Are hemodynamic goals viable in tailoring heart failure therapy?

Hemodynamic Goals Are Relevant
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The diversity of patient profiles and responses precludes a one-size-fits-all approach to heart failure. The randomized trials have provided us with some therapies that must be tried and others that can be tried. Offering significant although small benefits averaged over a population, these therapies are bolts of fabric stacked beside a tailor’s mannequin, the typical trial subject. The sequential patching of different medications in the order of their investigation, however, is not likely to yield the best regimen for any patient. There should be little disagreement on the principle of tailoring therapies for individuals, but what measurements should be taken?

Tailored to What?
The primary goal for asymptomatic and mildly symptomatic heart failure is to prevent or delay disease progression. Once symptoms and the risk of mortality dominate, the goals are to relieve symptoms and prolong survival. It has been proposed that hemodynamic goals are not appropriate in the care of these patients with heart failure. To construct the clearest case to the contrary, this discussion will focus on patients with advanced heart failure as those in whom hemodynamic abnormalities are most apparent (although a case can also be made for contributions of early rises in intracardiac pressures, blunting of natriuretic peptide responses, fluid retention, and valvular regurgitation and disease progression). Advanced heart failure will be defined here in those patients with dilated ventricles and low ejection fraction who have persistent or recurrent symptoms limiting daily life (New York Heart Association class III and IV) despite initiation of angiotensin-converting enzyme inhibitors, \( \beta \)-blockers, and diuretics that may include spironolactone. Most patients will have had a prior hospitalization for heart failure. Therapy is currently outlined around a pattern from survival trial protocols. The regimen is then tailored further to symptoms and signs, which themselves often reflect hemodynamic changes in heart failure, although in most cases exact hemodynamic measurement is not needed to confirm a skilled clinical assessment.

The challenge is to demonstrate the viability of any hemodynamic goals, regardless of how they are assessed, for tailoring therapy. Although it has been suggested that these goals have become obsolete, the population of heart failure patients seeking symptom relief is growing, as \( \beta \)-blocker use and implantable defibrillators have decreased early unexpected death. Although initially endorsed by theory and anecdote, hemodynamic goals are now supported by accumulating evidence as even more relevant in the modern era of advanced heart failure and outpatient heart failure management.

Tailored to Survival as Shown With Trial Protocols
The major trials in heart failure used mortality with or without hospitalization as a major end point. Mortality cannot be measured during life, and therefore therapy to affect it can...
only be patterned after the trial protocol. However, application of trial protocols to an individual is immediately limited. A recent study by Masoudi et al in older patients hospitalized with heart failure showed that fewer than one third would have qualified for the landmark trials with angiotensin-converting enzyme inhibitors, β-blockers, and spironolactone. Even patients who would not have been excluded often mirror those subjects at the fringes of the trial population in terms of renal function, age, and comorbidities. Meticulous monitoring is mandated and reimbursed during trials. Although based on trial results, decisions regarding potentially life-saving therapy for an individual may be altered by patient factors and constraints of the care environment.

In practice, multiple therapies are mixed differently than in the trials. Any combination outside that tested, such as spironolactone and β-blockers, extrapolates beyond evidence, but even for “typical subjects,” most clinical decisions reside outside randomized trials. Changes in doses and concomitant medications are discouraged during mortality trials but central to actual practice. The crucial details of diuretic adjustment are not specified. How should therapies be decreased for side effects? When can they be withdrawn for lack of benefit? β-Blockers, angiotensin-converting enzyme inhibitors, and, for some patients, spironolactone are life-saving elements of therapy to be used whenever possible. Until surrogates of disease progression and survival have been validated, however, designing therapy only to delay death minimizes both partners of the therapeutic relationship.

There has been a chasm between trials and practice in terms of the importance of symptoms. Most trials have been done in mild or mild to moderate heart failure, in which the primary limitation was in the capacity to sustain moderate exercise. This limitation is a complex function of cardiac reserve and peripheral muscle responses, which has not improved appreciably with medications that offer major survival benefit.

Tailored to Congestive Symptoms

In advanced heart failure, most of the symptoms that limit routine daily life and activity result primarily from elevated filling pressures. Immediate dyspnea on light exertion such as dressing usually indicates elevated left-sided filling pressures at rest. Orthopnea implies elevated left-sided filling pressures unless proven otherwise. Abdominal discomfort or loss of appetite often reflects elevated systemic venous pressures, as does head fullness when putting on socks. Edema and anasarca are symptoms for many. Although individuals vary in their tolerance of elevated filling pressures, relief of resting congestive symptoms can be closely correlated with reduction in filling pressures (Figure 1).

Tailored to Signs as Well as Symptoms of Congestion

However, symptoms represent only the most obvious target. For many patients, symptoms are relatively insensitive to elevated filling pressures (Figure 2). After resolution of resting dyspnea and the edema that may be evident to the patient, substantial elevations in filling pressures may remain unappreciated (Figure 2). These may be asymptomatic or contribute to the complex exertional limitation to which patients become accustomed as their “baseline.” Even without peripheral edema or resting dyspnea, further volume reduction has been associated with improvement in exercise capacity. Furthermore, patients with subclinical elevation of filling pressures are considered at risk for decompensation during the critical uptitration of β-blocker therapy, during which they may be incorrectly labeled as “intolerant” of this life-saving therapy.

Figure 1. Relationship of reduction in pulmonary capillary wedge pressures (PCW) during hospitalization to improvement in symptoms (Sx) measured at 3 months after discharge, from the ESCAPE trial. Average pulmonary capillary wedge pressures decreased from 25±9 to 17±7 mm Hg during a median of 1.9 days of monitoring during hospitalization, and more than half of patients had >33% reduction in pulmonary capillary wedge pressure. SOB indicates shortness of breath. 6MW indicates 6-minute walk.

Figure 2. Potential targets for therapy related to elevated filling pressures in heart failure, demonstrating the expanding circles defined by broader criteria beyond symptoms and physical signs. Unknown are the prevalence and clinical exercise limitation of patients in whom hemodynamic abnormalities are manifest only during exercise. Relative radii of the levels are for illustration only.
The jugular venous pressure is the most important component of this assessment. The prognostic value of jugular venous pressure elevation has been shown in outpatient heart failure. The ability of expert clinicians to estimate right atrial pressures from examination of the neck veins was reasonable but not perfect in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial. Right atrial pressures >10 mm Hg have been shown to track with pulmonary wedge pressures >22 mm Hg in ~80% of patients with chronic heart failure, although the prevalence of worsening right heart failure may be increasing with longer heart failure survival. Other qualitative indices that may be useful to expert examiners to reveal abnormally elevated filling pressures are the abdominal-jugular reflex, the Valsalva maneuver, and prominent radiation of the pulmonic component of the second sound.

A firm basis of expert consensus maintains that patients should be treated according to clinical signs of elevated filling pressures even in the absence of specific attributable symptoms. There will be no randomized trial of this theorem, as those caring for the relevant patient populations are convinced past a position of equipoise. Serial clinical assessment of fluid status is a level I recommendation of the American College of Cardiology/American Heart Association Guidelines for Chronic Heart Failure, and meticulous attention to fluid balance is the first recommendation for patients with late-stage disease. Assessment and treatment of fluid overload are primarily directed toward the hemodynamic parameters of elevated right- and left-sided filling pressures, for which confirmation by invasive measurement is rarely necessary in the outpatient setting.

Hospitalization for Heart Failure
Hospitalization is a common end point of clinical trials because of both intrinsic morbidity and association with mortality. More than 80% of hospitalizations for heart failure are characterized predominantly by symptoms associated with elevated left- or right-sided filling pressures, as shown in a large national registry. When these cannot be relieved by outpatient adjustment of medications, an efficient hospitalization allows diuresis to be escalated rapidly as blood pressure, electrolytes, and renal function are monitored. If needed, intravenous medications can be added to potentiate diuresis, and mechanical fluid removal has also been used effectively to remove fluid and relieve symptoms, even without other intervention. In the recent ESCAPE trial, therapy directed specifically toward clinical goals of reducing jugular venous pressure to <8 cm and eliminating peripheral edema led to an average 3.2 L of diuresis and major symptomatic improvement (Table 1 and Table 2). The majority of patients will respond well to adjustment of the aforementioned therapy, with the symptoms and signs of congestion used as surrogates for measured filling pressures, while adequate blood pressure and renal function are maintained.

### TABLE 1. Goals for Therapy During Heart Failure Hospitalization

<table>
<thead>
<tr>
<th>Clinical Assessment</th>
<th>All Patients</th>
<th>Monitored Hemodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of orthopnea</td>
<td>JVP &lt; 8 cm</td>
<td>PCW &lt; 16 mm Hg</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>Right atrial pressure</td>
<td>&lt; 8 mm Hg</td>
</tr>
<tr>
<td>Resolution of edema/ascites</td>
<td>Resolution of edema/ascites</td>
<td>(further diuresis to empty volume reservoir even if filling pressures at target)</td>
</tr>
<tr>
<td>Stable SBP usually</td>
<td>Stable SBP usually</td>
<td>≥ 80 mm Hg</td>
</tr>
<tr>
<td>Stable creatinine/BUN</td>
<td>Walking in hall without dyspnea or dizziness</td>
<td></td>
</tr>
</tbody>
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PCW indicates pulmonary capillary wedge pressure; JVP, jugular venous pressure; SBP, systolic blood pressure; and BUN, blood urea nitrogen.

### Why Do We Measure Hemodynamics?

**To Diagnose Hemodynamic Status**

For those uncommon patients in whom the initial hemodynamic profile is unclear or early responses are not as anticipated, hemodynamic measurement may be useful (Table 3). The most common unexpected information that changes the direction of therapy is the relative dominance of right over left ventricular dysfunction, intrinsic pulmonary hypertension, unappreciated very low or high systemic vascular resistance, or the contribution of heart failure to compromise from other conditions such as pulmonary disease or active ischemia.

**To Triage Patients in Acute Cardiogenic Shock**

Invasive hemodynamic measurement is routine during initial evaluation and management of life-threatening circulatory compromise. There is unlikely to be randomized data in this setting to demonstrate the utility of hemodynamic information, which will guide inotropic and pressor support while mechanical support or other surgery is considered.

**To Tailor Therapy During Decompensation of Chronic Heart Failure**

**Evaluation for Transplantation**

The strategy of optimizing loading conditions with intravenous agents with transition to oral vasodilators and diuretics was described by Kovick et al in 1976 and Pierpont et al in 1978. This approach was followed systematically in patients evaluated for transplantation, for whom effective reduction of left-sided filling pressures is key both to relieve disabling congestive symptoms and to demonstrate reversibility of pulmonary hypertension.

**Hemodynamic Goals of Tailored Therapy: How Dry**

For transplant evaluation, acceptable pulmonary vascular resistance for transplantation is usually achievable at pulmo-
nary capillary wedge pressures $\approx$20 mm Hg and slightly higher. However, serendipitous observation of the feasibility of further reduction led to systematic study of the impact of reducing filling pressures closer to normal levels.

It was thought at one time that a compromise needed to be made in chronic heart failure treatment between allowing symptomatic volume overload and maintaining filling pressures adequate for maintain cardiac output. It was demonstrated by Franciosa et al.21 and subsequently, however, that filling pressures can be reduced to near-normal levels ($\leq$16 mm) while maintaining or even improving stroke filling pressures can be reduced to near-normal levels (5) Optimization of diuretics and vasodilators to facilitate weaning from intravenous inotropic agents in patients with apparent dependence.

Redesign of therapy to filling pressure goals for patients with recurrent volume during decompensation.24–26 The regurgitant fraction is frequently reduced to only 25% of total stroke volume after effective therapy to reduce filling pressures because of a decrease in the effective regurgitant orifice.26

Reduction of filling pressures thus improves ventricular function while relieving congestive symptoms. Although marked variation exists in the relationship between filling pressures and symptoms, careful monitoring has confirmed the long-held clinical observation that improvement in resting symptoms is linked to reduction in filling pressures, as confirmed recently for symptomatic improvement at 3 months after hospital discharge (Figure 1). Because symptoms of congestion are usually absent at filling pressures still above normal, compromise is rarely necessary between symptomatic relief and adequate perfusion.

Compromise is sometimes necessary, however, between renal function and filling pressures in the cardiorenal compromise in which renal function worsens during diuresis despite persistence of excess filling pressures.27,28 A key observation, made in heart failure with both low and preserved ejection fraction, has been that worsening renal function is not primarily attributable to a fall in cardiac output. As this is increasingly recognized, the direct neural and hormonal factors contributing to this syndrome can be elucidated and more directly addressed with interventions focused on the kidney.

Decreased catecholamine levels and endothelin levels and increased exercise-induced blood flow were also demonstrated during aggressive reduction of filling pressures.29–31 For some transplant candidates, this strategy led to improvement in exercise capacity such that some left the waiting list.32 Sustained benefits in hemodynamics,33 echo parameters related to intracardiac filling pressures,34 and reduction in hospitalizations35 were evident both in transplant candidates.
and in the broader population of patients ineligible for transplantation. Because randomized trials were not performed in these early experiences, it was not possible to determine whether actual hemodynamic measurement resulted in more clinical improvement than therapy adjusted to the hemodynamic surrogates from clinical assessment.

**Current Hemodynamic Goals for Chronic Heart Failure Do Not Include Cardiac Output**

Previous efforts adjusted directly to increase cardiac output have failed to improve and appeared to worsen outcomes. Instead, the goal of tailored therapy has been to reduce filling pressures to pulmonary wedge pressure of ≤16 mm Hg and right atrial pressure ≤8 mm Hg (Table 1). Systemic vascular resistance has been a target of therapy only as necessary to reduce the filling pressures, with a goal being 1100 to 1200 in average-size individuals in whom the wedge pressure is still high. (If the filling pressures are not high, aggressive reduction of systemic vascular resistance often leads to symptomatic hypotension.) During the evolution of tailored therapy, systemic vascular resistance was frequently severely elevated, requiring high doses of combination vasodilators. More recent decompensated populations show less vasoconstriction, perhaps because of earlier renin-angiotensin system inhibition, and thus less need for monitored adjustment of vasodilator therapy.

Previous studies of tailored therapy and the recent ESCAPE trial confirm that cardiac output improves as filling pressures are reduced. The potential mechanisms described above may, however, have different impact than cardiac output increased by inotropic stimulation, which has consistently been associated with worse outcomes in previous experiences and in the ESCAPE population. The recent ESCAPE trial also confirms numerous previous studies regarding the prognostic importance of filling pressures, whereas cardiac output and index did not predict death or rehospitalization. It remains possible that new agents will be found to stimulate cardiac output with beneficial impact on outcomes. However, with the therapies currently available, the hemodynamic target remains reduction of intracardiac filling pressures.

**Tailoring to Clinical Assessment Versus Monitored Hemodynamics**

The ESCAPE trial compared therapy guided by clinical assessment of symptoms and signs with therapy guided by clinical assessment and invasive hemodynamic monitoring (Table 1) in patients with recurrent heart failure hospitalization, left ventricular ejection fraction ≤30%, systolic blood pressure ≤125 mm Hg, and 1 symptom and 1 sign of elevated filling pressures. All hemodynamic parameters had improved when the pulmonary artery catheter (PAC) was removed (median 1.9 days). Major clinical improvement occurred in both patient groups (Table 2). The PAC was implicated directly in adverse events in 4% of patients, and 22% had infections, compared with 11% without PAC.

Although there was a strong trend for benefit of hemodynamic monitoring in the higher-volume centers, PAC had no effect on in-hospital mortality or the end point of days alive out of hospital over the next 6 months. This result is consistent with a meta-analysis of 12 randomized trials of PAC in multiple settings, with an overall hazard ratio of 1.0.37 Patients whose therapy was adjusted with PAC had a trend for greater diuresis initially but significantly less deterioration in renal function and lower discharge diuretic doses. There was a consistent trend for better functional capacity and quality of life (Figure 3), with greater improvement in patients with greater reduction in filling pressures (Figure 1). At every time point after discharge, patients whose therapy was adjusted with the PAC preferred significantly more time alive than patients whose therapy was adjusted by clinical assessment alone.

Because neither deaths nor hospitalizations nor the primary end point of days alive out of the hospital during the next 6 months was neutral. There was a trend for benefit in the secondary functional end points, which was significant for all time points measured (1, 3, and 6 months) for the time tradeoff utility instrument, which determined how many months of 24 patients were willing to trade to spend the remaining time in better health. MLHF indicates Minnesota Living With Heart Failure score.

**Risk After Hospitalization**

Achievement of optimal volume status before discharge, identification of a stable oral regimen, and β-blocker therapy...
help to reduce rehospitalization, which occurs in up to 50% of patients. Education in the hospital focuses on daily weights and salt and fluid restriction and is reinforced during scheduled telephone contact from a dedicated heart failure management team, which is proven to decrease hospitalizations. During heart failure management after hospital discharge, most of the interventions within the first 3 months relate to change in diuretic doses based on inferences about filling pressures.

**Filling Pressures and Outcomes After Discharge**

Filling pressures and parameters related to them, such as jugular venous pressure, mitral and tricuspid regurgitation, and natriuretic peptide levels, are robustly linked to survival. Clinical class IV, characterized by symptoms from elevated filling pressures, is consistently associated with worse prognosis, as is persistent evidence of congestion at 1 month after discharge. Outcome after evaluation for transplantation is predicted by filling pressures, which are more predictive after therapy tailored to reduce wedge pressure toward a goal of 15 to 16 mm Hg. Among 2 groups with initial average wedge pressure of 30 mm Hg, those in whom it could be reduced to \( \leq 16 \) mm Hg had half the mortality of those in whom it could not. With hemodynamic monitoring during hospitalization in ESCAPE, lower pulmonary capillary wedge pressures achieved during therapy independently predicted lower 6-month event rates.

For any parameter used to guide heart failure therapy, it is difficult to determine whether treatment of that parameter itself improves outcomes or merely identifies a population whose responsivity predicts better outcomes, whether or not the parameter itself is actually treated. It has not been possible previously to determine the degree to which assessment and successful reduction of filling pressures create survivors or merely identify them. The recent completion of the randomized controlled single-blind Chronicle Offers Management to Patients With Advanced Signs and Symptoms of Heart Failure (COMPASS) trial of ambulatory monitoring of filling pressures provides some validation of treatment of elevated filling pressures in the outpatient setting. Right ventricular pressures and estimated pulmonary artery diastolic pressures were tracked via an implantable hemodynamic monitor and transmitted regularly from home to a central Web site, but they were available to the physician for only half of the patients. For patients without resting symptoms at randomization, regular review of the hemodynamic information led to an increased rate of diuretic adjustment and decreased hospitalization for heart failure.

**Can We Tailor to Newer Estimates of Filling Pressures?**

Multiple modalities have been introduced to estimate hemodynamic parameters without invasive measurement. Natriuretic peptides, related with wide interindividual variability to ventricular filling pressures, have been helpful in urgent care settings to suggest cardiac etiology of dyspnea and to identify patients at high or low risk for early adverse outcome. Several noninvasive techniques, including external and internal bioimpedance measurement and Doppler echocardiography, have generated estimates that correlate significantly with filling pressures and/or cardiac output across a specific population. Such techniques have lacked sufficient accuracy to guide therapies on the basis of serial changes.

**Tailoring to the Future**

The viability of hemodynamic goals remains apparent from the dominance of symptoms and therapies related to elevated filling pressures during hospitalization. The relevance of hemodynamic goals to life outside the hospital is actually increasing as fewer patients die suddenly and more survive to develop crippling symptoms of congestion. (A closely related goal about which little is known is the preservation of adequate renal function.) The hemodynamic goals of filling pressures thus dominate recurrent interventions and care for the patients with advanced disease. Neurohormonal antagonist therapy is crucial to maximize longer-term outcomes but is sometimes limited by the hemodynamic constraints of hypotension and renal perfusion. As the population ages, there will be an increasing proportion with preserved ejection fraction, for which the hemodynamic goal of optimal filling pressures is clearly key to reducing symptoms and hospitalization.

We are working now with primitive tools for tailoring. As we delineate the neurohormonal and cardiovascular adaptations that are beneficial and deleterious and validate measurable factors as targets or surrogates, it should be possible to select and dose therapies more precisely for an individual patient, before and beyond the hemodynamic goals for late-stage disease. New trial designs will be necessary to establish these tailoring strategies. At a more fundamental level, some genotypes have already been identified that appear sufficiently influential to guide treatment, particularly in the early stages of disease when the phenotype is not distinct. There will likely evolve a dynamic tension between therapy tailored to the static genetic profile and therapy tailored to changing protein expression and the integrated clinical profile.

**Tailoring to Patient Preferences**

Although the prognosis continues to improve, heart failure remains a progressive disease for many. Patient preferences increasingly come into play as they shift toward improved quality over length of life in severe disease. Although multiple physiological and psychosocial inputs contribute, there is a strong association between evidence of elevated filling pressures and patient focus away from survival, with those patients with jugular venous pressure estimated at >12 cm being willing to trade on average half of their remaining...
survival time to feel better, compared with 10% for patients with normal jugular venous pressure.42 A shift in the ratio of efforts toward palliation over prolongation of remaining life during late-stage disease includes reevaluation of therapy and its goals.

The dynamic aspect of heart failure applies not only to the circulation but also to integration of the individual life within its boundaries. In earlier times, craftsmen were more abundant than materials, and the tailors practiced their art at multiple stages during the life of a garment. As they did, however, we anticipate redesign of our therapies, beyond the current fashion, to the changing dimensions that will be measured and the changing occasions that mark a longer survival with heart failure.

References
Tailored Therapy for Heart Failure

Thierry H. Le Jemtel, MD; Eckhard U. Alt, MD

In the present era of evidence-based medicine, the usefulness of a therapeutic intervention is evaluated by the assessment of the mean effect in a selected cohort of patients. Evidence-based medicine may ascertain that a majority of patients derive some benefit from an intervention, but it cannot distinguish patients who truly benefit from those patients who either do not benefit or are harmed by the intervention. In contrast, a therapeutic scheme that consists of tailoring a pharmacological intervention to a patient’s individual response seems particularly attractive. This individualized therapy focuses on a single patient and his/her response to a given intervention to guide management. No one, even the most egalitarian mind, would argue against tailoring therapy to a patient’s individual characteristics and immediate response to medications when the immediate response accurately predicts long-term outcome.

Thus, the aim of the present review is not to dispute the sound principle of tailoring medical therapy to a patient’s individual response. Tailored therapy emphasizes an individual approach to treatment that is clearly worth pursuing. As presently recommended in patients with chronic heart failure (CHF), however, tailored therapy strongly emphasizes the need for invasive hemodynamic monitoring to guide therapy. The present article will outline the fallacy and futility of using acute hemodynamic monitoring, especially left ventricular (LV) filling pressure, to tailor medical therapy in patients with advanced CHF. The tenet of tailored therapy in CHF and its place in clinical practice will be reviewed first. LV filling pressure as a surrogate and a prognostic end point will then be discussed. Finally, the outcome of tailored therapy and its present evolution will be considered.

What Is Tailored Therapy?

Tailored therapy was originally reported as a therapeutic strategy for the management of patients hospitalized with advanced CHF. This approach involves right heart catheterization and subsequent administration of intravenous vasodilators to reduce pulmonary capillary wedge pressure to ≤15 mm Hg and to reduce systemic vascular resistance to ≤1200 dynes · s · cm⁻⁵ while maintaining systolic blood pressure ≥80 mm Hg. Nitroprusside or nitroglycerin has been described as the preferred vasodilator to lower LV filling pressure and systemic vascular resistance. The rate of administration of nitroprusside or nitroglycerin is adjusted to attain the hemodynamic goals within 24 to 48 hours of admission; most patients require a concomitant fluid negative balance of 3 to 4 L achieved with diuresis. In their earliest publications, the University of California at Los Angeles (UCLA) group did not initiate oral vasodilators or angiotensin-converting enzyme (ACE) inhibitors during the first 48 hours of hemodynamic monitoring, when fluid overload was the greatest. Treatment with oral vasodilators is only initiated once hemodynamic goals have been achieved. Intravenous nitroprusside or nitroglycerin is then weaned and discontinued. The floating pulmonary arterial catheter is removed when the oral vasodilator regimen has been demon-
strated to be effective for 24 hours. Patients ambulate for an additional 24 to 48 hours, under close supervision, before discharge.

Using this protocol, the UCLA experience was noteworthy. Ninety percent of patients who received tailored therapy were able to be discharged from the hospital on an oral regimen of vasodilators, diuretics, and, in most cases, digoxin. Less than 10% of patients required continued hospitalization. In contrast to the substantial risk of clinical deterioration recently noted in the months that follow hospitalization for CHF, the UCLA investigators reported that only 9% of patients discharged with a LV ejection fraction (EF) ≤ 20% deteriorated over the following 6 months after the hospitalization for tailored therapy. Moreover, only 5% of the patients who were stable at 1 month after having received tailored therapy deteriorated over the following 6 months after the hospitalization for tailored therapy.

What Happened to Tailored Therapy?
Tailored therapy has not gained wide acceptance in the practicing community, but in the absence of definite data, one can only speculate on the lukewarm attitude of clinical cardiologists toward this approach. Increasing awareness of publications reporting that pulmonary artery catheterization (PAC) is an expensive procedure that does not benefit critically ill patients is likely to have played a role. In addition, the need for tailored therapy may not have been readily apparent because patients with advanced CHF are mandated treatment with the same medications, eg, ACE inhibitors and other oral vasodilators, whether or not they underwent hemodynamic monitoring. Tailored therapy received more attention from the National Heart, Lung, and Blood Institute, however, which sponsored a randomized clinical trial entitled Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE). The findings of the ESCAPE trial have, until now, only been presented in abstract form. The ESCAPE trial did not provide supportive evidence that hemodynamic data collected by PAC are of any benefit in guiding therapy in patients with advanced CHF. The 30-day and 6-month mortality rates were similar, and there were no differences in complications, adverse events, or clinical outcomes among the 433 patients with advanced CHF who were randomized to PAC-directed therapy or clinical management without PAC.

Thus, the practicing community has not embraced tailored therapy as a fruitful approach to the management of patients with advanced CHF. In addition, the ESCAPE investigators could not demonstrate the benefit of PAC to guide therapy in the framework of a randomized trial. We are forced to conclude, therefore, that with these 2 groups tailored therapy for CHF is not an appropriate standard of care. The remaining outstanding issue is to understand why a therapeutic approach that was theoretically very attractive failed so soundly in practice.

Tailored therapy was based on 2 major assumptions. The first assumption was that the rise in LV filling pressure is the primary hemodynamic abnormality in patients with advanced CHF. A rational corollary of this first assumption was that reduction of LV filling pressure is the primary therapeutic target in patients with advanced CHF. The second assumption was that reducing LV filling pressure to ≤ 15 mm Hg within 48 hours of admission is of paramount importance for the long-term clinical outcome of patients with advanced CHF. Both assumptions evolved at a time when the syndrome of CHF was viewed as a hemodynamic entity. The hemodynamic paradigm of CHF did not survive the test of time, and neither did the aforementioned assumptions. The lack of relationship between acute hemodynamic effects and long-term clinical response was first appreciated during prolonged administration of ACE inhibitors. The dissociation between improvement in LV performance and functional capacity was subsequently confirmed with other therapeutic interventions in patients with CHF due to LV systolic dysfunction. Let us explore further each of these failed hypotheses.

LV Filling Pressure as a Primary Therapeutic Target
The primary goal of tailored therapy was to reduce LV filling pressure to ≤ 15 mm Hg as rapidly as possible. The original investigators demonstrated that near-normal LV filling pressures could be achieved in patients with advanced CHF without compromising the cardiac output. To the contrary, with time, stroke volume and thereby cardiac output increased after 24 to 48 hours of intravenous vasodilator therapy. In contrast to patients with LV diastolic dysfunction (normal LVEF), in whom the rise in LV filling pressure is directly related to the primary hemodynamic abnormality, the rise in LV filling pressure in patients with LV systolic dysfunction (low LVEF) is not directly related to the primary hemodynamic abnormality. The rise in LV filling pressure in patients with advanced CHF and low LVEF is primarily due to a reduction in cardiac output. Reduction in cardiac output and the resulting decreased fullness of the arterial circulation stimulates the renin-angiotensin-aldosterone and sympathetic nervous systems, as well as nonsmotic vasopressin release. In turn, renal and water excretions diminish, promoting fluid retention and increasing intravascular volume. With time, increased intravascular volume results in LV enlargement, which tends to reduce LV compliance, thereby contributing to further increase in LV filling pressure. Thus, the rise in LV filling pressure reflects the severity of volume overload in patients with advanced CHF and low LVEF but is neither the initial pathophysiologic event nor the primary hemodynamic abnormality. It is the fall in cardiac output that is primarily responsible for the rise in LV filling pressure in these patients.

Accordingly, the main therapeutic aim in patients with pulmonary and systemic congestion associated with LV systolic dysfunction is to restore a normal cardiac output and renal perfusion. Pharmacological interventions such as β-adrenergic blockade that, with time, reverse LV remodel-
ing and normalize LV systolic function have a far greater impact on clinical outcome than interventions that acutely improve LV systolic function by manipulating the loading conditions of the failing heart. Acute manipulation of cardiac loading conditions may immediately improve forward cardiac output by reducing the amount of functional mitral regurgitation that frequently accompanies marked LV dilatation. However, acutely manipulating the loading conditions of the failing heart, as done with tailored therapy, exerts only transient benefits. Lasting clinical improvement requires reversal of the LV remodeling process and return of the cardiac output and renal perfusion to near-normal values to prevent relapse of fluid retention and subsequent clinical deterioration. Thus, durable improvement in cardiac output and renal perfusion, rather than reduction in ventricular filling pressures (by pooling excess intravascular volume in splanchnic beds with venodilators), are the main therapeutic goal in patients with CHF due to LV systolic dysfunction. Similarly, at a very advanced stage of the syndrome of CHF and low LVEF, only interventions that restore a normal cardiac output such as cardiac transplantation or LV assist device implantation have been shown to improve long-term clinical outcome. In summary, the selection of LV filling pressure as the surrogate end point of tailored therapy focuses on an accompanying manifestation of clinical deterioration rather than on the cause of deterioration.

LV Filling Pressure as a Prognostic Index

The rationale advanced by the original investigators for targeting a reduction in LV filling pressure as the primary end point of tailored therapy was that the absolute change in LV filling pressure was a potent predictor of clinical outcome in hospitalized patients with advanced CHF. However, a better understanding of the reasons why patients with CHF decompensate will elucidate why the reduction in LV filling pressure is fully expected to correlate with a favorable clinical outcome in these patients. Nonadherence to medications and diet is a frequent precipitator of clinical deterioration and hospitalization in patients with CHF. Patients hospitalized for nonadherence to medications and diet with elevated LV filling pressures are likely to experience marked reduction in these pressures with resumption of medications and discontinuation of excessive sodium intake. On the contrary, patients with CHF who are hospitalized for nonadherence to medications and diet and presenting with elevated LV filling pressures are likely to experience marked reduction in these pressures with resumption of medications and discontinuation of excessive sodium intake. Thus, the emphasis on the predictive value of a change in LV filling pressure in response to therapy is somewhat of a self-fulfilling prophecy (ie, LV filling pressures decrease in patients destined to improve after resumption of medications after a period of outpatient nonadherence, whereas LV pressures remain unaltered in patients who have deteriorated while adherent to their medical regimen). The predictive value of a reduction of LV filling pressure in patients with advanced CHF led the original investigators to choose a reduction in LV filling pressure as the main target of tailored therapy. However, a different conclusion could have been reached if the investigators had not ignored the role of the events that led to clinical deterioration in these patients. These events are to a large extent indirectly responsible for the excellent predictive value of the changes in LV filling pressure. In other words, the emphasis on reducing LV filling pressure can be viewed as the result of biased analysis of outcome data. The initial publications did not establish a cause-and-effect relationship between fall in LV filling pressure and favorable prognosis in patients with advanced CHF.

The predictive value of a reduction in LV filling pressure may also be explained in part by the difficulties encountered in accurately measuring other hemodynamic parameters, especially cardiac output. In patients hospitalized for advanced CHF, LV filling pressure can be measured accurately. Moreover, the range of abnormal LV filling pressure is wide, from 15 to 40 mm Hg. The magnitude of the potential response to therapy is also broad. In contrast, the range of cardiac index is slim in patients hospitalized with advanced CHF. The cardiac index ranges from 1.6 to 2.3 L/min per meter. Furthermore, the cardiac index is notoriously difficult to measure accurately by thermodilution technique because of recirculation, respiratory-induced temperature changes, injection technique, and sampling errors. The error range is commonly estimated at 15% to 20%. Taking into consideration the narrow range of cardiac index in patients with advanced CHF and the inaccuracy of the measurement, one expects, from a statistical standpoint, changes in LV filling pressure to have a better predictive value than changes in cardiac output. The superior predictive value of LV filling pressure over cardiac index should not obscure the physiological importance of the reduction in cardiac output as the primary initiator for the rise in LV filling pressure.

Hemodynamic Profiling

A consequence of the tailored therapy concept is the heavy reliance on the hemodynamic profile of patients to guide therapy when they are hospitalized with advanced CHF. The management of patients with advanced CHF has focused on the detection and treatment of elevated LV filling pressure. Depending on the presence or absence of elevated filling pressure (wet or dry) and adequate or limited organ perfusion (warm or cold), patients are classified in 1 of the following 4 hemodynamic profiles: warm/dry, warm/wet, cold/dry, and cold/wet. This estimated hemodynamic profile is used to guide therapy. Notwithstanding how inadequate physical findings are for the detection of volume overload, one questions the importance of defining a precise hemodynamic profile to guide therapeutic interventions when clinical deterioration is severe enough to require hospitalization. Once intravascular depletion due to excessive diuresis is
persistent primary mechanism responsible for progressive deterioration evidence of cardiac myocyte loss that is presumably the in myocardial contractility or further impairment in LV performance. However, hemodynamic data collected during the transition from a decompensated state to a compensated (pre) state. Mean values are depicted by bold horizontal lines.

eliminated, systolic blood pressure dictates the therapeutic intervention: Vasodilator agents are preferred in patients with a systolic blood pressure ≥85 mm Hg, and careful positive inotropic therapy is reserved for patients with systolic blood pressure <85 mm Hg. Clarification of the events that lead to clinical deterioration is likely to be a more valuable guide to therapy than sorting out the precise hemodynamic profile. Patients who deteriorate because of nonadherence to medical regimen and diet will rapidly improve after intravenous and then oral administration of loop diuretics and resumption of other medications. Patients who deteriorate because of a specific comorbid condition require rapid recognition and treatment of the comorbid condition and adjustment of the heart failure medications depending on the nature of the comorbid condition.

Surprisingly, although hospitalizations for CHF represent 80% of the economic burden of heart failure, the events that trigger clinical deterioration are still poorly understood in 50% of patients hospitalized for CHF. One intuitively attributes clinical deterioration to a reduction in cardiac performance. However, hemodynamic data collected during the transition from a decompensated state to a compensated one in 8 patients with decompensated CHF do not support that hospitalizations were prompted by a transient reduction in myocardial contractility or further impairment in LV relaxation (Figure 1). Elevation of cardiac troponins provides evidence of cardiac myocyte loss that is presumably the primary mechanism responsible for progressive deterioration of LV systolic function in patients with CHF. Persistent elevation of cardiac troponins clearly identifies a subset of patients with CHF at risk for progressive LV dysfunction and death. Transient elevation of cardiac troponins occurs in patients with stable CHF and after strenuous exercise. In brief, elevation of troponins points to ongoing deterioration of LV systolic function in patients with CHF but does not seem to be responsible for abrupt clinical deterioration in these patients. Preliminary data suggest that clinical deterioration may be related in some patients to vascular endothelial activation resulting in diffuse vasodilatation at the expense of the essential organs. In summary, developing a precise understanding of the mechanisms that trigger clinical deterioration in patients with CHF is likely to yield a valuable approach to the management of advanced CHF. This approach may allow the clinician to select an intervention among existing therapies and devise new therapeutic interventions for the management and prevention of acute deterioration.

Current Trends in Tailored Therapy
Plasma brain natriuretic peptide (BNP) levels closely correlate with LV filling pressure in patients with advanced CHF. Thus, plasma BNP level–based tailored therapy is a logical alternative to LV filling pressure–based tailored therapy. The results of plasma BNP level–based tailored therapy were mixed in 2 randomized trials. The first trial involved 12 patients with a 12-week follow-up. The clinical outcome of the 6 patients randomized to plasma BNP level–guided therapy did not differ from that of the 6 patients randomized to conventional monitoring of therapy. The second study involved 69 patients and 6 months of follow-up. Patients who were randomized to BNP-guided therapy experienced significantly fewer cardiovascular events than did conventionally treated patients. In a randomized pilot study, we evaluated the effects of doubling the maximally recommended doses of ACE inhibitors in 36 patients with CHF who were selected for the stability of their symptoms. The end point of this pilot trial was the change in plasma BNP level over a period of 4 weeks. Although mean plasma BNP levels remained unchanged in the 19 patients who, randomized to maintenance of maximally recommended doses of ACE inhibitors, were remarkably stable over the 4-week period of the study, individual changes in plasma BNP level varied greatly (Figure 2). An equal number of patients experienced a decrease and an increase in plasma BNP levels. The magnitude of the individual increase and decrease in plasma BNP levels was remarkably similar. The spontaneous fluctuation of plasma BNP levels in patients selected for their clinical stability argues against using plasma BNP levels to guide therapy in ambulatory patients with CHF. There are presently not enough data to support measuring serial plasma BNP levels in patients with stable CHF. Several ongoing trials are addressing the value of BNP testing for outpatient CHF therapy. Their results will have a large impact on the future of BNP level–based tailored therapy.

Pharmacogenetics and pharmacogenomics are promising approaches to tease out the well-documented variability in drug response from patient to patient. Genetic polymorphisms can influence drug response by modulating drug absorption, distribution, or metabolism and drug target interaction. Most genetic polymorphisms in the human genome
occur at single nucleotide sites. These polymorphisms are designated single-nucleotide polymorphisms. They are encountered every 1000 base pairs, and their total number is currently evaluated at >3 million.51,52 This extreme prevalence makes it unlikely that an isolated single-nucleotide polymorphism can account for the variability in drug response from patients. Other genetic polymorphisms involve insertion/deletion or rearrangement of larger segments of DNA. Although the insertion/deletion polymorphism in the ACE gene was reported 15 years ago, its precise role in the pathogenesis of cardiovascular diseases and the response to therapies remains unresolved.53 Whether polymorphisms involving genes encoding for G proteins will better account for the variable response to antihypertensive medications is currently being investigated.54 The identification of genes that modulate response to cardiovascular therapies requires collecting a large DNA database in carefully conducted therapeutic trials with rigorous monitoring of the pharmacological intervention under investigation.

In conclusion, tailored therapy directed by hemodynamic goals is no longer an appropriate standard of care in patients with CHF. Hemodynamic-directed therapy was designed at a time when CHF was viewed as a hemodynamic disorder. Both the hemodynamic paradigm of CHF and hemodynamic-directed therapy did not survive the test of time. The complexity of the syndrome of CHF is now better appreciated with its neurohormonal and inflammatory components as well as the intricate interaction between the failing heart and the periphery.

References


Response to Le Jemtel and Alt

Lynne Warner Stevenson, MD

The differing position on the viability of hemodynamic goals is thoughtful and illuminating, reflecting the depth of clinical experience and contributions of its authors. As in most debates, there is a central arena of agreement, which I am persuaded by their arguments to broaden. We agree that the most profound and lasting impact is made by early therapy to counteract adverse neurohormonal responses, which remain the first and central target of intervention.

Once the disease has squeezed through our neurohormonal cordon, however, to symptoms that limit daily life, high filling pressures present the dominant target for relief. Fluid retention often develops without evident hypoperfusion, particularly in the elderly hypertensive patient. It is conceded that better ability to measure cardiac output might reveal its relevance, but only if there were better therapies to increase it without tachyarrhythmias or troponin leak.

There is complete agreement that short-term does not easily translate into long-term hemodynamic benefit. As indicated, noncompliance often precipitates early rehospitalization with fluid retention, again treated to lower filling pressures. The indwelling hemodynamic monitor study provides new evidence of the prevalence of rising pressures before hospitalization.

There is complete agreement that better techniques are needed for acute and chronic monitoring. Genotypic and proteomic information may increasingly guide individualization of therapy but will likely be more relevant during early progression than for crippling congestive symptoms. Congestion requires relief, as the responding authors and the strong legacy of fellows they have trained demonstrate daily their own commitment to compassionate care for heart failure.

Response to Stevenson

Thierry H. Le Jemtel, MD; Eckhard U. Alt, MD

In her present update on tailored therapy, Dr Stevenson is restricting the use of pulmonary artery catheterization (PAC) to a subset of patients with advanced heart failure (AHF). Physicians experienced in AHF will wholeheartedly agree with Dr Stevenson on the usefulness of PAC in selected patients. Demonstration of the usefulness of PAC is challenging in a randomized trial. Patients who need PAC to guide therapy are bound to miss enrollment, and patients with marginal need for PAC are bound to be enrolled. A controversial issue remains Dr Stevenson’s emphasis on left ventricular filling pressure (LVFP) as a therapeutic target and prognostic index in AHF. Elevated LVFP is not the primary hemodynamic abnormality when AHF is due to LV systolic dysfunction. A fall in cardiac output promotes fluid retention that results in elevated LVFP. Targeting LVFP as the key goal of therapy in AHF due to systolic dysfunction is akin to targeting temperature as the key goal of therapy in pneumonia. The prognostic value of a reduction in LVFP in AHF is driven by patients with high LVFP due to nonadherence to medications and diet. With resumption of medications, LVFP rapidly decreases. These patients have a good prognosis as long as they are adhering to their medical regimen. Meticulous follow-up, consideration of the events that led to deterioration, and adherence to medications are more valuable approaches than hemodynamic profiling for improving the prognosis of patients with AHF. Hemodynamic goals are groundless and gone. The future of tailored therapy may be in pharmacogenomics.
Hemodynamic Goals Are Relevant
Lynne Warner Stevenson

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