Heart failure in real life
Aim and Scope

Heart and Metabolism is a journal published three times a year, focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications. Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.

Website

www.heartandmetabolism.com

Heart and Metabolism is indexed in EMBASE, and SCOPUS, and PASCAL/INIST-CNRS until issue 65.

Design
Studio DTC - Servier

Layout
Blau Banquise

Printed
in France

© 2017 by
Les Laboratoires Servier

ISSN
1566-0338

All rights reserved throughout the world and in all languages. No part of this publication may be reproduced, transmitted, or stored in any form or by any means either mechanical or electronic, including photocopying, recording, or through an information storage and retrieval system, without the written permission of the copyright holder.

Opinions expressed do not necessarily reflect the views of the publishers, editors, or editorial board. The authors, editors, and publishers cannot be held responsible for errors or for any consequences arising from the use of the information contained in this journal.
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDITORIAL</td>
<td>Heart failure in real life</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>M. Marber</td>
<td></td>
</tr>
<tr>
<td>ORIGINAL ARTICLES</td>
<td>Assessing the breathless patient</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>M. R. Cowie</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart failure with mid-range EF (HFmrEF): a mildly reduced EF does not imply a mild disease</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>C. Tschöpe, B. Pieske</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal function in acute heart failure: what can go wrong and what we can do about it</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>S. R. Goldsmith</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preventing heart failure hospital readmissions: challenges and opportunities</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>B. Ziaeian, G. C. Fonarow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical benefits of trimetazidine in heart failure</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>G. M. C. Rosano</td>
<td></td>
</tr>
<tr>
<td>CASE REPORT</td>
<td>Team-based management to improve real-world outcomes in heart failure</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>M. Ryan</td>
<td></td>
</tr>
<tr>
<td>REFRESHER CORNER</td>
<td>Cellular metabolic and structural changes in heart failure</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>G. D. Lopaschuk</td>
<td></td>
</tr>
<tr>
<td>HOT TOPICS</td>
<td>Identifying heart failure in the emergency room</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>M. C. Scali</td>
<td></td>
</tr>
<tr>
<td>GLOSSARY</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>G. D. Lopaschuk</td>
<td></td>
</tr>
</tbody>
</table>
This issue of *Heart and Metabolism* is dedicated to heart failure in the real world and highlights the everyday problems faced in the identification of this syndrome and in its effective management. These issues are complex, so when the manuscripts arrived, I was amazed at their clarity. A good place to start is at the beginning: How do we diagnose heart failure?

Dr Cowie provides a comprehensive overview of the assessment of the breathless patient, offering a mixture of guideline pragmatism and personal opinion. The article is divided by mode of presentation—chronic breathlessness in the community/primary care setting versus acute breathlessness in the emergency room. Assessment in the community is particularly difficult due to the nonspecific nature of heart failure symptoms of breathlessness, fatigue, and ankle edema. Although a careful history and clinical examination are important, it is sobering how the use of B-type natriuretic peptide (BNP) dominates the guidelines; I think this probably reflects the difficulty in standardizing the clinical assessment of heart failure rather than indicating the infallibility of BNP. As Dr Cowie points out, the use of BNP is also problematic, as its concentration varies continuously across those with and without a heart failure diagnosis; therefore, any single cut-off value faces a sensitivity versus specificity conundrum. As a consequence, the European Society of Cardiology (ESC) guidelines mandate a cut off at a relatively low concentration, which provides a high sensitivity for rule-out, but low specificity for rule-in. This makes clinical assessment crucial, especially because the diagnosis of heart failure with preserved ejection fraction is not straightforward, even after echocardiography (see issue 71 of *Heart and Metabolism* where we address this topic). In my own practice, these patients (BNP above rule-out threshold but no severe left ventricular [LV] systolic or diastolic dysfunction on echocardiography) are very common and difficult to manage. Since they don’t meet the inclusion criteria for any of the trials showing a benefit with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor–neprilysin inhibitors (ARNI), β-blockers, or mineralocorticoid antagonists, treatment is based on improving symptoms. My own approach, if I think heart failure may be contributing to symptoms, is a short “diagnostic trial” of treatment with diuretics. Often, these patients have coincident chronic obstructive pulmonary disease that results in the same symptoms being treated in different specialist outpatient clinics. As Dr Cowie points out, exactly the same challenge occurs when patients present acutely, as chest sepsis also elevates BNP; all too often, the “solution” is treatment with “Lazy-cillin”—a concatenation of Lasix (furosemide) and cillin (antibiotic), a term used to tease the junior staff over their decision-making process—or “Lazy-heparocillin” (when heparin is added because the D-dimer is also elevated). Thus, any investigation that can increase the specificity of diagnosis and help select an appropriate therapy would be very useful.

In the Hot Topics article, Dr Scali comes to the rescue and introduces the use of lung ultrasound in

---

**Heart failure in real life**

Michael Marber, FRCP, FACC, PhD
BHF Center of Research Excellence, Cardiovascular Division, The Rayne Institute, St Thomas’ Hospital, London, United Kingdom

Correspondence: Michael Marber, BHF Center of Research Excellence, Cardiovascular Division, The Rayne Institute, St Thomas’ Hospital, London, SE1 7EH, United Kingdom
E-mail: mike.marber@kcl.ac.uk
the emergency room to differentiate between cardiac and pulmonary causes of breathlessness. Here, “comets,” also known as watery B-lines, appear on lung ultrasound as linear echogenic structures. They have a high sensitivity and specificity for a heart failure diagnosis, but it is unclear if they add to the diagnostic power of BNP. What is interesting, however, is the migration of diagnostic imaging to the emergency room setting with emergency physicians skilled in screening echocardiography (to complement focused assessment with sonography for trauma [FAST]) and computed tomography [CT] coronary and pulmonary angiography, all improving the appropriateness of referral to cardiology.

The diagnosis of heart failure can be difficult, as can its treatment; this is particularly the case when trying to resolve the fluid overload associated with congestive cardiac failure. I found that the article by Dr Goldsmith offered a new way of looking at the hemodynamics of renal glomerular filtration. Moreover, the concepts of renal preload and afterload are familiar to us as cardiologists. This article forces us to think of the pressure gradient across the glomerulus both in terms of systemic arterial pressure (as a surrogate for renal arterial pressure) and central venous pressure (as a surrogate for renal venous pressure). I always thought it a bit odd how patients with fluid overload, high central venous pressure, and acute kidney injury can paradoxically show an improvement in renal function with intravenous furosemide. The paradigm presented by Dr Goldsmith provides a clear explanation of this scenario and the trade-offs between arterial and venous pressure from the perspective of the kidney. This provides a very useful framework for managing these complex patients, especially when tight ascites exerts an additional external pressure on the system.

Preventing readmission is the topic of the article by Drs Ziaeian and Fonarow. They emphasize the high mortality and readmission rates after hospital discharge with a diagnosis of heart failure. They also point out that readmission within 4 weeks is used as a penalizing metric in a number of health care systems, despite the fact that the reasons for early readmission are multifactorial and not necessarily cardiac or even health related. As a consequence, a holistic approach to discharge planning must be taken. In addition, readmission rates can be reduced by early review and through use of other measures to monitor patients, including implantable devices. Ultimately, since approximately half of early readmissions are noncardiac, it is unclear if readmission from any cause is a valid quality metric. As Drs Ziaeian and Fonarow point out, it may inadvertently financially penalize those communities where need for health care investment is greatest, since increased probability of readmission is associated with lower socioeconomic status. Since heart failure is such a common condition, which degrades the individual's quality and quantity of life, as well as the health economy, shaping the care system with the correct incentives is crucial.

Drs Tschöpe and Pieske introduce the topic of heart failure with mid-range ejection fraction and the rationale for its inclusion in the latest ESC guidelines. In large part, this is to foster research and debate. Finally, Dr Lopaschuk provides a summary of the metabolic disturbances that occur within the myocardium in heart failure, and Dr Rosano, an overview of how they can be corrected by metabolic therapies, such as trimetazidine, which improves cardiac function and reduces hospital readmission with heart failure. What is clear from this issue is that we still have a long way to go and urgently require better diagnostic tests and therapies for this common condition.
Assessing the breathless patient

Martin R. Cowie, MD, FRCP, FRCP (Ed), FESC, FHFA
Clinical Cardiology, Imperial College London (Royal Brompton Hospital), United Kingdom

Correspondence: Prof Martin R. Cowie, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, United Kingdom
(E-mail: m.cowie@imperial.ac.uk)

Abstract
Breathlessness can be caused by many pathologies, and correctly identifying those patients who have heart failure can be a challenge in day-to-day practice in both the acute and chronic setting. The approach to the breathless patient should rely on good history taking and clinical examination, supplemented by investigations that help include or exclude particular diagnoses. The measurement of the plasma concentration of natriuretic peptides can be a very useful additional test, helping to rule out heart failure. If the levels are elevated, heart failure is not proven but is much more likely, and further investigation (typically including echocardiography and a specialist opinion) is required. The current European Society of Cardiology guidelines recommend a decision cut point of 125 pg/mL for N-terminal pro–B-type natriuretic peptide (NT-proBNP) and 35 pg/mL for B-type natriuretic peptide (BNP) in the chronic setting, and 300 pg/mL for NT-proBNP and 100 pg/mL for BNP in the acute setting. Recently published US guidelines are also strongly supportive of the use of natriuretic peptide testing to rule out heart failure as the cause of breathlessness. ■ Heart Metab. 2017;74:4-7

Keywords: diagnosis; heart failure; natriuretic peptide

Primary care/clinic setting
The diagnosis of heart failure can be challenging. In primary care, patients may present with symptoms of gradual-onset breathlessness, fatigue, or ankle swelling,¹ but these symptoms are not specific to heart failure, and many patients have several comorbidities.²,³ Making a timely and accurate diagnosis is key to identifying the underlying cause and starting potentially life-saving therapy. Most studies from general practice suggest that the diagnosis is only confirmed in around 30% of cases of suspected heart failure—which is appropriate, as the index of suspicion should be high.⁴

An individual meta-analysis of nine prospective studies reported that certain clinical features were highly specific for heart failure, including added heart sounds (99%), hepatomegaly (97%), history of myocardial infarction (89%), orthopnea (89%), and elevated jugular venous pressure (70%).⁵ Most of those features are not highly sensitive and so are helpful when present but may be absent in many patients with heart failure.

Clinical decision rules can help a clinician to decide whether a patient is likely to have a particular diagnosis. Several have been developed for heart failure arising in primary care.⁴,⁵ A decision rule based on meta-analysis was developed, suggesting that a patient presenting in primary care with symptoms that might be due to heart failure should be referred directly for echocardiography if they had one of the following: a history of myocardial infarction, basal crepitations, or ankle edema (in a man). Otherwise, an N-terminal pro–B-type natriuretic peptide (NT-proBNP-
**Abbreviations**

BNP: B-type natriuretic peptide; ECG: electrocardiogram; ESC: European Society of Cardiology; NICE: National Institute for Health and Care Excellence; NP: natriuretic peptide; NPV: negative predictive value; NT-proBNP: N-terminal pro–B-type natriuretic peptide.

The current European Society of Cardiology (ESC) guidelines provide an algorithm for the diagnosis of heart failure in the “nonacute” setting (Figure 1).9 The NP test should be performed, and depending on the NT-proBNP level, the patient should have echocardiography.4 This clinical decision rule was prospectively tested in 28 general practices and found to be less good than a simple cut off based on natriuretic peptides alone.1 At a decision cut point of plasma NT-proBNP under 125 pg/mL, the sensitivity for heart failure was 94% (95% confidence interval [CI], 88%-98%), and specificity was 49% (95% CI, 42%-56%), with an area under the receiver operating characteristics (AUROC) curve of 0.72.

The National Institute for Health and Care Excellence (NICE) in England currently recommends a primary care decision cut point of greater than or equal to 400 pg/mL for NT-proBNP and of greater than or equal to 100 pg/mL for B-type natriuretic peptide (BNP),6 but in the recent general practice prospective validation study,4 the sensitivity at this decision cut point was only 77%, albeit with a high specificity of 92%. Nearly all such patients will have heart failure (or other serious cardiovascular/renal problems), but up to 1 in 5 patients with heart failure may be missed. This is not ideal for a test to be used in primary care to rule out heart failure and further cardiological investigation. However, a Swiss study using similar cut points reported that the use of BNP testing in primary care leads to increased diagnostic certainty, less diagnostic work-up, and an accelerated initiation of appropriate treatment.7

An electrocardiogram (ECG) can also be used to rule out heart failure—a completely normal ECG is unlikely in a patient with heart failure (negative predictive value around 90% for systolic heart failure).8 However, ECG abnormalities become more common with advancing age, and the ECG is therefore not useful as a “rule in” test in the target population. Some ECG abnormalities may give a clue as to the etiology of heart failure (eg, myocardial infarction, atrial fibrillation) or indications for therapy (eg, anticoagulation for atrial fibrillation, cardiac resynchronization therapy for a broad QRS complex), adding value to this test.

---

**Fig. 1** Diagnostic algorithm for heart failure in a nonacute setting recommended by the European Society of Cardiology. Abbreviations: BNP, B-type natriuretic peptide; CAD, coronary artery disease; ECG, electrocardiogram; HF, heart failure; MI, myocardial infarction; NT-proBNP, N-terminal pro–B-type natriuretic peptide. Modified from reference 9: Adapted and reproduced with permission of Oxford University Press on behalf of the European Society of Cardiology. © European Society of Cardiology 2016. All rights reserved. For permissions, please email journals.permissions@oup.com. Oxford University Press and the ESC are not responsible for the adaptation in this work. Please visit www.escardio.org/Guidelines/ Clinical-Practice-Guidelines/Acute-and-Chronic-Heart-Failure.
pg/mL), then echocardiography should be performed to confirm the clinical diagnosis of heart failure. Such imaging provides information on global and regional ventricular function, chamber volumes, wall thickness, and valve function, and can identify pulmonary hypertension.

In routine practice, general practitioners may be reluctant to rely on their own cardiovascular examination or ECG interpretation and may wish to measure plasma NPs, even when they can find no abnormality on examination. In England, NICE makes the point that echocardiographic interpretation may not be straightforward and that a general practitioner should refer for "echocardiography AND a specialist assessment." This is likely to be particularly valuable for patients who have heart failure with preserved ejection fraction or due to valve disease.

The most recent North American guidelines also suggest that the NPs are useful in patients presenting with dyspnea to “support a diagnosis or exclusion of heart failure,” awarding it the highest possible level of recommendation. In the chronic ambulatory setting, the guideline states that NPs provide incremental diagnostic value to clinical judgment, particularly when the etiology of dyspnea is unclear. In the emergency setting, the NP value is included as a high-sensitivity “rule out” test, rather than for specificity, as there are many other causes of raised NPs. (Table I)

The acute setting

Breathlessness is a common symptom in those presenting in the emergency room or coronary care unit. Similarly to the more chronic setting, diagnosis should be based upon a thorough clinical examination (assessing symptoms, previous cardiovascular history, and potential cardiac and noncardiac precipitants) and a physical examination, including looking for signs of congestion and/or hypoperfusion. Further information from the ECG, chest radiograph, blood work, and echocardiography can be useful. Early diagnosis is key to early treatment and better outcome.

The current ESC guidelines make several recommendations regarding diagnostic investigations in the acute setting (Figure 2). All patients should have NPs measured on presentation to help distinguish cardiac from noncardiac causes of breathlessness. The high sensitivity of NPs is emphasized (good for a “rule out” test, with BNP <100 pg/mL or NT-proBNP <300 pg/mL making heart failure unlikely, except in some patients with end-stage decompensated heart failure, “flash” pulmonary edema, or right-sided heart failure). A recent meta-analysis suggests that at these cut points, the NPs have sensitivities of over 95% and negative predictive values of over 94%. Raised levels do not necessarily confirm the diagnosis as there are many causes of elevation (Table I).

The guidelines state that routine hemodynamic evaluation with a pulmonary artery catheter is not indicated but may be helpful in selected unstable patients with an unknown reason for deterioration. Despite much work on other biomarkers in heart failure, none other than the NPs have found their way into routine clinical practice, except for cardiac troponin, which is elevated in acute coronary syndrome but also in many patients with heart failure or pulmonary embolism. Interestingly, and in contrast to the chronic heart failure guideline, NICE recommends the same cut points in the acute setting as the ESC guidelines.

The benefit of the measurement of NPs in the diagnostic work-up of patients presenting with breathlessness in the acute setting has been further demonstrated by a shorter and less expensive inpatient length of stay in a randomized trial in Switzerland.

Conclusions

Careful history taking and physical examination remain at the core of the diagnosis of heart failure, in both the acute and chronic settings. Measurement of plasma NPs provide useful rule out information: nor-
mal levels make heart failure unlikely, although there is some debate about the critical decision cut points. Raised NP concentrations should trigger a search for cardiovascular/renal pathologies, and further blood tests and echocardiography are likely to be required. The ECG should also be mandatory because it may help to rule out heart failure, provide clues as to etiology of heart failure, or may indicate key treatment choices. A chest radiograph is generally of most value to exclude other pathologies that may contribute to symptoms. Adoption of the current approach recommended in the ESC guideline is likely to improve both the accuracy and speed of diagnosis and enable early commencement of targeted therapy.

**References**


Heart failure with mid-range EF (HFmrEF): a mildly reduced EF does not imply a mild disease

Carsten Tschöpe,1,2,3 MD, PhD; Burkert Pieske,1,2,4,5 MD, PhD
1Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin, Berlin, Germany
2German Center for Cardiovascular Research (DZHK), Partner Site Berlin, Berlin, Germany
3Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany
4Department of Cardiology, German Heart Center Berlin (DHZB), Berlin, Germany
5Berlin Institute of Health (BIH)

Correspondence: Prof Dr med Carsten Tschöpe, Medizinische Klinik mit Schwerpunkt Kardiologie, Charité – Universitätsmedizin Berlin, Campus Virchow Klinikum, Augustenburgerplatz 1, D-13353 Berlin, Germany
E-mail: Carsten.tschoepe@charite.de

Abstract
Chronic heart failure (HF) patients stratified by categories of left ventricular ejection fraction (EF) represent different phenotypes in terms of demographics, clinical presentation, etiology, mechanical and electrical remodeling, and pharmacotherapies. Until recently, there were two HF categories, distinguished on the basis of EF: HF with reduced EF (HFrEF; EF<40%) and HF with preserved EF (HFpEF; EF>50%). A “gray zone” remained for HF with EF values from 40% to 49%, and in clinical trials, patients within this zone were often assigned to one or the other defined groups. The new European Society of Cardiology Heart Failure 2016 guidelines have better defined this subentity as a separate group—HF with mid-range EF (HFmrEF), aiming to stimulate research into the underlying characteristics, pathophysiology, and, ultimately, treatment of HFmrEF. Some studies have already suggested that HFmrEF shows intermediate clinical characteristics falling between HFrEF and HFpEF. HFmrEF patients were often found to be younger, more likely to be male, and to have less frequent hypertension than HFpEF patients. Etiologically, HFmrEF resembles HFrEF more than HFpEF, with a higher prevalence of coronary artery disease and previous myocardial infarction or myocarditis, suggesting specific treatment strategies. HFmrEF can dynamically transition into HFpEF (recovery from disease) or HFrEF (progression of the disease); thus, subgroups of HFmrEF patients may represent a temporary state rather than an independent entity of HF. In conclusion, HF is a heterogeneous syndrome not sufficiently characterized by the measurement of EF alone. A deeper understanding of the underlying etiology and pathophysiological mechanisms, as well as the patient’s position on the disease trajectory, is mandatory to establish more precision-medicine–based therapeutic approaches. ■ Heart Metab. 2017;74:8-12

Keywords: diagnostic; HFmrEF; pathophysiology; treatment

Introduction
For heart failure (HF) patients with reduced ejection fraction (HFrEF; ie, HF with a left ventricular ejection fraction [LVEF] <40%), the accumulated therapeutic evidence has given rise to effective pharmacological and device therapies that have led to impressive improvements in survival.1 HF with preserved EF (HFpEF), defined in current guidelines as HF with an EF that meets or exceeds
HFmrEF: a mildly reduced EF does not imply a mild disease

the cut-off value of ≥50%,2 shows a similar reduced outcome; however, its management remains challenging, indicating that successful treatment targets differ between HFrEF and HFpEF.3 Between those defined categories of HF, there was an undefined gap for EF values falling within a middle range of 40% to 49%; in the American College of Cardiology/American Heart Association guidelines from 2013, HF with EF values falling within this range was referred to as an “intermediate group” but for management was treated according to what was known about HFpEF.4 Today, the recent 2016 European Society of Cardiology (ESC) guidelines refer to HF with EF values of 40% to 49% as a “gray area” to be regarded as mild systolic dysfunction but with features of diastolic dysfunction and needing further investigation; it reclassified this subentity as HF with mid-range EF (HFmrEF).1 Previously, HF clinical trials systematically either excluded such patients or assigned them to either the HFrEF or HFpEF group. Indeed, HFmrEF may share characteristics of both HFrEF and HFpEF5-7 to different extents; consequently, clinically, it is not clear which HF group individual HFmrEF patients belong to, what their prognosis will be, and which treatment options would be most relevant.8,9 Therefore, by identifying HFmrEF as a separate entity, the European Society of Cardiology (ESC) guidelines aim to stimulate research into its underlying characteristics, pathophysiology, and treatment. The main question is whether differentiation of patients with HF on the basis of LVEF can effectively separate them by underlying etiologies, demographics, and comorbidities with the ultimate aim of identifying a common response to therapies.

Prevalence and clinical characteristics of heart failure with mid-range EF

A number of data are available regarding the prevalence of HFmrEF. Although designs and settings differ between studies and registries, 14% to 24% of HF patients are characterized as having HFmrEF, as observed in Western countries, as well as in Asian trials. Thus, almost one-fifth, a substantial proportion of patients with HF, have a moderately reduced LVEF that falls between the commonly used cut offs for HFrEF and HFpEF.5-7,10-15

Clinical characteristics of heart failure with mid-range EF

Clinical presentation, burden of comorbidities, and quality of life were often shown to be similar for HFrEF, HFmrEF, and HFpEF.5-7,15 HFmrEF populations share some characteristics with HFpEF and some with HFrEF, but have also been found to have intermediate characteristics. Patients with HFmrEF are usually younger and more likely to be male than those with HFpEF. The HFmrEF group resembles the HFrEF group with regard to some features, including age and gender, but usually shows less left ventricular and atrial dilation. Several cardiovascular risk factors are shared among HFmrEF, HFrEF, and HFpEF, but patients with HFmrEF are more likely to have hypertension and diabetes than those with HFrEF. Most importantly, HFmrEF more closely resembles HFrEF with regard to both a higher prevalence of coronary artery disease and a greater risk of new cardiac ischemic heart disease events.6 A recent study from Sweden7 found that the prevalence of ischemic heart disease is similar between HFmrEF and HFrEF and that both are higher than in HFpEF (61%, 69%, and 52.4%, respectively). Among ischemic heart disease patients, previous myocardial infarction was more common in HFmrEF and in HFrEF than in HFpEF (88%, 71%, and 56%, respectively), and, consequently, patients were more often revascularized. Although ischemic heart disease is a significant prognostic factor across all HF types, it is important that coronary artery disease was found to be the principal primary cause of HFrEF and HFmrEF, whereas hypertensive heart disease was the principal etiology underlying HFpEF.7

Abbreviations

CHARM-Preserved: Candesartan in Heart failure—Assessment of morTality and Morbidity – Preserved [trial]; EF: ejection fraction; ESC: European Society of Cardiology; HF: heart failure; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro–B-type natriuretic peptide; NYHA: New York Heart Association; TOPCAT: Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist [trial]
Predictors and prognosis of heart failure with mid-range EF

The prognosis of HF is poor in general. However, data for the prognoses for the three HF forms differ. Some registries describing outcome in HFrEF show that all-cause hospitalization-free survival, overall survival, and HF hospitalization-free survival is similar to that found in HFmrEF and HFpEF without significant differences in outcome. However, others found that the HFmrEF mortality rate is intermediate, falling between the rates for the other two HF groups, with 1-year mortality rates being 8.8%, 7.6%, and 6.3% for HFrEF, HFmrEF, and HFpEF, respectively. Age, New York Heart Association (NYHA) class III/IV status, and chronic kidney disease predicted mortality across all LVEF groups. Low systolic blood pressure and high heart rate are predictors for mortality in HFrEF and HFmrEF. Although atrial fibrillation was found to be more common with increasing EF, it was associated with a similar increased risk of death, hospitalization rate, and stroke in all HF groups. However, HFmrEF resembles HFrEF rather than HFpEF with respect to ischemic heart disease as underlying cause, and HFmrEF was shown to be intermediate with regard to risk of new ischemic events. Established ischemic heart disease has an adverse impact on a majority of outcomes in all EF categories, but this is most prominent for new ischemic heart disease events in HFmrEF and in HFrEF. This is clinically relevant and calls for a diagnostic search for an ischemic etiology in patients with HF and EF values under 50%.

Treatment strategies for heart failure with mid-range EF

The overall finding that coronary heart disease, with a prevalence of 60%, is the most important driver in HFmrEF suggests, at least for this subgroup of patients, specific treatment strategies. Several registries and a recent individual patient-level analysis of double-blind randomized β-blocker trials have shown

<table>
<thead>
<tr>
<th>Drug</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>+</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>ARB</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
</tr>
<tr>
<td>BB</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>+</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>MRA</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
</tr>
<tr>
<td>Digitalis</td>
<td>+</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>ARNi</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Diuretics</td>
<td>+c</td>
<td>+c</td>
<td>+c</td>
</tr>
</tbody>
</table>

Table I EF-dependent pharmacological treatment responses. Data from registries or subgroup analysis show that treatments able to improve clinical outcome in HFrEF seem to also be beneficial in HFmrEF, but not in HFpEF. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNi, angiotensin-receptor neprilysin inhibitor; BB, β-blocker; HFmrEF, heart failure with midrange ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist. +, positive results for mortality and/or morbidity in prospective randomized controlled trials. (+), positive results from registries, subgroup analysis, or retrospective analysis. No data from randomized controlled trials available. -, negative results for mortality and/or morbidity in prospective randomized controlled trials. NA, not analyzed/data not available. +c, recommended to relieve symptoms and signs of congestion.
that the impact of cardiovascular medications, including the use of \(\beta\)-blockers, in HFmrEF is similar to that in HFrEF, but not in HFP EF (Table I).\(^6,7,23\) These findings are of clinical importance because there has been no evidence to guide HFmrEF management, and the ESC guidelines recommend therapies for HFrEF patients on the basis of evidence for HFP EF rather than that for HFmrEF. The effectiveness of classical HF drugs, including renin-angiotensin-aldosterone antagonists and \(\beta\)-blockers, on reverse remodeling has not been studied specifically in HFmrEF. It was shown that a decrease in N-terminal pro-B-type natriuretic peptide (NT-proBNP) was associated with an improved prognosis in HFmrEF.\(^24\) However, as summarized by Lam and Solomon,\(^6\) subgroup analyses from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist)\(^25\) and CHARM-Preserved studies (Candesartan in Heart failure—Assessment of mor tality and Morbidity – Preserved)\(^11,26\) have shown that HFmrEF patients had a benefit in prognosis similar to those with HFrEF with the use of spironolactone or candesartan, respectively. These findings support the hypothesis that treatment should be initiated according to the underlying etiology rather than the presenting LVEF.

**Conclusion**

One-fifth of HF patients belong to the HFmrEF group. A “mildly reduced EF” does not imply a “mild disease”: (i) clinical characteristics and prognosis of HFmrEF are intermediate between HFP EF and HFrEF; (ii) there are important LVEF transitions in HFmrEF toward HFrEF and HFP EF; (iii) HFmrEF is associated with worse prognosis when transitioned to HFrEF; and (iv) the prognostic impact of cardiovascular medications in HFmrEF resembles that in HFrEF.\(^5,7,15,16\)

Although guidelines have reclassified HF into at least three different groups, we should not forget that HF represents a heterogeneous syndrome, rather than a specific disorder. As discussed for HFP EF, it is also becoming more and more evident that in HFmrEF, a solely EF-based HF classification is probably not going to provide a sufficiently robust foundation on which to develop differential diagnoses and treatments.\(^27,28\) A deeper understanding of the underlying mechanisms is warranted. The establishment of a more precision-medicine–based approach, eg, the so-called phenomapping approach,\(^29\) combining of clinical profiles, new (dynamic) imaging investigations, biomarkers, and liquid biopsies may allow an improved classification of the individual HF patient in the future. The burden of ischemic heart disease in HFmrEF has an important clinical impact and should already be considered in our daily clinical diagnostic and treatment approaches.

**REFERENCES**

13. He KL, Burkhoft D, Leng WX, et al. Comparison of left ventricu-
HFmrEF: a mildly reduced EF does not imply a mild disease


Renal function in acute heart failure: what can go wrong and what we can do about it

Steven R. Goldsmith, MD
Professor of Medicine, University of Minnesota; Director, Heart Failure Program, Hennepin County Medical Center, Minneapolis, Minnesota; Director, Minnesota Heart Failure Consortium

Abstract
Renal dysfunction frequently occurs during treatment for acute heart failure. Baseline renal dysfunction and worsening renal function confer a poor prognosis in patients with acute heart failure. Renal dysfunction may be due to disturbances in intrinsic renal function, inadequate arterial pressure, excessive renal venous and intracapsular pressure, and/or the impact of therapy on intrarenal autoregulatory mechanisms. Distinguishing the precise mechanism or mechanisms that may be operative in each case of renal dysfunction in acute heart failure is critical to avoid further worsening of renal function and to provide optimum therapy for both the heart and the kidney. ■ Heart Metab. 2017;74:13-16

Keywords: acute heart failure; kidney; afterload/preload

Introduction

Acute heart failure (AHF) is characterized most commonly by an increase in left and right ventricular filling pressures. The vast majority of severe or acutely decompensated heart failure (HF) patients suffer primarily from congestion and elevated filling pressures and not from low blood pressure or decreased cardiac output. Increased filling pressures are transmitted to the pulmonary and systemic circulation and result in circulatory congestion. A primary change in cardiac function due to myocardial infarction or arrhythmia may initiate this sequence. However, circulatory congestion may develop independent of primary changes in cardiac function and in turn cause increases in cardiac filling pressures. Such congestion may arise from many different causes, including increased total body volume expansion, shifts of blood from reservoirs in the splenic and splanchnic beds to the central circulation, and/or a rise in blood pressure, which increases left and right ventricular afterload and may compromise systolic and/or diastolic function. Frequently, many of these mechanisms occur together and set up a number of feedback loops whereby they magnify their individual adverse effects.

Simple volume retention is probably the most common mechanism of circulatory congestion, and by far the most common treatment involves diuretics. The kidney is therefore at the center of the problem for most cases of AHF both as a contributor to congestion and as the target of therapy. The signal for volume retention arises from activation of the sympathetic nervous system (SNS) and the renin-angiotensin aldosterone system (RAAS), as well as secretion of the antidiuretic hormone arginine vasopressin, all of
which contribute to sodium and water reabsorption. As left ventricular filling pressure increases, causing increased respiratory rate and dyspnea, SNS activity rises further with additional stimulation of the RAAS and vasopressin, setting the stage for a vicious cycle. Data from several recent trials conducted by the National Heart, Lung, and Blood Institute Heart Failure Network demonstrate heightened activity of the RAAS in severely congested patients with AHF. In these studies, activation of the RAAS was linked to worsening renal function (WRF), suggesting a bidirectional relationship between neurohormonal activation and renally mediated congestion as AHF develops.

**A physiological approach to the heart and kidneys**

When we treat AHF, therapy is directed at removing volume and reducing arterial pressure (if elevated). Although it has not been a major focus of recent trials, therapy should probably include an attempt to mitigate the effects of neurohormonal activation. All of these interventions have effects on the kidney. A sound understanding of the influences on renal function in AHF and how it is affected by therapy is therefore critical in the treatment of AHF. Lack of appreciation of the ways in which AHF and the treatment for AHF may affect renal function may lead to failure to correct renal dysfunction when present, or worse, to WRF, which in turn may further aggravate volume retention and vasoconstriction.

When we approach a patient with AHF, we analyze the problem in terms of changes in preload, afterload, and ventricular function. This is because it makes little sense to give diuretics to a patient with acute diastolic HF whose main problem is hypertension from non-compliance with blood pressure medications. That patient primarily and perhaps only needs a reduction in blood pressure to alleviate the increase in cardiac filling pressure and pulmonary venous congestion. On the other hand, it may be risky to further lower blood pressure in a patient with a dilated ventricle and low ejection fraction presenting with a 30-kg weight gain, anasarca, and a blood pressure of 90/60 mm Hg. Furthermore, neither approach may be useful to a patient who had a normal blood volume and arterial pressure immediately before a massive myocardial infarction or the onset of an arrhythmia, such as atrial fibrillation, with rapid ventricular response. A similar analysis should occur when approaching renal function in a patient with AHF.

**Renal preload and afterload**

The kidney may be regarded as a sophisticated filtration system with many intrinsic components. However, for any given level of intrinsic renal function, renal loading conditions are important, just as they are for the left ventricle. One can therefore view renal function in AHF in terms of renal “preload,” intrinsic renal function, and renal “afterload” (Figure 1). Renal “preload” is the arterial inflow pressure and it has to be adequate to allow filtration to occur, although there are important autoregulatory factors that may preserve glomerular filtration rate (GFR) even when arterial inflow pressure in turn relates to the gradient between arterial inflow pressure, which can be considered as “renal preload,” and venous outflow pressure, which can be viewed as “renal afterload.” Although the kidney is a retroperitoneal structure, transmission of intra-abdominal pressure, if increased, may also influence perfusion and glomerular filtration and so may also be a component of renal “afterload.” In severe or acutely decompensated heart failure, renal function may decline purely on a hemodynamic basis, though typically used heart failure therapies may also influence intrarenal function. See the body of the paper for more detail.
Renal function in acute heart failure

As most patients with AHF are not overtly hypotensive, maintaining renal “preload” is not generally the most pressing problem in maintaining or improving renal function while treating AHF, though it does come into play with hypotensive patients or those who are in cardiogenic shock.

Frequently, however, one observes that despite a normal arterial pressure or renal “preload,” and with no known intrinsic renal disease, patients with AHF exhibit a decrease in GFR that reverses when they are decongested. The mechanism of this effect relates to renal “afterload”—the renal venous pressure, which in turn is related to the central venous pressure. A component of this renal afterload also seems to be related to the intra-abdominal pressure which may be transmitted to the retroperitoneal space and increase intracapsular pressure. It has been known for decades that an increase in renal venous pressure has an adverse effect on GFR, but until comparatively recently, the importance of this mechanism in both the presentation and treatment of AHF had been overlooked. The key to understanding renal dysfunction and WRF in many patients and its subsequent improvement with decongestive therapy lies with the beneficial effects from reducing renal “afterload” as a response to decongestive therapies whether they be pharmacologic, such as loop diuretics, or mechanical, such as ultrafiltration. To continue the analogy with HF, renal dysfunction due to increased renal venous pressure has an adverse effect on GFR, but until comparatively recently, the importance of this mechanism in both the presentation and treatment of AHF had been overlooked. The key to understanding renal dysfunction and WRF in many patients and its subsequent improvement with decongestive therapy lies with the beneficial effects from reducing renal “afterload” as a response to decongestive therapies whether they be pharmacologic, such as loop diuretics, or mechanical, such as ultrafiltration. To continue the analogy with HF, renal dysfunction due to increased renal venous/abdominal/intracapsular pressures might well be termed “congestive kidney failure.”

We can therefore modulate renal “preload” and “afterload” by paying attention to the mean arterial pressure and the central venous pressure, as well as to the intra-abdominal pressure if conditions such as tense ascites are present. Under most circumstances in AHF we may not be able to directly improve renal function because of renal injury from hypoxia, contrast dye, or intrinsic renal disease. However, our therapies may also have effects that appear independent of “preload” and “afterload,” as assessed by mean arterial and central venous pressure. As noted, autoregulatory factors allow for maintenance of GFR when arterial inflow pressure is decreased. Angiotensin II figures prominently here as it is a potent constrictor of the efferent arteriolar circulation within the glomerulus. When arterial pressure falls, and activation of the RAAS occurs, efferent arteriolar constriction may help to maintain intraglomerular filtration pressure. When an angiotensin II antagonist or angiotensin-converting enzyme inhibitor is given, GFR may then actually fall slightly because of a decrease in the glomerular filtration pressure despite a normal arterial pressure. This may occur more commonly at low arterial pressures where preferential dilation of the efferent arterioles occurs in response to these agents. This sort of renal “dysfunction” as reflected by a fall in GFR is generally not clinically important since the effect for the most part is small, and sodium and water excretion may continue because of a fall in the filtration fraction (GFR declining out of proportion to renal blood flow); also, since angiotensin II may constrict overall renal arterial input and limit intrarenal flow or renal “preload,” the net effect of using these drugs on renal filtration and excretory function may be neutral or even positive. It is not recommended that ACE inhibitor and angiotensin receptor blocker (ARB) be stopped in AHF unless severe renal dysfunction is present.

Respecting the heart and kidneys

It is therefore very helpful to approach the kidney in AHF in the same manner as we approach the heart and attempt to identify the mechanisms leading to renal dysfunction and address them selectively. Just as attempting to treat all AHF in the same manner will not produce uniformly positive results, lumping all cases of abnormal or WRF together will lead to misunderstanding and inappropriate or inadequate therapy. If the patient is hypotensive, arterial pressure must be raised. If the patient is grossly volume overloaded, aggressive diuresis is critical. RAAS inhibition should continue even if a transient fall in GFR due to efferent arteriolar dilation is seen.

One variable that does not seem to be important is cardiac output, since the kidney doesn’t respond to cardiac output per se, but rather to perfusion pressure. As elegantly shown by studies from the Cleveland Clinic, regardless of cardiac output, it is the renal perfusion pressure, ie, the difference between diastolic blood pressure and central venous pressure, that is the key determinant in maintaining GFR.

This point is illustrated nicely in an elegant brief review by Jessup and Costanzo. Considering the various factors that influence renal function in AHF, improving cardiac output (even if low) with the use of vasodilators and inotropes would probably not be of value, independent of improvement in arterial pressure.
Thinking beyond loop diuretics

Why is attention to the kidney so important in treating patients with AHF? As already stated, it is the kidney that causes much of the congestion in congestive HF. If renal function is inadequate, diuresis will be very difficult, particularly with loop diuretics, which themselves directly and adversely affect both renal function and neurohormonal imbalance. And if the patient is congested to the point of an increase in central venous pressure, this may be very difficult to overcome since more and more loop diuretics may simply cause more and more renal dysfunction, aggravating what has been called type I cardiorenal syndrome. It is for this reason that newer therapies, such as ultrafiltration and vasopressin antagonism, have been and are being explored in AHF, a topic beyond the scope of this discussion. However, the “bottom line” is that without adequate renal function, successful treatment of AHF is often very difficult.

Is worsening renal function always bad?

The last point to emphasize is the prognostic importance of renal function in AHF. Many studies have shown that abnormal or WRF is associated with an adverse prognosis. More recent studies have suggested that transient WRF, or WRF without persistent congestion, may not have the same adverse effects. Although these observations have not been substantiated or studied prospectively, it does seem that transient or mild WRF, if not associated with persistent congestion, may be acceptable. It is perhaps likely that in many of these situations, the WRF is due to the effects of neurohormonal inhibition triggered by the use of agents that interfere with activity of the RAAS. However, at least in theory, our goal in treating AHF should be to achieve adequate decongestion while improving or at least not significantly worsening renal function. We can do this most successfully by improving the loading conditions for both the heart and the kidney if we understand the impact of our treatments on each.

REFERENCES

Preventing heart failure hospital readmissions: challenges and opportunities

Boback Ziaeian, MD, PhD; Gregg C. Fonarow, MD

Division of Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, California; Division of Cardiology, Veteran Affairs Greater Los Angeles Healthcare System, Los Angeles, California; Ahmanson-UCLA Cardiomyopathy Center, University of California, Los Angeles Medical Center, Los Angeles, California

Correspondence: Gregg C. Fonarow, MD, Ahmanson-UCLA Cardiomyopathy Center, Ronald Reagan UCLA Medical Center, 10833 LeConte Avenue, Room A2-237 CHS, Los Angeles, CA 90095-1679 E-mail: gfonarow@mednet.ucla.edu

Abstract
Heart failure (HF) is a leading cause of hospitalization and readmission. As evidence-based treatments for the management of HF with reduced ejection fraction have evolved, the ability to reduce the HF readmission risk has improved. Clinical trials have shown measurable improvements in patient-centered outcomes through exercise, pharmacologic, and device therapies. In contrast, for HF with preserved ejection fraction, no medical therapy has been identified that improves survival, though aldosterone antagonists may reduce HF hospitalization risk. Thirty-day readmission rates have become a metric for hospital quality and financial penalties in the United States; however, reducing all preventable hospitalizations, improving health status, and prolonging survival should be the goal for HF patients. Nearly half of repeat hospitalizations for HF are secondary to noncardiovascular conditions. Careful attention to complicating comorbid conditions should be assessed before discharge for an acute decompensation. Optimizing the outpatient management of HF and providing careful transitions from the hospital to the outpatient setting are critical to minimizing readmission risk and improving patient-centered outcomes. Heart Metab. 2017;74:17-23

Keywords: heart failure; prevention; process measures; quality of care; readmission

Introduction
In the United States, heart failure (HF) is the fourth leading cause of all hospitalizations and the leading cause of hospitalization among cardiovascular diagnoses. According to Medicare, approximately one in four patients with a HF hospitalization will be readmitted at 30 days. Readmissions are a target for researchers and policy makers, as they are perceived as a marker of poor care quality and a source of preventable health care utilization. With HF prevalence projected to increase from 5.7 million to over 8 million American adults and costs ballooning from $20.9 billion to $53.1 billion between 2012 and 2030, reducing preventable hospitalizations for HF patients is a national priority.

Medicare uses hospital performance on 30-day HF mortality and readmissions as a quality metric and applies financial penalties to hospitals based on performance. Yet, strategies for effectively preventing or reducing readmissions are not agreed upon. Furthermore, the 30-day period of observation for readmis-
Heart failure hospitalizations

A hospital admission for HF portends a high risk for future morbidity and mortality. Among Medicare patients admitted for HF, 67% experienced a readmission and 36% died within 1 year. Readmission risk is highest on the third day following discharge. Not until 38 days after discharge is the readmission risk cut in half.4 Whereas hospital length of stay and inpatient mortality have decreased in the United States, discharges to skilled nursing facilities have increased (Figure 1).5 This reflects a sizeable population of chronically ill HF patients unable to live independently and at high readmission risk. The quality of a skilled nursing facility is known to influence hospital readmission rates, as well as mortality.6

HF management protocols prioritize cardiovascular care; only 17% to 35% of HF discharges are readmitted with a repeat HF exacerbation; however, 47% to 62% are readmitted for noncardiovascular causes.7,8 The diversity of readmission etiologies emphasizes the importance of a comprehensive assessment to prevent complications from other comorbidities and to identify specific patient needs. With the implementation of financial incentives to reduce readmissions, Medicare has reported modest decreases in the average 30-day HF readmission rate (Figure 2).9,10 The corresponding fall in the readmission rate also correlated with an increase in “observational stays,” which are not categorized as readmissions. The degree to which readmissions in HF patients are preventable is unclear. Less than a quarter of all 30-day readmissions were estimated as potentially avoidable based on chart review.11
Medical therapy to reduce HFrEF readmissions

The management of HF with reduced ejection fraction (HFrEF) has evolved over recent decades with additional medical therapies and interventions that improve long-term survival. A strong foundation exists for the use of evidence-based medical therapies to improve outcomes and reduce the hospitalization burden for HFrEF patients (Table I).12 Therapies that reduce the hospitalization burden are expected to reduce readmissions as well.

The cornerstone of guideline-directed medical therapy for HFrEF includes the inhibition of the renin-angiotensin and cardiac β-adrenergic systems.13,14 Angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) were found in clinical trials to improve mortality and reduce hospitalizations.15,16 β-Blockers are effective in reducing both mortality and readmissions.17-19 Of the performance measures recommended by the American College of Cardiology and the American Heart Association, only β-blockers and ACE inhibitors/ARB were significantly associated with reductions in mortality and readmissions.20 The new angiotensin II receptor neprilysin inhibitor (ARNI) sacubitril-valsartan improved mortality and hospitalization risk beyond the benefits of ACE inhibition among symptomatic HFrEF patients in the large PARADIGM-HF trial (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure).21 Both American and European guidelines endorse the use of ARNIs in appropriately selected patients.13,14

Additional medical therapies have been found to reduce hospitalization risk. Aldosterone inhibitors such as spironolactone and eplerenone have both been shown in clinical trials to reduce death and hospitalizations, with benefits seen within 30 days of therapy initiation.22,23 Observational data confirms that the addition of an aldosterone inhibitor reduces HF readmissions, but remains underutilized in clinical practice.24 Among African Americans with HFrEF, the combination of hydralazine and isosorbide dinitrate was found to improve mortality and reduce hospitalizations on top of optimal medical therapy.25 Optimization of guideline-directed medical therapy dosing and monitoring is also essential for improving outcomes, and better ensuring the efficacy of therapies demonstrated in trials translates into real-world clinical effectiveness.

HFrEF patients with elevated heart rates are observed to be at increased risk for adverse outcomes.26 A new sodium-potassium inward channel (I_f, also called the funny current) blocker, ivabradine, was found to reduce hospitalizations for medically optimized HFrEF patients with a sinus rate greater than 70 beats per minute.27 Although an older medication, there is fair evidence for recommending digoxin as an add-on therapy in symptomatic or at-risk patients. The Digitals Investigators Group trial found a 6% absolute risk

reduction in hospitalization with digoxin after an average of 37 months of follow-up. Although β-blockers were not routinely used during the study period, more recent observational data suggest that digoxin may be effective in reducing readmissions. With respect to diuretic therapy, torsemide has a higher bioavailability compared with furosemide. Small nonblinded trials suggest that patients discharged with torsemide have a lower readmission risk.

Nutritional supplementation with n-3 polyunsaturated fatty acids was found to provide a small mortality and hospitalization benefit after a median observation period of 3.9 years. Lifestyle interventions through exercise were evaluated in the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of exercise training). The addition of a regimented exercise program reduced HF hospitalizations and improved quality of life. Pooled findings from other monitored exercise trials facilitated Medicare’s approval of cardiac rehabilitation in chronic HFrEF patients.

Whereas device therapies such as implantable cardioverter defibrillators (ICD) are indicated for the prevention of sudden cardiac death, cardiac resynchronization therapy (CRT) is useful for improving cardiac function and symptoms. In the trials CARE-HF (CAdiac RESynchronization-Heart Failure) and MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), CRT markedly reduced HF hospitalization risk. When compared with ICD therapy alone, CRT therapy is associated with a lower risk of death and all-cause readmission.

The potential for new technologies to monitor congestion and prevent readmissions is a developing field. The CardioMEMS device (St. Jude Medical, Inc, St. Paul, Minnesota) is the first implantable pulmonary artery sensor that wirelessly transmits pulmonary artery hemodynamics to monitor cardiac pressures. Usage of the device reduced HF hospitalizations by 37% after 15 months among patients previously hospitalized for HF compared with usual care. Both the fidelity of data and an advanced care team receiving the transmitted information resulted in improved fluid management and patient outcomes.

In patients with HF with preserved ejection fraction (HFrEF), no therapy has been shown to reduce mortality. However, there is some data to suggest that aldosterone antagonist therapy may reduce HF hospitalization risk in these patients. Implantable hemodynamic monitoring also has been demonstrated to reduce HF hospitalizations.

### Table 1

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-HeFT</td>
<td>ACE inhibitor</td>
<td>African-American Heart Failure Trial</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>ARB</td>
<td>Chronic Heart Failure: A Controlled Trial Investigating Outcomes of exercise training</td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>ARNI</td>
<td>Multicenter Automatic Defibrillator Implantation Trial with cardiac resynchronization therapy</td>
</tr>
<tr>
<td>CHAMPION</td>
<td>β-Blockers</td>
<td>HF-ACTION</td>
</tr>
<tr>
<td>CHARM</td>
<td>Drug</td>
<td>SOLVD</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Digoxin</td>
<td>RALESH, EPHESUS-HF</td>
</tr>
<tr>
<td>Hydralazine-isosorbide dinitrate</td>
<td>Hydralazine-isosorbide dinitrate</td>
<td>SHIFT</td>
</tr>
<tr>
<td>n-3 PUFA</td>
<td>n-3 PUFA</td>
<td>GISSI-HF</td>
</tr>
<tr>
<td>CRT</td>
<td>Devices</td>
<td>CARE-HF, MADIT-CRT</td>
</tr>
<tr>
<td>CardioMEMS</td>
<td></td>
<td>CHAMPION</td>
</tr>
</tbody>
</table>

### Abbreviations

- ACE: angiotensin-converting enzyme
- ARB: angiotensin II receptor blocker
- ARNI: angiotensin II receptor neprilysin inhibitor
- n-3 PUFA: n-3 polyunsaturated fatty acids
- CRT: cardiac resynchronization therapy
- COPERNICUS: Carvedilol Prospective Randomized Cumulative Survival; DIG: Digitalis Investigation Group
- EPHESUS-HF: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
- GISSI-HF: Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico
- HF-ACTION: Heart Failure: A Controlled Trial Investigating Outcomes of exercise training
- MADIT-HF: Multicenter Automatic Defibrillator Implantation Trial with cardiac resynchronization therapy
- MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
- PARADIGM-HF: Prospective comparison of ARNI with ACE-I to Determine Impact on Global Mortality and morbidity in Heart Failure trial
- RALES: Randomized Aldosterone Evaluation Study
- SHIFT: Systolic Heart failure treatment with the l, inhibitor ivabradine Trial
- SOLVD: Studies Of Left Ventricular Dysfunction

### Hospital interventions to reduce readmissions

Transforming care delivery to provide more information and resources to discharged patients has also been associated with lower readmission rates. A review of interventions (such as patient education, discharge planning, medication reconciliation, scheduling follow-up before discharge, communication with outpatient providers, and follow-up telephone calls) implemented to reduce readmissions found that no single intervention alone reduced the 30-day readmission risk. Generally, more interventions are as-
associated with greater success.\textsuperscript{38} Most research in this realm has been observational, and further research is warranted in order to understand the effectiveness and costs of resource intensification.

Certain hospital characteristics have been associated with lower readmission risks. Higher nurse staffing ratios were associated with 41\% lower odds of receiving Medicare penalties for excessive readmissions when controlling for case-mix and hospital characteristics.\textsuperscript{39} Hospitals with a greater proportion of patients receiving follow-up care within 7 days of discharge have a lower risk of 30-day mortality and readmission, controlling for patient and hospital factors.\textsuperscript{40} Appropriate follow-up after hospitalization remains integral to reducing repeat hospitalizations.

Peri-discharge interventions may improve clinical outcomes and reduce HF readmissions, as shown in small trials. A multidisciplinary, nurse-directed intervention including comprehensive education for patients and families, medication review, and intensive follow-up reduced readmissions by over half and improved quality of life scores.\textsuperscript{41} Another small randomized trial found formal education that used nurse-directed patient education and intermittent patient contact after discharge for 1 year reduced readmissions by 39\%.\textsuperscript{42} A meta-analysis of interventions among older HF patients reported that comprehensive discharge planning with post-discharge support reduces readmissions and improved outcomes without increasing costs.\textsuperscript{43} Publication bias remains a concern regarding the external validity of these interventions, especially for smaller studies. Overall, the literature suggests that more support and careful outpatient monitoring may reduce the readmission burden and improve patient quality of life.

**Perspective on HF readmission reduction efforts**

Whether the 30-day HF readmission is an appropriate metric of hospital care quality is debatable. Critics have argued that the 30-day readmission measure does not adjust for medical complexity, disability, and socioeconomic status. Models that risk adjust on the basis of characteristics during hospitalization perform poorly, with C-statistics well below acceptable discrimination standards.\textsuperscript{44} Hospitals in lower socioeconomic regions are disadvantaged and more likely to receive Medicare penalties.\textsuperscript{45-47} Over half of the national variation in hospital readmission rates may be explained by the county socioeconomic factors.\textsuperscript{48} Financially penalizing hospitals that have limited resources is a perverse disincentive that may exacerbate disparities in the quality of care delivered.

Nearly half of HF patients are readmitted for non-cardiovascular conditions. The importance of a complete medical evaluation should be emphasized, as HF is only one of many comorbidities that may increase the readmission risk. A HF hospitalization should not only address the acute cardiovascular issues. Before discharge, outpatient challenges should be evaluated. Patients should have an assessment of their comorbid conditions, health literacy, cognitive impairment, mental health, financial barriers, functional status, and be provided early outpatient follow-up.\textsuperscript{49} The potential impact that such multidimensional assessments and interventions may have on rehospitalization risk for HF patients requires further evaluation in clinical trials.

**Conclusions**

A number of medical and device therapies are known to improve HF outcomes in HFrEF patients and to reduce readmission risk. These therapies are frequently underutilized in eligible patients. Hospital strategies that increase support at discharge, improve communication, and provide close outpatient follow-up are associated with lower readmission risk. Whether the 30-day readmission rate is an appropriate quality metric for inpatient care is debatable. Evidence suggests that variations in hospital performance are mostly unexplained and may relate to patient and regional factors. Nevertheless, a hospitalization is a major life event that portends future adverse outcomes. All potentially avoidable hospitalizations should be prevented through careful outpatient HF management. Health system strategies that improve the quality of care and reduce the hospitalization burden are needed and require further research.

**REFERENCES**


2. Writing Group Members; Mozaffarian D, Benjamin EJ, Go AS, et al; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statis-
Preventing heart failure hospital readmissions


36. Masoudi FA, Mi X, Curtis LH, et al. Comparative effectiveness...


Clinical benefits of trimetazidine in heart failure

Giuseppe M.C. Rosano, MD, PhD, FESC, FHFA
Cardiovascular Clinical Academic Group, St George’s Hospitals NHS Trust University of London, United Kingdom – Dept of Medical Sciences, IRCCS San Raffaele, Rome, Italy

Correspondence: Giuseppe M.C. Rosano, MD, PhD, FESC, FHFA, Cardiovascular Clinical Academic Group, St George’s Hospitals NHS Trust University of London, Cranmer Terrace, London SW15 1BA, United Kingdom
E-mail: grosanosgul.ac.uk

Abstract

Heart failure is a clinical condition associated with an impaired ability to convert metabolic substrates into high-energy substrates. The metabolic alterations occurring in heart failure result in a 30% to 40% decrease in cardiac adenosine triphosphate (ATP) levels and in a significant decrease in phosphocreatine, the heart’s main store of high-energy phosphates. It is becoming evident that modulation of cardiac metabolism is an important tool for the treatment of patients with heart failure and/or with conditions that increase the risk of developing it, such as ischemic heart disease and diabetes. Unlike hemodynamic drugs, trimetazidine acts directly at the cardiac-cell level; by increasing high-energy phosphate availability, it improves contractility and reduces angina. Four meta-analyses have evaluated the effect of trimetazidine on left ventricular function, exercise tolerance, and clinical outcomes in patients with heart failure, all concluding that trimetazidine improves New York Heart Association class, functional capacity, and left ventricular ejection fraction, and reduces the occurrence of hospitalization for heart failure and cardiovascular mortality. The effects of trimetazidine on functional parameters and clinical outcome in heart failure are associated with a good safety profile. Therefore, trimetazidine represents an important therapeutic resource for the treatment of patients with heart failure in whom it has a significant benefit on quality and quantity of life. ■ Heart Metab. 2017;74:24-28

Keywords: cardiac energy metabolism; heart failure; trimetazidine

Heart failure is a clinical condition associated with an impaired ability to convert metabolic substrates into high-energy substrates. Ample evidence suggests that in heart failure and in most of its predisposing conditions such as diabetes, arterial hypertension, and coronary artery disease, there is an elevated rate of myocardial fatty acid oxidation and reduced glucose oxidation.

Metabolic alterations in heart failure

The preferential myocardial utilization of free fatty acid (FFA) in heart failure is the consequence of a mal-adaptive process that leads to an impaired production of high-energy phosphates. This maladaptive process is more evident in diabetic patients. Studies have shown that, despite higher plasma levels of glucose, these patients exhibit a greater FFA extraction and utilization by their cardiac myocytes and that a direct relationship exists between the degree of insulin resistance and left ventricular dysfunction. These changes are associated with an increased oxygen utilization and decreased energy production and metabolic efficiency. Studies in patients with congestive
heart failure found a 50% increased extraction and uptake of FFA coupled with a 60% decreased glucose uptake compared with subjects without heart failure.5

Glucose oxidation requires less oxygen per mole of adenosine triphosphate (ATP) generated than FFA oxidation; thus, FFA utilization is less metabolically efficient than glucose utilization and leads to a reduced production of ATP, which translates into a lower availability of high-energy phosphates for cellular processes and cardiac contraction than that afforded by glucose utilization. Therefore, glucose oxidation is preferable to FFA oxidation when oxygen availability is limited, such as in underperfused cardiac tissue. The metabolic alterations occurring in heart failure result in a 30% to 40% decrease in cardiac ATP concentration and in a significant decrease in its main storage molecule, phosphocreatine.1-4

ATP is required for almost all cellular processes; its reduced availability within the cardiac myocyte leads to diminished activity of the sarcoplasmic/endoplasmic reticulum calcium (Ca2+)–ATPase (SERCA) with a consequent impairment of active relaxation in early diastole. It also leads to reduced availability of ATP for actin-myosin cross-bridge cycling, leading to a further impairment of left ventricular function. The impact of glucose oxidation on left ventricular function is shown by the fact that, in animal models, after coronary artery ligation, the heart shows a better recovery of left ventricular function compared with patients on placebo.16 Our group has been the first to provide extensive evidence that metabolic modulation of the failing heart with trimetazidine has beneficial effects on cardiac function and on clinical events.17-23 We have shown that trimetazidine is effective in improving left ventricular systolic and diastolic function in diabetic patients with heart failure and/or with conditions, such as ischemic heart disease and diabetes, that increase the risk of developing it.

**Therapeutic approaches to modulating cardiac energy metabolism**

Several drugs have been shown to affect the metabolic processes in the failing heart, acting at different levels of glucose or FFA utilization. These include etomoxir, perhexiline, ranolazine, pyruvate, dichloroacetate, and trimetazidine.13 Out of all these drugs, trimetazidine is the only one that has been consistently found to improve cardiac metabolism and to have relevant clinical cardiovascular effects in ischemic heart disease and in heart failure. Trimetazidine is approved for clinical use in more than 100 countries worldwide except in the United States, where it has never been filed for approval.1 All the remaining small molecules have limited clinical application or significant safety issues that limit their use. Ranolazine is approved for the treatment of angina but has not shown efficacy in heart failure.

**A closer look at trimetazidine**

Several studies have shown that trimetazidine leads to a significant increase in cardiac ATP production and that this effect is associated with a significant clinical improvement and cardioprotection.14,15 Fraga et al have shown that the phosphocreatine/ATP ratio, an index of cardiac energy production, is lower in patients with coronary artery disease and in those with failing hearts than in normal subjects; they also show that in these patients, trimetazidine administration increases high-energy phosphate production by 33%, bringing it to the same level of that in normal subjects.14

Brottier et al first assessed the effect of long-term treatment with trimetazidine on top of standard treatment in 20 patients with advanced ischemic cardiomyopathy (New York Heart Association [NYHA] class III-IV) and found that it improved clinical status and left ventricular function compared with patients on placebo.16 Our group has been the first to provide extensive evidence that metabolic modulation of the failing heart with trimetazidine has beneficial effects on cardiac function and on clinical events.17-23 We have shown that trimetazidine is effective in improving left ventricular systolic and diastolic function in diabetic patients with heart failure, in those with ischemic heart failure, and in elderly patients with left ventricular dysfunction (Figure 1).17,19 These initial findings have been confirmed by subsequent studies extending the evidence to patients with nonischemic heart failure and post myocardial revascularization.24-30

Patients with heart failure and reduced left ventricular function show a natural history of a progressive decline in left ventricular function, often despite
optimal medical therapy. Left ventricular function can be improved by interventions that directly increase cardiac contractility or reduce oxygen consumption. Drugs of the first class—such as amrinone, milrinone, flosequinan, and ibopamine—increase oxygen consumption and, in the long term, exhaust high-energy phosphate stores, leading to an impaired function of SERCA and Ca\(^{2+}\) accumulation that in turn increases the risk of arrhythmia. This is the reason why all these drugs have consistently shown an increase in the risk of death (mainly arrhythmic) in patients with heart failure. On the other hand, drugs that reduce oxygen consumption through different mechanisms (reduction in heart rate, reduction in preload or afterload) like angiotensin-converting enzyme (ACE) inhibitors, β-blockers, mineralocorticoid-receptor antagonists, ivabradine, and sacubitril/valsartan (LCZ696), improve contractility and long-term outcome. Trimetazidine has been shown to improve left ventricular function over the long term. Unlike the traditional approach, trimetazidine acts directly at the cardiac-cell level and, by increasing high-energy phosphate availability, it improves contractility and reduces angina. The increased ATP availability also leads to an improved diastolic function and decreases the levels of free Ca\(^{2+}\) in the sarcoplasmic reticulum during diastole, thereby decreasing the risk of arrhythmia.

**Fig. 1** Effect of trimetazidine on left ventricular function in patients with heart failure. (A) Percent change in left ventricular function (various measures) in patients with ischemic heart failure treated with trimetazidine (compared with placebo). P<0.05 for all comparisons. (B) Percent change (from baseline) in left ventricular ejection fraction in diabetic patients with heart failure treated with trimetazidine. P<0.01 vs placebo.

**Abbreviation:** LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; WMSI, wall motion score index.


**Fig. 2** Effect of trimetazidine on exercise capacity and muscle strength in patients with heart failure with reduced ejection fraction (HFrEF). Gray bars indicate trimetazidine treatment. Red bars indicate placebo.

**Abbreviation:** 6MWT, 6-minute walk test; NYHA, New York Heart Association; TMZ, trimetazidine.

The improvement in left ventricular function across the studies has been assessed in a meta-analysis by Gao et al that concluded that trimetazidine therapy was associated with a significant improvement in left ventricular ejection fraction in patients with both ischemic and nonischemic heart failure (weighted mean difference compared with placebo, 7.4% and 8.7% respectively).33 These benefits are similar to those observed with ACE inhibitors. The beneficial effect of inhibition of FFA oxidation with trimetazidine is not limited to the heart; it extends to skeletal muscle where trimetazidine increases muscle strength and reduces loss of muscle mass.22,23 Overall, the central and peripheral effect of trimetazidine leads to an improvement in exercise capacity, NYHA class, and quality of life (Figure 2).34

Trimetazidine improves prognosis in patients with heart failure and reduced ejection fraction (HFrEF), as shown by a collaborative multicenter study coordinated by Fragasso.35 In this international multicenter cohort study, trimetazidine reduced overall mortality and cardiovascular mortality by 30%; it also reduced hospitalization for heart failure by 10.4% at 5 years, with an improvement in hospitalization-free survival of 7.8 months at 5 years. Other studies have subsequently shown similar results, and recent meta-analyses have confirmed the effect of trimetazidine on mortality and morbidity. Four meta-analyses have evaluated the effect of trimetazidine on left ventricular function, exercise tolerance, and clinical outcomes in patients with heart failure, and all have concluded that trimetazidine improves NYHA class, functional capacity, and left ventricular ejection fraction, and reduces the occurrence of hospitalization for heart failure and cardiovascular mortality.33,36-38 Three of these meta-analyses have also found a beneficial effect of trimetazidine on overall mortality.

The relevance of the body of evidence on trimetazidine in heart failure has also been endorsed by the recent guidelines of the European Society of Cardiology, which have included the drug in the algorithm for the treatment of patients with HFrEF.39 Furthermore, during the assessment of the benefit/risk of trimetazidine, the European Medicines Agency acknowledged the beneficial effect of trimetazidine in patients with ischemic heart failure.40

### Summary

The effects of trimetazidine on functional parameters and clinical outcome in heart failure are associated with a good safety profile. Because of the absence of an effect on heart rate or blood pressure, trimetazidine can be safely and effectively added to all cardiac medications used in heart failure. The modulation of cardiac metabolism with trimetazidine should always be considered in the treatment of patients with heart failure, when indicated. The evidence of trimetazidine in heart failure supports the well-established role of this drug in ischemic heart disease, where it can be used throughout the continuum of the disease from angina to heart failure. Its efficacy in patients with diabetes and cardiovascular disease suggests that it should be used as early as an alteration of cardiac function is detected. Its added benefits in the elderly are well proven and are associated with a sustained improvement in quality of life. Therefore, trimetazidine is an important therapeutic resource for the treatment of patients with heart failure, in whom it has a significant benefit on quality and quantity of life.

### REFERENCES

8. Peyton RB, Jones RN, Attarian D, et al. Depressed high-energy phosphate content in hypertrophied ventricles of animal and man: the biologic basis for increased sensitivity to ischemic
Clinical benefits of trimetazidine in heart failure


Team-based management to improve real-world outcomes in heart failure

Matthew Ryan, BSc, MBChB, MRCP
Department of Cardiology, Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom; Cardiovascular Division, King’s College London, London, United Kingdom

Correspondence: Dr Matthew Ryan, The Rayne Institute, 4th Floor Lambeth Wing, St Thomas’ Hospital, Westminster Bridge Road, London, SE1 7EH, UK
E-mail: matthew.ryan@kcl.ac.uk

Abstract

Adopting a team-based strategy in the management of heart failure has been demonstrated to improve patient outcomes through greater guideline adherence, better patient adherence, and closer monitoring of clinical status. We describe the case of a young patient who had repeated presentations with symptomatic heart failure, followed by disengagement from care. The cycle of deterioration was halted through the work of our multidisciplinary heart failure team. ▪ Heart Metab. 2017;74:29-31

Keywords: Team-based management in heart failure

Case

A 47-year-old Ghanaian woman attended our emergency department with dyspnea at rest. Her symptoms had developed over a few hours, before which she reported feeling well, apart from a dry cough. There was no history of edema, chest pain, or syncope. Her past medical history was remarkable for hypertension, hypercholesterolemia, and recurrent urinary tract infections with a previous episode of acute kidney injury. Her hypertension was treated with once-daily amlodipine (10 mg) as monotherapy. She had been taking thrice-daily amoxicillin (500 mg), prescribed by her general practitioner for a presumed pneumonia and initiated 24 hours earlier. She smoked five cigarettes per day and consumed alcohol infrequently.

On initial assessment she was found to be in extremis, with a resting tachypnea of 40 breaths per minute and profound hypoxemia with oxygen saturations of 60% on air. Mean arterial pressure was elevated at 110 mm Hg. Clinical examination revealed bilateral end-inpiratory crackles, wheeze, and a third heart sound. She was euvoletic with no signs of systemic hypoperfusion. An anteroposterior chest radiograph (Figure 1) demonstrated pulmonary edema and marked cardio-

Fig. 1 Chest radiograph demonstrating marked cardiomegaly and pulmonary edema.

Abbreviation: AP, anteroposterior.
megaly, even considering the projection. A 12-lead electrocardiogram (ECG) confirmed sinus rhythm, with left axis deviation but no evidence of ischemia.

She was initially resuscitated in the emergency department with high-concentration oxygen, intravenous furosemide, and an intravenous infusion of glyceryl trinitrate (GTN). Broad spectrum antibiotics were administered to cover for superadded infection. Despite this, her oxygen saturation deteriorated, and she was sedated and intubated in the emergency department 4 hours after presentation. She was transferred to our intensive care unit for stabilization.

A review of her medical notes elicited important aspects of her case. She had presented to cardiology services on a number of occasions over the previous 6 years. The first of these presentations was an admission to hospital with atypical chest pain, where she was found to have an abnormal ECG (T-wave inversion in the anteroseptal leads) and a hypokinetic apical anterior left ventricle segment on echocardiography. An invasive coronary angiography performed at the time revealed unobstructed epicardial coronary arteries. The episodes of chest discomfort resolved, and she remained well at follow-up 12 months later, though she described intermittent episodes of dyspnea, which were thought at the time to represent panic attacks. Ventricular function had normalized on echocardiography. A review was offered a year later, but the patient declined to attend. She had attended hospital on one further occasion with a suspected lower respiratory tract infection, and an ECG performed at the time showed mild left ventricular dysfunction. Follow-up was arranged, but she missed a number of appointments. There were also concerns regarding adherence to her antihypertensive medication regime during this period.

Given the repeated presentations, we investigated her for alternative causes of flash pulmonary edema. Renal duplex ultrasound demonstrated normal flow in the renal arteries, and dynamic mitral regurgitation was felt to be unlikely given the normal valve morphology and unobstructed coronary arteries. A 24-hour urine collection excluded pheochromocytoma.

Echocardiography was repeated during intensive care. The left ventricle was found to be dilated and globally hypokinetic with an ejection fraction (EF) of 30%. The right ventricle's function appeared well preserved and there were no significant valvular lesions or pericardial effusion. Her hypertension was controlled and she had a brisk diuresis. This led to a rapid improvement in gas exchange, permitting successful extubation after 12 hours. Guideline-directed heart failure therapy (angiotensin-converting enzyme [ACE] inhibitor and β-adrenoceptor blocker) was initiated and uptitrated quickly to maximum tolerated doses, along with a small dose of loop diuretic. Amlodipine was discontinued. She was discharged 8 days after admission.

After discharge, the patient’s ongoing monitoring was supervised through our heart failure multidisciplinary team (MDT). She received support from our community heart failure nurses, including regular contact and extensive education and encouragement to adhere to her medication regime. At an early outpatient review with her heart failure consultant, she was asymptomatic and her blood pressure was well controlled. A cardiac magnetic resonance imaging (MRI) scan showed persistent left ventricle dilatation but an improvement in EF, measured at 45%. No myocardial scar or right ventricular dysfunction was seen. MRI aortography again excluded renal artery stenosis and coarctation of the aorta. A formal diagnosis of dilated cardiomyopathy was made, and she will remain under follow-up with review by the MDT where necessary.

Heart failure in the real world

Managing heart failure in real clinical practice often feels a world away from the apparent perfection achieved in clinical trials. Optimally titrated doses and robust follow-up find themselves replaced with challenging adherence issues and missed opportunities to optimize care. This case highlights a number of these issues, as well as strategies that can be adopted with the aim of improving outcomes.

As in this case, the real-world diagnosis of heart failure is often delayed but apparent in retrospect. This is particularly true for younger patients, who with a greater physiological reserve will adapt to a certain level of dysfunction until a “tipping point” is reached and florid symptoms develop. It is not uncommon for episodes of dyspnea to be diagnosed as panic attacks or lower respiratory tract infections. Chest pain, though seen in-

**Abbreviations**

BNP: B-type natriuretic peptide; ECG: electrocardiogram; EF: ejection fraction; GTN: glyceryl trinitrate; MDT: multidisciplinary team; MRI: magnetic resonance imaging
frequently, may result from microvascular dysfunction in early dilated cardiomyopathy. The combination of chest pain, normal coronary arteries, and an abnormal ECG merits consideration of detailed investigation and close follow-up even if initial investigation is unremarkable. Other nonspecific but important symptoms in this demographic are generalized fatigue, exertional dyspnea despite a relatively preserved exercise capacity, and upper abdominal fullness. It is not infrequent to see new referrals in our heart failure clinic where pulmonary edema or cardiac chamber dilatation are detected on an upper abdominal computed tomography scan performed for chronic abdominal pain.

The transient nature of these symptoms further challenges clinicians, as the patient will often look well at the time of clinical assessment. Many clinicians will have a low index of suspicion of heart failure in relatively young patients with transient symptoms, meaning that opportunities to diagnose are missed. Under a busy clinical workload, how can we ensure that critical time is not lost due to diagnostic delay? The key components must be a greater awareness and consideration of the condition, coupled with the use of B-type natriuretic peptide (BNP) screening tests. The use of BNP measures to make timely diagnoses prevents hospitalizations and critical care admissions of the sort seen in this case, in turn significantly reducing the cost of care. There is evidence that even in mildly symptomatic, well-compensated patients, the use of disease-modifying therapy is strongly associated with positive clinical outcomes.

It is notable that this patient presented with significant hypertension. This is a positive prognostic sign in patients with systolic heart failure, predicting a good treatment response. Hypertensive patients have greater capacity to tolerate vasodilation and therefore up titration of medication to optimal doses.

Even with a prompt diagnosis and the initiation of gold-standard pharmacological therapy, a positive outcome will still not be achieved if the patient does not engage with treatment. This is the true real-world problem of managing heart failure. Reported rates of nonadherence vary widely, but average around 30%, with associated costs in both rehospitalization and outcomes. Attendance at follow-up for disease surveillance is equally important, though less widely investigated and reported than medication adherence. Missed reviews result in suboptimal therapy, and adverse outcomes go unnoticed.

These factors contribute significantly to the difference in mortality observed between randomized trials and real-world registries. Trial patients derive significant benefit from often-mandated guideline-directed medical therapy, structured follow-up, and close monitoring for adverse outcomes. There can be no denying that adopting these processes in the real world is challenging, but there is good evidence that such integrated management can break a cycle of repeated hospitalization and improve clinical outcomes.

**REFERENCES**

Cellular metabolic and structural changes in heart failure

Gary D. Lopaschuk, PhD  
Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada

Correspondence: Dr Gary D. Lopaschuk, 423 Heritage Medical Research Building, University of Alberta, Edmonton, Alberta T6G 2S2, Canada  
E-mail: gary.lopaschuk@ualberta.ca

Abstract
The myocardium undergoes dramatic metabolic and structural changes in patients with heart failure. These metabolic and structural changes can be major contributors to the contractile dysfunction seen in heart failure. These changes include dramatic alterations in mitochondrial function and energy metabolism, as well as structural changes in the myocyte itself and the collagen matrix. Alterations in calcium handling and excitation-contraction coupling are also hallmarks of the failing heart. Part of these alterations result from accelerated apoptosis, autophagy, mitochondrial production of reactive oxygen species, mitophagy, and mitofission that occur in heart failure. This Refresher Corner paper provides a review of some of the metabolic and structural changes in the failing heart. ■ Heart Metab. 2017;74:32-36

Keywords: apoptosis; autophagy; excitation-contraction coupling; mitochondria; mitofission; mitofuson; mitophagy

Introduction
Despite the differing etiologies involved in the development of heart failure, there are a number of common metabolic and structural changes that can occur in the failing heart (Figure 1). These include: (i) changes in cardiac energy metabolism; (ii) changes in myocardial structure (eg, increased cardiomyocyte hypertrophy, increased fibrosis, and alterations in the collagen network); (iii) alterations in cardiac contractile proteins and calcium handling; (iv) alterations in myocardial signaling pathways; and (v) alterations in apoptotic, autophagic, and mitophagic pathways. Many of these metabolic and structural changes are an initial attempt to allow the heart to adapt to the underlying etiology causing the heart failure; however, these changes can also result in an adverse remodeling of the myocardium that can also be maladaptive and contribute to the severity of heart failure. As a result, many of the therapeutic approaches used, or being developed, to treat heart failure are aimed at preventing this adverse remodeling of the failing heart. The goal of this Refresher Corner article is to provide an overview of some of the metabolic and structural changes that occur in the failing heart.

Metabolic remodeling in the failing heart
Heart failure can result in a significant remodeling of cardiac energy metabolism. Some of this remodeling may be considered “adaptive” remodeling, whereas some may be considered “maladaptive.” A prominent metabolic change that occurs in the failing heart is a decrease in mitochondrial integrity and oxidative function.1-3 Mitochondrial dysfunction can occur for a
number of reasons, including in response to increased reactive oxygen species production, decreased mitochondrial biogenesis, increased posttranslational modifications such as acetylation, and alterations in mitophagy, mitofusion, and mitofission.\textsuperscript{4,5} Impaired mitochondrial function can lead to a decrease in mitochondrial fatty acid and glucose oxidation, which can then impair cardiac energy production.\textsuperscript{1-3} Overall oxidative metabolism is impaired in heart failure; however, glucose oxidation is impaired to a greater extent than fatty acid oxidation.\textsuperscript{1} The failing heart attempts to increase energy (adenosine triphosphate [ATP]) production independent of mitochondrial metabolism by increasing glucose uptake and glycolysis. The rise in glycolysis primarily occurs via insulin-independent processes, such as by upregulation of glucose transporter 1 (GLUT1), a glucose transporter that is not dependent on insulin. In fact, the failing heart actually becomes insulin resistant, showing a marked decrease in insulin-stimulated glucose metabolism, particularly glucose oxidation.\textsuperscript{6} Despite the increase in glycolysis in the remodeled failing heart, only a small amount of ATP is produced compared with mitochondrial oxidative phosphorylation, resulting in an energy-deficient state. In addition, since pyruvate from glycolysis cannot be adequately metabolized by the mitochondria, it is shunted toward lactate production, with the resultant by-product being an increased proton (H\textsuperscript{+}) production.\textsuperscript{1} This can have the negative effect of decreasing cardiac efficiency, which contributes to the energy-starved state of the failing heart.

**Structural remodeling in the failing heart**

Heart failure is also associated with marked changes in structural remodeling. This can include increased cardiac fibrosis and increased cardiomyocyte hypertrophy (especially under conditions of pressure overload).\textsuperscript{7,9} Although increased fibrosis and hypertrophy may initially be an adaptive response, excessive remodeling contributes to the severity of heart failure.

The cellular mechanisms involved in increased cardiac fibrosis in heart failure are numerous and are not yet fully defined. Cardiomyocytes, vascular cells, and fibroblasts are interconnected in the heart via a matrix of fibrillar collagen. In heart failure, collagen deposition increases due to alterations in collagen turnover (increased synthesis and decreased degradation) by myofibroblasts.\textsuperscript{8} The

![Metabolic and structural changes in the failing heart](image)

**Fig. 1** Metabolic and structural changes in the failing heart that contribute to contractile dysfunction. Abbreviation: SERCA2, sarcoplasmic reticulum Ca\textsuperscript{2+}-ATPase.
increased deposition of collagen can be adaptive in the heart during compensatory concentric hypertrophy in order to create a stress-tolerant myocyte scaffold to enhance systolic force generation. However, accumulation of interstitial and perivascular collagen fibers and disruption of the collagen network can contribute to left and right ventricular dysfunction and the development of heart failure. Myocardial fibrosis alters the myocardial architecture, leading to myocyte disarray, as well as mechanical, electrical, and vascular dysfunction. The pathways that control collagen synthesis are complex and involve a number of cell types, including myocytes, myofibroblasts, and macrophage/leukocytes/mast cells, which secrete factors, cytokines, and hormones that trigger and maintain fibrosis. In addition, resistance of collagen to degradation by matrix metalloproteinases also occurs in heart failure, thus favoring matrisome expansion.

When cardiac function is reduced in the failing heart, the heart typically remodels and myocyte hypertrophy occurs. Although this hypertrophy may temporarily improve heart function and reduce ventricular wall stress, prolonged cardiac hypertrophy is a strong predictor of arrhythmias, sudden death, dilated cardiomyopathy, and heart failure. Cardiac hypertrophy is initiated by a complex series of signal transduction pathways that are regulated in response to either neuroendocrine factors or mechanical wall tension or stretch-sensing pathways. Neuroendocrine and cytokine hypertrophic signaling includes alterations in β-adrenergic signaling, angiotensin II signaling, aldosterone-receptor signaling, cytokine signaling, and natriuretic peptide signaling. These neuuropeptides and cytokines act on multiple receptors and signal second messenger signaling pathways in the myocytes, inducing hypertrophic growth. Receptor and second messenger pathways include, but are not limited to, β-adrenergic receptor activation, angiotensin II receptor activation, natriuretic peptide receptor activation, tumor necrosis factor α (TNFα) receptor activation, Gαq-coupled receptor activation, protein kinase C α (PKC) activation, mitogen-activated protein kinase (MAPK) kinase signaling pathway activation, increased calcium (Ca2+)/calmodulin-dependent kinase II signaling, phosphodiesterase 5 activation, nuclear histone deacetylase activation, and activation of many cardiac nuclear transcription factors that affect cardiovascular stress responsiveness (eg, nuclear factor of activated T-cells [NFAT], myocyte enhancer factor-2 [MEF2], GATA binding protein 4 [GATA4]).

As these complex signaling pathways become better defined, they could provide new pharmacological targets to attenuate the hypertrophic response in heart failure.

Remodeling of the contractile proteins and calcium handling

Contractile function of the heart is critically dependent on an efficient excitation-contraction coupling, with Ca2+ being a key mediator of contractile protein function. In heart failure, there are marked defects in this excitation-contraction coupling, including defects in Ca2+ handling by the cardiomyocytes. Whereas the sarcoplasmic reticulum (SR) ryanodine receptor (RyR) releases Ca2+ in order to initiate contraction, the SR Ca2+-ATPase (SERCA2) is critical in sequestering cytoplasmic Ca2+ into the SR to mediate muscle relaxation. In the failing heart, decreased expression and activity of SERCA2 and an increased Ca2+ leak through RyR leads to decreased Ca2+ transients that result in both reduced and slowed force generation, impaired muscle relaxation, increased potential for arrhythmogenesis, and increased Ca2+ signaling of the hypertrophic pathway (which includes calcineurin activation). These changes are also associated with upregulation of the sodium (Na+)/Ca2+-exchanger (NCX1), which is also associated with contractile dysfunction.

Significant changes also occur in the contractile proteins during the development of heart failure. Myosin is a key motor molecule that generates force by cyclic interactions with actin and tropomyosin, and it consists of two myosin heavy chains (MHC) and two regulatory light chains (MLC). In the failing heart, there is a transition from a fast α-isoform of MHC to a slow β-isoform, resulting in a decrease in contractile velocity. Heart failure also induces changes in contractile regulatory proteins. The troponin complex consists of a Ca2+-binding protein, troponin C (TnC); an inhibitory protein, troponin I (TnI); and a tropomyosin-binding protein, troponin T (TnT). In the failing heart, TnT shifts to a more fetal isoform (TnT4), which has the potential to impact cardiac contractility. Although shifts in TnI to a more fetal isoform have also been demonstrated in rodent hearts, a similar switch has not been observed in the human heart. Changes in structural proteins, such as titin, can also occur in the
failing heart. In particular, titin, a very large sarcomeric protein important in the elastic recoil of the cardiomyocyte, can switch toward a more fetal isoform, which can lead to increased ventricular stiffness.17

Apoptosis, autophagy, mitophagy, and mitofusion in the failing heart

There are a number of processes in the heart that aim to maintain quality control of the cardiomyocyte. This includes: (i) apoptosis, or programmed cell death, which is a normal physiological process that eliminates DNA-damaged or unwanted cells; (ii) autophagy, a cellular degradation process in which cytoplasmic constituents are recycled by lysosomal enzymes for reuse; (iii) mitophagy, a process where damaged mitochondria undergo selective degradation; (iv) mitofission, a process where mitochondrial fragmentation occurs; and (v) mitofusion, a process where mitochondria fuse to form larger mitochondria. In the failing heart, all of these pathways are adversely altered.

Apoptosis has been extensively studied in the failing heart; in this condition, numerous markers of apoptosis and enzymes identified in the apoptotic pathways have been shown to be upregulated.17 Although controversial, it is generally believed that excessive apoptosis in the failing heart augments contractile dysfunction and decreases cardiomyocyte numbers in the heart.18 Autophagy is also upregulated in response to stresses such as heart failure.19,20 As a result, both apoptosis and autophagy are increased in the failing heart. Although increased autophagy may be an attempt to degrade protein aggregates and defective organelles as part of a protective homeostatic mechanism to maintain cell survival, excessive autophagy may contribute to the pathology of heart failure. It is not clear as to whether autophagy is a sign of failed cardiomyocyte repair or a suicide pathway for failing cardiomyocytes. Mitophagy, which is the selective degradation of mitochondria by autophagy is also accelerated in the failing heart. This may initially be adaptive, serving to remove defective mitochondria following damage or stress. Defective mitochondria may in part, arise from the increased production of mitochondrial reactive oxygen species that occurs in the failing heart.21 However, emerging studies suggest that excessive autophagy may also contribute to the severity of heart failure, due to an excessive loss of mitochondria in the failing heart.5,20

Considerable recent interest has focused on the role of mitofission and mitofusion in the control of mitochondrial quality.4 Mitochondrial fission leads to mitochondrial fragmentation, whereas mitochondrial fusion results in the formation of enlarged mitochondria and in the fusion of damaged mitochondria with healthy organelles. Growing evidence suggests that fusion/fission factors in cardiomyocytes are critical in mitochondrial quality control and cell death. As such, impairment of these pathways can result in cardiomyocyte dysfunction and death, contributing to heart failure. Heart failure can result in small and fragmented mitochondria associated with an increase in the proteins involved in the mitofission pathway.22 In contrast, mitofusion decreases in heart failure, and the ratio of mitofusion proteins to mitofission proteins decreases.23 This increase in the rate of mitofission compared with mitofusion may explain the small fragmented mitochondria seen in the failing heart.

Summary

Dramatic metabolic and structural changes occur in the failing heart. This includes impaired mitochondrial function and oxidative metabolism, which results in an increased reliance of the heart on glycolysis as a source of energy. Increased fibrosis and cardiac hypertrophy are also two common structural changes seen in the failing heart. In addition, remodeling of Ca2+-handling and contractile proteins also occurs in heart failure. Accelerated apoptosis, autophagy, mitochondrial reactive oxygen species production, mitophagy, and mitofission also occur in heart failure. Combined, these metabolic and structural changes contribute to the severity of this condition. Thus, targeting these pathways has potential as a therapy to lessen the severity of contractile dysfunction in heart failure.

REFERENCES

4. Dorn GW II, Vega RB, Kelly DP. Mitochondrial biogenesis and
Cellular metabolic and structural changes in heart failure


Identifying heart failure in the emergency room

Maria Chiara Scali, MD, PhD
Cardiovascular Medicine Division, United Hospitals of Valdichiana, Montepulciano, 53045 Siena, Italy

Correspondence: Maria Chiara Scali, MD, PhD, Cardiothoracic Department, Pisa University, Via Paradisa 2, 56100 Pisa, Italy
E-mail: chiarascal11@gmail.com

Abstract
Acute dyspnea is a frequent diagnostic challenge for physicians. Ultrasound lung comets, also called B-lines, are a simple marker viewable by lung ultrasound that can help in the differential diagnosis between cardiac dyspnea and pulmonary dyspnea. B-lines reliably indicate a cardiac origin in patients presenting with acute dyspnea in the emergency room, with accuracy comparable to cardiac natriuretic peptides. The single most frequent source of false positives is represented by the so-called “dry B-lines,” which are visible in interstitial lung disease or lung fibrosis, but these B-lines can be distinguished from watery B-lines because the latter increase with exercise and decrease with diuretics. This innovative, low-cost imaging tool has been recently recognized by the 2016 European Society of Cardiology heart failure guidelines, which assign a class II a, level of evidence C, to lung ultrasound with B-lines for diagnosis of cardiac origin of acute dyspnea in the emergency room. ■ Heart Metab. 2017;74:37-39

Keywords: B-line; emergency room; heart failure; lung comet

Lung comets in heart failure

Counting of ultrasound lung comets (also called B-lines), first proposed in 2004, is an attractive method for assessing pulmonary congestion.\(^1\,^2\) They are a useful, practical, appealingly simple way to detect extravascular lung water, a key yet elusive parameter helpful in prognostic stratification and therapy tailoring in heart failure patients.\(^3\) B-lines, as shown in Figure 1, are described as “discrete laser-like vertical hyperechoic reverberation artifacts that arise from the pleural line..., extend to the bottom of the screen without fading, and move synchronously with lung sliding.”\(^4\) A total of 28 chest sites are scanned from the second to sixth intercostal space, and the total number of B-lines is recorded as the B-lines score.\(^3\)

Fig. 1 Six B-lines (indicated by white arrows) departing from the horizontal pleural line in a lung ultrasound scan taken at the third intercostal space in the right hemithorax of a patient with acute dyspnea.
Up to five B-lines can be counted in normal subjects. In pulmonary congestion of cardiac origin, more than 30 B-lines can be counted. A B-line–based score has been proposed in which pulmonary congestion would be graded mild when six to 15 B-lines are counted, moderate when 16 to 30 B-lines are counted, and severe when more than 30 B-lines are counted.

Pulmonary congestion–related B-lines are a very dynamic marker that changes within minutes or seconds: they decrease during dialysis or after diuretic challenge and may increase during exercise, especially in the presence of stress-induced left ventricular dysfunction. Several studies have confirmed the presence of B-lines in heart failure patients at rest, the negative prognostic impact of B-lines, and their agreement with established markers of severity, such as increased plasma concentration of cardiac natriuretic peptides, elevated pulmonary artery systolic pressure, and decreased exercise capacity.

**Lung comets in the emergency room**

A recent systematic meta-analysis of seven studies for a total of 1075 patients showed 94% sensitivity and 92% specificity of B-lines for the identification of pulmonary congestion of cardiac origin in patients presenting with acute dyspnea in the emergency room. The single most frequent source of false positives is represented by interstitial lung disease or lung fibrosis; however, it is possible to distinguish between such B-lines and watery B-lines, as only the latter change rapidly with posture (increasing in the supine position versus the upright position), stress (increasing with exercise), or therapy with diuretics or dialysis. In patients admitted with acute dyspnea and pulmonary congestion, B-lines are significantly correlated with N-terminal pro–B-type natriuretic peptide (NT-proBNP) values. The accuracy of B-lines in predicting the cardiac origin of dyspnea is high and comparable to cardiac natriuretic peptides.

**Take-home message**

B-lines are a reliable and inexpensive tool for the assessment of pulmonary congestion in patients with heart failure, both at rest and during exercise. By counting B-lines, the reduction in exercise capacity due to increasing extravascular lung water can easily be differentiated from that due to other causes, including interstitial lung disease, physical deconditioning, and anemia, for example. Patients with 30 or more B-lines during stress usually have greater functional impairment at baseline and during stress and a greater chance of transition to acute decompensated heart failure and other events within a short-term follow-up period.

B-lines can be easily evaluated in patients, both at rest and after a dynamic challenge, such as posture change, exercise, or diuretic therapy. Lung B-lines allow the noninvasive detection, in real time, of even subclinical forms of pulmonary edema with a low-cost, radiation-free approach. Given the recent endorsement by 2016 European Society of Cardiology (ESC) guidelines on heart failure, assessment of B-lines is expected to gain in popularity among cardiologists and emergency room specialists, who frequently face the difficult challenge of identifying the cause of acute dyspnea. Given the low cost, the high diagnostic and predictive value, the easy access to echo machines, and the short learning curve for sonographers, assessment of ultrasound B-lines promises to quickly become an essential method to evaluate patients with acute dyspnea. The large-scale validation of B-lines in patients at rest and after stress is currently in progress with large-scale, multicenter, international effectiveness studies targeted to show the outcome impact of B-line–driven intervention versus standard therapy in heart failure patients.

**REFERENCES**


**B-type natriuretic peptide (BNP)**

B-type natriuretic peptide (BNP) is a 32-amino-acid vasoactive peptide secreted by the atria and ventricles in response to ventricular volume expansion and/or to increased wall stress (cardiomyocyte stretch) due to pressure overload. BNP elicits its biological actions—eg, natriuresis, vasodilation, diuresis, inhibition of the renin-angiotensin-aldosterone system, enhanced myocardial relaxation, inhibition of fibrosis and hypertrophy, promotion of cell survival, and inhibition of inflammation—by activating specific natriuretic peptide receptors (NPR-A)/guanylate cyclase (GC-A) that utilize cyclic guanosine monophosphate (cGMP) as an intracellular second messenger. Circulating BNP levels have been demonstrated to be a marker for prognosis and risk stratification in the setting of heart failure.

**Heart failure with midrange ejection fraction (HFmrEF)**

Heart failure with midrange ejection fraction (HFmrEF) is a new category of heart failure defined as heart failure with an ejection fraction between 40% and 49%. This new class of heart failure is meant to apply to patients in a “gray zone,” where the benefits of therapies on morbidity and mortality have not been conclusively proven as they have been for patients with heart failure with reduced ejection fraction (HFrEF).

**Heart failure with preserved ejection fraction (HFpEF)**

Heart failure with preserved ejection fraction (HFpEF) is usually defined as heart failure with an ejection fraction higher than 50% and is characterized by diastolic dysfunction rather than systolic dysfunction. It is primarily accompanied by concentric remodeling and defects in left ventricular compliance. Approximately 50% of all heart failure cases are classified as HFpEF.

**Heart failure with reduced ejection fraction (HFrEF)**

Heart failure with reduced ejection fraction (HFrEF) is usually defined as heart failure with an ejection fraction lower than 40% and is characterized by systolic dysfunction. It is primarily accompanied by eccentric remodeling and a decreased left ventricular wall thickness. Approximately 50% of all heart failure cases are classified as HFrEF.

**Mitofission**

Mitofission occurs in response to changes in mitochondrial dynamics and represents the process by which a mitochondrion divides into two daughter mitochondria that are often not equal in size. Dynamin-related protein 1 is the best characterized regulator to date of the mitochondrial division machinery involved in fission. Mitofission is essential for organelle distribution during the process of mitosis; it also appears to be an important process for mitophagy, the autophagic process by which defective mitochondria are degraded by the cell.

**Mitofusion**

Mitofusion occurs in response to changes in mitochondrial dynamics and represents the process by which mitochondria fuse and elongate. Mitofusion is regulated by three evolutionarily conserved GTPases of the dynamin family: mitofusin-1 and mitofusin-2, which are located on the outer mitochondrial membrane; and optic atrophy-1 (OPA1), located on the inner mitochondrial membrane. Mitofusion can allow the redistribution of mitochondrial contents and mitigate mitochondrial DNA mutations.

**Mitophagy**

Mitophagy is a quality control pathway that removes damaged and/or dysfunctional mitochondria through autophagy-mediated degradation of the organelle (ie, mitochondrial-specific autophagy). Autophagic machinery is targeted to the outer mitochondrial membrane via protein and lipid interactions and subsequently sequesters and delivers damaged/dysfunctional mitochondria to lysosomes for degradation.

**N-terminal pro–B-type natriuretic peptide (NT-proBNP)**

N-terminal pro–B-type natriuretic peptide (NT-proBNP) is a 76-amino-acid peptide generated from the cleavage of 108-amino-acid proBNP (the storage form of BNP). Therefore, the cleavage of proBNP generates 76-amino-acid NT-proBNP and 32-amino-acid BNP.
NT-proBNP is not biologically active; however, circulating NT-proBNP levels have been demonstrated to be a marker for prognosis and risk stratification in the setting of heart failure.

**Sensitivity**

Sensitivity is also known as “true positive rate” and is a statistical measure of the performance of a binary classification test, which measures the percentage of actual positive outcomes/end points that are correctly identified as being a positive outcome/end point, hence the “true positive rate.”

**Specificity**

Specificity is also known as “true negative rate” and is a statistical measure of the performance of a binary classification test, which measures the percentage of actual negative outcomes/end points that are correctly identified as being a negative outcome/end point, hence the “true negative rate.”
In the next issue:
Acute coronary syndromes: changing face