

Acute cardiogenic pulmonary edema – an important clinical entity with mechanisms on debate

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1. INTRODUCTION

1.1. Definition, classification

Acute cardiogenic pulmonary edema (ACPE) represents a severe form of acute heart failure which is defined by an increase of pulmonary capillary wedge pressure (PCWP) over 18 mmHg. Although ACPE is a frequent clinical syndrome, the exact mechanisms by which it appears and its precipitating factors sometimes remain obscure. Regarding its causes, ACPE has been classified into valvular (in patients with significant mitral and/or aortic mitral disease) and non-valvular ACPE (in patients without significant mitral and/or aortic mitral disease). Non-valvular ACPE can further be classified into ACPE associated with systolic left ventricular dysfunction (defined as a left ventricular ejection fraction, LVEF < 45%) and ACPE with preserved LVEF (defined as a LVEF ≥ 45%) (Figure 1).

In this article we will discuss the current perspectives regarding the possible mechanisms

involved in the appearance of ACPE with preserved LVEF. This form of ACPE is the subject of certain hypothesis on debate in the literature. □

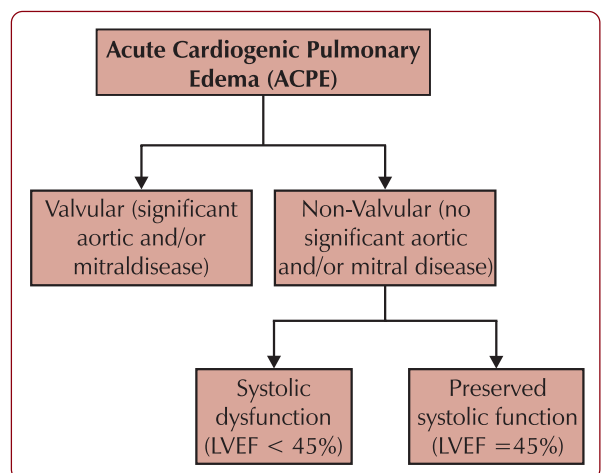


FIGURE 1. Classification of acute cardiogenic pulmonary edema.

Note: LVEF, left ventricular ejection fraction.

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1.2. Basic physiology

The fluid balance between intravascular and extravascular spaces at capillary level is governed by the Frank-Starling law (Figure 2). The intravascular and extravascular spaces are separated by the endothelial barrier. This barrier is characterized by an intrinsic resistance to water filtration (defined by the filtration coefficient, K_f) and the property of reflecting electrical negatively charged proteins (defined by the protein reflection coefficient, σ_p). According to Frank-Starling law the main forces acting on the barrier between the intravascular and extravascular space are the hydrostatic pressure and the oncotic pressure. Hydrostatic pressure pushes water out of the space where it is measured. Oncotic pressure is a direct cause of the presence of electrically negative charged proteins (mainly albumin); it has the opposite effect as the hydrostatic pressure, keeping water in the space where it is measured.

In the pulmonary capillary vascular bed, an increase of hydrostatic intravascular pressure (measured as PCWP) leads to increased extravasations of fluid in the pulmonary interstitial space, through the endothelial barrier. If the increase is large enough (if it overcomes lymphatic drainage), this first step is followed by fluid extravasation in pulmonary alveoli, through the

alveolar epithelium and franc pulmonary edema. The increase of the hydrostatic intravascular pressure defines ACPE and is not encountered in acute non-cardiogenic pulmonary edema. In the latter, pulmonary edema is primarily a consequence of the increased permeability of the alveolar-capillary membrane (defined as the endothelial capillary, the alveolar endothelial and the interstitium in-between). This leads to an increase of the filtration coefficient (K_f) of the membrane and a decrease of the protein reflection coefficient (σ_p) with an increase of the transudate rate (Q_{iv-int}) from the vessel to the interstitium (Figure 2). The result is exudation of fluid in the pulmonary interstitium and alveoli, but with normal hydrostatic pressure. In clinical practice, a decrease of oncotic pressure (e.g. severe hypoalbuminemia) is never severe enough to produce ACPE.

In ACPE, the increase of PCWP is a direct consequence of the increase of the end-diastolic LV pressures. Left atrium (LA) empties during LV diastole and during this time the pressures in the LA and LV are at their lowest values. Thus, the increase of PCWP above normal values is a diastolic pathological process. \square

2. THE CONCEPT OF HEART FAILURE WITH PRESERVED LEFT VENTRICULAR FUNCTION

2.1. Definitions of systolic and diastolic heart failure

Heart failure (HF) with preserved LVEF (i.e. LVEF > 50%) is encountered in 40% to 50% of the total cases of heart failure (1-6). The same percentages are encountered in ACPE (7,8).

LVEF is a marker of systolic LV function because it measures the ratio between end-diastolic LV volume minus end-systolic LV volume and end-diastolic LV volume (Figure 3). Systolic HF (SHF) is defined as clinical HF associated with decreased LVEF (generally defined as LVEF < 45%). In HF, dyspnea is a sign of pulmonary congestion and hence, a sign of increased PCWP and LV end-diastolic pressures. Thus, dyspnea is a sign of diastolic LV dysfunction regardless of the LV systolic function. However, signs and symptoms of heart failure can appear in the absence of overt systolic dysfunction as defined by the LVEF. The cardiac origin of these symptoms is proved by

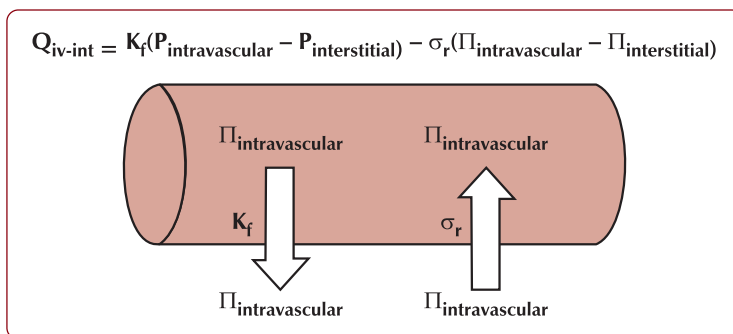


FIGURE 2. Frank-Starling law.

The net transudate rate from the vessel to the interstitium (Q_{iv-int}) is the difference between the net hydrostatic pressures and the oncotic pressures (given primarily by albumin) encountered in these spaces. These pressures have opposite effects: hydrostatic pressure tends to push water outside the vessel, while oncotic pressure tends to keep water inside the vessel. The difference of the hydrostatic pressures between the vessel and the interstitium ($P_{intravascular} - P_{interstitial}$) is corrected for a specific constant of filtration of the alveolar-capillary membrane (K_f). The difference of the oncotic pressures between the vessel and the interstitium ($\Pi_{intravascular} - \Pi_{interstitial}$) is also corrected with a specific constant of protein reflection (σ_r).

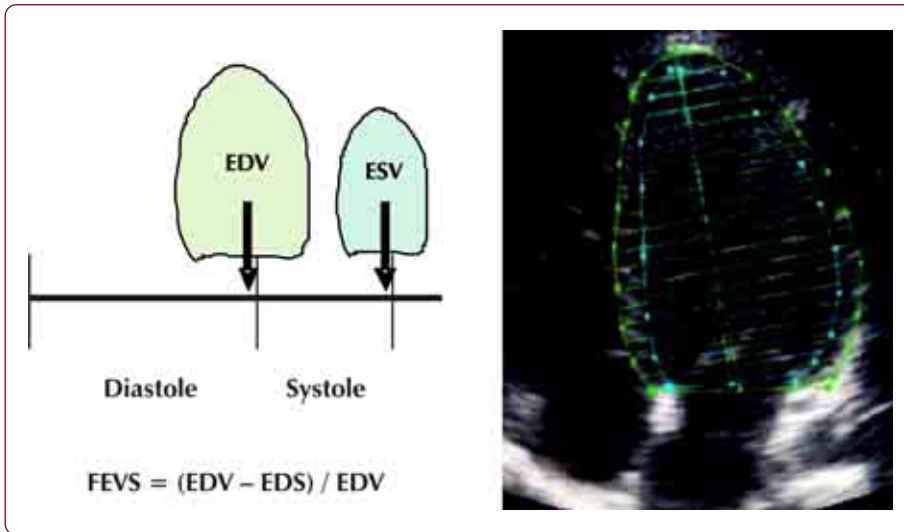


FIGURE 3. The formula for computing left ventricular ejection fraction and the corresponding echocardiography image.
 Note: ESD, end-diastolic left ventricular volume; ESD, end-systolic left ventricular volume

the presence of high levels of brain natriuretic peptide (BNP), diagnostic for HF (15-18). BNP is a useful clinical marker when the clinician is faced with the differential diagnosis of causes of dyspnea: an increased value indicates HF regardless of the LVEF.

HF in the presence of normal LVEF is called diastolic HF (DHF). The term DHF is frequently used in cardiology; and its existence is almost axiomatic today, although some investigators are not so convinced (1, 2, 4, 5, 9, 10, 12-14). It is very surprising how few data are known and proven about the causes of DHF. ACPE is an acute, extreme form of DHF.

At present, 3 hypotheses exist regarding SHF and DHF: 1. they are separate pathological entities; 2. they are consequent stages of evolution of the same disease, with diastolic HF preceding systolic HF, and 3. they represent the same pathological process in which both systolic and diastolic dysfunction coexist but manifest themselves in different proportion depending on the stage of evolution of HF. □

2.2. Pure diastolic heart failure

It has been suggested that DHF is a particular and specific form of HF with different characteristics from SHF: in DHF LV dysfunction happens only during diastole. The concepts of this theory are best summarized in an excellent review recently published by Zile and Brutsaert (11, 11a). Recently, in a study on 47 patients, Zile

also proved that HF with preserved LVEF is associated, as expected, with increased end-diastolic LV pressures and LV diastolic relaxation dysfunction (20). This study proposed the hypothesis that ACPE with preserved LVEF is a consequence of decreased LV compliance, which, at little volume increase (e.g. increased sodium intake) leads to large pressure increase and consequent ACPE. The study of Zile (20) is extremely important as it clearly proves that *chronic* HF with preserved LVEF has increased end-diastolic LV pressures, rigid LV and LV relaxation dysfunction. However, this study does not prove that *acute* HF with preserved LVEF has the same main mechanism and, as we will show, it does not report anything about the longitudinal LV systolic function during ACPE. This hypothesis relies mainly on the assumption that systolic LV dysfunction can be excluded when LVEF is normal. However, it has been proven that normal LVEF is not a reliable marker of systolic function mainly because of the way LVEF is computed (15, 16, 22-25). The myocardial fibers of the LV are predominantly disposed in two directions: longitudinal (the subendocardial fibers) and radial (the subepicardial fibers) (Figure 4). Systolic LV function is a consequence of the contraction of both the radial and the longitudinal myocardial fibers. However, it has been proven that because of the way it is calculated, LVEF largely underestimates the longitudinal function of the LV (15,16). In other words, LVEF is predominantly

a marker of LV radial systolic function, and not of the LV longitudinal systolic function. □

2.3. Diastolic and systolic dysfunctions – part of a continuum

The fact that LVEF does not necessarily represent the complete absence of systolic dysfunction led to the hypothesis that diastolic heart failure is part of the continuum that begins with diastolic LV dysfunction associated with systolic longitudinal dysfunction, progresses to overt systolic LV dysfunction with depressed LVEF and culminates with refractory systolic HF. An important editorial which supports this hypothesis has recently been published by Burkhoff et al (21). This theory suggests that LV diastolic dysfunction represents in fact LV systolic dysfunction of the subendocardial longitudinal myocardial fibers, and that, in reality, pure diastolic dysfunction, without longitudinal systolic dysfunction is very rare if nonexistent (15,16,21,23-25). It has been proven that longitudinal systolic function provides 30 to 40% of the LV stroke volume (15,16).

In this concept, diastolic relaxation is regarded mainly as a passive process opposite to longitudinal systolic contraction (15,16). The LV is compressed like a spring during systole and relaxes passively during diastole. By affecting longitudinal systolic contraction, the opposite diastolic relaxation is also affected (the spring reversal to the original position is affected because the whole spring is defective) (Figure 5). As a consequence, it seems that diastolic and systolic dysfunction represents only different stages of evolution of the same pathological condition, heart failure (15,16,23,26). In fact, diastolic HF (HF with preserved LVEF) has the same prognosis as systolic HF (HF with decreased LVEF) (1,3-5,27,28) again suggesting that they are only different stages of the same disease. Moreover, diastolic dysfunction is rare in patients that do not have diabetes, hypertension, obesity or ischemic heart disease, even if they are elderly – risk factors that are common with the development of systolic heart failure (6). □

2.4. Coexistence of systolic and diastolic HF with different clinical expression at different stages of the evolution of HF.

In summary, it seems that HF always consists of both forms of LV dysfunction, systolic and diastolic, but in different proportions in respect to the stage of evolution of HF. In other words, it appears that there is no pure systolic, nor

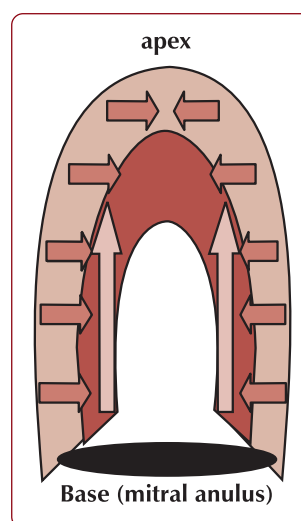


FIGURE 4. Left ventricular (LV) longitudinal and radial systolic function. The subendocardial myocardial fibers are disposed longitudinally, from the base of the LV towards the apex. They provide the longitudinal systolic function which is responsible for 30% to 40% of the LV stroke volume. Subendocardial, longitudinal fibers are most sensible to ischemia. Radial myocardial fibers are disposed subepicardially. They are responsible for the radial systolic function, which is the main function depicted by LV ejection fraction as computed by echocardiography.

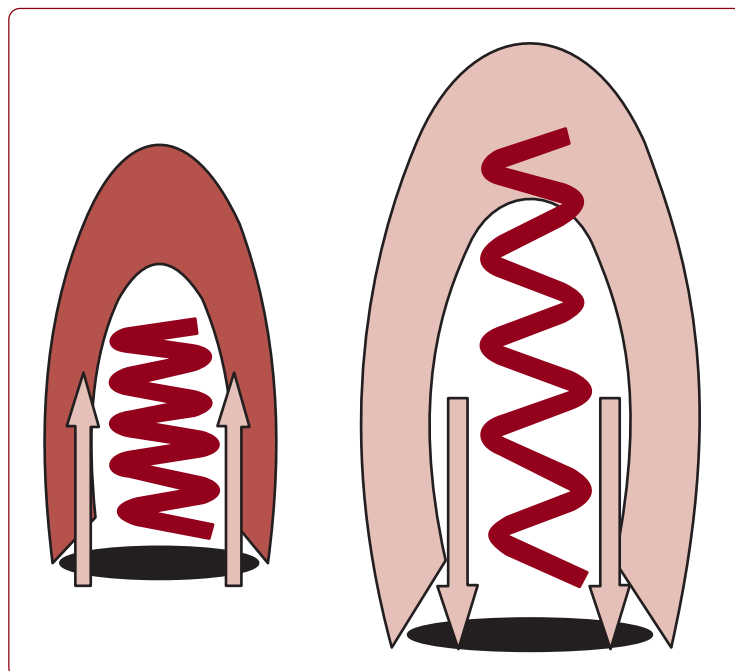


FIGURE 5. Diastolic relaxation represented as a passive relaxation of the longitudinal compression of the LV during systole (through the longitudinal systolic function).

pure diastolic HF. The two different manifestations of HF (systolic and diastolic HF) seem to represent different stages of evolution of the same pathologic process. In HF with preserved LVEF, there is an important LV relaxation dysfunction with increased end-diastolic LV pressures, decreased LV compliance and non-dilated LV (20), LV longitudinal systolic dysfunction (of the subendocardial myocardial fibers) (15,16) but maintained LV radial systolic function (hence, normal LVEF). As the disease progresses, LV radial systolic function becomes affected, with progressive deterioration of global LV systolic function and decreased LVEF, with eventually dilated LV (hence, a more compliant LV) – those phenomena are present in systolic HF. In this stage of evolution diastolic dysfunction does not disappear, but persists (29), being responsible for increased end-diastolic LV pressures, pulmonary congestion and dyspnea of cardiac origin.

However, the majority of the studies included patients with chronic HF. When the studies included patients with acute HF, these patients were investigated after acute HF has been compensated, or, if the patients were evaluated during the acute episode the studies relied on the false premise that normal LVEF excludes systolic HF (8). As a consequence, the exact role of each type of cardiac dysfunction in ACPE remains unknown. □

3. MECHANISMS AND CAUSES OF ACUTE CARDIOGENIC PULMONARY EDEMA WITH PRESERVED EJECTION FRACTION

Three main mechanisms have been cited as a cause of ACPE with preserved LVEF:

1. acute systolic dysfunction;
2. diastolic dysfunction (including systolic longitudinal dysfunction) and
3. dynamic mitral regurgitation. Another theoretical mechanism, a decrease of left heart stroke volume below right heart stroke volume has not been studied in clinical trials.

ACPE with preserved LVEF is predominantly associated with:

1. severe hypertension,
2. myocardial ischemia and
3. renal artery stenosis.

These 3 entities have frequently been cited as the causes and aggravating factors of ACPE. They act through the previously mentioned mechanisms.

3.1. Acute systolic and diastolic LV dysfunction in ACPE

In a landmark study, Gandhi et al. (8) measured LV systolic function by LVEF, and the conclusion was that there is no aggravated systolic dysfunction during ACPE with preserved LVEF. However, this conclusion relies LVEF. This study proves the fact that LVEF during ACPE, and LVEF after ACPE are identical in ACPE with preserved LVEF. However, because LVEF is not a perfect marker for LV systolic dysfunction, there can be LV longitudinal dysfunction during ACPE. The effect of the potential 30 to 40% of the stroke-volume that are lost during LV longitudinal dysfunction in the pathogenesis of ACPE is unknown. In conclusion, the exact grade of LV acute systolic dysfunction during ACPE is not known. □

3.2. Dynamic mitral regurgitation

Dynamic mitral regurgitation can precipitate ACPE (7, 41, 42). However, a recent study denied the existence of dynamic mitral regurgitation in ACPE with preserved LVEF (8). The principal limitation of this study is the subjective assessment of the severity of mitral regurgitation (by Color Doppler). Another study suggested the presence of aggravated mitral regurgitation (up to two times) in ACPE with preserved LVEF (7). This study quantitatively evaluated the increase of the severity of mitral regurgitation after physical effort in patients recovering after ACPE, as compared with the lack of aggravation after physical effort in patients without a history of ACPE. This is also the main limitation of the study. The patients were not evaluated during ACPE, but afterwards, during treadmill test. This is indirect proof that increased mitral regurgitation during physical effort can lead to ACPE. This study does not bring data on the causes of ACPE unrelated to physical effort. An old study, that included patients with ACPE with both preserved and depressed LVEF, showed that almost 2/3 of them had moderate or severe mitral regurgitation (41). The cause of acute mitral regurgitation appeared to be myocardial ischemia (40% of the patients had myocardial infarction), but this was not definitively proven. However, hypertensive crisis, frequently encountered during ACPE, leads to increased LV to left atrium systolic gradient and hence increased mitral regurgitation on Color Doppler, although the

regurgitant orifice area remains constant. In other words, aggravated mitral regurgitation during ACPE can be a consequence of hypertensive crisis and not a direct cause of ACPE. However, its appearance can have a role in aggravating ACPE. □

3.3. The difference between the left and the right heart stroke volumes

There is only a very limited number of studies that evaluated the role of right ventricle (RV) in the pathogenesis of left heart failure, and none of these studies have evaluated the possible involvement of RV in the pathogenesis of ACPE (44, 45). Theoretically, ACPE can not take place if the RV stroke volume is not higher than LV stroke volume, because the increase of PCWP would not take place. This fact can be intuited from the relative protection against ACPE that appears in organic pulmonary arterial hypertension (as in severe mitral stenosis or right heart failure in biventricular Dilated Cardiomyopathy). Therefore, theoretically, during ACPE, LV dysfunction is more severe than the eventual RV dysfunction, leading to a smaller increase of LV stroke volume as compared with RV stroke volume. Thus, instantaneous RV stroke volume should be higher than instantaneous LV stroke volume, leading to increased PCWP and ACPE. □

3.4. Hypertensive crisis

Arterial hypertension > 160mmHg (systolic) is encountered in almost 85% of patients with ACPE (30, 31) and it is the rule in ACPE with preserved LVEF. Arterial pressure (AP) is a resultant of cardiac debit (CD) and peripheral vascular resistance (PVR). PVR is increased in ACPE due to vasoconstriction of the accompanying adrenergic syndrome. To maintain AP, CD has to be maintained. CD is the product of stroke-volume and heart rate. The maintenance of an efficient DC is the characteristic of ACPE with preserved LVEF, and this is the reason why it almost invariably is associated with hypertension. The lack of hypertension in ACPE suggests severe systolic LV dysfunction. This suggests that hypertension is an accompanying phenomenon of ACPE and not the predisposing factor (32). In fact, the incidence of preexisting severe hypertension in ACPE is not very high. A normal fundoscopic exam formally excludes severe preexisting hypertension or present hypertensive emergency as the cause of ACPE (33). However, hypertensive crisis associated with ACPE can aggravate LV systolic dysfunction

by aggravating subendocardial ischemia through increased LV wall stress (34, 35). □

3.5. Myocardial ischemia

Acute myocardial ischemia has been cited as a cause of non-valvular ACPE. Besides acute coronary syndromes and acute myocardial infarction, where the presence of myocardial ischemia is without doubt, an important group of patients develop ACPE without an apparent precipitating factor, with preserved LVEF, negative myocardial necrosis markers, no angina and non-specific ECG changes. In the lack of proof for other causes, myocardial ischemia is frequently believed to be involved. In ACPE with preserved LVEF the ECG displays negative T waves in anterior precordial leads without ST changes, with subsequent regression (43) in the presence of normal coronary arteries. We illustrate such an example in Figure 6. The

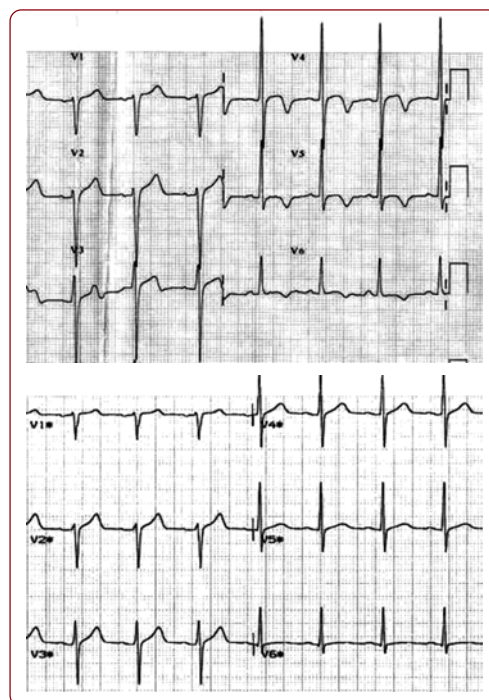


FIGURE 6. ECG changes acute cardiogenic pulmonary edema with preserved left ventricular ejection fraction (LVEF): negative T waves in anterior leads that disappeared after remittance of pulmonary edema. A case of a 38 year old male with new diagnosed diabetes, no angina and normal epicardial coronary arteries at angiography. LVEF, measured after remittance of pulmonary edema was normal.

Courtesy of Dr. Darabont RO, MD, PhD, Department of Cardiology, University Hospital of Bucharest.

causes of the ECG changes are unknown. Coronary X syndrome (microvascular angina, angina with normal coronary arteries) can present ECG changes that are typical of ischemia in the absence of epicardial artery stenosis. The role of this disease in the development of ACPE is unknown. However, microvascular angina predominantly affects the subendocardium, which can lead to LV longitudinal systolic dysfunction. The subendocardial myocardium is also very sensitive to ischemia induced by increased wall stress which appears in hypertensive crisis. These mechanisms might have a role in ACPE.

Even if significant epicardial coronary artery disease is present, there are cases where ACPE appears despite successful myocardial revascularization (31). □

3.6. Critical renal artery stenosis

Renal artery stenosis was first described as a rare cause of severe, brisk ACPE in 1988 (36) (also known as “flash” pulmonary edema). It is estimated that 41% of patients with bilateral renal artery stenosis, and 12% of patients with unilateral renal artery stenosis will develop ACPE (37, 46). There are no prospective studies that have evaluated this association; the literature consists only of case reports and small series (19, 36, 38-40, 46). The cause-and-effect relation between critical artery stenosis and ACPE was made upon the disappearance of ACPE after interventional treatment of renal artery stenosis (36, 40). In this association, ACPE is characteristically associated with preserved

LVEF and severe hypertension. These patients frequently have coronary artery disease, potentially severe (36); however, there are reports where ACPE appeared on structurally normal hearts and normal coronary arteries (40). There are also reports of patients with severe renal artery stenosis and renal failure where pulsus alternans appeared as a sign of severe LV dysfunction in the presence of normal LVEF (19). The mechanism of ACPE in renal artery stenosis is unknown. Hypertension and myocardial ischemia might play a role. It is also unknown how many patients with ACPE without apparent cause have significant renal artery stenosis. □

4. CONCLUSION

In conclusion, ACPE represents a syndrome of acute heart failure characterized by increased PCWP and pulmonary edema. About 50% of ACPE have preserved LVEF. The mechanisms and precipitating factors are still largely in debate. The presence of acute LV longitudinal systolic dysfunction associated with diastolic dysfunction is very likely; however, it has not been proven conclusively. This mechanism can be precipitated by hypertension crisis and myocardial ischemia (including microvascular angina). Hypertension also aggravates mitral regurgitation which further increases pulmonary capillary pressure and pulmonary edema. The role of the right ventricle in ACPE is unknown. Renal artery stenosis is responsible for an unknown number of cases of ACPE with preserved LVEF. The exact mechanism of this association is unknown, although hypertension and volume overload can be involved. □

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