The pathophysiology of acute heart failure—Is it all about fluid accumulation?

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Despite significant advancements in chronic heart failure (HF), no breakthroughs have occurred in the last 2 decades in our understanding of the pathophysiology, classification, and treatment of acute HF (AHF). Traditional thinking, which has been that this disorder is a result of gradual fluid accumulation on a background of chronic HF, has been called into question by recent large registries enrolling less selected patient populations. It is increasingly recognized that many patients with this syndrome are elderly, have relatively preserved ejection fraction, and have mild or no preexisting chronic HF. In this review, we propose 2 primary subtypes of AHF: (1) acute decompensated cardiac failure, characterized by deterioration of cardiac performance over days to weeks leading to decompensation; and (2) acute vascular failure, characterized by acute hypertension and increased vascular stiffness. Registry data suggest that the latter is the more common form of AHF in the general population, although the former is often overrepresented in studies focused in academic tertiary care centers. Regardless of the clinical subtype, a variety of pathophysiologic mechanisms may play a role in this disorder, many of which remain poorly understood. In this review, we describe current understanding of the pathophysiology of AHF, including a critical evaluation of the data supporting both traditional and novel mechanisms, and suggest a framework for integrating these mechanisms into an overall model of AHF. (Am Heart J 2008;155:9-18.)

Acute heart failure (AHF) is the most common cause for hospital admission in patients >65 years. There are approximately 1000000 admissions to US hospitals for AHF each year, accounting for >6000000 hospital days and $12 billion in costs. Moreover, the prognosis of patients admitted with AHF is dismal, with >20% of patients being readmitted with heart failure (HF) and >20% dying during the first year after admission. This outcome is worse than that reported for patients with stage D severe chronic systolic HF enrolled in the Copernicus study, suggesting that an AHF event is associated with an abrupt worsening in HF prognosis. Despite this, data regarding the pathogenesis, etiologic factors, subclassification into specific disorders, risk stratification, and effective treatment of AHF are lacking.

Most studies on the epidemiology of AHF have been small, retrospective, or highly selective. Although larger registries have recently been performed, these data are limited by lack of detail and short-term follow-up. In these registries, the mean age of patients admitted with AHF is 71 to 76 years, half are women, and half have preserved ejection fraction (EF; >40%). These results are in contrast to data on patients with chronic HF, in which the mean age is lower, most patients are men, and the EF is significantly lower. Notably, AHF frequently occurs even when chronic HF symptoms are mild or absent—in the European registry and the ADHERE registry, the index admission was the first time HF was diagnosed in 25% to 27% of the patients. In the recent IMPACT-HF study and registry, 70% of patients at 1-month follow-up were in New York Heart Association class I or II. Clearly, in some patients, AHF may be the result of a specific pathologic process (in the absence of chronic HF), whereas in others, it is the end result of a slow deterioration in severe chronic HF. At present, our ability to define and distinguish various clinical subtypes of AHF is limited by the paucity of data and limitations in our understanding of the pathophysiology of AHF.

Two general categories of AHF have been previously suggested by us and used in the recently published European Society of Cardiology guidelines on the diagnosis and treatment of AHF.

1. Acute decompensated cardiac failure: In many patients, AHF is the end result of a relatively slow (days to weeks) deterioration of severe chronic HF. This deterioration has traditionally been attributed to nonadherence with diet, pharmacologic therapy, or fluid restriction or to decreased contractility due to ongoing myocardial injury (eg, ischemia). This
type of AHF may be able to be managed in the outpatient setting by administration of diuretics, resumption of proper diet and fluid restriction, and improved pharmacotherapy or other interventions (such as revascularization, resynchronization).

2. Acute vascular failure: This rapidly progressive disorder of high blood pressure (BP) accompanied by severe acute dyspnea is commonly encountered in emergency settings. It is most likely caused by a combination of increased vascular resistance superimposed on decreased cardiac contractility (in many cases despite relatively preserved EF), leading to severe hypertension, afterload mismatch, and increased diastolic left ventricular (LV) failure. Very importantly, data from recent registries such as ADHERE5 have suggested that this presentation is the most common type of AHF in unselected populations.

Pathophysiology of AHF

The existing paradigm for understanding AHF has focused primarily on acute decompensated cardiac failure rather than vascular failure. This paradigm suggests that AHF is caused by either an acute or chronic decrease in LV contractility (typically induced by ischemia or arrhythmia) or progressive fluid accumulation. Although these triggers almost certainly play a role in some patients with AHF, data to support the relative importance of different AHF triggers are lacking. Here we will review existing data on both traditional and novel mechanisms that may contribute to the pathogenesis of AHF (of either category) and suggest a framework for integrating them into a comprehensive disease model.

Traditional mechanisms of AHF

Fluid overload

Volume overload is considered a hallmark of AHF, and almost all patients hospitalized with AHF receive diuretic therapy. A simplistic view of AHF pathophysiology suggests that gradual increase in total body volume leads to symptoms of congestion and that normalization of volume status through treatment with diuretics results in restoration of homeostasis. Surprisingly, available data do not provide abundant support for this simplified model of AHF pathophysiology.

In a recent small study, Verwey et al11 have demonstrated that even in patients with severe chronic HF monitored by invasive and noninvasive measures, worsening symptoms of HF (fatigue and increased shortness of breath) and increase in pulmonary pressure occurred days to weeks before weight gain was first observed. Furthermore, when weight gain did occur, it was in the range of only 2 kg. Similarly, Lewin et al12 have demonstrated that weight gain did not differ in a prospective cohort of patients between patients developing AHF and those who did not. Recent data using chronically implanted hemodynamic monitors have confirmed that a dramatic rise in cardiac filling pressures often occurs preceding an AHF hospitalization, even in the absence of any significant change in weight (R. Bourge, MD, personal communication 2006). Studies of hospitalization for AHF have generally demonstrated only modest degrees of weight loss (approximately 2 kg) during AHF hospitalization.13 We have recently analyzed the amount of weight loss in the IMPACT-HF study and registry (W. Gattis-Stough, unpublished data, 2005). Comparing patients with weight loss above and below median, these data suggest that the degree of weight loss was not associated with the degree of improvement in fatigue, paroxysmal nocturnal dyspnea, or rest dyspnea. Only orthopnea (P < .001) and dyspnea on exercise (P = .028) improved more in patients who lost more weight. A greater degree of weight loss during hospitalization was not associated with a reduction in recurrent HF or death at 60 days. In support of the hypotheses of limited fluid accumulation in most patients admitted with AHF, the use of more aggressive diuretic treatment either during the initial stabilization period or as continuous maintenance therapy has not been associated with improved outcome.14 Moreover, aggressive diuretic treatment of AHF has been has correlated with more adverse events, especially renal failure.15 Taken together, these data suggest that the pathogenesis of AHF (and thus the optimal treatment) is substantially more complicated than volume overload alone.

Nonadherence

Nonadherence may be a significant precipitating factor in some patients with AHF, especially those with severe chronic HF. Data on this topic are limited because of the inability to measure adherence reliably. Nonadherence is reported in 20% to 60% of patients with chronic HF and is often quoted as the leading cause for hospital admission. In a prospective study, higher readmission rates, more hospitalization days, and a lower EF after 6 years were found in HF patients who were noncompliant with digoxin (which suggests higher noncompliance with other aspects of the medical regimen16). Cline et al17 reported that half of a cohort of patients with chronic HF could not recall the correct dose of the prescribed medication, and more than half could not remember the correct time for taking the medication. We have examined compliance by pill count in patients post-MI who required captopril treatment for HF and prospectively found nonadherence to be associated with more adverse outcome and readmission due to AHF.18 Similar findings are reported for nonadherence with fluid and diet recommendations.19 In a large prospective study, even nonadherence with
placebo was associated with worst outcome in patients with CHF. To date, the importance of nonadherence in AHF pathophysiology remains poorly defined because no large prospective studies have directly addressed the role of nonadherence in an unselected cohort of patients with AHF. This distinction is important because, as noted, AHF may frequently occur on a background of minimal or mild chronic HF. Although such patients may be less sensitive to nonadherence with diet or diuretic therapy, nonadherence to other treatments (such as hypertension) may still be a significant factor in the genesis of AHF.

**Myocardial ischemia**

Most patients admitted for AHF have a history of chronic ischemic heart disease, and ischemia is often invoked as an important trigger for AHF. Surprisingly, however, little data exist on the incidence of acute ischemia during an AHF event. However, in the large European registry, only 32% of patients admitted with AHF had chest pain at admission, and acute myocardial infarction was diagnosed in only 12%. Surprisingly, few other data exist on the occurrence of frank acute coronary syndrome (ACS) during an AHF event. This may be related in part to the fact that electrocardiographic changes and troponin release may occur in patients with HF without coronary disease (and may be the result rather than the cause of the AHF syndrome). Available data suggest that the incidence of troponin above the threshold for ACS diagnosis in patients with AHF is approximately 20%. In the PRESERVED-HF study, a multicenter, prospective, randomized, open-label trial of nesiritide or dobutamine in 51 patients with chronic ischemic (but not acute) heart disease admitted with AHF, detectable troponin T was present in 43.5%, and troponin I was present in 73.9% of patients at baseline. In the patients with undetectable baseline troponin, 7.7% developed detectable troponin T, and 41.7% developed detectable troponin I during the hospitalization. Only 15% of patients completed the study without evidence of troponin release. Although the study was not powered to evaluate clinical events, baseline and peak values of troponin were significantly higher in patients experiencing death or worsening HF as compared with patients with no event. However, as alluded to previously, low levels of detectable troponin may not be direct evidence of ACS because they may also be seen in patients with AHF without coronary disease.

RITZ is the only prospective study that evaluated patients admitted with AHF who also have ACS, randomizing 200 patients admitted with AHF accompanied by ACS to placebo or the endothelin antagonist tezosentan. During the first 72 hours after enrollment, 3% of patients died, 12% sustained a recurrent event of HF, and 12% had recurrent ischemia, of which 3% were frank myocardial infarctions. In these patients, troponin increase was a strong predictor of adverse outcome. More data exist on the occurrence of AHF during admission for ACS. Khot et al reported on the incidence and outcome of clinical HF (by Killip class) in a large cohort of patients (n > 20,000) with non-ST-elevation ACS enrolled in the GUSTO IIb, Paragon A and B, and PURSUIT studies. Acute HF (Killip class ≥ 2) was observed in 11% of the patients, leading to a 9% one-month mortality and 16% six-month mortality—more than triple the mortality observed in patients without HF. Acute HF was correlated with 30% of the overall mortality in the study, being the strongest independent negative prognostic factor in the cohort.

The exact incidence of frank myocardial ischemia in AHF remains unknown, in part because of difficulty of diagnosing ischemia in patients admitted with AHF. Although observational data cited suggest ischemic complications in 20% of AHF admissions, this number may be lower (troponin spillage can occur even when ischemic heart disease is not present) or higher (ischemia may occur without significant troponin leakage). Clearly, patients with both ACS and AHF have a poor prognosis, and more study of this patient group is needed.

**Arrhythmias**

The contribution of arrhythmias to the pathophysiology of AHF has not been studied in detail. Most registries have reported that atrial fibrillation occurs in 30% to 42% of patients admitted with AHF. In a large study by Cleland et al, 42% of patients had atrial fibrillation at admission, of whom approximately half did not previously have chronic atrial fibrillation. A quarter of these patients had atrial fibrillation that was judged to be rapid and presumably the cause of the AHF event. In the same study, malignant ventricular arrhythmias were reported in 8% of patients. Because of the retrospective nature of the study, the investigators were not able to demonstrate a cause-and-effect relationship between arrhythmias and the occurrence of AHF or its outcome. Recently, Benza et al have shown that the occurrence of new arrhythmias, mainly atrial fibrillation, was a strong predictor of recurrent events and death in patients admitted for AHF. Conceptually, transient arrhythmias may result in steep decreases in cardiac contractility and deterioration in diastolic dysfunction, both of which could contribute to an AHF event. Given that such transient events may be difficult to detect, the precise role of arrhythmia in the pathogenesis of AHF remains unknown. The proliferation of implantable devices in patients with chronic HF may provide important insights into the role of arrhythmia in AHF.

**Mechanical lesions**

In some patients, the decreased myocardial effective contractility leading to AHF may be caused by a significant mechanical lesion that evolves or deteriorates rapidly. The most common such mechanical lesion is
acute mitral regurgitation. In a recent study on patients with recent acute pulmonary edema, stress echocardiographic evaluation revealed significant stress-induced mitral regurgitation in comparison with control patients with similar degrees of HF but no pulmonary edema. These findings are in contrast with those of Gandhi et al., who did not observe significant new valvular lesions in serial echocardiographic evaluations performed in patients admitted with AHF and high BP. Other causes of mechanical lesions that may cause an AHF event are ischemic or nonischemic papillary muscle rupture, mechanical valve malfunction due to thrombosis or pannus, infective endocarditis, ventricular septal rupture, and aortic dissection causing severe ischemia or aortic regurgitation. Although no large prospective echocardiographic study was performed in patients admitted for AHF, the prevalence of such mechanical lesions as the primary cause of AHF appears to be low.

**Novel mechanisms of AHF**

**Vascular resistance and afterload mismatch**

Our knowledge of the hemodynamic events preceding AHF is limited by the selective use of right heart catheterization. In unselected registries such as ADHERE, the main hemodynamic observation related to AHF onset is a significant increase in BP. In ADHERE, the median first systolic BP reported (in many cases after some treatment was administered by emergency medical services) was 143 mm Hg. We have recently completed a registry of 341 consecutive patients who were admitted during a period of 3 months to a community hospital, in which initial BP measured before treatment by EMS was 164/88 mm Hg. Mean BP in the highest quartile was 212/115 mm Hg. Similar findings have been reported in other studies enrolling patients in whom BP was measured early in the course of AHF, suggesting that high BP is a key feature in most patients with AHF.

In recent years, accumulated evidence has suggested that measurements of forward contractility power and flow are significant predictors of short- and long-term outcome in patients with AHF. The calculation of cardiac power output (CPo; the product of simultaneously measured cardiac output [CO] and mean arterial pressure [MAP]; CPo = MAP × CO) and SVR might be important in the diagnosis, risk stratification, and monitoring of patients with both chronic HF and AHF. Cardiac power output integrates considerations of both contractility (CO) and afterload (MAP), potentially providing an integrated means of assessing hemodynamic state in AHF. In a recent study, CPo and vascular resistance were invasively measured in 100 patients with AHF at baseline and for 30 hours.

AHF episode during invasive hemodynamic monitoring had lower CPo at baseline and deterioration in CPo leading up to the acute event (Figure 1). Superimposed on this low and decreasing CPo, we observed a steep increase in SVR immediately before the AHF event.

These core hemodynamic events lead to an acute “mismatch” between rapidly increasing afterload and impaired systolic performance, resulting in an acute increase in LV end-diastolic pressure and a decrease in CO. This hemodynamic model may explain the presence of pulmonary congestion despite modest fluid accumulation. Afterload mismatch and reduced contractility can lead to fluid redistribution from the peripheral circulation to the pulmonary circulation due to increased pulmonary venous pressure transferred backward to the alveoli, overwhelming the absorptive capabilities of the alveolar cells, inducing pulmonary congestion and low peripheral perfusion, the main symptoms of AHF.

The exact causes for the observed sudden increases in SVR are not known. Some studies have suggested that in patients with chronic HF, increased arterial stiffness may be one of the causes of increased vascular resistance. This mechanism may also be important in AHF. The incidence of both AHF and arterial stiffness increases with age. Inflammatory activation, which has been suggested as a potential trigger of AHF, has recently been demonstrated to result in an abrupt increase in arterial stiffness. Regardless of cause, the paradigm of acute rise in SVR, leading to afterload mismatch and decreasing cardiac performance, appears to fit the observational data about the epidemiology of AHF. Future prospective studies are needed to further evaluate this hypothesis.

**Diastolic dysfunction**

Traditionally, EF measured by echocardiography has been regarded as an important measure of LV contractility. Surprisingly, detailed data on echocardiographic parameters in patients with AHF are sparse. In the only
significant prospective study reported to date, Gandhi et al assessed EF, valvular function, and simple measures of diastolic function in 38 patients admitted with AHF accompanied by high BP. Comparing admission measurements to 3-day follow-up, there was no change in EF or valvular function (Figure 2), whereas some measures of diastolic dysfunction were more severe at admission than at 3-day follow-up. A retrospective study of clinical, hemodynamic, and neurohormonal correlations of EF in patients with AHF showed that EF was only weakly correlated with hemodynamic measures of contractility (i.e., cardiac power) as well as outcome. In another study, Logeart et al demonstrated that EF had no value in predicting the short-term prognosis of patients with AHF. The studies of both Gandhi et al and Logeart et al did demonstrate a correlation between measures of diastolic (rather than systolic) function and outcome in AHF. In a recent review, Banerjee et al suggested that acute exacerbation of diastolic dysfunction may be one of the core echocardiographic findings in patients with AHF. It is unknown whether diastolic dysfunction represents a primary mechanism of AHF or a secondary phenomenon to the acute increases in afterload described. Regardless, deterioration in diastolic function may clearly contribute to increases in LV filling pressure, with subsequent pulmonary congestion due to fluid redistribution rather than fluid accumulation.

Cardiorenal syndrome

In patients with chronic HF, the presence of concomitant chronic renal dysfunction has been one of the strongest risk factors for mortality. Although renal dysfunction predicts all-cause mortality, it is most predictive of death from progressive HF, suggesting that in chronic HF, renal dysfunction may be a marker of HF severity. Indeed, the strongest predictor of creatinine clearance in patients with chronic HF is CO. In the setting of hospitalization for AHF, multiple analyses have confirmed the prognostic value of renal dysfunction as measured by increase in serum urea nitrogen level and/or creatinine. Although the relationship between renal dysfunction and adverse outcomes appears to be linear, several studies have used a threshold of a 0.3-mg/dL rise in serum creatinine over baseline to define this phenomenon. Changes of this magnitude generally occur in about a third of patients admitted for AHF and are associated with a prolonged and complicated hospital course as well as high rates of morbidity and mortality. In one multicenter cohort study, a creatinine level increase of 0.3 mg/dL had a sensitivity of 65% and specificity of 81% for predicting inhospital mortality. The exact cause for the association between renal dysfunction and poor outcome in patients with AHF is not known. On one hand, renal dysfunction may occur more frequently in patients with more severe AHF and, therefore, may be a marker of severity. In support of this concept, increased serum urea nitrogen level, which integrates both renal perfusion and intrinsic impairment, was found to be a stronger predictor of adverse outcome than creatinine in most analyses. Alternatively, greater degrees of renal dysfunction may represent greater burden of comorbidity (such as diabetes and hypertension), resulting in acute deterioration in renal function despite relatively modest hemodynamic insult. Regardless of cause, worsening renal function may play an important role in the progression and propagation of an AHF episode by leading to greater fluid and sodium retention and neurohormonal activation.

Neurohormonal and inflammatory activation in AHF

Activation of neurohormonal pathways and inflammatory cascades is known to be a central feature of the chronic HF syndrome. Blockade of neurohormonal activation has been the major driver of therapeutic success in drug development for chronic HF. The interaction between neurohormones, inflammation, and AHF is complex and has not been studied in detail. In experimental models, acute increases in inflammatory cytokines can recapitulate many aspects of the HF phenotype, including decreased contractility, diastolic dysfunction, and increased capillary permeability leading to pulmonary edema. Small observational studies in patients with AHF support a potential role for acute changes in inflammatory stress in the pathophysiology of AHF. In a study on 30 patients admitted with AHF, we demonstrated that both classic neurohormones (norepinephrine, brain natriuretic peptide, and
endothelin 1) and inflammatory markers (interleukin 6, C-reactive protein) were significantly increased during the acute phase of AHF both at time zero (before treatment) and at 48 hours (Figure 3). In a separate study on 340 patients admitted with AHF, our group has observed interactions between leukocytosis and lymphocyte ratio on admission and specific characteristics of AHF (O. Milo-Cotter, unpublished data 2007). Higher lymphocyte ratio was related to higher admission systolic BP, whereas lower lymphocyte ratio was related to higher troponin and more severe recurrent HF and death. The correlation between increased systolic BP and increased lymphocytes is in line with recent studies demonstrating a possible interaction between inflammatory activation and increased arterial stiffness, suggesting a link between inflammatory and hemodynamic events in AHF.

A notable finding in these studies has been the persistence of inflammatory and neurohormonal activation beyond the acute event. In the study by Milo et al., inflammatory and neurohormonal activation persisted >48 hours and was still incompletely resolved at 60 days. This pattern was also seen in analysis of data from the PRESERVED-HF study, in which elevated values of neurohormones and inflammatory markers persisted at 5 days of follow-up. These data suggest that persistent elevation of neurohormonal and inflammatory axes in patients with AHF may explain the high (50%) short-term rates of recurrence in this disorder.

Ventricular dyssynchrony

It has become apparent in recent years that the synchronization of cardiac contraction including atrioventricular, interventricular (right ventricle and LV), and intraventricular (different segments of the LV) is an important determinant of cardiac contractility. Dyssynchrony has been repeatedly shown to be associated with adverse outcomes in patients with chronic HF, an association that may be improved with cardiac resynchronization therapy. The importance of dyssynchrony in patients with AHF has not been examined. Theoretically, acute changes in cardiac contractility and conduction may induce dyssynchrony, which could potentially contribute to the progression of AHF after an initial insult. In support of this concept, Brophy et al. found that intraventricular conduction delay is associated with more adverse outcome in patients admitted with AHF. To date, no study has evaluated the interaction of AHF and dyssynchrony in detail.

Platelet activation

In patients with chronic HF, many measures of platelet activation (particularly P-selectin) have been shown to be increased and related with outcome. In AHF, platelet activation may lead to microvascular reduction in myocardial blood flow, leading to decreases in cardiac contractility and myocardial ischemia. O’Connor et al. found a significant increase in both soluble and platelet-bound P-selectin in patients admitted with AHF as compared with controls (Figure 4). In the second study, Milo et al. found the same increase when comparing values during an AHF event with values measured in the same patients at 2-month follow-up. These increases in platelet activation, which have been related to poor outcome,
suggest a possible avenue for the evaluation of antiplatelet therapies in AHF.

**Putting it together—initiation and amplification of an AHF event**

Consideration of the data summarized suggests a new framework for understanding the pathophysiology of AHF events. We suggest that AHF can be understood in 2 phases—an “initiation phase” that provides the initial trigger and an “amplification phase” in which various mechanisms contribute to the viscous cycle of deterioration leading to an AHF event.

**Initiation phase**

As described in Figure 5, our hypothesis suggests that AHF is initiated by a combination of 2 pathways. The “cardiac pathway” is fundamentally initiated by a low cardiac contractility reserve. This low contractility reserve can be amplified by an acute decrease in cardiac contractility. A variety of mechanisms may contribute to this decrease, including ischemia, arrhythmia, inflammatory activation, or progressive deterioration in myocardial dysfunction due to the underlying mechanism causing the HF process. In many cases, such decrease in contractility will be accompanied by a plasma troponin leak. This leak represents sometimes a true acute ischemic event, although in many cases, it is the result of nonischemic myocardial necrosis. Rarely, patients with low contractility reserve will develop AHF without a further decrease in contractility, related to pure nonadherence and fluid accumulation. As previously alluded to, such cases are nowadays more commonly treated in outpatient HF disease management programs by resumption of appropriate dietary and diuretic treatment. An important inherent mechanism in the cardiac pathway relates to renal impairment. A decrease in contractility will invariably lead to lower renal perfusion and fluid accumulation. Many clinicians will address the fluid accumulation by an increase in diuretic therapy. Sometimes, this combination may lead to progressive renal impairment, which, by numerous mechanisms, may cause further deterioration in the HF process, instigating a viscous cycle of more HF.

In contrast, the “vascular pathway” is commonly the main pathophysiological mechanism for AHF in patients with mild to moderate decrease in cardiac contractility reserve, which by itself would rarely lead to an AHF episode. This vascular pathway is fundamentally related to increased vascular resistance in the periphery associated with increased vascular stiffness. Again, a variety of mechanisms (including neurohormonal activation, inflammatory stress, and aging-associated changes in vascular stiffness) may contribute to the development of this component. This would lead to an acute afterload mismatch impairing the forward-pumping ability of the heart and, hence, redistribution of fluid to the pulmonary circulation and lungs. By echocardiography this pathway will lead to a mild decrease in LV EF and concomitant signs of significant, sometimes acute, diastolic dysfunction.

Although one or the other of these pathways may predominate in different clinical scenarios, in most patients, both pathways are active in the initiation phase of an AHF event. This combination will culminate into reduction in both forward perfusion of many organ systems as well as increased LV pressures. This increased intracavitary pressure of the LV will manifest as worsening diastolic dysfunction by echocardiography and increased wedge pressure by right heart catheterization. Although these variables can be quantitated relatively easily, for the large part these changes are only epiphenomena related to the AHF event and not its immediate cause.

Once initiated, multiple mechanisms contribute to the amplification of the AHF event as described.

**Amplification phase**

Once initiated, the AHF process is amplified through several mechanisms:

1. **Myocardial necrosis and progressive LV failure:** Although in some cases, acute coronary syndrome is the cause of the AHF event, in other cases, AHF, by inducing hypoxia, acidosis, hypoperfusion, significant neurohormonal-inflammatory activation, or increased LV pressure causing subendocardial ischemia or platelet activation, may cause additional myocardial necrosis, leading to
troponin release and further reduction in cardiac contractility, amplifying the AHF syndrome.

2. Right ventricular failure: Although in some cases, an acute event of RV failure is caused by pulmonary embolism, triggering an AHF event, in most cases, RV failure is the result rather than the cause of AHF. During such an event, increased fluid content in the lungs and decreased oxygen saturation induce pulmonary vasoconstriction. This process leads to an increase in RV pressure that further compromises LV function through the ventricular interaction mechanism.\(^{57}\)

3. Respiratory failure: Decreased oxygenation, presence of acidosis, and reduced CO may lead to depressed central respiratory drive, failure of the respiratory muscles, and eventually respiratory failure superimposed on cardiovascular failure.

4. Leakage of the alveolar-capillary membrane and decreased alveolar fluid clearance: The significant hypoxia and possibly acute inflammatory process related to AHF may depress the rate of alveolar fluid clearance, further enhancing pulmonary congestion.\(^{58}\)

5. Renal failure: As previously described, patients with AHF who develop acute renal failure during the course of their admission (defined by an increase of $\geq 0.3$ mg/dL in serum creatinine) have worse outcomes.\(^{47}\) Although the exact reason for this association is not known, it is possible that renal failure is a marker of more severe HF but also an important amplifier of the syndrome trough fluid accumulation and activation of neurohormonal and inflammatory mechanisms.

6. Arrhythmias: Arrhythmias, especially atrial tachyarhythmias, are very common in patients with AHF. Recently, Benza et al\(^ {59}\) have shown that the occurrence of new arrhythmias, mainly atrial arrhythmias, was a strong predictor of recurrent events and death. Hence, development of arrhythmia during the AHF event is an important cause for further deterioration in these patients.

Conclusions

Acute HF is a collection of clinical syndromes with varying and poorly understood pathophysiologic mechanisms. Despite its high prevalence and morbidity, limited understanding of the fundamental underlying pathophysiology has led to a lack of development of new therapies in this field. Existing data suggest that some traditional triggers, such as fluid accumulation, ischemia, and arrhythmias, may play a limited role in the initiation of this syndrome, whereas other mechanisms such neurohormonal activation, increased vascular stiffness, and fluid redistribution may play a larger role. Further elucidation of the role of these various mechanisms will require carefully designed, prospective studies. Greater understanding of fundamental mechanisms contributing to AHF may be helpful in defining subtypes that may be amenable to specific therapies, leading to improved care for this disorder.

References


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