The literature provides multiple definitions of heart failure (1). A recent attempt to describe this syndrome posited that heart failure is a mechanical and neurohumoral syndrome in which the heart fails as a pump, resulting in stasis of blood in the lungs and venous system, fatigue, effort intolerance, and reduced longevity. From a purely mechanical perspective, heart failure is defined as a clinical syndrome that can result from any structural or functional cardiac disorder impairing ventricular filling or ejection of blood (2). Incidence of structural heart disease is high in patients with advanced chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD) requiring dialysis. In large observational cohort studies, more than 80% of patients with ESRD are reported to have cardiovascular disease (3,4). This observation is of paramount clinical relevance because the leading causes of death for patients with ESRD are due to...
cardiovascular disease, including heart failure, myocardial infarction, and sudden cardiac death (3,5–7).

In CKD, and particularly ESRD, 3 major mechanisms induce and exacerbate cardiomyopathy: volume overload, pressure overload, and nonhemodynamic factors associated with CKD. The nonhemodynamic factors are manifold, and include activation of the renin-angiotensin system, catalytic iron–dependent oxidative stress, inflammation, and stimulation of profibrogenic factors (5,7) These pathological mechanisms cause direct and immediate effects and affect long-term disease progression in these patients (5,7).

The American Heart Association (AHA), American College of Cardiology (ACC), and European Society of Cardiology (ESC) have developed guidelines recommending that heart failure be classified in a manner that reflects its risk factors, severity, and natural history (2,8,9). In the AHA/ACC guidelines, stage C heart failure defines patients with current or prior symptoms of heart failure. The primary form of maintenance renal replacement therapy (RRT) worldwide is hemodialysis, and a smaller proportion of patients use peritoneal dialysis. With rare exceptions, lack of fluid removal by RRT in patients undergoing dialysis leads to dyspnea and congestion due to salt and water retention. Thus, by definition, all patients undergoing dialysis, even those with no structural heart disease, experience New York Heart Association (NYHA) functional class (FC) III to IV symptoms if fluid removal by RRT is delayed. Thus, management and treatment of patients undergoing dialysis with heart failure is difficult due to the dynamic nature of fluid overload.

A “real world” example is illustrated by the following clinical vignette: a patient undergoing dialysis is referred to the cardiologist because of worsening heart failure symptoms. Because of transport to and from the dialysis clinic in addition to the time required for dialysis, which usually exceeds 6 h, patients on dialysis rarely schedule non-nephrology doctor’s visits on the same day as dialysis sessions. Thus, visits to the cardiologist almost always occur prior to a dialysis day. During the visit, the cardiologist correctly identifies fluid overload, and the patient is likely to be returned to the nephrologist for “better” dialysis and more ultrafiltration. This is problematic because the nephrologist likely sent the patient to the cardiologist because the patient was already receiving the maximal tolerable ultrafiltration.

The incidence, severity, and outcomes of heart failure in patients undergoing dialysis are poorly characterized and potentially undertreated, because the severity of symptoms relative to the frequent changes in volume status occurring before and after RRT are not witnessed and remain poorly documented (5,7). In addition, none of the existing practice guidelines for the treatment of fluid overload in patients on dialysis comment on whether it is appropriate to apply the AHA/ACC/ESC stages of heart failure or the NYHA FC system (10).

For advancement in the treatment of heart failure in patients on dialysis, a methodology that improves the characterization of heart failure in these patients is essential and urgently required. The implementation of classification systems for any disease syndrome can have a positive impact on disease management (10–12). For example, introduction of the CKD staging system and the Risk, Injury, Failure, Loss, End-stage renal disease (RFLE) (11,12) staging system for acute kidney injury have allowed clinical investigators to better characterize disease processes, conduct epidemiological studies, guide clinical trial enrollment, standardize practice guidelines, and improve clinicians’ ability to track disease progression (13,14).

The 11th Acute Dialysis Quality Initiative (ADQI) meeting was convened to focus on cardiorenal syndrome (15). The working group that focused on cardiorenal syndrome type IV (advanced CKD and progressive heart disease) identified this clinical and research issue as a critical unmet need in the care of patients on dialysis with heart failure. We based this assessment on the fact that accurate risk stratification of patients with any given disease state is essential to improve clinical status and outcomes.

Workgroup Methodology

The specific methods for the ADQI conferences were developed and refined over the first 4 international conferences (16). Briefly, our methods comprise: 1) a systematic search for evidence, with review and evaluation of the available literature; 2) establishment of clinical and physiological outcomes and of measures to be used for treatment comparisons; 3) description of current practice and the rationale for use of current techniques; and 4) analysis of areas in which evidence is lacking and future research is required to obtain new information. The topics chosen for each conference are selected on the basis of the following criteria: 1) prevalence of the clinical problem; 2) estimates of variation in clinical practice; 3) potential influence on outcome; 4) potential for development of evidence-based guidelines; and 5) availability of scientific evidence. A detailed report of the ADQI process has been published previously (16).

Before the conference and according to the structure of previous ADQI consensus meetings, we performed a systematic review of the literature (11,17). Specifically, we used the search terms “heart failure,” “peritoneal dialysis,” “hemodialysis,” “renal replacement therapy,” “chronic kidney disease,” “dialysis,” “guidelines,” “consensus,” and “end-stage renal/kidney disease,” combined with “prognosis,” “major
adverse cardiovascular events,” “myocardial infarction,” “stroke,” “volume overload,” “fluid overload,” “sudden cardiac death,” “death,” and “mortality.” In view of the volume of retrieved literature, only representative publications are cited in this proposal. Furthermore, we opted to base our staging proposal on clinical scenarios for which data are ample. We also excluded the specific clinical situations pertaining to renal or heart transplant or to mechanical circulatory support.

Based on the literature identified prior to the conference, the following key questions were considered:

1. Are there current heart failure staging systems that can be applied specifically to patients undergoing dialysis?
2. What are the critical features of a staging system that can be easily used by clinicians to establish appropriate diagnostic and therapeutic approaches?
3. How can a new heart failure staging system specifically address the unique nature of nonphysiological periodic volume removal, which characterizes all forms of dialysis?

Current Staging Systems of Heart Failure

Multiple heart failure staging systems and classification schemes have been proposed. In 1977, Wagner and Cohn (18) proposed a classification system based on 3 broad pathophysiological mechanisms: systolic dysfunction, diastolic dysfunction, and volume overload. These 3 conceptual etiologies remain relevant in the current assessment and treatment of heart failure. Since 2005, the ESC/ACC/AHA have developed consensus guidelines that include a staging system for heart failure to reflect its severity as well as its natural history (2). However, the most commonly used system to characterize the severity of heart failure symptoms is the NYHA FC (10) (Table 1), which is based on a grading of dyspnea relative to the intensity of physical activity. The ESC/ACC/AHA and NYHA classification systems have proven to be robust and have been used successfully to assess the epidemiology and severity of heart failure. They have been the basis for establishing inclusion criteria and response to therapy in seminal clinical trials conducted in patients with heart failure (19–21).

However, neither of these staging systems can be used in their current forms to assess the severity of heart failure in patients on dialysis because dyspnea in these patients is not solely attributable to heart failure and its severity changes in relation to the timing of volume removal. For nearly all patients undergoing dialysis, delay in or absence of RRT results in dyspnea due to fluid overload even if the patient’s heart is structurally normal. Thus, all patients on dialysis can theoretically be considered in NYHA FC III to IV, which can improve to NYHA FC I after fluid removal. In patients not on dialysis with acutely decompensated heart failure, euvoolemia can be restored and maintained for variable periods of time with appropriate medical therapies; however, all patients undergoing dialysis begin to retain salt and water immediately after RRT treatment, and accumulation continues until the next prescribed RRT (this occurs in both peritoneal dialysis and hemodialysis to varying degrees). We concluded that a staging system for heart failure in patients on dialysis must be able to define heart failure symptoms in relation to the response to the periodic nonphysiological volume removal that occurs with all forms of dialysis. Thus, the timing of assessment and the periodicity of dialysis must be taken into account. In addition, we sought to develop a patient-centered staging system that was easily understandable by care providers and therefore easily usable for planning further diagnostic evaluations and treatment for patients with coexisting heart failure and dialysis-requiring ESRD.

Proposed Staging System

We considered a number of possible solutions to the problem outlined in the previous text. To specifically exclude patients with normal hearts on dialysis, the proposed classification system incorporates echocardiographic criteria that indicate the presence of underlying structural heart disease. We modified the NYHA FC of dyspnea severity into a new system with a description of heart failure symptoms and their response to fluid removal by RRT/ultrafiltration. The 3 elements of our proposed staging schema are as follows:

1. Standardized echocardiographic evidence of structural and/or functional heart abnormalities;
2. Dyspnea occurring in the absence of primary lung disease, including isolated pulmonary hypertension; and
3. Response of congestive symptoms to RRT/ultrafiltration.

The standardized echocardiographic criteria are based on the evidence of mild to moderate echocardiographic disease cutoffs that are detailed in the American Association of Echocardiography consensus guidelines (which are consistent with the European Society of Echocardiography
guidelines) (22,23). The echocardiographic criteria that suggest or are supportive of cardiac disease are summarized in Table 2.

The classification system that we propose is summarized in Figure 1.

Patients who present with severe dyspnea that is relieved by RRT/ultrafiltration are categorized by their post-therapy status. For example, a patient with echocardiographic evidence of left ventricular hypertrophy who presents to the dialysis clinic with dyspnea at rest, undergoes RRT, and then experiences no symptoms would be classified as ADQI class 2R. In addition, the RRT/ultrafiltration metric does not necessarily suggest a single therapy. Symptomology relieved by RRT/ultrafiltration assumes that the patient is receiving RRT at the appropriate frequency.

**Strengths and limitations.** Like previously published staging systems, the proposed classification system will require prospective testing and validation in appropriate patient cohorts. In addition, because echocardiographic findings are a prerequisite for entry into the classification system, standardization of the collection and documentation of these echocardiographic data is imperative.

Studies in patients undergoing dialysis that deployed continuous hemodynamic monitoring before, during, and after RRT with ultrafiltration have demonstrated that interdialytic volume accumulation results in increased pressures in the pulmonary artery and right ventricle (Fig. 2) (24,25). The proposed staging system accommodates the "tidal nature" of nonphysiological volume removal. Another strength of this proposed system is that symptom grading is similar to grading in other heart failure symptom scales (e.g., the NYHA FC system) that are familiar to clinicians. In addition, the proposed staging system is based on patient-reported symptomology and is thus patient centered.

Patients with heart failure on dialysis pose unique diagnostic and therapeutic challenges; for example, a patient

<table>
<thead>
<tr>
<th>Table 2 Echocardiography Criteria*</th>
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<tbody>
<tr>
<td>LVH (LV mass index &gt;110 g/m² for women and &gt;130 g/m² for men or &gt;47 g/m²² for women and &gt;50 g/m²² for men). Latter measure is LV mass calculated by the area-length method and indexed to height (22,38,39).</td>
</tr>
<tr>
<td>Increased LV volume index &gt;86 ml/m² diastolic or &gt;37 ml/m² systolic.</td>
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<tr>
<td>Left atrial enlargement (left atrial volume index &gt;34 ml/m²).</td>
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<tr>
<td>Diastolic dysfunction (ASE grade ≥2).</td>
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<tr>
<td>Moderate to severe mitral or aortic valvular disease (stenosis or regurgitation).</td>
</tr>
<tr>
<td>RV systolic dysfunction by accepted criteria (e.g., TAPSE &lt;17 mm).</td>
</tr>
<tr>
<td>LV ejection fraction ≤45%.</td>
</tr>
<tr>
<td>Regional wall motion abnormality of LV (&gt;10% of the myocardium).</td>
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</table>

*At least 1 (of 8) listed criteria must be abnormal to fulfill the definition of echocardiographic evidence of heart disease.

LV — left ventricle; LVH — left ventricular hypertrophy; RV — right ventricle; TAPSE — tricuspid annular plane systolic excursion.

Figure 1 ADQI Heart Failure in ESRD Classification System

Classification is determined by a dyspnea assessment before and after renal replacement therapy (RRT)/ultrafiltration (UF). When patients have the same class assessment before and after RRT/UF, they are scored by their post-treatment assessment. The classification scheme assumes that the class assignment represents the patient’s achievement of optimized UF and is representative of the patient’s usual level of dyspnea before and after RRT/UF. *If dyspnea symptoms improve to class I levels, the patient would be classified as class 2R. **If dyspnea symptoms improve to class II levels, the patient would be classified as class 3R. ADQI — Acute Dialysis Quality Initiative; ESRD — end-stage renal disease; NYHA — New York Heart Association.
with mild left ventricular dysfunction undergoing dialysis who becomes dyspneic may be deemed to have fluid overload and referred back to the nephrologist for standard thrice-weekly hemodialysis and additional ultrafiltration. Thus, RRT is a form of treatment for ESRD with heart failure. However, in some cases, this therapy fails to improve or resolve the symptoms of dyspnea. This clinical scenario raises multiple questions regarding presence and severity of heart failure, type of monitoring required, and therapeutic approaches needed to treat the persistent symptoms. A validated classification system would prove useful here and could potentially be useful for uniform assessment of heart failure in patients undergoing dialysis. In addition, surveillance of these patients will allow better understanding of the temporal aspects of heart failure and ESRD. Specifically, does heart failure usually precede ESRD, is it the reverse, or is this a cardiorenal interaction?

Validation of the proposed system would start with classification of a large cohort of patients undergoing dialysis. The initial assessment would include collection and documentation of appropriate echocardiographic data. Echocardiography is recommended for all patients on dialysis within 1 to 3 months of starting RRT (5,7). In addition, patients would be queried about the presence of dyspnea pre- and post-RRT/ultrafiltration. Simple tools such as the Likert scale and visual analogue scale have been shown to be useful in the assessment of dyspnea in patients with heart failure and could be used as appropriate (26,27). Assessment of patient symptoms pre- and post-RRT is routine and considered standard of care. However, these data may not always be gathered in standard database data fields, and standardization may be required. Once the prevalence of the various stages of the new classification system is determined, follow-up to assess outcomes would be needed. Our operating hypothesis is that mortality risk would increase through each of the proposed stages. After initial longitudinal assessment, the proposed staging system might be useful for clinical trial entry and design. For example, does more frequent hemodialysis improve ADQI class function? Are outcomes for patients with advanced heart failure and ESRD improved with peritoneal dialysis versus hemodialysis? In addition, certain standard heart failure medications (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers) might be better suited for certain ADQI heart failure stages than for others. Recent data suggest that treating patients with ESRD with spironolactone may improve structural heart disease and improve survival, and the proposed classification schema should be deployed in conjunction with future studies of aldosterone blockade in patients with ESRD (28,29).

In addition to future research concerning the descriptive epidemiology and prognosis of patients on dialysis classified with this new scheme, future studies may use novel technologies such as advanced imaging and biomarkers to aid in support of the classification or in the traditional domains of testing (screening, diagnosis, prognosis, and management) (30,31).
Future Directions

Important therapies for patients with heart failure on dialysis may include more frequent hemodialysis, preference for peritoneal dialysis, or polyelectrolytes that remove sodium via the gut (32). For patients who are dyspneic even with good volume control, standard heart failure therapies may require additional adjustments. However, before treatment advances can be made, it is essential to be able to differentiate patients with fluid overload alone in the absence of structural heart disease from patients in whom fluid overload and dyspnea can be directly attributed to underlying cardiac disease.

The precise criteria that define echocardiographic evidence of structural heart disease are an important component of any proposed classification, specifically, the differentiation of heart failure with preserved ejection fraction versus volume overload alone. Both clinical entities can present with clinical and echocardiographic features of “diastolic dysfunction.” For the subset of patients in whom this distinction is required, we propose a diagnostic pathway to ascertain the correct diagnosis (Online Appendix). The distinction can be particularly important in patients undergoing dialysis due to the high prevalence of left ventricular hypertrophy. Schwartzenberg et al. (33) demonstrated that 35% of patients with heart failure with preserved ejection fraction, despite elevated left ventricular end-diastolic pressure values, experienced a drop in stroke volume with intravenous nitroprusside. This appears to be due to excessive reduction in filling pressure and thus filling volume (end-diastolic volume) due to diastolic dysfunction. Many patients on dialysis would be expected to experience something similar with volume removal during RRT.

The dynamic assessment (i.e., before and after ultrafiltration) is particularly important given that asymptomatic diastolic dysfunction is prevalent in the community and may be more prevalent in the ESRD population (34). As suggested in the Kidney Disease: Improving Global Outcomes consensus guideline, echocardiography should be performed in all incident patients on dialysis (5). Novel and known cardiac biomarkers, along with dynamic exercise testing, may be more prevalent in the ESRD population (34). As suggested in the Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80:572–579.


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Key Words: chronic kidney disease • classification • dyspnea • ESRD • fluid overload • heart failure.

APPENDIX

For a complete list of the ADQI Consensus Group members, as well as supplemental information, please see the online version of this article.