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Review Article

Hemodynamic characteristics and early warnings in very old patients

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Abstract: The hemodynamic characteristics of very old patients (VOPs) are unique. With increasing age, patients may experience reduced diastolic function, increased rates of valvular heart disease and coronary atherosclerosis, stiffer vessels, and a reduced heart response to stimulations. Structural and functional modifications are linked to cardiac aging; echocardiography reveals concentric remodeling of the left ventricle, dilation of the left atrium, thickening and calcification of the valves, modification of the large vessels, and abnormal ventricular relaxation. According to a comprehensive understanding of the insufficient compensatory mechanisms of the aging heart, arrythmia should be avoided to the maximum extent and "conservative" fluid therapy should be provided together with appropriate blood pressure control. Considering these factors will improve the success rate of resuscitation and significantly reduce economic loss. In addition, more attention should be paid to the diastolic blood pressure in VOPs.

Keywords: Hemodynamic, very old patients, resuscitation, early warning, fluid therapy

Life expectancy has been gradually extended with improvements in quality of life, so there has been an increase in the size of the extremely old population (aged ≥80 years). Therefore, the prevalence of chronic diseases and organ dysfunction has correspondingly increased, along with the hospitalization rate and demand for intensive care units (ICUs) [1]. Very old patients (VOPs) suffer more underlying diseases than younger people, with the organ function in a state of decline, so they face a high mortality rate even after positive treatment. A meta-analysis showed that approximately 25%-45% of patients over 65 years old die during hospitalization. Among them, 15%-25% die in the ICU and 97% of VOPs die within 1 year of discharge [2]. Aging also increases the risk of cardiovascular disease (CVD). According to the heart disease and stroke statistics from the American Heart Association, the morbidity of CVD significantly increases with age, and mortality due to CVD in those over 75 years old exceeds 70% [3].

It is crucial to understand the underlying changes that occur with aging. VOPs have unique characteristics. During therapy of this population, two main points should be taken into account: disease and aging. Relatively healthy VOPs are already in a state of hemodynamic compensation, so the addition of stress and diseases on this basis lead to different characteristics from those of younger patients. Fundamental changes in cardiac structure and function may result in higher requirements for hemodynamic therapy. Thanks to critical ultrasound, diagnostic accuracy and the quality of healthcare are improved in the ICU [4, 5]. Critical ultrasound can help doctors to identify the details of complicated underlying diseases and improve the success rate of treatment [6, 7]. Aging itself can lead to hemodynamic changes. When VOPs develop acute and serious diseases such as sepsis and severe pneumonia and thus suffer shock and respiratory failure, these diseases will exert severe impacts on their hemodynamics. As staff members in a

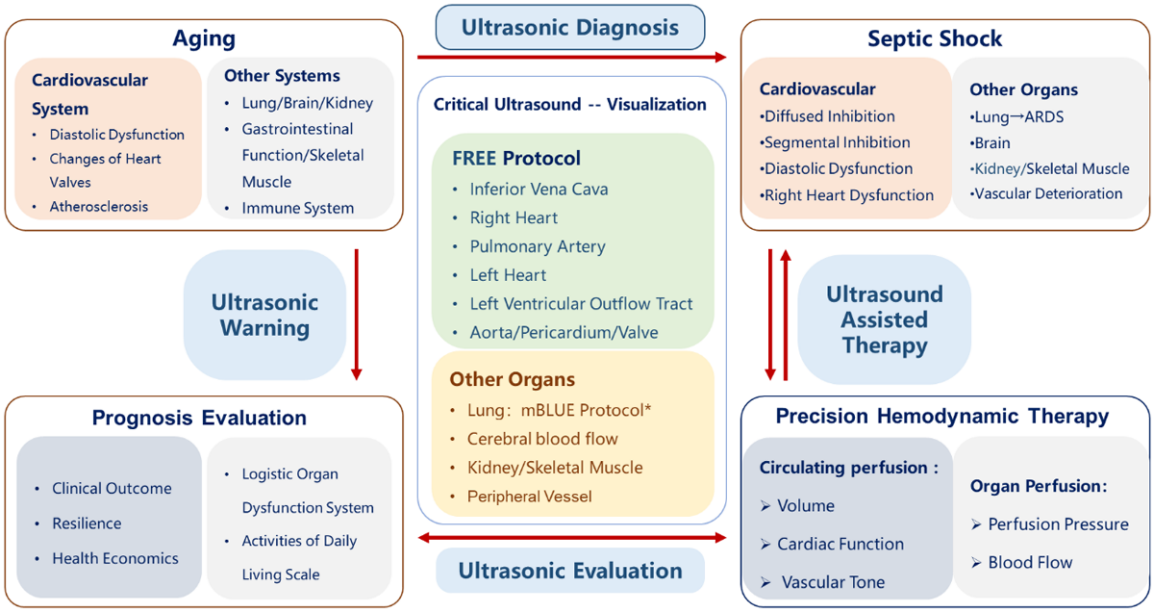

Figure 1. Precision Hemodynamic Therapy System. *mBLUE protocol: modified bedside lung ultrasound examination, including the upper BLUE point, lower BLUE point, phrenic point, PLAPS point, and the back BLUE point of both sides.

Table 1. The structural and functional changes in very old patients (VOPs) and early warning signs in hemodynamic therapy

Key Points
Pathophysiological Changes in VOPs
➢ Diastolic function declines with age.
➢ Degeneration is predominant in valvular heart disease.
➢ Coronary atherosclerosis is a degenerative form of coronary artery disease.
➢ A progressive decline in the maximal response with age occurs in the arteries.
➢ Regulation of the cardiovascular system is greatly affected.
Echocardiographic characteristics in VOPs
➢ Increased myocardial thickness.
➢ Left atrium enlargement.
➢ Sclerosis of the valves.
➢ Decreased aortic valve area.
➢ Decreased E/A ratio.
➢ Increased E/Ea ratio.
Hemodynamic early warnings in VOPs
➢ There is a poor connection between CVP and blood volume.
➢ Conservative fluid therapy should be administered.
➢ AF is an age-related manifestation that may be caused by increased atrial pressure and leads to major hemodynamic changes.
➢ For patients with valvular heart disease, the indications need to be followed and surgical treatment should be promptly provided.
➢ Appropriate blood pressure, especially diastolic blood pressure, is a major determinant of tissue perfusion.

geriatric ICU that has discharged nearly 500 VOPs, we are skilled in ultrasonic hemodynamic assessment techniques that are favored because they are visual and noninvasive. On the basis of our experience, we constructed a precision hemodynamic therapy system (**Figure 1**). In this article, we summarize the structural and functional changes in VOPs and their influence on hemodynamic therapy, and we relay our experience regarding early warning signs (**Table 1**).

Pathophysiologic changes in VOPs

Diastolic and systolic function

Systolic function is almost unaffected by the aging process over an individual's lifetime [8].

Additionally, at rest, the ejection fraction (EF) is preserved [9]. However, diastolic function declines with age, partly because cardiac diastole is less complete [8]. The prevalence and severity of diastolic dysfunction (DD) increase sharply after the age of 50 years old. One study showed that more than half of the population between 70 and 80 years old suffered DD, and the proportion increased to more than two-thirds of those over 80 years old [10]. Ventricular diastolic function declines with age for the following reasons: first, decreased phosphorylation of troponin and ventricular stiffening in the senescent myocardium leads to ventricular diastolic dysfunction in older adults, resulting in diastolic dysfunction physiologically [11]. Second, ventricular wall thickness increases with age. Previous studies have reported that, in healthy adults aged 20-29 years, the ventricular wall thickness is 7-8 mm, while in people at 70 years [12], it increases to 9-10 mm. Third, increased fibrosis and increased pericardial adipose tissue deposition promote the development of DD [13], which gives rise to morphologic changes in the left atrium and increased diameter (volume).

In older adults, DD is associated with certain diseases. First, hypertension, which can cause LV hypertrophy, is very common in older patients. Hypertensive heart disease is a common abnormality leading to heart failure with preserved ejection fraction (HFpEF), also called diastolic heart failure. DD often develops when the cardiac structure is normal. In the stiff aged heart, the process of collagen deposition accelerates structural changes based on the original LV hypertrophy. Second, atrial fibrillation (AF), an age-related condition, also correlates with many physiologic and pathologic factors in DD, such as diabetes mellitus. Atrial enlargement due to DD leads to AF, which is also triggered by disorders of the sinus node and conduction system [14]. Up to 30% of patients with DD are confirmed to have AF at the time of suffering heart failure symptoms [15]. The association between DD and AF has been confirmed in older patients, with a positive association between the severity of DD and AF [16].

HFpEF, which has recently been described as a geriatric syndrome, is a common presentation of HF in patients aged over ≥65 years old, characterized by reduced exercise tolerance, and high rehospitalization rate and mortality in VOPs [17]. This condition elevates the risk for hospitalization and is more common in the older adult population [18, 19].

Changes in heart valves

People face a higher prevalence of VHD as they age, and the disease affects less than 1% of patients aged 18-44 years old, but impacts more than one eighth of those over 75 years old [20, 21]. Degeneration is predominant in VHD, especially aortic stenosis and mitral regurgitation [22]. As the life expectancy increases, the incidence of degenerative VHD has also increased gradually. Aging-related changes in the valve are triggered by a number of factors. Different valves suffer different damage under a shear force [23]. For example, in an 80-year-old man, the heart valve has opened and closed approximately 2.9 billion times, which eventually leads to valve degeneration due to damage from different shear forces. Calcification is seen in 25% of individuals over 65 years old and is found in up to 50% of those over 85 years old [24]. Calcium phosphate deposition compromises all valves with aging [25]. Calcification also promotes the process of fibrosis, accelerating degeneration [26]. Regarding the aortic valve, significant regurgitation is rarely seen because the cusps are anchored to the annulus while commissural fusion is minimal [24]. In terms of the mitral valve, the mitral apparatus differs from the aortic apparatus; atrial dilatation can result from DD, resulting in regurgitation [27].

Coronary atherosclerosis

Coronary atherosclerosis is a degenerative form of coronary artery disease, characterized by remodeling of the coronary arteries, which disrupts the oxygen supply to the myocardium. Endointimal hyperplasia, collagenization of the media, and deposition of calcium in the elastic fibers ultimately lead to arterial changes [28]. A study from the Mayo Clinic showed that nearly 60% of patients aged over 60 years old suffered severe coronary atherosclerosis [29]. Among various risk factors for atherosclerosis that have been established, age is probably the most significant. Compared to younger patients, VOPs are more likely to have inadequate coronary blood supply under stress as a result of this structural change.

Arteries

A progressive decline in the maximal response occurs with age. Arterial wall compliance declines with increasing age [30, 31]. Thus, the stroke volume propagates more rapidly, and the pulse wave velocity is increased [32]. The age-related stiffness of vessels results not only from mechanical factors such as pressure, but also from pressure-independent factors [33]. Several processes including abnormal endothelial function and vascular inflammation also underlie this change in stiffness [34, 35]. Age-related impairment of endothelial function has been reported in conduit arteries such as the brachial [36], femoral [37] and popliteal arteries [38]. Many studies have explored the role of nitric oxide in age-related vascular dysfunction [39]. A recent meta-analysis revealed a significant age-related impairment in the smooth muscle function of resistance arteries [31]. Intimal-medial thickness increases linearly with age, not only in carotid arteries but also in peripheral vessels in the upper and lower extremities [40, 41]. Age-related thickening seems to occur similarly in both central and peripheral arteries. Aging generally gives rise to reduced vascular compliance, which lowers the ability of VOPs to respond appropriately to acute alterations in cardiac output (CO), blood pressure (BP), and fluid status.

The changes with age in arterial resistance are smaller than those in stiffness. Reportedly, a 5% increase per decade starts at the age of 20 years [42], which helps maintain organ perfusion, compensating for the decline in diastolic pressure due to increased arterial stiffness[43]. Not only do the intrinsic attributes of the large arteries change with age, but also the shape and geometric configuration change, with relatively little effect on BP [44, 45].

Autonomic nervous system

Regulation of the cardiovascular system is under heavy influence of age. The autonomic nervous system is essential in cardiac modulation. However, it undergoes numerous age-associated changes, and greatly affects the regulation of the cardiovascular (CV) system. An age-associated decline in parasympathetic modulation and a reduced heart response occur partly because of a decline in β-adrenergic receptor responsiveness [46-48]. Sympathetic activation appears during senescence, which may be a compensatory mechanism for the restoration of cardiac function. In response to exercise, a diminished secretion of adrenaline in older individuals means the subsequent increase in stroke volume may not be sufficient to meet the increased demand [49].

Aging is also associated with impaired baroreflex sensitivity, resulting in a greater postural fall in BP in older patients [50]. Arterial stiffening that accompanies aging may also give rise to decreased angiotensin levels. Aging also has an effect on the cardiac response to exercise or increased physical activity. As described above, normal aging diminishes both cardiac chronotropic and inotropic responses [49].

Rare congenital heart diseases

Nearly one third of the German population suffers at least one type of congenital heart disease, as indicated by the German National Register for Congenital Heart Defects [51]. Hemodynamics in this group remains relatively stable most of the time. However, stress and diseases, such as shock and respiratory failure, may lead to major hemodynamic changes. Accordingly, understanding the hemodynamic changes in these patients is important.

Echocardiographic characteristics of VOPs

A number of structural and functional modifications are related to cardiac aging, including concentric remodeling of the left ventricle (LV), dilation of the left atrium, thickening and calcifications of the valves, modification of the large vessels, and abnormal ventricular relaxation (**Figure 2**).

There is a progressive increase in the thickness of the developed myocardium with age, while there is a slight reduction or no change in LV internal dimensions, which leads to an increased thickness/radius ratio and concentric LV remodeling [52]. Left atrial enlargement, which occurs simultaneously with LV structural changes, induces stroke and AF [53]. Sclerosis of the aortic and mitral valves is common in VOPs, which may cause a decrease in valve mobility or moderate leakage. Changes at the mitral level ranging from a small calcium spicule to a large mass are associated with a greater risk of thromboembolism, heart block, valvu-

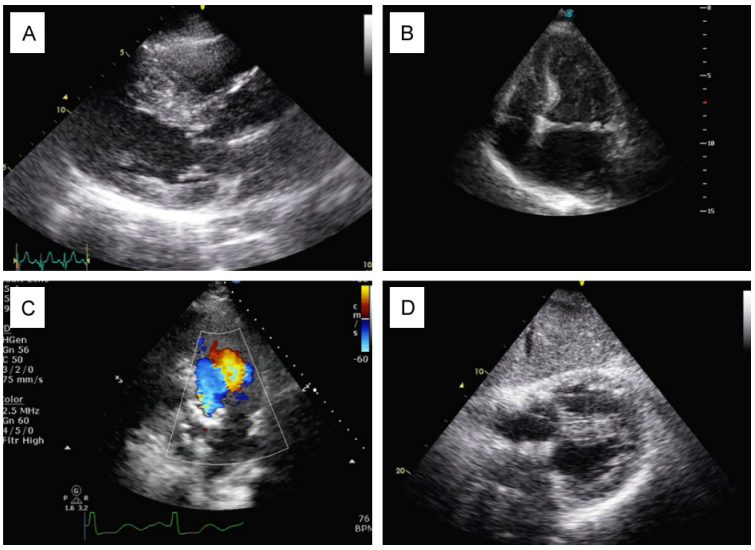

Figure 2. Ultrasonic Images of Very Old Patients. (A) Increased myocardial thickness; (B) left atrial enlargement; (C) aortic regurgitation; and (D) right ventricular hypertrophy.

lar dysfunction, and infective endocarditis [54]. A decrease in aortic valve area is accompanied by a reduction in the LV outflow tract diameter, resulting in a rise in aortic velocity [55]. Progressive dilation of the ascending thoracic aorta and a decrease in arterial compliance occur with an increase of age. This predicts incident heart failure, stroke and CV events, and all-cause mortality [56].

Notably, LV diastolic function declines, while the LV ejection fraction does not change much with age. The gradual reduction of the E wave reflects changes in the mitral valve inflow velocity, while the atrial contribution increases in the meantime [57], leading to an equilibrium in E and A velocity when individuals reach around 50 years old, with a reversal in the E/A ratio after this age. As a result, E/A <1 is common (87%) in the older population [58]. Because the compliance of the LV cavity decreases, a longer time is needed to accommodate the necessary blood volume during diastole, leading to an increase in deceleration time. Similarly, tissue Doppler showed lower early diastolic mitral and tricuspid annular velocities (Ea) in VOPs. In a cohort of asymptomatic older people who received routine screening, Ea decreased by approximately 1 cm/s and E/Ea increased by approximately 1 unit per decade [59]. In addition, increasing age leads to an increase in systolic wave reflection and systolic afterload and a decrease in Ea, ultimately giving rise to an increase in the E/Ea ratio [60], while late diastolic velocities on tissue Doppler do not change with age. Tissue Doppler also shows a lower systolic mitral annular velocity in older people who have subclinical LV systolic dysfunction [61]. However, the compensatory rise in radial thickening normalizes the LV ejection fraction [62].

Because of the pathophysiologic changes that occur with the aging of the heart, an abnormal relaxation pattern may be detected. An E/A ratio >1 would be unusual in this group. In that case, pseudo normal filling should always be taken into account. In some cases, an E/A ratio >1 indicates a worse prognosis in patients over 65 [63].

In terms of the effect of age on the right ventricle (RV), tricuspid annular plane systolic excursion (TAPSE), global systolic strain, and systolic velocity of the tricuspid annulus, as shown by tissue Doppler imaging (RV S'), all decline with age [64]. Additionally, the peak E velocity of tricuspid inflow, early diastolic strain rate, and RV free wall e' velocity also decline with age. Although the RV fractional area change remains unaffected, aging compromises the systolic/diastolic function of the RV.

By ultrasound examination, people at an older age show increases in myocardial thickness, left atrial enlargement, sclerosis of the valves, decreases in aortic valve area and E/A ratio, and an increase in E/Ea ratio.

Hemodynamic early warnings in VOPs: preload and volume management

There is a weak relationship between central venous pressure (CVP) and blood volume. The evaluation of volume state and fluid responsiveness is an important part of hemodynamic therapy. Usually, pressure measures including CVP and pulmonary artery wedge pressure (PAWP) are used to evaluate preload and guidance of the fluid therapy. However, these indi-

ces are under influence of multiple factors. For example, a gradual decrease in diastolic function with age may lead to an increase in LV filling pressure, and chronic pulmonary hypertension leads to an increase in RV pressure, which affects CVP. In fact, CVP is weakly associated with blood volume, and CVP/ΔCVP cannot be adopted to predict the hemodynamic response to a fluid challenge, especially in older patients [65]. Functional hemodynamic parameters, including stroke volume variation (SVV) and pulse pressure variation (PPV), are useful to predict fluid responsiveness in older patients with septic shock. Furthermore, the passive leg raise test is an effective method for accurately predicting fluid responsiveness [66].

Conservative fluid therapy should be administered to VOPs. Fluid management is also important in older patients because an impaired LV diastolic function has clinical implications in the ability of an aging heart to manage increased preload. A reduction in early LV filling may lead to a decrease in distension in the LV. This may result in a failure of the Frank-Starling mechanism, as well as an age-associated reduction in LV compliance. This situation can result in an increase in left atrial and LV end-diastolic pressure, and finally, pulmonary congestion and edema [67]. Therefore, "conservative" fluid therapy should be administered for these patients, which may also prevent age-associated ventilator-induced mortality [68, 69].

Myocardial contractility

The LV contractile reserve declines with age. Despite the preservation of the LV ejection fraction in older people without clinical heart disease, a sharp increase in systemic BP triggered by low-dose phenylephrine infusion during concurrent β-blockade still results in a decline in LV contractile reserve. One study revealed a change in pharmacologic and physiologic responses to adrenergic stimulation in the aging heart, and the imbalance of heart rate (HR) and myocardial contractility in VOPs [70]. Thus, the end-diastolic and end-systolic volumes increase significantly to compensate for CO, and the contractile capacity of an aging heart can no longer meet the metabolic requirements. Meanwhile, CO reserves decline in the aging heart; the CO reserve and HR reactivity are 20%-30% lower than those in younger individuals [71]. In the older patients, the physiological response to exercise is declined in cardiac diastolic time and responsivity to adrenergic stimulation, which leads to a weaker response to stress, resulting in a smaller stroke volume and a smaller maximum HR [72, 73]. However, older individuals also experience a decline in resting HR with age. As a result, the systolic and diastolic filling times of the heart are prolonged, and the end-diastolic and end-systolic volume can be maintained [74]. Thus, in the older patients, compensatory mechanisms ensure an adequate metabolic support in the resting state. Furthermore, it is clear that the mechanism by which cardiac functional reserve is insufficient to cope with stress.

The aging heart is unable to compensate completely under stress. In the pathologic state, the decline of cardiac function reserve in older patients exerts a great impact. In the early stages of hypovolemic shock, the CO of patients significantly increases because of sympathetic excitation, which manifests as an increase in HR and myocardial contractility. Similarly, in the early stages of septic shock, the decrease in afterload triggered by vasodilation also requires a compensatory increase in CO. The maximum HR is significantly reduced by depressed excitability of individual sinoatrial node myocytes [75] and adrenergic stimuli caused by a reduced β-adrenergic response and a reduced functional response. Circulating catecholamine concentrations are often elevated under stress, but this cannot be completely compensated for, leading to an insufficient CO response to stress [11].

AF is an age-related manifestation probably triggered by increased atrial pressure, which leads to major hemodynamic changes. As a special condition in VOPs, it is usually an age-associated presentation of underlying cardiac and non-cardiac disease. A wide spectrum of pathophysiologic changes commonly found in older people, including left atrial structural remodeling, ion channel dysfunction, autonomic neural dysregulation, and decreased LV diastolic filling, facilitate the onset of AF [76]. AF is positively correlated with aging, with an increase in the prevalence and incidence of AF among people after 65 years old, and more than 10% of patients aged ≥85 years suffer AF [77]. There is a special relationship between AF and HF. They have similarities in risk factors

and epidemiology and are both risk factors for one another [78]. AF and HF are also associated with changes in structure, electrophysiology, and neurohormones, so they have mutual evolution and perpetuation [79]. The association between AF and LV DD is of particular importance in the older population. A loss of the atrial contribution to ventricular filling and an irregular and often rapid HR result in a less and irregular ventricular filling [80]. Rapid AF mainly shortens the LV diastolic time. LV filling is further exacerbated by the progression of AF and consequent loss of efficacious atrial contraction. The use of β-blockers in patients with DD may yield more benefits because of their antiarrhythmic properties and HR-lowering capacity [81].

For patients with VHD, the indications need to be followed up and surgical treatment should be promptly provided. In patients with VHD, CO is affected, regardless of whether there is valvular stenosis or regurgitation, so simply adjusting the hemodynamic status is sometimes of limited significance for improving CO.

Afterload

Appropriate BP, especially diastolic BP, is a major determinant of tissue perfusion. BP, especially systolic BP, rises with age, which increases pulse pressure ([PP] difference between systolic and diastolic pressure). Therefore, VOPs are predisposed to isolated systolic hypertension [82]. With aging, vascular changes in the aorta and its major branches (e.g., a loss of viscoelastic characteristics of conduit vessels resulting in stiffening of the arteries and promoting early wave reflection from the peripheral arteries [83]), increase systolic pressure. These changes result in an increase in systolic pressure and a reduction in diastolic pressure, resulting in an increase in PP, which is an effective index for evaluation of arterial stiffness and prognosis in older people [84]. Diastolic BP is a major determinant of tissue perfusion [85]. Aging can also give rise to an increase in peripheral vascular resistance and the LV mass index, as well as a reduction in CO, HR, and stroke and vascular volume. Compared with younger patients, the pathophysiologic features of essential hypertension in VOPs are characterized by a hypertrophied heart, low systemic and renal blood flow, and high total peripheral resistance. Furthermore, there is a continuous and positive correlation of CV events with BP above baseline (approximately 115/75 mmHg) at all ages. Additionally, the absolute difference in CV risk between the highest and lowest BP levels is much greater in older adults [14].

Conclusion

Aging brings about morphologic and functional cardiac changes. A decline in diastolic function, degeneration in the heart valve, sclerosis, and changes in the conduction system bring alter the hemodynamic status. Therefore, aging poses a great influence on the resuscitation process. With a deeper understanding of aging-related changes, we realize common insufficient compensatory mechanisms in the aging heart and the necessity to avoid arrythmia to the maximum extent and administer "conservative" fluid therapy together with appropriate BP control, which will improve the success rate of resuscitation in extremely old critically ill patients, and reduce economic loss.

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Disclosure of conflict of interest

None.

Abbreviations

AF, atrial fibrillation; BLSA, Baltimore Longitudinal Study on Aging; CO, cardiac output; BP, blood pressure; HH, heart rate; CV, cardiovascular; CVD, cardiovascular disease; CVP, central venous pressure; DD, diastolic dysfunction; Ea, early diastolic mitral and tricuspid annular velocities; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICU, intensive care unit; LV, left ventricular; PAWP, pulmonary artery wedge pressure; PPV, pulse pressure variation; RV, right ventricular; PP, pulse pressure; SVV, stroke volume variation; TAPSE, tricuspid annular plane systolic excursion; VHD, valvular heart disease; VOPs, very old patients.

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