EDITORIAL

Beyond the Four Quadrants: The Critical and Emerging Role of Impedance Cardiography in Heart Failure

Heart failure (HF) is a disorder characterized by hemodynamic abnormalities including a reduction in the heart's ability to deliver oxygenated blood to the body. HF is also associated with important neurohormonal abnormalities, including activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and their resulting effects on the heart and vascular endothelium. Our understanding of the neurohormonal role in the progression of HF has greatly improved in the past 10 years,[1] and many of the therapies that significantly improve the symptoms and prognosis of patients with HF now target the underlying neurohormonal abnormalities. As shown in Figure 1, neurohormonal activation can lead to progression of hemodynamic abnormalities resulting in reduced cardiac output (CO); increased filling pressures; and ultimately worsening symptoms of fatigue, dyspnea, and decreased exercise tolerance. Although the neurohormonal mechanisms may cause progression of the disease process, nearly all medications used in HF treatment have demonstrable effects on hemodynamics. Current acute HF treatment is aimed directly at stabilizing and improving a patient's short-term hemodynamic condition; chronic HF treatments can alter short-term and improve long-term hemodynamics.

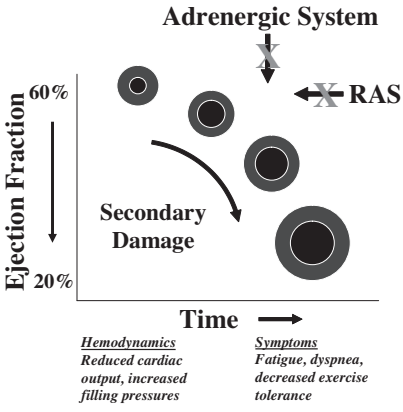

Figure 1. Neurohormonal activation and resultant hemodynamic and symptom changes. RAS=renin-angiotensin-aldosterone system

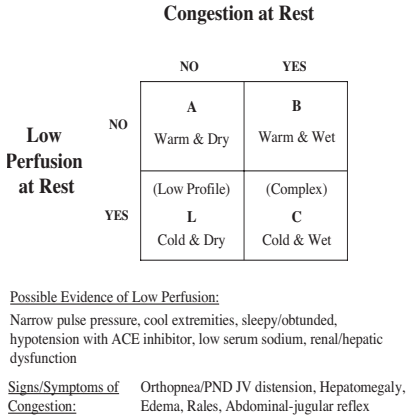

Figure 2. Clinical profiles in heart failure. PND=paroxysmal nocturnal dyspnea; JV=jugular vein; ACE=angiotensin-converting enzyme. Adapted from *J Am Coll Cardiol*. 2003;41(10):1797–1804.[5]

Specific hemodynamic measurements such as CO and systemic vascular resistance are generally obtained for only the most critically ill HF patients, in large part due to the risk, discomfort, and cost of invasive procedures such as pulmonary artery catheterization.[2] Nonetheless, understanding and measuring the factors that affect CO are central to the assessment, prognosis, and treatment of patients with HF. The four determinants of CO are the rate of the pump (heart rate), the volume of blood available to pump (preload), the pumping strength (contractility), and the force the heart must overcome to pump (afterload, generally approximated by systemic vascular resistance). Symptoms—physical findings like vital signs—and laboratory findings such as blood tests and chest radiographs are imprecise measures of hemodynamic function. Unfortunately, they are the only data many clinicians have at their disposal when making important decisions in the care of patients with HF.

The direct cost of treating HF is estimated to be $56 billion per year in the United States[3] and the number of HF patients in this country may reach 10 million by 2010.[4] A significant portion of the cost of HF care is the high cost of hospitalizations for patients with acute decompensation. Through careful surveillance of patients with chronic HF using improved methods for measuring hemodynamic and neurohormonal

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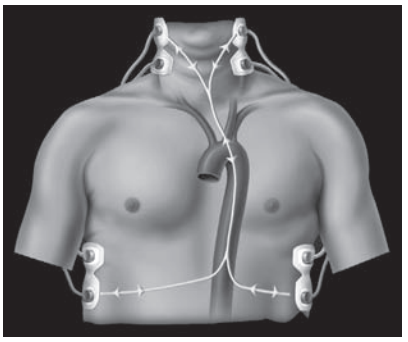

Figure 3. Front view of impedance cardiography method

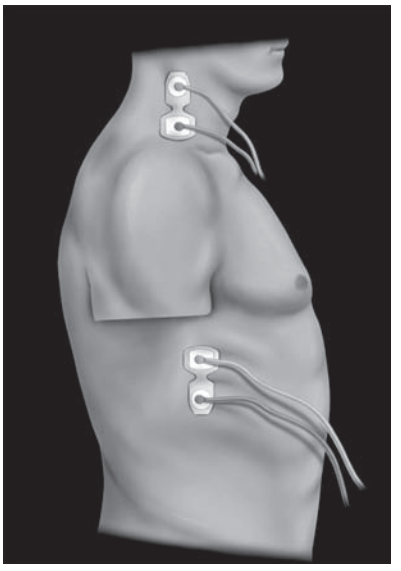

Figure 4. Lateral view of impedance cardiography method

status, primary care physicians and cardiologists may be able to intervene in a timely manner and prevent acute episodes leading to hospitalization, major morbidity, or death.

Warner-Stevenson[5] has developed and popularized the concept of categorizing HF patients by hemodynamic subset based on perfusion with CO (warm vs. cold) and congestion with pulmonary artery wedge pressure (wet vs. dry). The four quadrants, representing the four hemodynamic classes, are shown in Figure 2. Studies have suggested that these profiles provide a useful framework to risk stratify patients with HF, predict outcomes, and identify therapeutic options. However, this framework is based on invasive pulmonary artery catheterization, with its requisite risk and cost, or on physical examination and patient history, which have been shown to lack sensitivity and specificity, even in the hands of experienced clinicians.[6] HF management using hemodynamic subsets could be substantially improved by the existence of more objective data with which to classify patients and evaluate the effectiveness of subsequent pharmacologic and implantable interventions.

Impedance cardiography (ICG) is a noninvasive method of determining hemodynamic status. In the past, studies questioned the reliability of ICG technology,[7,8] leading some to conclude that the technology did not have value in clinical decision making. However, refinements in signal processing and CO algorithms have greatly improved the reliability of ICG technology. The latest generation of ICG devices (BioZ ICG Monitor, CardioDynamics, San Diego, CA; and BioZ ICG Module, GE Medical Systems Information Technologies, Milwaukee, WI) are both highly reproducible and accurate in a number of clinical settings, including HF.[9–11] A recent search of the literature failed to show a single citation since US Food and Drug Administration 510(k) clearances of these particular devices that suggests they are not valid for clinical applications.

ICG is a form of plethysmography that utilizes changes in thoracic electrical impedance to estimate changes in blood volume in the aorta and changes in fluid volume in the thorax. As shown in Figures 3 and 4, the ICG procedure involves the placement of four dual

Table I. Impedance Cardiography Parameters

Parameter	Abbreviation	Measurement/Calculation	Units
Flow			
Stroke volume	SV	VI × LVET × VEPT (Z MARC algorithm)	mL
Stroke index	SI	SV/body surface area	mL/m^2
Cardiac output	CO	SV × heart rate	L/min
Cardiac index	CI	CO/body surface area	$L/min/m^2$
Resistance			
Systemic vascular resistance	SVR	([MAP – CVP]/CO) × 80	$dyne \times s \times cm^{-5}$
Systemic vascular resistance index	SVRI	([MAP – CVP]/CI) × 80	$dyne \times s \times cm^{-5} \times m^2$
Contractility			
Preejection period	PEP	ECG Q wave to aortic valve opening	ms
Left ventricular ejection time	LVET	Aortic valve opening to closing	ms
Systolic time ratio	STR	PEP/LVET	No units
Velocity index	VI	First time $derivative_{max}$/baseline impedance	$/1000/s$
Acceleration index	ACI	Second time $derivative_{max}$/baseline impedance	$/100/s^2$
Left cardiac work index	LCWI	(MAP – PCWP) × CI × 0.0144	$kg \times m/m^2$
Fluid Status			
Thoracic fluid content	TFC	1/baseline impedance	/kOhm

VEPT=volume of electrically participating tissue; Z MARC=impedance modulating aortic compliance; CVP=central venous pressure (estimated value of 6 mm Hg); MAP=mean arterial pressure; ECG=electrocardiogram; PCWP=pulmonary capillary wedge pressure (estimated value of 10 mm Hg)

sensors on a patient's neck and chest. A low-amplitude, high-frequency alternating current is delivered from the four outer sensors and the four inner sensors detect instantaneous changes in voltage. As suggested by Ohm's law, when a constant current is applied to the thorax, the changes in voltage are directly proportional to the changes in measured impedance. The overall thoracic impedance, called base impedance (Z_0) is the sum of the impedances of the components of the thorax, including fat, cardiac and skeletal muscle, lung and vascular tissue, bone, and air. Changes from Z_0 occur due to changes in lung volumes with respiration and changes in the volume and velocity of blood in the great vessels during systole and diastole. The rapidly changing component of chest impedance (ΔZ) is filtered to remove the respiratory variation, leaving the impedance changes due to ventricular ejection. Figure 5 details the elements contributing to Z_0 and ΔZ, and Figure 6 illustrates how the first derivative of the impedance waveform ($\Delta Z/\Delta t$) is used with an electrocardiogram to determine the beginning of electrical systole, aortic valve opening, maximal deflection of the $\Delta Z/\Delta t$ waveform, and the closing of the aortic valve. From these fiducial points, a variety of measured and calculated parameters (Table I) are continuously displayed on the ICG device screen for monitoring purposes, or in a printed report for review (Figure 7).

The hemodynamic parameters derived from ICG can aid in the diagnostic and prognostic evaluation of patients with HF. Using ICG, a clinician is able to evaluate direct or indirect measures of each of the four major determinants of CO (preload, afterload, contractility, and heart rate). Figure 8 is a conceptual diagram of CO and its determinants, ICG parameters associated with the determinants, and the effects of pharmacologic agent classes on each determinant. Due to greater acceptance of ICG in clinical and research settings, clinicians are now able to use ICG-derived hemodynamic data to help decide when to initiate and titrate these types of medications. A summary of applications of ICG in HF is presented in Table II, demonstrating its broad clinical applicability.

Table II. Summary of Impedance Cardiography Applications in Heart Failure

Application	Description
Assessment and diagnostic	Establish baseline hemodynamics Trend changes to gauge level of hemodynamic decompensation Determine whether symptoms are due to hemodynamic deterioration Aid in differentiation of systolic vs. diastolic dysfunction
Prognostic	Emergency department values predictive of length of stay and hospital charges Improvements associated with improving NYHA class, quality-of-life measures Abnormal values associated with mortality
Treatment	Determine stability for initiation and up-titration of β-blocker and ACE-inhibitor therapy Assist in selection of drug agents and dosing Measure response to adjustments in therapy Determine need and optimal selection/dosing of IV therapy (dobutamine, milrinone, nesiritide) Optimize LVAD settings and wean patients from LVAD support Determine optimal pacemaker settings in patients with AV sequential pacemakers Detect hemodynamic changes due to compensation, medication, and diet compliance Provide an adjunct to post-transplant myocardial biopsies

NYHA=New York Heart Association; ACE=angiotensin-converting enzyme; LVAD=left ventricular assist device

Adapted from Yancy C, Abraham W. Noninvasive hemodynamic monitoring in heart failure: utilization of impedance cardiography. *Congest Heart Fail.* 2003:9(5):241–250.

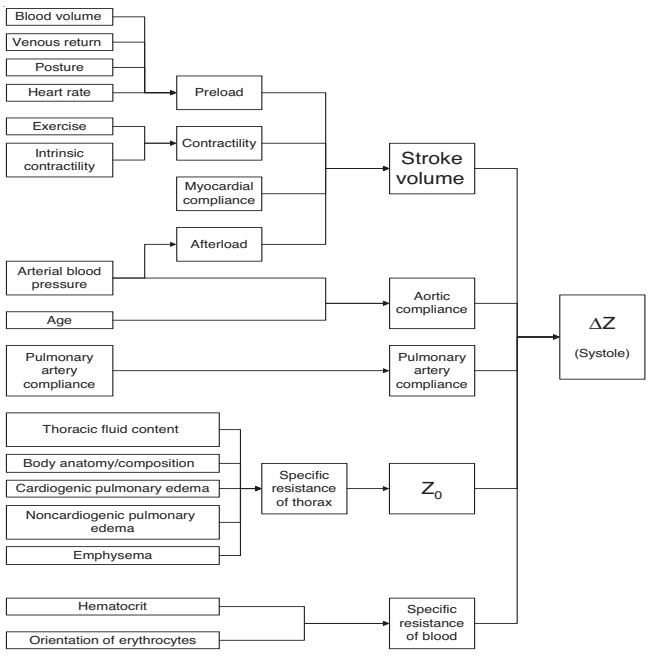

Figure 5. Contributing elements to thoracic impedance. Z_0=baseline impedance; ΔZ=change in impedance
Adapted from Osypka MJ, Bernstein DP. Electrophysiologic principles and theory of stroke volume determination by thoracic electrical bioimpedance. *AACN Clin Issues*. 1999;10(3):385–399.

In this supplement to *Congestive Heart Failure*, we seek to further define the role of ICG through a series of original contributions. The study by

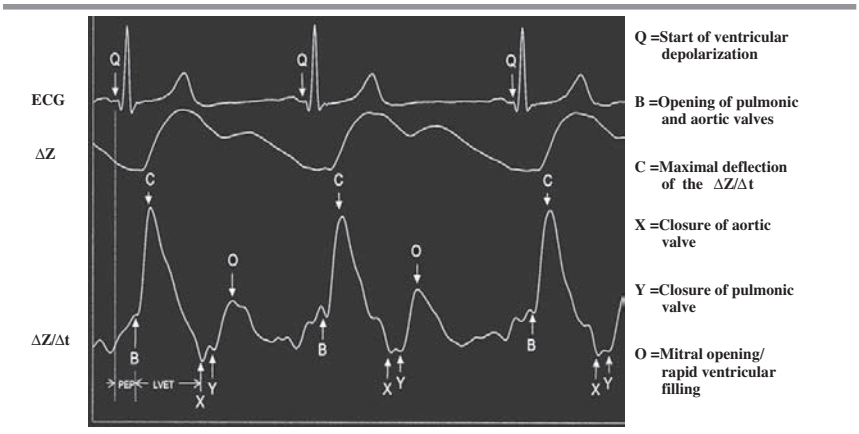

Figure 6. Fiducial points derived from electrocardiogram (ECG) and impedance waveforms. ΔZ=change in impedance; ΔZ/Δt=first derivative of the impedance waveform; PEP=preejection period; LVET=left ventricular ejection time

Hemodynamic Status Report

Name: **ID:** **Age:** 63 **Sex:** Female **Height:** 5 ft 2 in **Weight:** 145 lb **BSA:** 1.67 m²

30 Beat Average **Page 1 of 1**

Parameter	Description	Value	Low	Normal	High
HR	Heart Rate	70	68		86
SBP	Systolic Blood Pressure	135	100		140
DBP	Diastolic Blood Pressure	90	60		90
MAP	Mean Arterial Pressure	105	84		100
CI	Cardiac Index	2.2	2.5		4.7
CO	Cardiac Output	3.7	4.2		7.8
SI	Stroke Index	32	35		65
SV	Stroke Volume	52	58		108
SVRI	Systemic Vascular Res. Index	3562	1337		2483
SVR	Systemic Vascular Resistance	2159	742		1378
ACI	Acceleration Index	106	90		170
VI	Velocity Index	48	33		65
TFC	Thoracic Fluid Content	64.6	21.0		37.0
LCWI	Left Cardiac Work Index	3.0	3.0		5.5
LCW	Left Cardiac Work	5.0	5.4		10.0
STR	Systolic Time Ratio	0.45	0.30		0.50
PEP	Pre-Ejection Period	121			
LVET	Left Ventricular Ejection Time	265			

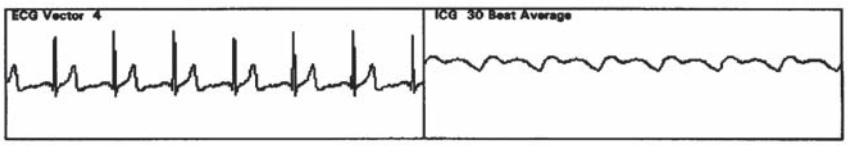

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Figure 7. Impedance cardiography hemodynamic status report (BioZ ICG Monitor, CardioDynamics, San Diego, CA)

Yung et al. (p. 7) validates the accuracy of ICG in patients with pulmonary hypertension by comparing ICG to both direct Fick method and thermodilution CO. In doing so, the authors demonstrate the potential hazard of using thermodilution as the only reference standard for CO measurement. Parrott et al. (p. 11) compare changes in ejection fraction by echocardiography to changes in ICG parameters in established HF patients. Their findings demonstrate the ability of ICG to simply and cost-effectively identify changes in ventricular function. While pulmonary artery catheterization in patients with HF has been criticized and is largely unproven by clinical trial, an estimated 2 million such catheters are sold worldwide each year.[12] Springfield et al. (p. 14) illustrate the role of ICG in the differential diagnosis of patients with dyspnea. Although B-type natriuretic peptide testing has gained wide attention recently as an aid to diagnose HF in the emergency department,[13] ICG may also have a diagnostic role and provides additional value because of its ability to identify appropriate therapeutic options and monitor the response to therapy in real time. Silver et al. (page 17) report on the ability of ICG to replace pulmonary artery catheterization, which has tremendous cost implications for hospitals caring for such patients. Vijayaraghavan et al. (page 22) demonstrate the prognostic role of ICG in patients with chronic HF, and show strong association of ICG changes to changes in functional status and quality-of-life measures. Summers et al. (page 28) provide a series of case reports that illustrate ICG's practical role in the initiation and titration of neurohormonal agents and their patient-specific hemodynamic effects.

This compilation of studies adds to the growing body of data supporting the role of ICG in the management of patients with HF. Within a year, the results of two multicenter trials studying key roles for ICG should be available: PRospective Evaluation and identification of Decompensation by Impedance Cardiography Test (PREDICT), conducted in patients with chronic HF; and the BioImpedance cardioGraphy (BIG) substudy of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE).[14] PREDICT specifically addresses the ability of ICG-derived hemodynamic data to

identify patients at risk for death, hospitalization, or emergency department visit. The BIG substudy will evaluate the diagnostic and prognostic role of ICG in both arms of a randomized, controlled trial in pulmonary artery catheter–hemodynamic-guided management of patients admitted with an acute episode of HF.

There is now a compelling body of literature that demonstrates the validity of ICG using the most current technology. More and more studies have shown the value of ICG in clinical settings in addition to HF, including dyspnea,[15] hypertension,[16] and atrioventricular sequential pacemakers.[17] The studies presented in this issue of *Congestive Heart Failure* further define the role of this valuable, noninvasive technology in clinical medicine. It is likely that these and other studies of ICG in HF will be used to refine our understanding and ability to assess patients and predict prognosis, expanding on the concept of the four quadrants presented in Figure 2. The impact of adding ICG hemodynamic data to the four quadrants is depicted in Figure 9. Knowledge of stroke index, cardiac index, systemic vascular resistance index, and changes in fluid with thoracic fluid content would likely provide more quantitative, objective, and sensitive measurements of hemodynamic factors, and has significant implications for the management of patients with HF.

Incorporating this model of assessment into a proposed therapeutic algorithm is shown in Figure 10. Ideally, a baseline measurement of ICG in addition to other standard clinical variables would be collected and utilized in combination to more precisely assess a patient's perfusion, congestion, and vasoactive status. This assessment would lead to a categorization of the patient's absolute or relative change in hemodynamic profile, facilitating assessment of short-term risk for adverse HF-related events. The change in hemodynamic status and assessment of higher risk may lead to increased clinical surveillance or a decision to intervene to prevent a negative patient outcome. In addition, ICG parameters may aid in the assessment of a stable, low-risk hemodynamic profile toward the initiation and up-titration of neurohormonal agents that are often underprescribed but are known to improve event-free survival.

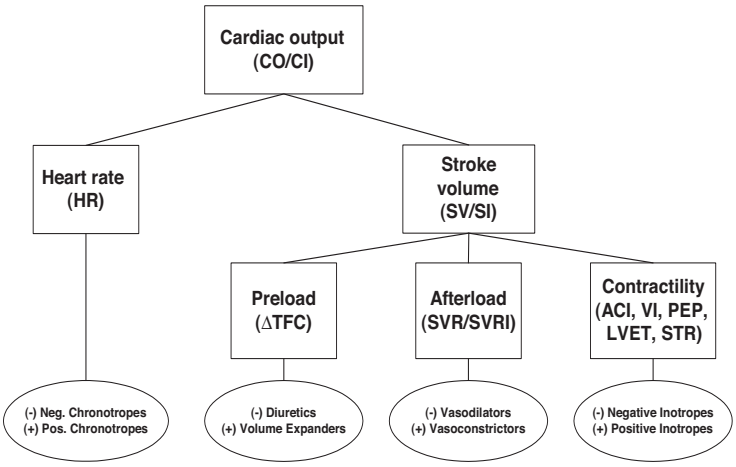

Figure 8. Pharmacologic agent effect on cardiac output determinants and impedance cardiography parameters. CO=cardiac output; CI=cardiac index; HR=heart rate; SV=stroke volume; SI=stroke index; ΔTFC=change in thoracic fluid content; SVR=systemic vascular resistance; SVRI=systemic vascular resistance index; VI=velocity index; PEP=preejection period; ACI=acceleration index; LVET=left ventricular ejection time; STR=systolic time ratio

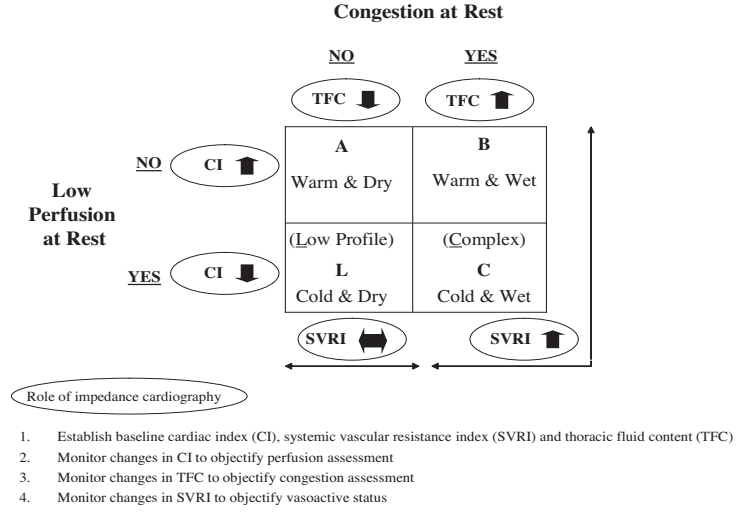

Figure 9. Model for clinical profiles in heart failure utilizing impedance cardiography hemodynamic measurements

Note: This supplement to Congestive Heart Failure *contains articles dealing with ICG. Readers are reminded that positive statements about the clinical utility of ICG, and the BioZ ICG Monitor in particular, are solely the opinions of the authors and do not represent an official endorsement by* Congestive Heart Failure, *its Editors or Editorial Board, or the Heart Failure Society of America.*

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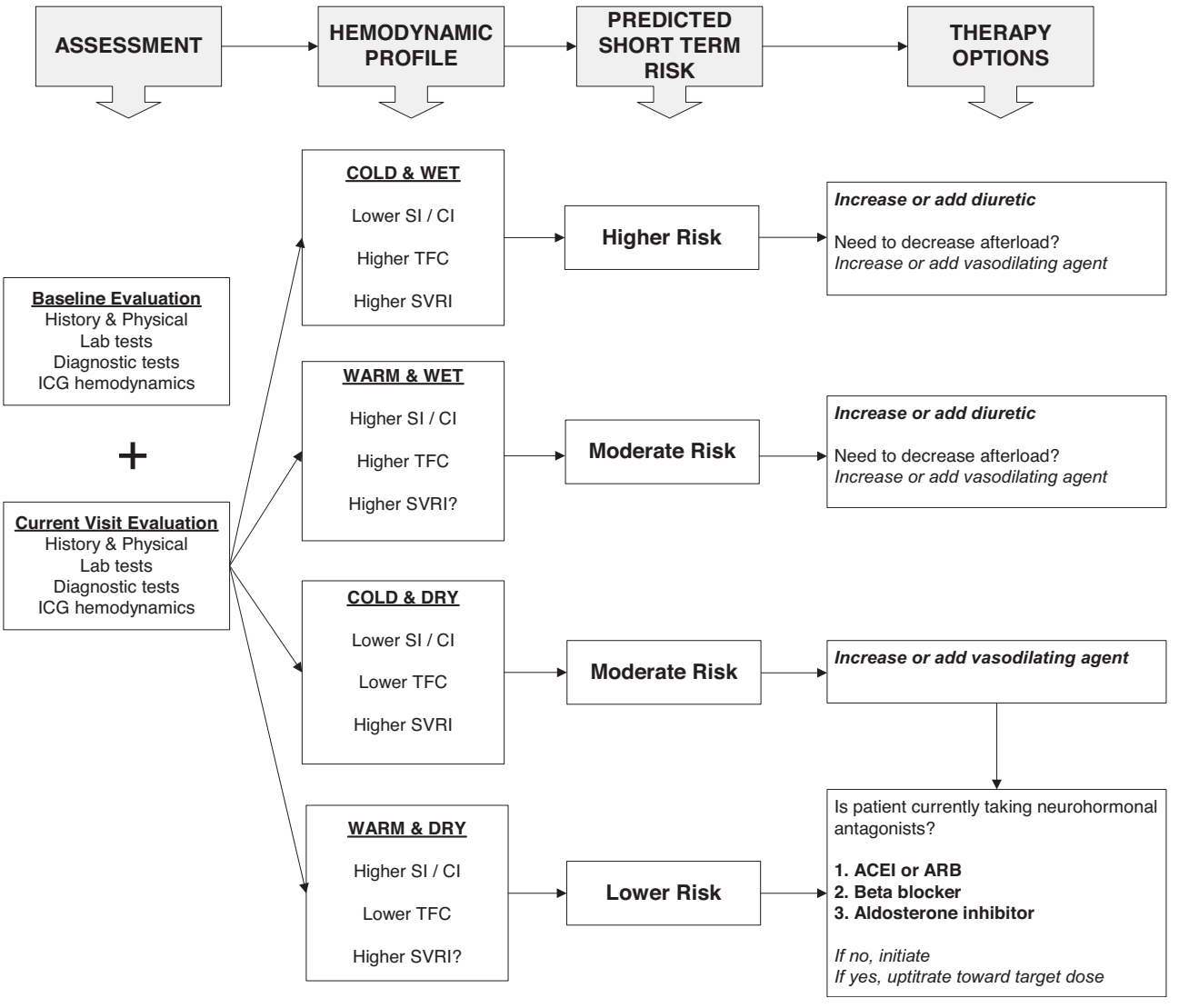

Figure 10. Therapeutic algorithm for incorporating impedance cardiography (ICG) parameters into clinical assessment of heart failure. SI=stroke index; CI=cardiac index; TFC=thoracic fluid content; SVRI=systemic vascular resistance index; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin-receptor blocker

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