart failure and coexisting central with obstructive sleep apnea. *Chest* 2012; **142**: 440-447 [PMID: 22281801 DOI: 10.1378/chest.11-2089]

114 **Arzt M**, Schroll S, Series F, Lewis K, Benjamin A, Escourrou P, Luigart R, Kehl V, Pfeifer M. Auto-servoventilation in heart failure with sleep apnoea: a randomised controlled trial. *Eur Respir J* 2013; **42**: 1244-1254 [PMID: 23222879 DOI: 10.1183/09031936.00083312]

115 Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure (ADVENT-HF). ClinicalTrials.gov Identifier, NCT01128816. [accessed at May 01128828, 01122014]. Available from: URL: https: //clinicaltrials.gov/ct2/show/NCT01128816?term=ADVENT-HF&rank=01128811

116 **Khayat R**, Abraham W, Patt B, Brinkman V, Wannemacher J, Porter K, Jarjoura D. Central sleep apnea is a predictor of cardiac readmission in hospitalized patients with systolic heart failure. *J Card Fail* 2012; **18**: 534-540 [PMID: 22748486 DOI: 10.1016/j.cardfail.2012.05.003]

117 **Khayat RN**, Abraham WT, Patt B, Pu M, Jarjoura D. In-hospital treatment of obstructive sleep apnea during decompensation of heart failure. *Chest* 2009; **136**: 991-997 [PMID: 19567491 DOI: 10.1378/chest.09-0597]

118 **Ohmura T**, Iwama Y, Kasai T, Kato T, Suda S, Takagi A, Daida H. Impact of predischarge nocturnal pulse oximetry (sleep-disordered breathing) on postdischarge clinical outcomes in hospitalized patients with left ventricular systolic dysfunction after acute decompensated heart failure. *Am J Cardiol* 2014; **113**: 697-700 [PMID: 24342759 DOI: 10.1016/j.amjcard.2013.10.048]

119 Cardiovascular Improvements With MV ASV Therapy in Heart Failure (CAT-HF). ClinicalTrials.gov Identifier, NCT01953874. [accessed at May 01953828, 01952014]. Available from: URL: http: //clinicaltrials.gov/ct2/show/NCT01953874?term=CAT-HF&rank=01953871

120 **Arzt M**, Bradley TD. Treatment of sleep apnea in heart failure. *Am J Respir Crit Care Med* 2006; **173**: 1300-1308 [PMID: 16528015 DOI: 10.1164/rccm.200511-1745PP]

121 **Bradley TD**, Holloway RM, McLaughlin PR, Ross BL, Walters J, Liu PP. Cardiac output response to continuous positive airway pressure in congestive heart failure. *Am Rev Respir Dis* 1992; **145**: 377-382 [PMID: 1736745 DOI: 10.1164/ajrccm/145.2_Pt_1.377]

122 **Koyama T**, Watanabe H, Igarashi G, Terada S, Makabe S, Ito H. Short-term prognosis of adaptive servo-ventilation therapy in patients with heart failure. *Circ J* 2011; **75**: 710-712 [PMID: 21266785 DOI: 10.1253/circj.CJ-10-0956]

123 Randomized controlled Study of Adaptive-servo Ventilator in patients with congestive heart failure: Confirmatory trial of efficacy on cardiac function (SAVIOR-C). UMIN-CTR ID, UMIN000006549. [accessed at May 000007728, 000002014]. Available from: URL: http: //upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000007761&language=E

124 **Masip J**, Páez J, Merino M, Parejo S, Vecilla F, Riera C, Ríos A, Sabater J, Ballús J, Padró J. Risk factors for intubation as a guide for noninvasive ventilation in patients with severe acute cardiogenic pulmonary edema. *Intensive Care Med* 2003; **29**: 1921-1928 [PMID: 13680119 DOI: 10.1007/s00134-003-1922-9]

125 **Parissis JT**, Andreoli C, Kadoglou N, Ikonomidis I, Farmakis D, Dimopoulou I, Iliodromitis E, Anastasiou-Nana M, Lainscak M, Ambrosio G, Mebazaa A, Filippatos G, Follath F. Differences in clinical characteristics, management and short-term outcome between acute heart failure patients chronic obstructive pulmonary disease and those without this co-morbidity. *Clin Res Cardiol* 2014; **103**: 733-741 [PMID: 24718849 DOI: 10.1007/s00392-014-0708-0]

126 **Antonelli M**, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, Pelaia P, Principi T, Gregoretti C, Beltrame F, Pennisi MA, Arcangeli A, Proietti R, Passariello M, Meduri GU. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med* 2001; **27**: 1718-1728 [PMID: 11810114 DOI: 10.1007/s00134-001-1114-4]

127 **Padeletti M**, Jelic S, LeJemtel TH. Coexistent chronic obstructive pulmonary disease and heart failure in the elderly. *Int J Cardiol* 2008; **125**: 209-215 [PMID: 18221802 DOI: 10.1016/j.ijcard.2007.12.001]

128 **Hill NS**. Noninvasive ventilation for chronic obstructive pulmonary disease. *Respir Care* 2004; **49**: 72-87; discussion 87-89 [PMID: 14733624]

129 **Clini E**, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, Ambrosino N. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; **20**: 529-538 [PMID: 12358325 DOI: 10.1183/09031936.02.02162001]

130 **Tuggey JM**, Plant PK, Elliott MW. Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: an economic analysis. *Thorax* 2003; **58**: 867-871 [PMID: 14514940 DOI: 10.1136/thorax.58.10.867]

131 **Chebbo A**, Tfaili A, Jones SF. Hypoventilation syndromes. *Med Clin North Am* 2011; **95**: 1189-1202 [PMID: 22032434 DOI: 10.1016/j.mcna.2011.09.002]

132 **Marik PE**, Desai H. Characteristics of patients with the "malignant obesity hypoventilation syndrome" admitted to an ICU. *J Intensive Care Med* 2013; **28**: 124-130 [PMID: 22564878 DOI: 10.1177/0885066612444261]

133 **Kessler R**, Chaouat A, Schinkewitch P, Faller M, Casel S, Krieger J, Weitzenblum E. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. *Chest* 2001; **120**: 369-376 [PMID: 11502631 DOI: 10.1378/chest.120.2.369]

134 **Ayappa I**, Berger KI, Norman RG, Oppenheimer BW, Rapoport DM, Goldring RM. Hypercapnia and ventilatory periodicity in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2002; **166**: 1112-1115 [PMID: 12379556 DOI: 10.1164/rccm.200203-212OC]

135 **Norman RG**, Goldring RM, Clain JM, Oppenheimer BW, Charney AN, Rapoport DM, Berger KI. Transition from acute to chronic hypercapnia in patients with periodic breathing: predictions from a computer model. *J Appl Physiol* (1985) 2006; **100**: 1733-1741 [PMID: 16384839 DOI: 10.1152/japplphysiol.00502.2005]

136 **O'donnell CP**, Schaub CD, Haines AS, Berkowitz DE, Tankersley CG, Schwartz AR, Smith PL. Leptin prevents respiratory depression in obesity. *Am J Respir Crit Care Med* 1999; **159**: 1477-1484 [PMID: 10228114 DOI: 10.1164/ajrccm.159.5.9809025]

137 **Piper AJ**, Wang D, Yee BJ, Barnes DJ, Grunstein RR. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. *Thorax* 2008; **63**: 395-401 [PMID: 18203817 DOI: 10.1136/thx.2007.081315]

138 **Hida W**, Okabe S, Tatsumi K, Kimura H, Akasiba T, Chin K, Ohi M, Nakayama H, Satoh M, Kuriyama T. Nasal continuous positive airway pressure improves quality of life in obesity hypoventilation syndrome. *Sleep Breath* 2003; **7**: 3-12

[PMID: 12712392 DOI: 10.1007/s11325-003-0003-1]
139 **Banerjee D**, Yee BJ, Piper AJ, Zwillich CW, Grunstein RR. Obesity hypoventilation syndrome: hypoxemia during continuous positive airway pressure. *Chest* 2007; **131**: 1678-1684 [PMID: 17565018 DOI: 10.1378/chest.06-2447]
140 **Heinemann F**, Budweiser S, Dobroschke J, Pfeifer M. Non-invasive positive pressure ventilation improves lung volumes in the obesity hypoventilation syndrome. *Respir Med* 2007; **101**: 1229-1235 [PMID: 17166707 DOI: 10.1016/j.rmed.2006.10.027]
141 **Priou P**, Hamel JF, Person C, Meslier N, Racineux JL, Urban T, Gagnadoux F. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. *Chest* 2010; **138**: 84-90 [PMID: 20348200 DOI: 10.1378/chest.09-2472]

P- Reviewer: Cheng XW, Gaetano S, Kolettis TM
S- Editor: Yu J **L- Editor**: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

© 2014 Baishideng Publishing Group Inc. All rights reserved.