

## CASE REPORT

## Use of Noninvasive Hemodynamics to Aid Decision Making in the Initiation and Titration of Neurohormonal Agents

*Angiotensin-converting enzyme inhibitors,  $\beta$  adrenergic blockers, and nesiritide are pharmacologic agents for heart failure with both short- and long-term neurohormonal and hemodynamic effects. Angiotensin-converting enzyme inhibitors and  $\beta$  adrenergic blockers reduce morbidity and mortality in chronic heart failure. Higher doses may result in better outcomes than lower doses, but concern about hemodynamic tolerance is a major barrier to the initiation and up-titration of these agents. Nesiritide is a newer neurohormonal agent with proven efficacy and safety for use in decompensated heart failure, but appropriate patient selection has been challenging for clinicians. Like vasodilators, nesiritide may be underutilized in heart failure treatment. Impedance cardiography is a newer, noninvasive monitoring technology that can accurately measure hemodynamic parameters. Impedance cardiography is being used with increasing frequency by clinicians to guide therapy in patients with heart failure and has been proposed in heart failure treatment algorithms. Three case reports are presented to illustrate how hemodynamic data using impedance cardiography can be utilized in the initiation and titration of neurohormonal agents. (CHF. 2004;10(2 suppl 2):28–31) ©2004 CHF, Inc.*

**H**ear failure (HF) is characterized by both hemodynamic and neurohormonal abnormalities and manifests with symptoms such as peripheral edema, shortness of breath, fatigue, and weight gain. The progression of HF results from the activation of multiple neurohormonal regulatory processes, including an increase in sympathetic nervous system activity and activation of the renin-angiotensin-aldosterone system, endothelins, and natriuretic peptides.<sup>1</sup> Angiotensin-converting enzyme (ACE) inhibitors,  $\beta$  adrenergic blockers, and nesiritide are pharmacologic agents for HF which have both short- and long-term neurohormonal and hemodynamic effects.

Hemodynamic factors can play prominently in clinical decision making, and knowledge of hemodynamics may be illuminating during initiation and up-titration of various HF medications. The concept of hemodynamic goal-directed therapy for HF has been shown to

improve outcomes,<sup>2</sup> and may be analogous to the use of hemodynamics and oxygen delivery in septic shock, where goal-directed therapy improved mortality in a randomized series of patients.<sup>3</sup>

Initial and ongoing hemodynamic tolerance, as well as hemodynamic improvement associated with therapy, can now be noninvasively and reliably monitored with impedance cardiography (ICG). ICG provides the unique ability to continuously monitor a patient's hemodynamic status without the requisite risks and cost of right heart catheterization and therefore extends the possibility of using hemodynamics on a much broader range of patients, including outpatients. ICG hemodynamic monitoring has been proposed as a valid option in HF treatment algorithms.<sup>4,6</sup> Here we present three cases as practical examples in which clinicians used ICG hemodynamic information to help guide treatment of neurohormonal agents.

### Case One: Nesiritide Therapy

A 58-year-old African-American woman was brought to the hospital emergency department (ED) by ambulance after becoming acutely short of breath at home. The patient could not list her routine medicines but it was determined that she had been prescribed a pill for diabetes, some type of blood pressure (BP) medicine, and a water pill after her most recent hospitalization. Upon questioning, she admitted that she had not taken her medicines in the past few days. In the ED, the patient was severely dyspneic with an oxygen saturation of 88% and extremely hypertensive to a BP of 198/122 mm Hg.

Upon examination, her heart rate was 113 bpm, and her respiratory rate was 32 BPM. She weighed 296 lb. Cardiac auscultation revealed a quiet, mid-systolic murmur and summation gallop; her lungs had diffuse rales, and she had mild pitting edema to the

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PARAMETER	BASELINE	POST-THERAPEUTIC INTERVENTION
Heart rate (bpm)	113	88
Respiration rate (BPM)	32	20
SpO <sub>2</sub> (%)	88	97
BP (mm Hg)	198/122	132/66
CO (L/min)	3.8	5.6
SVR (dyne × s × cm <sup>-5</sup> )	2854	1488

SpO<sub>2</sub>=saturated oxygen by pulse oximetry; BP=blood pressure; CO=cardiac output; SVR=systemic vascular resistance

knees. The chest radiograph showed a large cardiac silhouette and prominent vascular markings with moderate interstitial edema; the electrocardiogram showed evidence of left ventricular hypertrophy. She was placed on ICG monitoring for hemodynamic assessment to aid in determining appropriate therapy.

The initial ICG data revealed cardiac output (CO) of 3.8 L/min and systemic vascular resistance (SVR) of 2854 dyne × s × cm<sup>-5</sup>. Both the hemodynamic and ED physician assessments were consistent with acute decompensated HF and pulmonary edema. The patient was given a bolus of nesiritide 2 μg/kg followed by a continuous infusion of 0.01 μg/kg/min. Table I shows the clinical and hemodynamic findings at baseline and with intervention. During nesiritide treatment, respiratory rate decreased to 20 BPM, heart rate decreased to 88 bpm, BP decreased to 132/66 mm Hg, and SVR decreased to 1488 dyne × s × cm<sup>-5</sup> × m<sup>2</sup>. Her CO rose significantly to 5.6 L/min/m<sup>2</sup>. These objective changes in hemodynamic endpoints coincided with dramatic improvements in symptoms of dyspnea and orthopnea. Urine output of 1500 mL was documented over the next 2 hours. The patient was admitted to the observation unit for continued nesiritide treatment and reinstatement of oral medications guided by ICG. She was discharged after a 23-hour observation to follow up for further adjustment of her therapy for hypertension and HF.

## Discussion

HF, by definition, is the inadequacy of the CO to meet the needs of the tissues under normal filling pressures.

Reduced CO is paired with neurohormonal activation and is the hallmark of HF decompensation. This patient had clinical signs of elevated filling pressures and ICG data showed that she had a very low CO in relation to her body size. Her markedly elevated SVR was possibly the inciting factor for decompensation and caused by noncompliance with BP medications.

In acute HF with volume overload, the high preload and abnormally high filling pressures cause the symptoms of dyspnea and edema.<sup>7</sup> Diuretic agents lower preload in such patients, helping congestive symptoms, but do not significantly decrease afterload and may not adequately improve cardiac output. BP is not a reliable indicator of CO, and a wide range of SVR values can exist at various BP levels.<sup>8</sup> Nesiritide, with effects on afterload as well as preload, resulted in not only significant improvement in symptoms due to preload reduction but significant improvements in CO and SVR.<sup>9</sup> Since each patient may respond uniquely, utilizing ICG to follow beat-by-beat changes in CO and SVR during therapy allows real-time titration of medications during observation. In this case, ICG demonstrated that the therapy was successful in restoring hemodynamic stability. Rapid improvement in ICG-measured hemodynamic parameters provided an early signal of patient response, which resulted in the early reduction in her nesiritide dosing with the prompt resumption of her oral medications. Sustained hemodynamic stability provided additional rationale for discharge rather than admission for further observation.

## Case Two: Titration of Carvedilol Therapy

A 79-year-old white man, 6 ft tall and weighing 160 lb, was referred to an outpatient HF clinic with New York Heart Association (NYHA) class IV symptoms. He had been diagnosed with ischemic HF and mild mitral regurgitation; ejection fraction (EF) by echocardiogram was 27%. Serum creatinine was 2.42 mg/dL. His medication regimen upon entry into the clinic included enalapril 5 mg b.i.d., furosemide 20 mg q.d., and digoxin 0.125 mg q.d. Due to continued severe symptoms, he had recently been treated with IV milrinone 0.375 μg/kg/min and IV dopamine 2.5 μg/kg/min for 4 hours twice a week. In the clinic, ICG hemodynamic measurements were conducted as part of his initial evaluation. The hemodynamic parameters included heart rate of 57 bpm, BP of 159/58 mm Hg, cardiac index (CI) of 3.6 L/min/m<sup>2</sup>, systemic vascular resistance index (SVRI) of 1904 dyne × s × cm<sup>-5</sup> × m<sup>2</sup>, and thoracic fluid content (TFC) of 35.0/kOhm. TFC is a patient-specific measurement of thoracic impedance and reflects the fluid volume in the thorax, allowing for quantitative intrapatient fluid trending.<sup>10</sup>

Using ICG guidance, carvedilol was initiated and increased in a stepwise fashion, ultimately achieving the targeted dose of carvedilol 25 mg b.i.d. with the discontinuation of inotropic medications. The patient had symptoms of fatigue during drug titration; however, the continued stability of ICG parameters helped the patient achieve the target dosage. Upon reaching the targeted dose of carvedilol, the patient had less fatigue and exertional dyspnea, and end organ perfusion was validated by a serum creatinine level decrease to 1.7 mg/dL. Table II provides a trend summary of the patient's hemodynamic changes during carvedilol titration. The patient had no hospitalizations or ED visits during the up-titration period, and hemodynamics at the end of treatment were similar to the beginning but, importantly, were accomplished without the aid

of inotropic agents and their known negative effects on mortality.<sup>11</sup> A subsequent echocardiogram was obtained and showed that his EF had increased to approximately 45%.

## Discussion

Treatment with  $\beta$  blockers decreases the risk of worsening HF caused by prolonged activation of the sympathetic nervous system.<sup>12</sup> Studies on carvedilol report a consistent reduction in death and hospitalization in patients with HF when taken in efficacious doses.<sup>13</sup> Despite the overwhelming evidence for the benefit of carvedilol, there is a gap in treatment between those who can benefit and those who are actually treated with the drug.<sup>14</sup> Patient response to  $\beta$ -blocker therapy differs and efforts to predict which patients will respond to the therapy are imprecise.<sup>15</sup> Clinicians who struggle with  $\beta$  blocker initiation and up-titration in HF are often concerned about whether a particular patient can hemodynamically tolerate the agent<sup>16</sup> and are also lacking real-time quantitative tools to aid this assessment.

In this case example, monitoring and trending of the hemodynamic parameters provided by ICG assisted the clinicians in reaching the recommended therapeutic dose of carvedilol. This patient's prior requirement of IV inotropic therapy with both milrinone and dopamine initially caused question as to whether he would tolerate increasing doses of carvedilol. The ICG indication of elevated SVRI also indicated a potential hemodynamic benefit from carvedilol's additional  $\alpha$ -

**Table II.** Hemodynamics Changes With Carvedilol Therapy

PARAMETER	3.125 MG B.I.D.	6.25 MG B.I.D.	25 MG B.I.D.
Heart rate (bpm)	57	66	51
BP (mm Hg)	159/58	146/57	158/48
CI (L/min/m <sup>2</sup> )	3.6	4.1	3.8
SVRI (dyne $\times$ s $\times$ cm <sup>-5</sup> $\times$ m <sup>2</sup> )	1904	1574	1656
TFC (/kOhm)	35.0	39.3	38.4

BP=blood pressure; CI=cardiac index; SVRI=systemic vascular resistance index; TFC=thoracic fluid content

blocking effects, and the subsequent SVRI reduction validated this perception. Serial ICG measurements allowed for the up-titration with greater confidence and success than might have been achieved without hemodynamic data. While the patient's weight did not change appreciably, the significant rise in TFC during  $\beta$  blocker up-titration may provide some rationale for further augmentation of diuretic agents.

## Case Three: Initiation of ACE Inhibitor Therapy

A 64-year-old white woman was referred to the HF clinic in May 2001. Her diagnosis was nonischemic cardiomyopathy and she was NYHA classification IIIb with an EF of 32.5% by multiple gated acquisition. Upon initial assessment, she had a score of 67 on the Minnesota Living with Heart Failure Questionnaire and was limited by severe dyspnea at 91 m on her 6-minute walk test. Her medications at clinic entry were digoxin 0.125 mg q.d., spironolactone 12.5 mg q.d., carvedilol 31.25 mg b.i.d., and furosemide 20 mg q.o.d. By order of her previous physician, she was also receiving milrinone infusions of 0.375  $\mu$ g/kg/min for 4 hours twice a week as palliative

care. Her hemodynamic parameters by ICG included a heart rate of 60 bpm, BP of 118/65 mm Hg, CI of 1.9 L/min/m<sup>2</sup>, SVRI of 3228 dyne  $\times$  s  $\times$  cm<sup>-5</sup>  $\times$  m<sup>2</sup>, and TFC of 38.5/kOhm. High SVRI helped identify vasoconstriction in the presence of normal BP, and lisinopril 2.5 mg q.d. was initiated. Furosemide was increased to 20 mg q.d.

One week later, her hemodynamics showed improvement in CI and SVRI to 2.2 L/min/m<sup>2</sup> and 2461 dyne  $\times$  s  $\times$  cm<sup>-5</sup>  $\times$  m<sup>2</sup>, respectively, and a decrease in TFC to 30.3/kOhm. Lisinopril was increased to 5 mg q.d. 2 weeks later, and the milrinone was reduced to a 6-hour infusion, 1 day a week. At a routine clinic visit about 3 weeks later, further up-titration of lisinopril was made to 5 mg in the morning and 2.5 mg in the afternoon. Milrinone was discontinued. NYHA class was improved to II and she was able to increase her distance on the 6-minute walk to 225.5 m.

One month later, lisinopril was prescribed at 5 mg b.i.d., and at her next visit the hemodynamic report indicated BP of 112/69 mm Hg; CI of 2.5 L/min/m<sup>2</sup>; SVRI of 2475 dyne  $\times$  s  $\times$  cm<sup>-5</sup>  $\times$  m<sup>2</sup>; and TFC of 28.4/kOhm. Her 6-minute walk distance increased to 343 m, which

**Table III.** Hemodynamic Changes With Addition and Up-Titration of ACE Inhibitor Therapy

PARAMETER	BASELINE	2.5 MG Q.D.	5 MG Q.D.	5/2.5 MG A.M./P.M.	5 MG B.I.D.
Heart Rate (bpm)	60	64	90	59	65
BP (mm Hg)	118/65	93/64	107/62	107/68	112/69
CI (L/min/m <sup>2</sup> )	1.9	2.2	2.7	2.3	2.5
SVRI (dyne $\times$ s $\times$ cm <sup>-5</sup> $\times$ m <sup>2</sup> )	3228	2461	2104	2609	2475
TFC (/kOhm)	38.5	30.3	29.3	34.5	28.4
NYHA	3b	3	2	3	3a
6-Minute walk test (m)	91	ND	211.8	225.5	342.9

ACE=angiotensin-converting enzyme; BP=blood pressure; CI=cardiac index; SVRI=systemic vascular resistance index; TFC=thoracic fluid content; NYHA=New York Heart Association Class; ND=not determined

corresponded with a Minnesota Living with Heart Failure Questionnaire score that improved to 22. A summary of the hemodynamic changes during the titration phase of the ACE inhibitor is listed in Table III. During this time, the patient had no hospitalizations or ED visits. One year following initial referral to the clinic her EF had increased to 42%.

## Discussion

ACE inhibitors should be prescribed to all patients with HF who do not have contraindications. It is well known that ACE inhibitors are significantly underutilized,<sup>17</sup> and many patients are treated with lower doses than those shown to be most beneficial in clinical trials.<sup>18</sup> However, during titration of ACE inhibitors patients can develop symptoms of dizziness and hypotension, or require hospitalization. Concerns over side effects can often prevent clinicians from initiating or up-titrating the drug, so knowledge of hemodynamics before increasing drug dose during titration may help physicians identify patients with

hemodynamic need and tolerance for higher doses.<sup>19</sup> In this specific case study, ICG findings of persistently elevated SVRI helped the clinicians increase the ACE inhibitor in a stepwise fashion. Of significance is the fact that the patient was already at a maximum dose of carvedilol when the ACE inhibitor was reinitiated. The case also demonstrates an initial improvement in SVRI may be transient, and that continued surveillance may lead to the need for continued up-titration of the ACE inhibitor. The decreased afterload from initial to final was at least in part responsible for the patient's demonstrated improvement in EF from 30% to 42%. The patient's functional status improved, as shown by her increased walking distance on the 6-minute test. Importantly, she did not experience any untoward symptoms or require hospitalization.

There is debate over the most appropriate dosing of ACE inhibitors for individual patients.<sup>20</sup> Comparison of group characteristics, as is the case in most clinical trials, often tells us

little about a specific patient's optimal ACE inhibitor dose. Because BP itself can be a poor guide to hemodynamic status, ICG-measured SVRI may be a more valuable parameter for determining which patients will benefit from higher doses of ACE inhibitors. In this case, both CI and SVRI provided important information that aided in optimal dose titration and tissue perfusion leading to improved functional status and quality of life.

## Conclusion

Although HF is both a hemodynamic and neurohormonal disorder, it is the hemodynamic effects of various medications that are readily measurable and that can limit therapy during drug titration. ICG provides accurate noninvasive hemodynamic information that can guide physicians during neurohormonal agent therapy in both chronic and acutely decompensated HF. These three cases demonstrate that ICG can be a valuable tool to aid decision making by clinicians caring for HF patients.

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