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## THE PRESENT AND FUTURE

### JACC REVIEW TOPIC OF THE WEEK

# Diaphragmatic Function in Cardiovascular Disease



## JACC Review Topic of the Week

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### ABSTRACT

In addition to the diaphragm's role as the primary respiratory muscle, it also plays an under-recognized role in cardiac function. It serves as a pump facilitating venous and lymph return, modulating left ventricular afterload hemodynamics and pericardial pressures, as well as regulating autonomic tone. Heart failure (HF) is associated with diaphragmatic changes (ie, muscle fiber atrophy and weakness, increased ratio of type I to type II muscle fibers, and altered muscle metaboreflex) that lead to diaphragmatic dysfunction with subsequent symptomatic manifestations of HF. Herein, it is proposed that targeting the diaphragm in patients with HF via inspiratory muscle training or device-based stimulation can provide a novel treatment pathway for HF. Reviewed are several potential mechanisms through which therapies targeting the diaphragm can be beneficial in HF (ie, improving preload reserve, atrial and ventricular synchrony, and metaboreflex activity; reducing pericardial restraint; and restoring diaphragm strength). (J Am Coll Cardiol 2022;80:1647-1659)

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The diaphragm is among the largest muscles in humans. It is a dome-shaped fibromuscular structure separating the thoracic and abdominal cavities. The diaphragm functions as the primary respiratory muscle. Motor neural activation results in diaphragmatic contraction, forcing abdominal contents caudally and increasing the transverse and longitudinal dimensions of the chest cavity. This reduces

intrathoracic pressure that draws air into the lungs during inspiration.<sup>1</sup> Relaxation of the diaphragm allows for elastic recoil of the chest wall, reducing thoracic cavity size, increasing intrathoracic pressure, and causing exhalation.<sup>1</sup> The diaphragm also plays an important role in coughing, speech, swallowing, and abdominal straining; acts as the “external sphincter” of the lower esophagus; and aids in blood return to



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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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## ABBREVIATIONS AND ACRONYMS

**ASDS** = asymptomatic  
synchronized diaphragmatic  
stimulation

**AT** = aerobic training

**CSA** = central sleep apnea

**HF** = heart failure

**HFref** = heart failure with  
reduced ejection fraction

**HRV** = heart rate variability

**IMT** = inspiratory muscle  
training

**LV** = left ventricle

**LVEF** = left ventricular ejection  
fraction

**NYHA** = New York Heart  
Association

**PIDS** = pacing-induced  
diaphragmatic stimulation

**P<sub>max</sub>** = maximal inspiratory  
pressure

the heart and lymph return to the thoracic duct from the abdominal lymph vessels during inhalation.<sup>1</sup> The diaphragm plays an under-recognized role in cardiac function and its hemodynamics. In this review, we discuss the role of the diaphragm on hemodynamics and the diaphragm as a potential novel therapeutic target in heart failure (HF).

## ROLE OF THE DIAPHRAGM IN CARDIOVASCULAR FUNCTION

The diaphragm plays a major role in modulating hemodynamics via acting as a respiratory pump that increases systemic venous and lymph return, regulating left ventricular (LV) afterload, modulating pericardial pressure, regulating heart rate variability (HRV), and modulating arterial baroreflex sensitivity.

### ACTING AS A RESPIRATORY PUMP: INCREASING SYSTEMATIC VENOUS AND

**LYMPH RETURN.** Diaphragmatic motion drives changes in intrathoracic pressure during inspiration and expiration. In healthy individuals, pleural pressure at end-expiration is estimated to be about  $-4$  mm Hg.<sup>2</sup> However, pleural pressure varies substantially from lung apex to base, with posture, age, sex, comorbidities and disease state (eg, emphysema, obesity), and time within the respiratory cycle.<sup>2</sup>

Respiration acts as a pump for both systemic and pulmonary venous systems. Inspiration reduces intrathoracic pressure and increases intra-abdominal pressure creating a pressure gradient that enhances venous return to the right atrium. The fall in intrathoracic pressure also increases the pressure gradient across the right atrial and right ventricular walls, increasing myocardial stretch (preload), and increasing right-sided stroke volume.<sup>3</sup>

Inspiration has similar effects on lymphatic return.<sup>4</sup> The right lymphatic duct drains lymph from the right side of head and neck, right thorax, and right upper extremity and empties into the junction of the right subclavian vein and right internal jugular vein; the thoracic duct drains lymph from the rest of the body and empties into the junction of the left subclavian vein and the left internal jugular vein.<sup>4</sup> Drainage of lymph into the venous system is a passive process driven by pressure gradients (Figure 1).

Inspiration is also associated with a reduction in LV stroke volume. This may reflect pooling of blood in pulmonary veins, reducing venous return to the left atrium, an increase in aortic diastolic pressure

## HIGHLIGHTS

- The diaphragm plays a key role in modulating cardiovascular hemodynamics.
- HF is associated with diaphragmatic dysfunction.
- Device-based stimulation of the diaphragm can improve preload reserve, enhance atrioventricular synchrony, and reduce pericardial restraint, with potential therapeutic implications for HF.

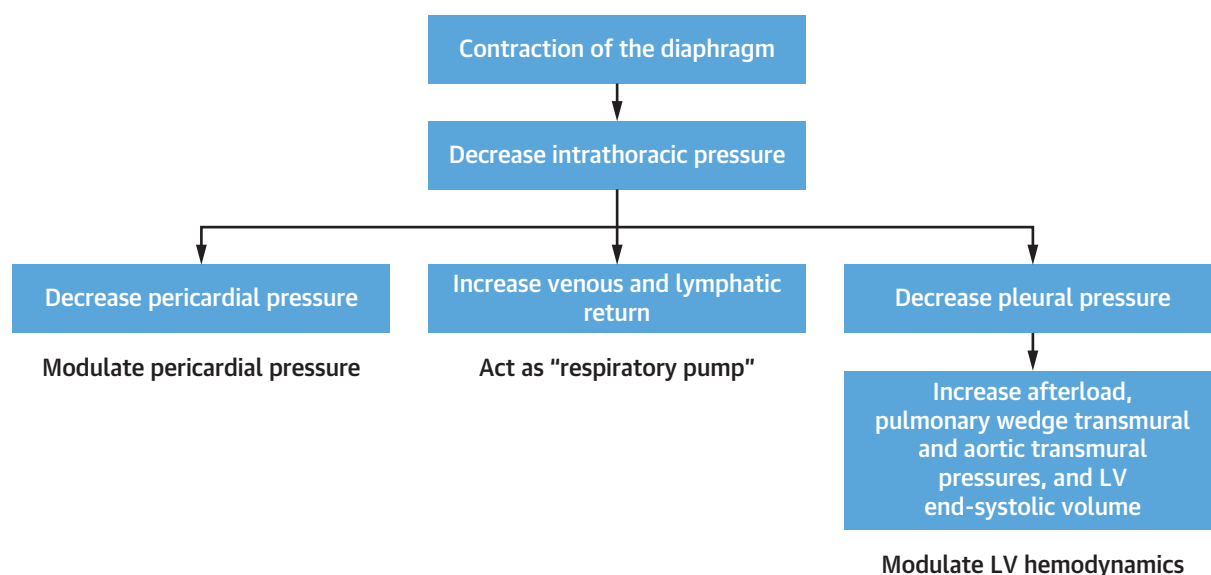
and LV afterload, or increased right ventricular filling during inspiration causing septal displacement into the LV, leading to reduced LV diastolic filling and stroke volume (ventricular interdependence).<sup>5</sup> The fall in LV stroke volume may be partially offset by an increase in transmural wall pressure and hence preload. During expiration, blood flow to the left atrium increases, septal displacement favors LV filling, and aortic diastolic pressures drop, leading to an increase in LV stroke volume (Figure 1).<sup>5</sup>

**REGULATING LV AFTERLOAD.** Contraction of the diaphragm results in a reduction in intrathoracic pressure, which imposes an afterload burden on the LV, resulting in a reduction in LV systolic performance.<sup>6</sup> It also results in a decrease in pleural pressure, which is inversely associated with the gradient between intrathoracic and extrathoracic vasculatures.<sup>7</sup> The afterload is highly dependent on this gradient; therefore, contraction of the diaphragm (and subsequently reduction in pleural pressure) would increase the afterload.<sup>7</sup>

**MODULATING PERICARDIAL PRESSURE.** Pericardial pressure is closely related to heart volumes. At normal physiological heart volumes, pericardial pressure is fairly stable. However, an increase in the heart volumes beyond the normal range results in a marked increase in pericardial pressure because the inflection point on the compliance curve is exceeded.<sup>8</sup>

Pericardial pressure varies with respiration; it rises with expiration and falls with inspiration.<sup>9</sup> Thus, it is closely related to changes in pleural pressure,<sup>10</sup> which are highly influenced by diaphragmatic movements. In preclinical studies, pleural and pericardial pressures have a close relationship in the normal resting state throughout the respiratory cycle (maximum difference during inspiration/expiration  $\sim 3$  mm Hg).<sup>10</sup> This correlation persists even during positive pressure ventilation.<sup>10</sup> In clinical studies of

**FIGURE 1** Cardiovascular Physiological Roles of the Diaphragm



The diaphragm exerts cardiovascular physiological roles (eg, modulates pericardial pressure and left ventricular (LV) hemodynamics and acts as a “respiratory pump”).

mechanical ventilation, progressively higher tidal volumes led to greater pericardial pressures with parallel change in pleural pressures.<sup>11</sup> This suggests an essential role for the diaphragm in modulating pericardial pressures and the possibility to use this mechanism in addressing conditions marked by pericardial restraint (**Figure 1**).

**REGULATING HRV AND MODULATING ARTERIAL BAROREFLEX SENSITIVITY.** HRV refers to the natural fluctuations in the intervals between consecutive heartbeats and provides an indirect assessment of autonomic nervous system activity.<sup>12</sup> Decreased HRV indicates a heightened sympathetic tone, is commonly encountered in HF, and is associated with increased cardiovascular morbidity and mortality.<sup>13</sup> The diaphragm modulates HRV via its effect on respiration and the resultant hemodynamic changes during inspiration and expiration. Fluctuations in blood pressure subsequently modulate the baroreceptor reflex system, resulting in HRV. In healthy individuals and patients with ischemic heart disease and diabetes, diaphragmatic breathing has been shown to improve HRV significantly.<sup>13</sup>

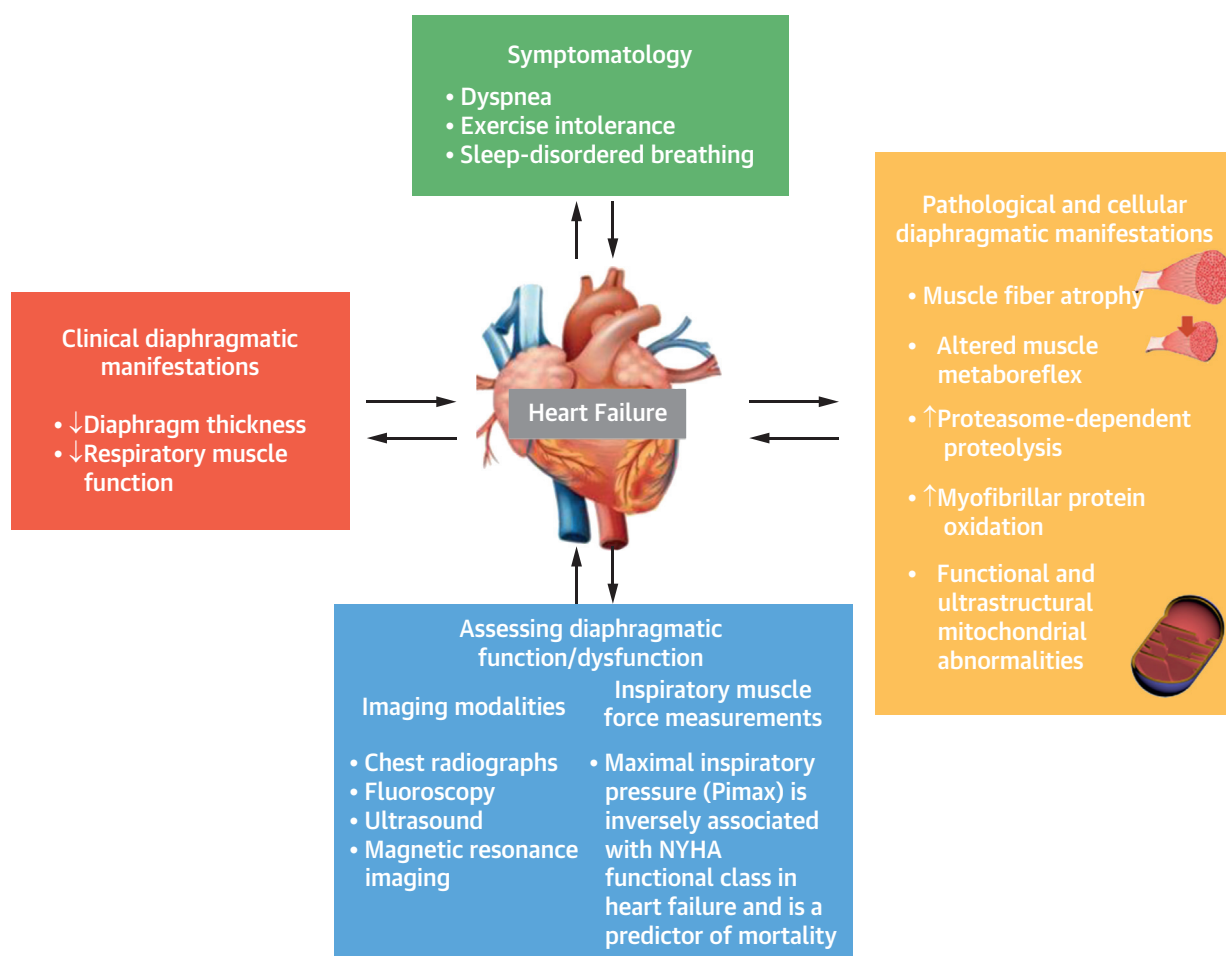
The diaphragm is also involved in modulating arterial baroreflex sensitivity. In a study of patients with hypertension, slow breathing at 6 breaths/min reduced blood pressure and increased baroreflex sensitivity.<sup>14</sup>

## DIAPHRAGMATIC ABNORMALITIES IN HF

The effect of HF on the diaphragm manifests in an “afferent” and “efferent” components. HF is typically associated with structural and physiological changes in the diaphragm (ie, efferent effect) that results in mechanical diaphragmatic dysfunction. The afferent input from the diaphragm plays an important role in mediating different reflexes (eg, metaboreflex); such reflexes trigger complex hemodynamic and respiratory cascades during exercise. Impairment of this afferent input results in disturbance in exercise-related hemodynamics (**Figure 2**).

**MUSCLE FIBER ATROPHY AND WEAKNESS.** Whereas the global respiratory muscle strength is generally well preserved in patients with HF at rest, diaphragm weakness is commonly encountered in patients with HF and predicts exercise intolerance independently from pulmonary dysfunction in these patients.<sup>15</sup> In a study of patients with heart failure with reduced ejection fraction (HFrEF) scheduled for LV assist device implantation, maximum inspiratory and maximum expiratory forces were significantly reduced by 38% and 25% in patients with HFrEF compared with in control subjects.<sup>16</sup> Furthermore, patients with HFrEF had diaphragm wasting with a mean diaphragm thickness that was 23% lower compared with diaphragm thickness in control

**FIGURE 2** Clinical, Pathological, and Cellular Diaphragmatic Associations With Heart Failure



Heart failure is associated with several physiological and cellular diaphragmatic changes. NYHA = New York Heart Association; P<sub>imax</sub> = maximal inspiratory pressure.

subjects.<sup>16</sup> At the cellular level, diaphragm biopsies in patients with HFrEF showed severe fiber atrophy with increased proteasome-dependent proteolysis, myofibrillar protein oxidation, and severe functional and ultrastructural mitochondrial abnormalities.<sup>16</sup>

**INCREASED RATIO OF TYPE I TO TYPE II MUSCLE FIBERS.** HF is associated with a high proportion of type I muscle fibers (slow twitch type) in the diaphragm.<sup>17</sup> Compared with type II muscle fibers (fast twitch type), type I muscle fibers have higher oxidative and lower glycolytic capacities.<sup>17</sup> Even though these changes may represent an adaptive mechanism to chronic hypoxia, the implications are not well understood.

**ALTERED MUSCLE METABOREFLEX.** Muscle metaboreflex is a key regulator of the cardiovascular exercise response and is triggered by metabolic by-

products (eg, lactic acid) in skeletal muscles that stimulate afferent nerve fibers leading to sympathetic stimulation with a resultant increase in cardiac output and vasoconstriction of nonactive muscles.<sup>18</sup> In a healthy state, baroreceptor unloading during muscle metaboreflex activation results in an increase in mean arterial pressure primarily via an increase in cardiac output, whereas in an HF state, baroreceptor unloading during muscle metaboreflex activation increases mean arterial pressure primarily via vasoconstriction. In a canine model of HF, baroreceptor unloading was simulated by bilateral carotid occlusion;<sup>19</sup> this resulted in a pressor response caused by peripheral vasoconstriction of all vascular beds (including the ischemic active skeletal muscle) with no preferential vasoconstriction of the nonischemic vasculature,<sup>19</sup> suggesting that restoration of blood

flow to ischemic active muscles is remarkably attenuated in HF because of the absence of preferential vasoconstriction of the nonischemic vasculature. Because the diaphragm is metabolically more active during exercise, altered diaphragm metaboreflex can contribute to limited exercise capacity in patients with HF (**Central Illustration**).

**ASSESSING DIAPHRAGMATIC DYSFUNCTION.** Several imaging modalities can be used to assess the diaphragm and its dysfunction. Chest radiographs can be used to assess diaphragmatic shape, position, and contour and are typically used for the initial assessment of diaphragmatic dysfunction.<sup>20</sup> Fluoroscopy is a functional imaging modality that is typically used as a next step in assessing diaphragmatic elevation seen on chest radiographs.<sup>20</sup> Ultrasound is an inexpensive and readily available modality that provides data related to the diaphragmatic function, excursion, thickness, and thickening and can be used during exercise (**Figure 3**).<sup>21</sup> Magnetic resonance imaging can be used to study the excursion, synchronicity, and velocity of diaphragmatic motion.<sup>20</sup> While these modalities were predominantly studied in the context of pulmonary diseases, their utility in assessing diaphragmatic dysfunction in patients with HF is still uncertain.

In addition to imaging modalities, inspiratory muscle force measurements, such as maximal inspiratory pressure ( $P_{i,max}$ ), can be used to assess the degree of diaphragmatic dysfunction in HF.<sup>22</sup>  $P_{i,max}$  is typically reduced in patients with HF, and its degree of reduction correlates with worsening New York Heart Association (NYHA) functional class and is a strong predictor of mortality.<sup>22</sup>

## TARGETING THE DIAPHRAGM AS TREATMENT IN PATIENTS WITH HF

Given the vital relationship between the diaphragm and cardiac hemodynamics, there is the potential to use the diaphragm to treat cardiovascular diseases associated with the disturbance of cardiac hemodynamics, such as HF.

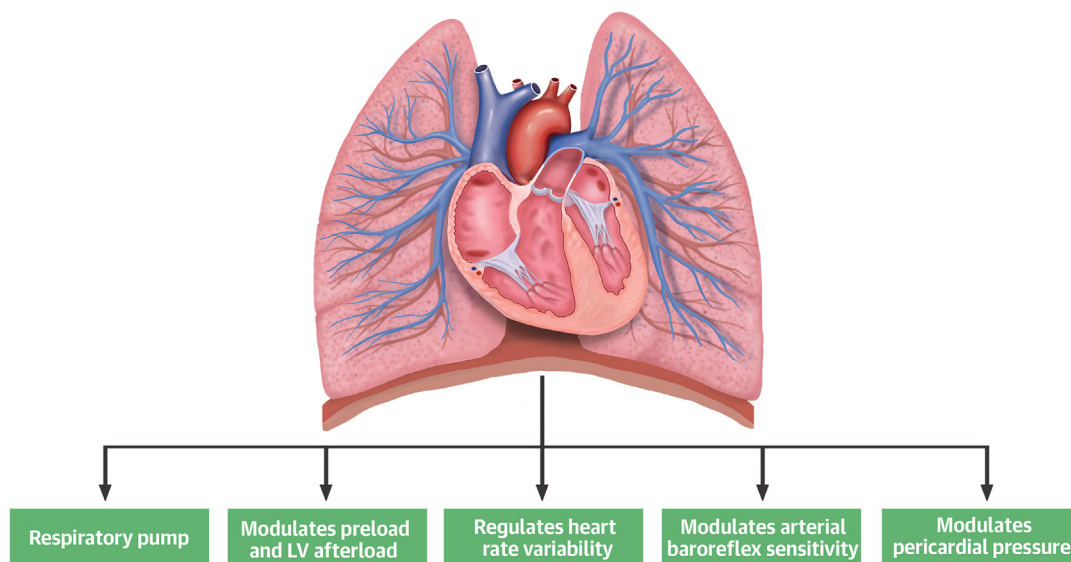
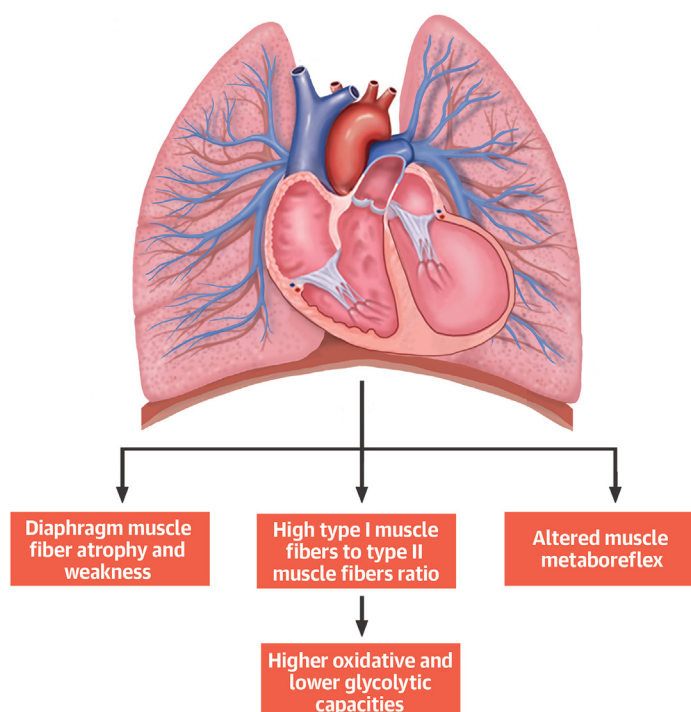
**INSPIRATORY MUSCLE TRAINING IN HF.** The structural and biochemical changes of the diaphragm seen in HF can result in inspiratory muscle weakness, which may be among the main drivers for dyspnea, fatigue, and exercise intolerance that is observed in patients with HF. There is a growing body of evidence suggesting that inspiratory muscle training (IMT) in patients with HF may counteract these changes and restore normal/semi-normal diaphragmatic and respiratory muscle function.<sup>23</sup> In patients

with HF and inspiratory muscle weakness (in whom maximal inspiratory pressure was <70% of predicted) exhibiting altered activity of the respiratory muscle metaboreflex, which is shown by significant reduction of blood flow to resting and exercising limbs, a 4-week course of IMT resulted in hypertrophy of the diaphragm and improvement in the blood flow to the resting and exercising limbs with inspiratory muscle loading.<sup>24</sup> These results suggest that IMT in patients with HF can improve the thickness of the diaphragm, restore diaphragmatic strength, and improve the activity of the respiratory muscle metaboreflex. Furthermore, this study showed that IMT in patients with HF can increase the ventilatory load needed to induce the respiratory muscle metaboreflex-mediated peripheral vasoconstriction;<sup>24</sup> this suggests that IMT may be associated with reduction in the accumulation of the metabolic by-products of muscles (eg, lactic acid), which are key regulators of metaboreflex activity. IMT also exerts favorable effect on the inspiratory muscle force measurements. In a meta-analysis, isolated IMT showed a statistically significant increase in  $P_{i,max}$  by 25.12 cm H<sub>2</sub>O.<sup>25</sup>

Subsequent studies have shown that an exercise program that consists of combined aerobic training (AT), resistance training performed on a treadmill or bicycle at an intensity of 60% to 80% of maximum heart rate, and IMT is superior to either AT/resistance training, AT/IMT, or AT alone in improving aerobic capacity and circulatory power in patients with HFrEF.<sup>26</sup> Although the effect of AT, resistance training, and IMT on the cellular and molecular levels of the diaphragm in humans has not been explored, in a mice model of HF, aerobic exercise training prevented contractile dysfunction of diaphragm fiber bundles and reduced markers of oxidative stress and proteolysis.<sup>27</sup>

Some of the mechanisms that may underlie the beneficial effects of IMT in patients with HF may relate to: 1) attenuation of metaboreflex (thus improving blood flow distribution to skeletal muscles and delaying muscle fatigue); 2) enhancement of ventilatory efficiency; and 3) reduction of ventilatory oscillations.<sup>28</sup>

**DIAPHRAGMATIC STIMULATION.** In a study in 14 patients undergoing cardiac surgery, diaphragm pacing, using a transvenous pacing catheter to stimulate the right and left phrenic nerves resulted in reduced pulmonary artery pressure, right atrial pressure, left atrial pressure, and total pulmonary vascular resistance with a significant augmentation in cardiac output.<sup>29</sup>

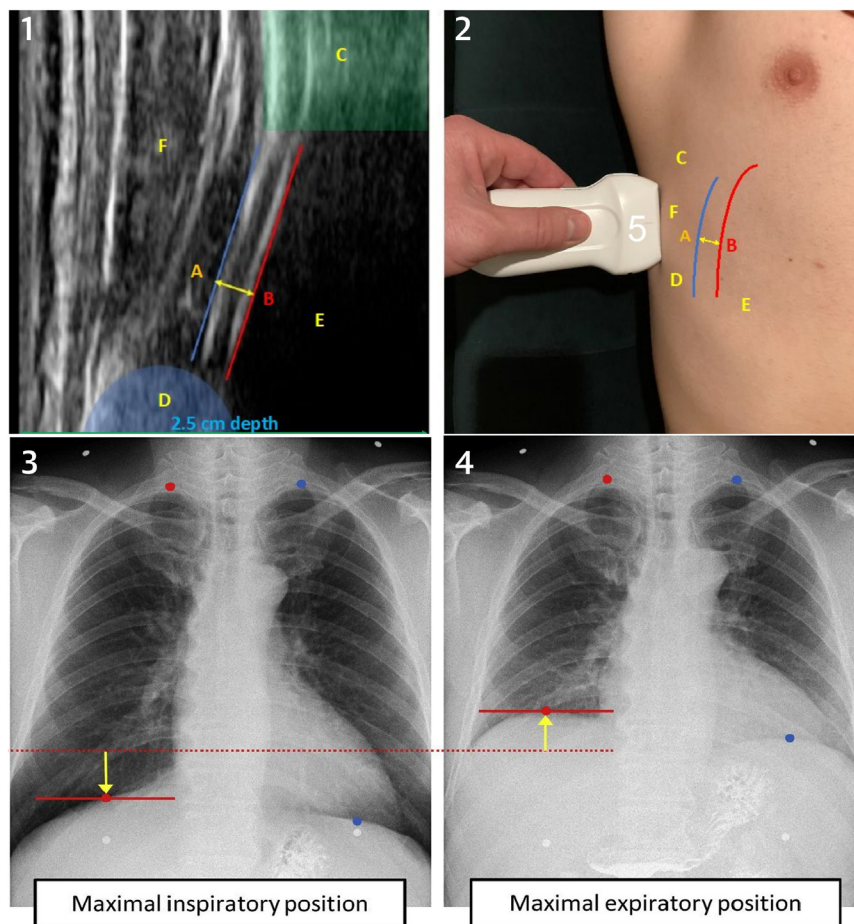
**CENTRAL ILLUSTRATION** Diaphragm as a Therapeutic Target in Cardiovascular Disease**Diaphragm in a Physiological State****Diaphragm in a Heart Failure State**

Salah HM, et al. *J Am Coll Cardiol.* 2022;80(17):1647-1659.

A summary of the physiological cardiovascular roles of the diaphragm, diaphragm abnormalities in heart failure, clinical benefits of diaphragm stimulation therapy and inspiratory muscle training, and proposed mechanisms for these benefits. LV = left ventricle.



**FIGURE 3** Imaging Modalities to Assess the Diaphragm Function and Structure

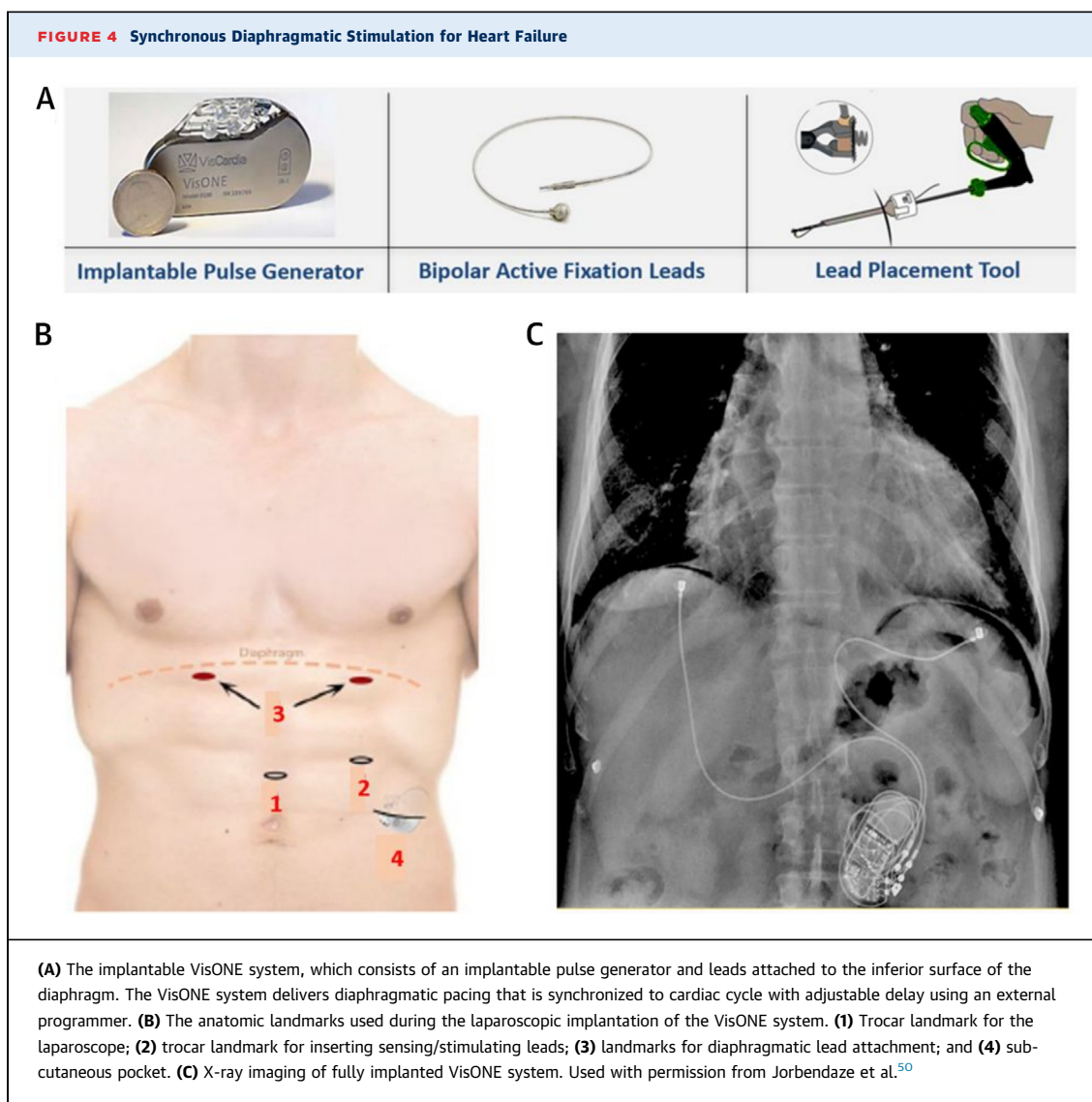


(1, 2) Evaluation of the diaphragm function and structure using bedside ultrasound: (A) pleural side; (B) peritoneal side; (C) lung; (D) rib; (E) liver and visceral organs. The **arrows** represent the diaphragm. (3, 4) Evaluation of the diaphragm function and structure using fluoroscopy. The **dashed line** represents the diaphragm rest expiratory position (baseline). In (3), the **solid line** represents the diaphragm position with maximal inspiration. The **arrow** represents the change in the diaphragm position from the rest expiratory position to maximal inspiration. In (4), the **solid line** represents the diaphragm position at maximal expiration. The **arrow** represents the change in the diaphragm position from the rest expiratory position to maximal expiration. (3) and (4) reproduced with permission from Hida et al.<sup>49</sup>

The hemodynamic effects of pacing-induced diaphragmatic stimulation (PIDS) was first observed on patients with permanent pacemakers who are ambulatory and later confirmed on patients who are hospitalized and undergoing temporary pacing during electrophysiologic examination.<sup>30</sup>

Subsequently, the same group investigated the effect of PIDS on cardiac hemodynamics in patients undergoing open-heart surgery, during which a temporary stimulation lead was attached to the left dorsal location of the diaphragm.<sup>31</sup> PIDS 20 milliseconds after the onset of ventricular pacing significantly improved electromechanical activation time with no observed desensitization of the

diaphragm following PIDS, suggesting that PIDS can potentially improve LV systolic function.<sup>31</sup> This favorable effect was achieved regardless of whether subjects were symptomatic or asymptomatic from the diaphragmatic contraction in response to pacing, suggesting comparable efficacy. The randomized, open-label, crossover Epiphrenic-II Pilot trial, which included patients with HFrEF who were scheduled for open cardiothoracic surgery and implantation of a combined pacemaker/cardiac resynchronization therapy or implantable cardioverter-defibrillator/cardiac resynchronization therapy for chronic HF, showed that optimized PIDS modes (ie, optimized delay to ventricular cardiac resynchronization



therapy pulse) resulted in a significant improvement in left ventricular ejection fraction (LVEF), improvement in the NYHA functional class, and an increase in the maximal power and oxygen consumption during exercise testing.<sup>32</sup>

Recently, the pilot VisONE Heart Failure Study investigated the VisONE asymptomatic synchronized diaphragmatic stimulation (ASDS) system, which consists of an implantable pulse generator and leads attached to the inferior surface of the diaphragm, and showed that a transabdominal laparoscopic implantation of the VisONE ASDS system in patients with HFrEF (LVEF  $\leq 35\%$ ), NYHA functional class II–III symptoms, and no ventricular dyssynchrony results in an acute improvement in LVEF, cardiac output, and 6-minute walk distance, and a decrease in heart rate at 1 month following the implantation.<sup>33</sup> Follow-

ups at 12-months showed consistent improvement in these outcomes with larger effect when diaphragmatic synchronization was  $>80\%$  of pacing.<sup>34</sup> Based on these results, the U.S. Food and Drug Administration granted ASDS a breakthrough device designation status in 2020 (Figure 4, Table 1).<sup>35,36</sup>

Phrenic nerve stimulation is also used in the management of central sleep apnea (CSA), which is prevalent in HF.<sup>35</sup> Phrenic nerve stimulation during sleep using the remedē System (Respica Inc), an implantable device that results in diaphragmatic contraction with restoration of normal breathing pattern during sleep. The cumulative evidence from the pilot and pivotal trials with moderate to severe CSA demonstrated that phrenic nerve stimulation significantly reduces apnea-hypopnea index, improves quality of life, and oxygenation at 6 months

**TABLE 1 Studies Investigating the Role of Long-Term Diaphragmatic Stimulation on Cardiovascular Outcomes in Humans**

Study, Ref. #	Year	Population	Intervention	Number of Participants	Major Results
Ishii et al <sup>29</sup>	1990	Patients undergoing cardiac surgery	Bilateral diaphragm pacing	14	Bilateral diaphragm pacing reduced pulmonary artery pressure, right atrial pressure, left atrial pressure, and total pulmonary vascular resistance with a significant augmentation in cardiac output
Roos et al <sup>31</sup>	2008	Patients undergoing cardiac surgery	Pacing-induced diaphragmatic stimulation	35	Stimulation improved electromechanical activation time with no observed diaphragm desensitization
Beeler et al, <sup>32</sup> Epiphrenic II Pilot Trial	2014	Patients with chronic heart failure and cardiac resynchronization therapy	Attaching an additional electrode to the left diaphragm for diaphragm stimulation	24	Diaphragm stimulation improved left ventricular ejection fraction, dyspnea, and working capacity
Zuber et al, <sup>33</sup> Pilot VisONE Heart Failure Study	2019	Patients with LVEF $\leq$ 35%, moderate-severe heart failure symptoms, and no evidence of ventricular dyssynchrony	Laparoscopic implantation of the VisONE ASDS system	15	VisONE ASDS system resulted in an improvement in LVEF, cardiac output, and 6-minute walk distance, and a decrease in heart rate at 1 month with consistent improvement in these outcomes at 3, 6, and 12 months with larger effect when diaphragmatic synchronization was $>80\%$ of pacing

ASDS = asymptomatic synchronized diaphragmatic stimulation; LVEF = left ventricular ejection fraction.

with sustained results through 5 years following implantation (Figure 5).<sup>37,38</sup> These benefits were consistent in patients with CSA and HF, and in parallel, phrenic nerve stimulation resulted in a significant improvement in HF quality of life as measured by the Minnesota Living With Heart Failure Questionnaire.<sup>39</sup> Whereas hospitalizations for HF were numerically lower with treatment (4.7% in the treatment group vs 17% in the control group) at 6 months, this difference did not reach a statistical significance ( $P = 0.065$ ).<sup>39</sup> These findings signal a possible direct or indirect effect for phrenic nerve stimulation on HF beyond the effect on CSA.

#### POTENTIALS MECHANISMS BY WHICH DIAPHRAGMATIC STIMULATION IMPROVES CARDIAC OUTCOMES IN PATIENTS WITH HF

The exact mechanisms by which diaphragmatic stimulation drive the cardiovascular benefits and improved hemodynamics in HF are not well understood, partially because of the lack of studies exploring its pathophysiology and partially because, until recently, there was a lack of therapeutic options. We propose the following mechanisms that may individually and/or cumulatively drive such benefits in patients with HF:

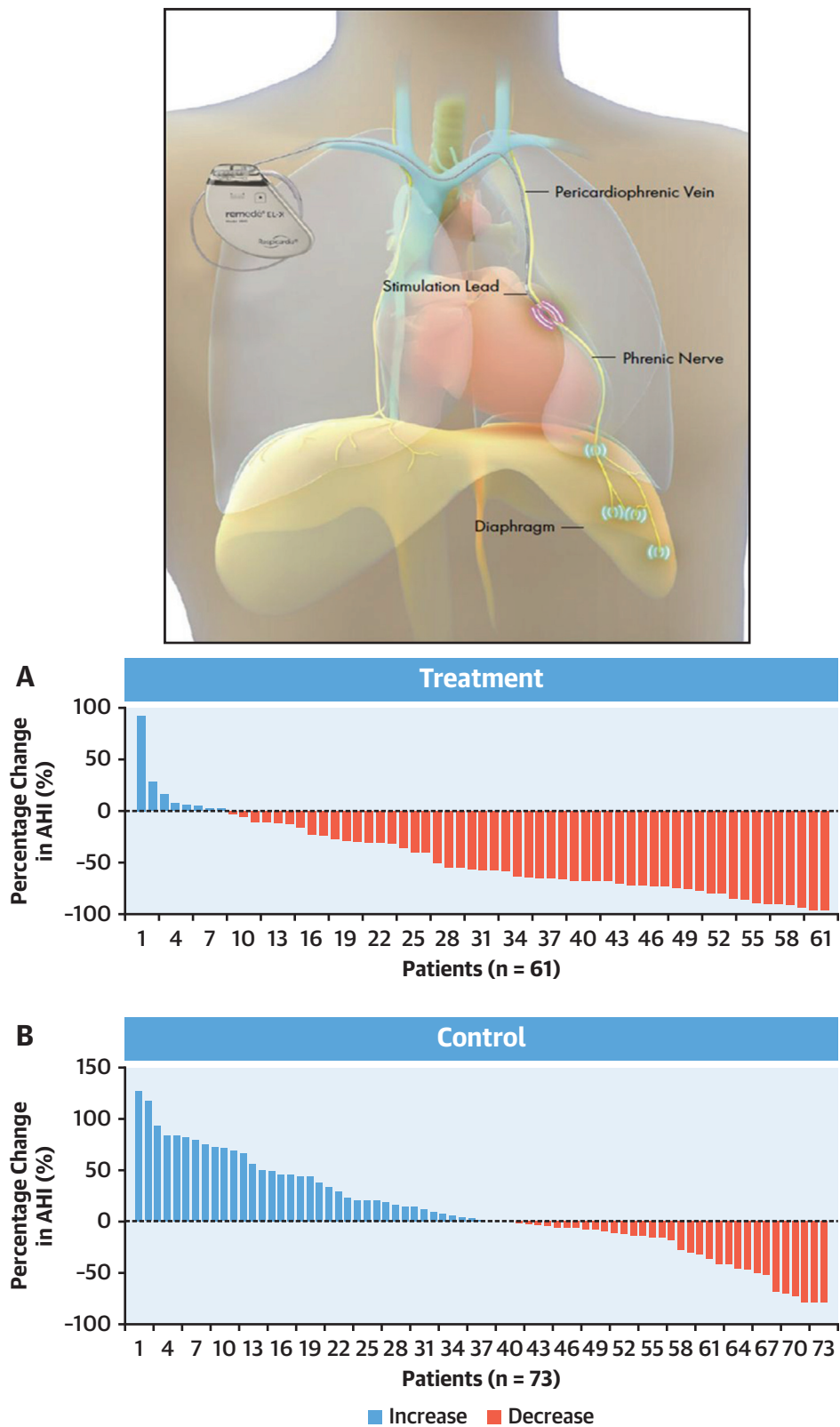
**IMPROVING PRELOAD RESERVE.** ASDS results in an asymptomatic but palpable diaphragmatic movement, which is characterized by a focal caudal diaphragmatic movement followed by backward cranial movement superimposed on the regular respiration movements.<sup>32</sup> These movements can favorably affect loading and unloading of the heart.

In healthy individuals, augmentation of cardiac output during physical activity depends largely on

the conversion of unstressed to stressed blood volume by means of central blood volume recruitment (eg, from lower extremities and abdominal compartment) with resultant increase in preload.<sup>40</sup> The central blood volume recruitment process occurs in response to venous constriction via baroreflex- and chemoreflex-mediated sympathoactivation.<sup>40</sup> In the lower extremities, this process is aided by skeletal muscle contraction.<sup>41</sup> In the abdominal compartment, almost 400 mL of blood volume is recruited centrally from the splanchnic circulation in response to physical activity.<sup>42</sup> This shift is, in large part, aided by the contraction of the diaphragm.<sup>43</sup> Preload reserve refers to the ability of the cardiovascular system to enhance cardiac output in response to increased preload without a significant increase in ventricular filling pressure and is typically impaired in patients with HF.<sup>40</sup> ASDS-induced diaphragmatic movement can potentially increase preload as a result of the central blood volume recruitment from the splanchnic circulation.<sup>44</sup> In patients with HF, the Frank-Starling mechanism plays a limited role in augmenting cardiac output in response because the failing heart typically operates on the relatively flat portion of the Frank-Starling curve. ASDS likely overcomes this limitation by mechanically aiding cardiac function, decreasing the heart's work burden, and improving cardiac energy expenditure with subsequent favorable cardiac remodeling. Favorable cardiac remodeling (reduction in LV end-systolic dimension) in response to mechanical aid with ASDS may be among the mechanisms underlying the improvement in LVEF and LV end-systolic volume seen with ASDS.

Diaphragmatic contraction generated by ASDS may also function as an "auxiliary heart" in series with the native heart that aids in pumping blood from the

**FIGURE 5** Phrenic Nerve Stimulation in Central Sleep Apnea



Phrenic nerve stimulation in patients with central sleep apnea results in restoration of normal breathing pattern. Modified with permission from Costanzo *et al.* <sup>51</sup> AHI = apnea/hypopnea index.

trunk into the extremities. In a study of healthy individuals performing plantar flexion exercise at 4 METS, plethysmography was used to measure changes in body and trunk volumes during 3 types of breathing (spontaneous breathing, rib cage breathing, and abdominal breathing).<sup>45</sup> During spontaneous and rib cage breathing, blood was displaced from the extremities into the trunk (an average of 160 mL during spontaneous breathing and 478 mL during rib cage breathing), whereas an average of 225 mL of blood was displaced from the trunk into the extremities during abdominal breathing (predominantly diaphragm breathing).<sup>45</sup> Collectively, these mechanisms likely result in overcoming preload reserve failure, improving cardiac output, and enhancing perfusion.

**IMPROVING ATRIOVENTRICULAR SYNCHRONY.** ASDS potentially exerts beneficial effects by improving atrial and ventricular synchrony. With dual-chamber pacing alone, it has been demonstrated that a properly timed, effective atrial contraction is important for optimal LV systolic function because such contraction increases LV end-diastolic pressure while maintaining a low mean left atrial pressure.<sup>46</sup> This optimal mechanical atrial and ventricular synchrony can be re-established in patients with severe LV dysfunction with a resultant increase in cardiac output by atrioventricular sequential pacing.<sup>46</sup> With diaphragmatic pacing, swings in intrathoracic and pericardial pressures affect cardiac loading conditions and atrioventricular synchrony. Initial caudal diaphragmatic movement induced by ASDS generates a negative intrathoracic pressure gradient that is transmitted to the pericardium, pulling outward on the ventricles during late diastole and allowing for an increase in the atrial contribution to LV filling during diastole.<sup>32</sup> This initial ASDS-induced caudal diaphragmatic movement and changes in loading conditions with improved atrial contribution to LV filling in late diastole may also be able to re-establish the mechanical synchrony lost in HF states. Following caudal displacement, the diaphragmatic movement induced by ASDS is cranial and is typically much faster than the regular diaphragmatic movement. Cranial displacement of the diaphragm increases intrathoracic and pericardial pressure, which acts as an extracardiac compressive force, augmenting ventricular contraction during systole.<sup>41</sup>

**REDUCING PERICARDIAL RESTRAINT.** The pericardium plays an important and under-recognized role in the pathophysiology of HF via its compressive contact force on the surface of the myocardium (ie, pericardial restraint).<sup>8</sup> Pericardial restraint is involved in modulating the hemodynamics of cardiac

function throughout the cardiac cycle. It is typically exaggerated in different phenotypes of HF because of an increase in cardiac volumes.<sup>8</sup> In patients with normal LVEF undergoing pericardiectomy for elective coronary artery bypass surgery, there was an increase in LV end-diastolic volume and LV mass indices with no change in end-systolic circumferential wall stress or end-systolic volume, suggesting that targeting pericardial restraint could improve diastolic filling and result in myocardial growth with no adverse cardiac remodeling.<sup>47</sup>

ASDS-induced diaphragmatic movement can result in a negative intrathoracic pressure with subsequent “micro” reduction in pericardial pressure, which would improve cardiac filling conditions and systolic performance. A decrease in the intrathoracic pressure results in a similar decrease in the pericardial pressure even in conditions of increased pericardial restraints, such as tamponade.<sup>10</sup> The decrease in intrathoracic pressure transmitted to the pericardial space generates an increased atrial transmural pressure gradient that works to reduce atrial pressure and augment atrial filling with more volume at lower pressures. Because atrial pressure and volume reflects loading conditions of the ventricles, an increase in atrial blood volume at a lower pressure allows the corresponding ventricle to subsequently fill at lower pressure with higher volumes as well, reflecting increased ventricular compliance. This salutary change in ventricular compliance works in conjunction with preload to recruit the other beneficial changes of LV afterload reduction, preload reserve, and increased cardiac output.

**IMPROVING METABOREFLEX ACTIVITY AND RESTORATION OF DIAPHRAGM STRENGTH BY MUSCLE TRAINING.** As we already discussed, HF is associated with altered metaboreflex activity, weakness and atrophy of the diaphragm muscle fibers, and increased type-I muscle fibers to type-II muscle fibers ratio. Prospective studies showed that inspiratory muscle training in patients with HF can lead to significant improvement in metaboreflex activity.<sup>48</sup> It is possible that chronic stimulation of the diaphragm with ASDS would result in diaphragm training with subsequent improvement in metaboreflex activity, tissue remodeling, and optimization of diaphragmatic energy metabolism. This may translate clinically to an improvement in exercise capacity that is independent from pulmonary function.

## FUTURE DIRECTIONS

This review highlights the underappreciated role of the diaphragm in the cardiovascular system and its



potential as a target therapy in patients with HF. However, there is a need for studies investigating the diaphragmatic changes associated with different HF phenotypes (eg, HFrEF vs HF with preserved ejection fraction). Most of the current evidence supporting diaphragm-based therapies as a potential therapeutic pathway in patients with HF is driven by studies that included an HFrEF population, which underscores the need for studies examining the effect of these therapies in patients with HF with preserved ejection fraction. Additionally, more studies are needed to understand the effect of IMT (isolated or in combination with other forms of exercise) and device stimulation therapy on the functional inspiratory muscle force measurements and the diaphragmatic cellular and molecular changes that are associated with these therapies. Furthermore, the proposed mechanisms underlying the favorable effects of IMT and device stimulation therapy in this review are mainly postulation, which underscores the need for studies exploring the mechanisms of these therapies.

## CONCLUSIONS

The diaphragm is a key but overlooked component of not only the respiratory system but also the cardiovascular system. It plays a role as a pump that increases venous and lymph return, modulates LV afterload hemodynamics and pericardial

pressures, regulates HRV, and improves baroreflex sensitivity. HF is commonly associated with diaphragmatic dysfunction; targeting the diaphragm (via device stimulation therapy or inspiratory muscle training) may provide a novel treatment pathway for HF.

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