



# Ultrasonographic assessment of organs other than the heart in patients with heart failure

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## Abstract

The number of patients with heart failure has been dramatically increasing in Japan in association with aging of the society. This phenomenon is referred to as a heart failure pandemic. The fundamental origin of heart failure is cardiac dysfunction. Echocardiography is widely used to assess cardiac function, as well as to diagnose heart diseases that cause cardiac dysfunction. However, the severity of heart failure is not necessarily correlated with that of cardiac dysfunction. This is partly explained by the fact that heart failure induces dysfunction of organs other than the heart through hemodynamic deterioration and neurohumoral changes. In addition, one of the characteristics of patients with heart failure, particularly elderly patients, is the presence of numerous comorbidities. Symptoms of heart failure are not specific, and assessment of cardiac function, particularly left ventricular diastolic function, has not been established. Thus, ultrasonographic assessment of organs other than the heart helps the diagnosis of heart failure, assessment of the severity of heart failure, and development of our understanding of the pathophysiology in each patient. This review summarizes current knowledge about the usefulness of ultrasonographic assessment of organs other than the heart in heart failure.

**Keywords** Liver · Kidney · Intestinal tract · Diaphragm · Lung

Heart failure is a clinical syndrome caused by structural and/or functional abnormalities of the heart, but an association with structural and/or functional abnormalities of other organs is not rare. The severity and prognosis of heart failure are determined not only by the degree of cardiac abnormality but also by that of abnormalities of other organs, which results in a variety of symptoms, physical findings, pathophysiology, and treatment efficacy in heart failure. For better understanding of heart failure, assessment of cardiac function and structure is not sufficient, and information obtained from other organs may help us in the diagnosis and evaluation of heart failure.

In the field of ultrasonographic assessment of patients with heart failure, echocardiography is indispensable [1]. Although echocardiographic assessment of cardiac function

and structure is fundamental for evaluation of heart failure, some limitations remain. For example, assessment of left ventricular (LV) diastolic function has not been established, and thus evaluation of the degree of LV diastolic dysfunction is quite difficult. In addition, echocardiographic assessment of hemodynamics such as LV and right ventricular filling pressures is still inaccurate. To detect elevation of filling pressures, ultrasonographic assessment of other organs suffering from congestion provides additional information. Exercise tolerance is a key parameter of the severity of heart failure, but it is well known that indices derived from echocardiography at rest are not necessarily correlated with exercise tolerance, partly due to the load dependency of echocardiographic indices. Ultrasonographic assessment of other organs provides an alternative index, helps us develop an understanding of reasons for exercise intolerance, and suggests new interventions to improve exercise tolerance.

In this review, we provide an overview of the current paradigm of ultrasonographic assessment of organs other than the heart in patients with heart failure.

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## Assessment of lung by ultrasonography

Elevation of LV filling pressure is a typical phenomenon associated with heart failure and results in pulmonary congestion. Although detection of elevated LV filling pressure is crucial in the diagnosis of heart failure and assessment of its severity, echocardiographic assessment of LV filling pressure has not been established, particularly in patients with preserved LV ejection fraction [2, 3]. Pulmonary congestion leads to an accumulation of extravascular lung fluid. Chest X-ray is usually used to assess pulmonary congestion; however, the detection of pulmonary congestion with chest X-ray is insensitive and imprecise. For example, Chakko et al. reported inadequate sensitivity, specificity, positive predictive value, and negative predictive value of venous redistribution and interstitial edema on chest X-ray to detect pulmonary congestion (Table 1) [4].

The “comet-tail artifact” or “B-line” on lung ultrasonography has emerged as a simple and useful sign to detect pulmonary congestion [5]. B-line is density related and likely originates from interfaces between fluid-filled and well-aerated alveoli [6, 7]. In normal lungs, lung ultrasound shows A-line (Fig. 1a). B-line appears following an increase in extravascular lung fluid (Fig. 1b, c). An experimental study demonstrated a linear correlation between extravascular lung fluid and the number of B-lines [8], and a clinical study supported this result [9]. In another experimental study, B-line preceded pulmonary deterioration in gas exchange or changes in chest X-ray in association with

accumulation of extravascular lung fluid [10]. Although typical measurements during stress echocardiography are limited to indices obtained from cardiac imaging [11], a recent study has suggested that the appearance of B-line during stress echocardiography is a sign of stress-induced pulmonary edema [12]. As the same probe can be used for echocardiography and lung ultrasonography, B-line is a simple and easy marker for detection of pulmonary congestion and diagnosis of heart failure. Pleural effusion can be also observed on lung ultrasonography. Therefore, ultrasonographic assessment of the lung is useful in the diagnosis of heart failure through detection of pulmonary congestion and pleural effusion.

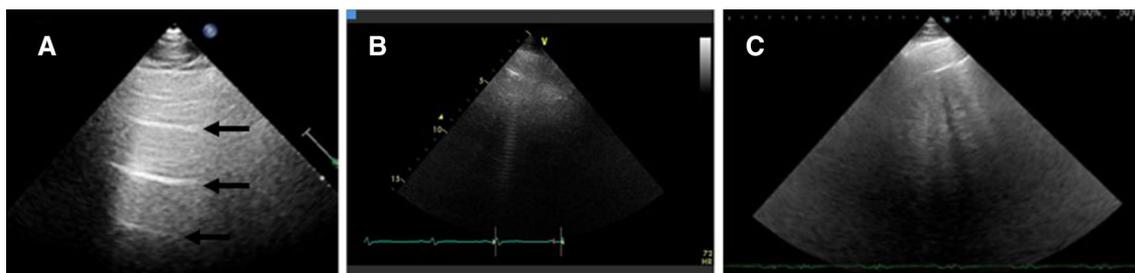
Recently, the number of elderly patients with heart failure has increased, and home care for elderly patients has been promoted in Japan. Symptoms of heart failure are not specific, and the diagnosis of heart failure should be supported by objective abnormalities. However, chest X-ray cannot be used when a doctor sees a patient at the patient’s home. Portable ultrasonographic devices are now available, and ultrasonographic assessment of the lung will likely be helpful in the diagnosis of heart failure at a home visit.

Interstitial changes in the lung are induced by not only pulmonary congestion but also lung diseases such as acute respiratory distress syndrome and connective tissue diseases. Therefore, B-line can be observed in such primary pulmonary diseases (Fig. 2). In primary pulmonary diseases, B-line is irregular and thickened, and its number does not change with postural changes [13]. In pulmonary congestion, B-line is regular and thin, and its number decreases in association with the change from supine to upright position. Hubert et al. have recently suggested that the diagnostic capacity of B-line to identify elevation of LV filling pressure is superior to that of conventional echocardiographic parameters in patients with significant dyspnea [14]. Although B-line is not necessarily specific for pulmonary congestion, lung ultrasonography is likely to provide additional information in the differentiation of heart failure.

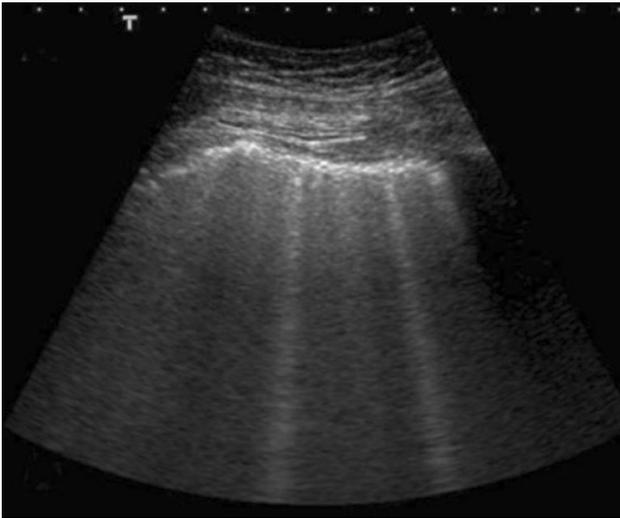
**Table 1** Sensitivity, specificity and predictive value of radiographic signs of congestion

	Predictive value			
	Sensitivity	Specificity	Positive	Negative
Redistribution	60	68	75	52
Interstitial edema	60	73	78	53

Adapted from Ref. [4]



**Fig. 1** A-lines, normal lung appearance (A, arrow), and B-lines (B mild pulmonary congestion, C severe pulmonary congestion) in lung ultrasound



**Fig. 2** Lung appearance of pneumogenic interstitial syndrome (pulmonary silicosis) recorded with a 6-MHz convex probe. Irregular pleural line and multiple blurred, uneven B-lines are observed. Permission from [46]

### Assessment of liver by ultrasonography

Examination of the inferior vena cava (IVC) is recommended to semi-quantitatively evaluate right atrial pressure [15], but its poor accuracy has been widely recognized [16].

Elevation of right atrial pressure induces liver congestion. The liver is assumed to become stiff in association with liver congestion as it is covered with a membrane. Several studies have demonstrated that ultrasonographic assessment of liver stiffness (Fig. 3) is useful in the evaluation of right atrial pressure. Millonig et al. reported that liver stiffness assessed with transient elastography was well correlated with central venous pressure in an animal study [17]. Taniguchi et al. demonstrated a close curvilinear relation between right atrial pressure and liver stiffness assessed with transient elastography in patients with heart failure (Fig. 4), and indicated liver stiffness  $\geq 10.6$  kPa was sensitive and specific for detecting right atrial pressure  $> 10$  mmHg [18]. They also showed the superiority of assessment of liver stiffness over examination of IVC in the evaluation of right atrial pressure. Yoshitani et al. reported a significant correlation between central venous pressure and liver stiffness assessed with shear wave elastography in patients with heart failure [19].

Recently, Taniguchi et al. showed that elevation of liver stiffness assessed with transient elastography was associated with poorer clinical outcome in patients with heart failure, and concluded that liver congestion was related to the prognosis [20]. However, Hopper et al. showed that liver stiffness did not change in association with alteration in volume status in patients with acute decompensated heart failure and in patients under hemodialysis [21]. The liver is

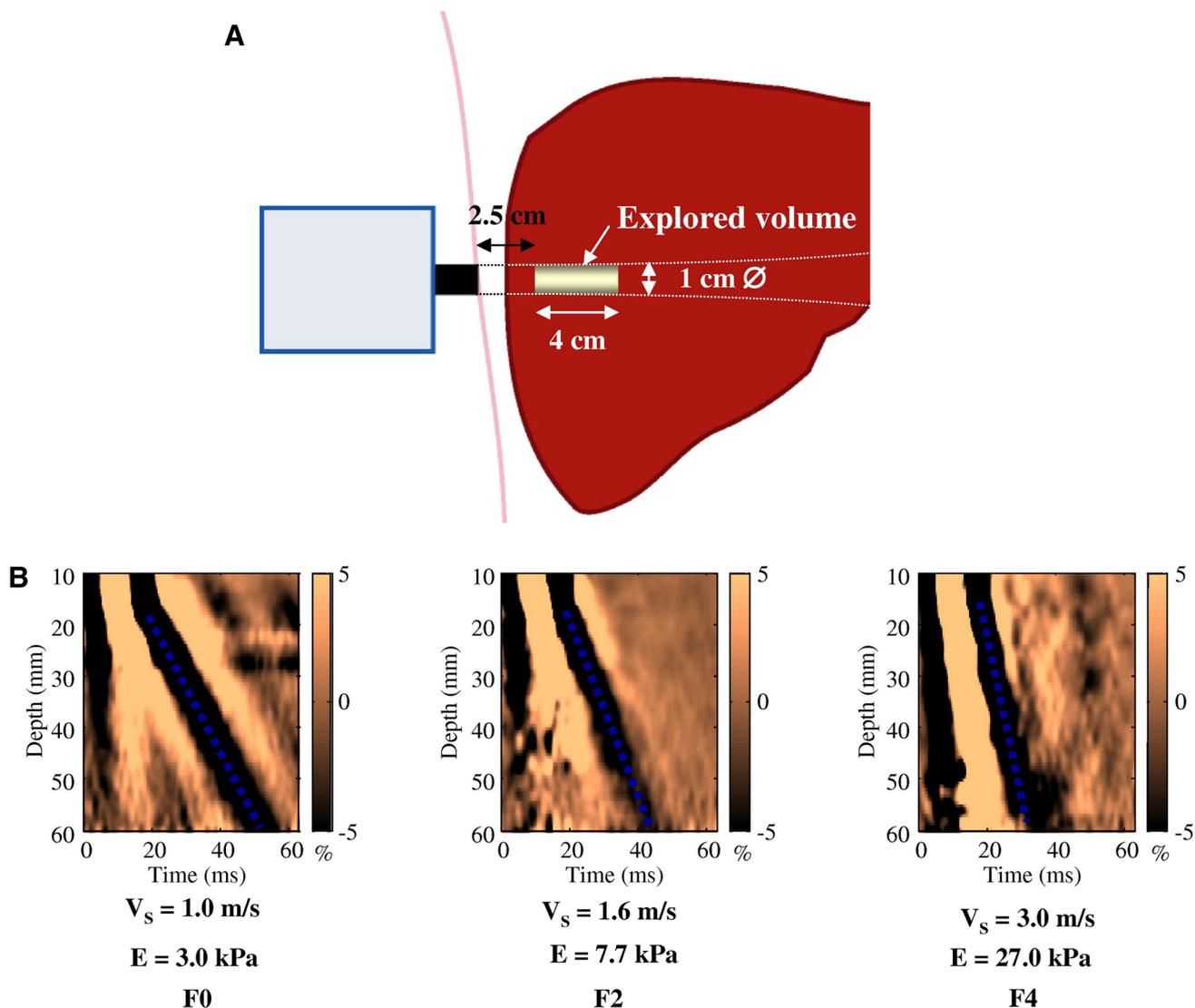
stiffened in association with progressive liver fibrosis due to primary liver diseases [22], suggesting that the increase in liver stiffness does not necessarily indicate elevation of right atrial pressure and liver congestion. Chronic liver congestion in association with advanced heart failure is well known to induce liver fibrosis and cirrhosis [23], and severe liver fibrosis and dysfunction were associated with poor prognosis in patients with advanced heart failure listed for heart transplantation [24]. Future studies are necessary to incorporate ultrasonographic assessment of liver stiffness into clinical evaluation of patients with heart failure, but ultrasonographic liver stiffness is likely a useful parameter that reflects the severity of heart failure, particularly right-sided heart failure.

### Assessment of carotid artery by ultrasonography

Wave intensity is defined as  $(dP/dt) \times (dU/dt)$  at any site of the circulation, where  $dP/dt$  and  $dU/dt$  are the time derivatives of blood pressure and flow velocity, respectively. As arterial pressure waveforms and arterial diameter-change waveforms are similar, wave intensity can be calculated with ultrasonographic measurement of carotid artery diameter and blood flow (Fig. 5). Ohte et al. demonstrated that (1) wave intensity in the carotid artery has two peaks, (2) the first peak reflects LV contractility, and (3) the second peak reflects the early diastolic performance of the left ventricle [25]. Indices derived from cardiopulmonary exercise testing are well known to reflect the severity of heart failure. Recently, Nogami et al. reported that the first peak of wave intensity in the carotid artery at rest significantly correlated with minute ventilation (VE)/carbon dioxide production (VCO<sub>2</sub>) slope at cardiopulmonary exercise testing, and suggested that wave intensity was useful in assessing the pathophysiology of heart failure [26]. Vríz et al. reported that the carotid wave intensity predicted the prognosis of patients with heart failure and reduced ejection fraction [27]. These clinical studies suggest that wave intensity serves as an additional parameter for the assessment of heart failure.

### Assessment of kidney by ultrasonography

Deterioration of renal function is frequently observed during the progression of heart failure, and it is well known that renal dysfunction is an independent predictor of poor outcome in heart failure patients. Although the kidneys are membrane-covered like the liver, Yoshitani et al. demonstrated a lack of correlation between central venous pressure and kidney stiffness assessed with shear wave elastography in patients with heart failure [19]. However,



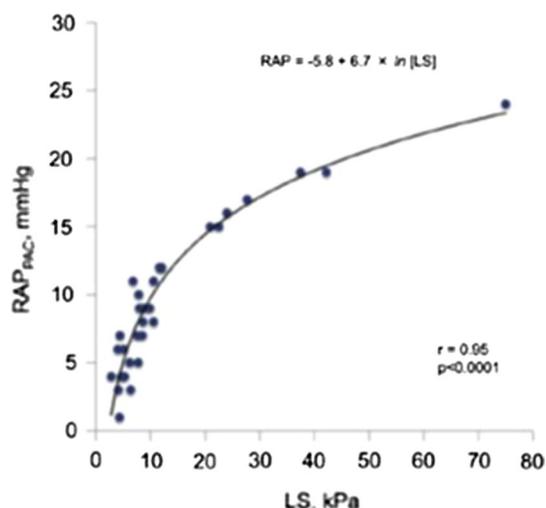
**Fig. 3** Liver stiffness measurements. **a** Position of probe and explored volume. **b** Shear wave propagation velocity according to the severity of hepatic fibrosis. The elastic modulus  $E$  expressed as  $E=3qV^2$ , where  $V$  is the shear velocity and  $q$  is the mass density (constant for tissues): the stiffer the tissue, the faster the shear wave propagates.

Hence, for absent fibrosis (F0), velocity is 1.0 m/s and elasticity is 3 kPa, whereas for cirrhosis (F4), velocity is 3.0 m/s and elasticity is 27 kPa.  $V$  velocity,  $E$  elastic modulus, and is calculated as  $E=3 \times V^3$ . Permission from [47]

ultrasonographic assessment of the kidneys is likely to provide important information in heart failure.

Iida et al. focused on the changes in intrarenal blood flow in patients with heart failure [28]. They found that the intrarenal venous flow pattern was useful in semiquantitative assessment of right atrial pressure and prediction of clinical outcomes in patients with heart failure. Although previous studies have shown the usefulness of the resistive index derived from the intrarenal arterial flow pattern as a predictive index in patients with chronic kidney diseases [29, 30], Iida et al. found that the intrarenal venous flow pattern was superior to the resistive index in predicting clinical outcomes [28].

Kidney volume is decreased with glomerular sclerosis and tubular atrophy, and is a simple estimate of renal reserve and function in patients with suspected renal diseases [31]. Our and other studies have suggested a relation between kidney size and diuretic response in patients with acute decompensated heart failure [32, 33] (Fig. 6). In particular, our study suggested that left kidney volume more accurately predicted the required dose of furosemide than right kidney volume, although the mechanisms underlying this difference remain unclear. These findings are not yet established, and it should be investigated in future studies whether kidney size can serve as a predictor of the response to diuretics in heart failure.

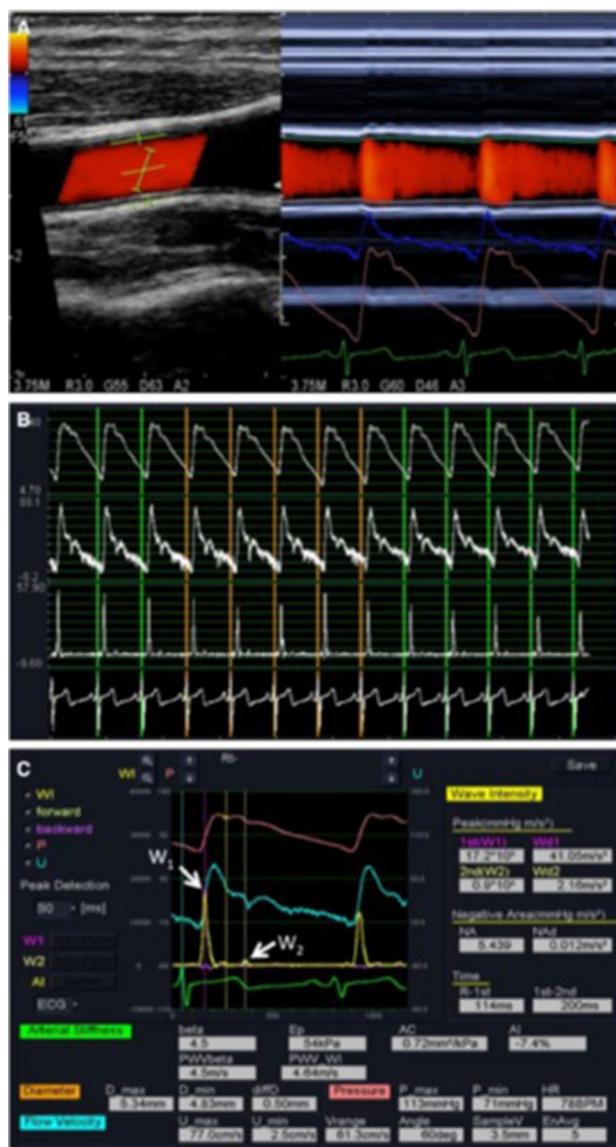


**Fig. 4** Relation between liver stiffness (LS) and right atrial pressure (RAP) in patients with heart failure. Scatter plots showing the relation between LS as assessed by transient elastography and RAP determined using a pulmonary artery catheter (RAP<sub>PAC</sub>). Permission from Ref. [18]

### Assessment of intestine by ultrasonography

Sandek et al. showed an increase in intestinal wall thickness, intestinal permeability, and intestinal bacterial biofilm in patients with heart failure (Fig. 7), and suggested that such changes contributed to the origin of chronic inflammation and malnutrition in heart failure [34]. Intestinal wall thickening, suggestive of intestinal wall edema, was closely related to gastrointestinal symptoms and inflammatory markers, and was associated with cachexia in patients with heart failure [35]. Another article reported that intestinal blood flow measured with ultrasound was decreased in patients with heart failure, and that its decrease was associated with gastrointestinal symptoms and cachexia [36]. Although there was no correlation between intestinal blood flow and intestinal wall thickness, both were interrelated with inflammatory markers [34, 36]. Recently, Ikeda et al. showed that the increase in intestinal wall thickness was independently related to a higher incidence of clinical events in patients with heart failure [37].

These results suggest that the reduction in intestinal blood flow and the increase in wall thickness are not necessarily induced by the same mechanisms in patients with heart failure, but that they are highly associated with gastrointestinal symptoms, malabsorption, and gut microbial imbalance, and lead to malnutrition, systemic inflammation, impaired quality of life, and poor prognosis. Ultrasonographic assessment of intestinal wall thickness and intestinal blood flow may help us more deeply understand the pathophysiology of heart failure in each patient.

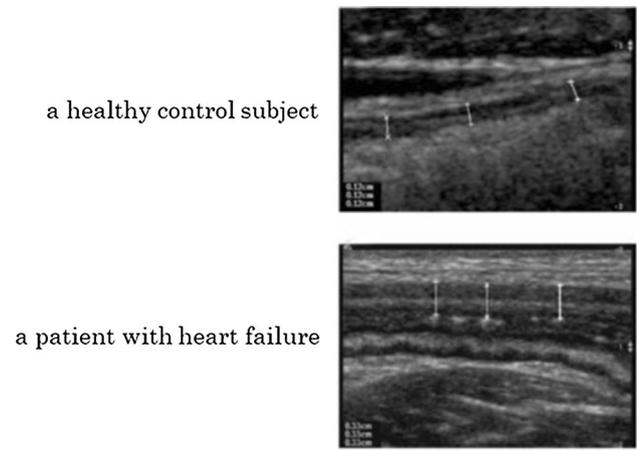
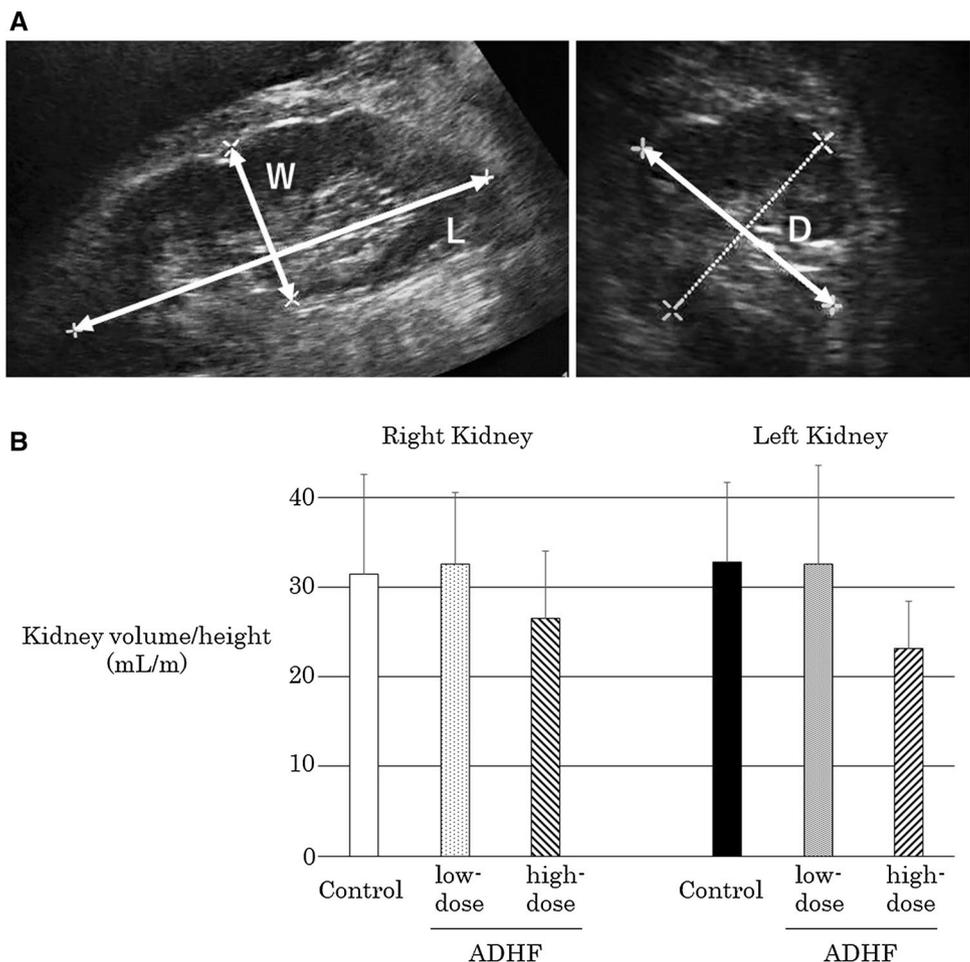


**Fig. 5** Visualization of the wave intensity with carotid arterial blood flow. W1: the first peak of wave intensity, W2: the second peak of wave intensity. Permission from Ref. [26]

### Assessment of diaphragm by ultrasonography

Our and other studies have demonstrated that inspiratory muscle weakness is closely related to symptoms and exercise intolerance in patients with heart failure [38, 39]. The inspiratory muscle weakness is not a part of generalized muscle atrophy [39, 40]. Experimental studies have demonstrated the different effects of heart failure on diaphragm and limb skeletal muscles [41, 42]. Therefore, assessment of inspiratory muscle function is useful in evaluating the severity of heart failure in each patient.

**Fig. 6 a** Ultrasonographic images of the kidney to show the measurement of kidney size. *D* depth, *L* maximum length, *W* width. **b** Patients with acute decompensated heart failure (ADHF) were divided into two groups according to the required dose of diuretics during the first 3 days from admission, i.e., patients in whom a high dose of furosemide was required for the treatment of ADHF (high dose) and those in whom a low dose was required (low dose). This figure shows height-adjusted right and left kidney volumes in control subjects without heart failure (control), the high-dose group, and the low-dose group. Although both right and left kidney volumes were significantly lower in the high-dose group than in the low-dose group ( $p=0.043$ ,  $p=0.009$ , respectively), multivariate logistic regression analysis for predicting the requirement of high-dose furosemide revealed that left kidney volume, but not right kidney volume, was an independent predictor (odds ratio: 0.856, 95% confidence interval: 0.735–0.997,  $p<0.05$ ). Reproduced from data of Ref. [33]

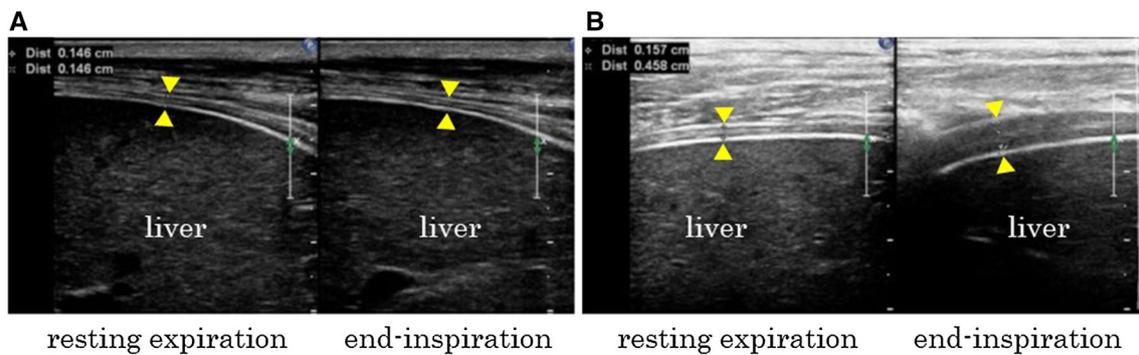


**Fig. 7** Measurement of bowel wall thickness in a healthy control subject (upper) and a patient with heart failure (lower) Permission from Ref. [34]

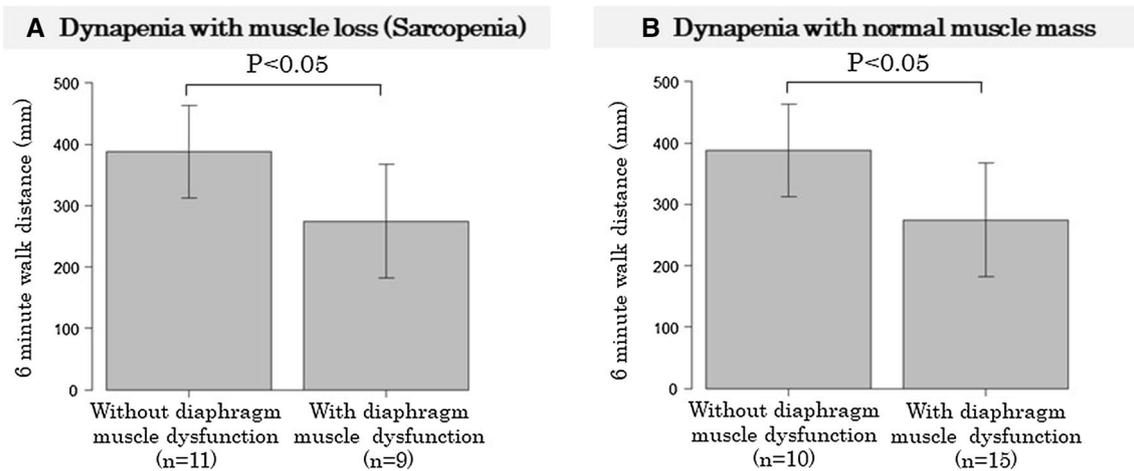
Respiratory muscle function is usually evaluated with spirometry, and the maximal inspiratory pressure is used as the gold standard in the assessment of inspiratory muscle

function. The diaphragm is the principal inspiratory muscle [43], and we found a significant correlation between maximal inspiratory pressure and diaphragm function assessed with ultrasound [44] (Fig. 8). In addition, we reported that impairment of diaphragm function was associated with exercise intolerance in heart failure patients without dynapenia, with dynapenia but without sarcopenia, and with sarcopenia [44, 45] (Fig. 9). In our study, exercise tolerance was impaired in heart failure patients with dynapenia regardless of skeletal muscle mass, and the effects of diaphragm dysfunction on exercise tolerance could not be explained by the decrease in diaphragm muscle mass. Thus, ultrasonographic assessment of diaphragm function is helpful in understanding the severity of heart failure in each patient, particularly in patients with discrepancy between the severity of symptoms and the echocardiographic data. In addition, although both the diaphragm and the limbs are made of skeletal muscle, limb function cannot be used as a substitute for diaphragm function.

Heart failure is based on cardiac dysfunction, but it is a syndrome derived from dysfunction of not only the heart but also several other organs. Current guidelines divide heart



**Fig. 8** Ultrasonographic images of the diaphragm (arrowed) at resting expiration and at end-inspiration in a heart failure patient (a) with and (b) without diaphragm dysfunction



**Fig. 9** Effects of diaphragm muscle dysfunction on 6-min walk distance in heart failure patients with dynapenia and muscle loss (sarcopenia) (a) and with dynapenia and normal muscle mass (b). Permission from Ref. [45]

failure into three phenotypes according to ejection fraction, because the effects of cardioprotective medications such as angiotensin-converting enzyme inhibitors,  $\beta$ -blockers, angiotensin receptor blockers, and mineralocorticoid receptor blockers are likely different between heart failure with reduced ejection fraction and that with mid-range or preserved ejection fraction. Lung, liver, and intestine congestion is induced by hemodynamic deterioration independent of LV ejection fraction. Currently, there is no evidence that the difference in LV ejection fraction modulates the effects of diaphragm dysfunction or kidney size on the pathophysiology of heart failure or the relation between wave intensity and LV function. Thus, although future studies are needed, ultrasonographic assessment of organs other than the heart may provide valuable information independent of LV ejection fraction, may be useful to fully understand the pathophysiology in each patient with heart failure, and may aid the discovery of new therapeutic approaches to improve the prognosis and/or quality of life of heart failure patients.

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### Compliance with ethical standards

**Conflict of interest** The authors have no relationships relevant to the contents of this paper to disclose.

**Ethical statements** All the procedures followed were in accordance with the Helsinki Declaration of 1964 and later versions.

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