Cardiorenal Syndrome in Heart Failure

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Foreword

Heart failure continues to be a major medical problem across the globe. In the United States (US), it is the most common reason for patients to be hospitalized. Hospital cases of heart failure with preserved ejection fraction (HFpEF) are increasing in the US, while hospitalization for heart failure with a reduced ejection fraction (HFrEF) may be decreasing. Both conditions often present with fluid overload, pulmonary congestion, edema, and some renal function impairment. Most physicians know that aggressive diuretic therapy or other means of reducing excessive circulating volume can at times lead to worsening renal function and even acute kidney injury. When this occurs in the setting of acute decompensated heart failure, outcomes can be poor, and management can be challenging.

This important new book brings together the clinician-scientists that have been actively studying the "cardio-renal syndrome" at various universities around the world. The authors know each other well and have been at the "front lines" in various laboratories trying to better understand what is really happening and how it can be best managed. It is most appropriate that they have come together to put forth their thinking into this book in 18 extraordinary chapters.

I know most of these investigators. Some, such as John Burnett, I have known for longer than John and I would care to divulge. In the early days of heart failure research, John's lab group in Rochester (Mayo Clinic) and ours at the University of Minnesota used to meet regularly to share data to better understand the important role of the kidney in heart failure. The effervescence of the lab meetings was stunning! We learned a great deal from each other and uncovered the things we did not know!

When I moved to the Cleveland Clinic, I worked closely with W. H. Wilson Tang and Wilfried Mullens. It was a time of extraordinary focus on the kidney in heart failure, which Wilson and Wilfried have continued, now on both sides of the Atlantic. Other prominent investigators have participated in elegant studies on the kidney in patients with heart failure, and many of them have contributed their insights in this book. The cast is really quite remarkable. Most are still very actively investigating this complex interplay between the kidney and the failing heart.

I am honored that I was asked to write this short forward for this important new book. These authors are the people that have done the work, and we need to listen to them. There are other investigators, not represented here, who of course have also made major contributions to the field and we are most grateful for their work over the years. Credit goes to Drs. Tang, Verbrugge, and Mullens for updating the field and for putting this book together. It is outstanding!

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Contents

Introduction: Refining Physiologically Based Individualized Management of Cardio-Renal Syndrome

The topic of cardio-renal syndrome has been reviewed extensively in the literature especially the past few decades. There is general agreement that adverse and dynamic interactions between the kidneys and circulatory compartments promote increased circulating volume, exacerbate heart failure symptoms, and accelerate subsequent disease progression, while the contribution of noncardiac factors is also under-recognized. Nevertheless, this complex and diversified condition cannot be confined to a "one-fits-all approach" when patients presents with a wide range of manifestations. Often, thorough insight and understanding of cardiac and renal pathophysiology in heart failure and kidney disease is key for making the right therapeutic decisions. Many classic theses of congestive failure and edema have been developed since the 1940s, among them were writings from legends like Issac Starr and Eugene Stead to address these age-old bedside dilemmas [1, 2]. These elegant masterpieces often read like "fireside chats" and reminded us the importance of logical reasoning and pathophysiologic deductions that was based on astute bedside observations and presentations of individual patients or case series. As clinicians, there is a need to look back at the often-forgotten wisdom from the past and to better integrate them with new tools and insights now available in the pursuit of precision medicine.

Like such master clinicians, this book seeks experts in various topics of cardio-renal syndrome to incorporate pathophysiologic insights in describing their approaches to various clinical scenarios that clinicians often encounter in managing heart failure. As editors, we are honored to bring together a group of international experts in which every senior author has made a huge contribution to advance the field of cardio-renal medicine while bringing together many of the learnings we have collectively made over the past decades. By design, we commenced this book with a historical perspective on the evolving evidence and concepts regarding cardio-renal syndrome, combined with perspectives on the contemporary understanding of cardio-renal interactions in the setting of heart failure. These introduction chapters set the stage for some in-depth discussions of traditional and novel pathophysiological insights on neurohormonal and autonomic mechanisms as well as clinical pharmacology perspectives – all forming

the backbone for later case-based chapters. It has been the aim to offer a thorough mechanistic understanding of problems that are frequently encountered in clinical practice and directly apply this knowledge through practical recommendations. Each starts with a realistic case vignette of a patient with cardio-renal syndrome. Building from the cases, key questions are posed that are relevant to the clinical management. This is followed by a brief discussion of the available evidence for diagnosis and/or treatment, citing key insights over the years from research groups across the globe. Finally, a treatment strategy is proposed with a link back to the case vignette and the pathophysiology that is discussed in the earlier chapters.

Inevitably there will be overlap across the chapters, but the interpretation varies from different points of view and perhaps even described in different clinical scenarios. This is intentional, with the hope to provide the reader with the breadth and depth of our international experts' opinions. There is no single "right" answer to each case – but there are different ways to interpret the published evidence, and even different ways to synthesize the optimal treatment strategies – some even with completely conflicting approaches based on the same published data! It is simply fascinating.

Indeed, there are some interesting observations when compiling this series of chapters. First, we still have very limited armamentarium of diagnostic and therapeutic tools to tackle cardio-renal syndrome. Indeed, there is only so much we can do to change the dose, route, and sequence of diuretic therapy. We certainly need more precise and impactful ways to clarify the underpinnings of this syndrome. Second, we do not have a good grasp of the fundamental defect(s) in each of the cases besides observing how their clinical manifestations unfold. Specifically, there are some abnormalities that may indeed drive the syndrome while others may be iatrogenic from responding to the syndrome. Sorting them out may be a key aspect moving forward in our explorations. Third, we seemed to have a challenge in naming the conditions themselves. Terms like "worsening renal function" and "acute kidney injury" have inadequately captured the true conditions that the heart and the kidneys are facing in the setting of acute or chronic heart failure, and have led investigators astray in putting too much faith in those terminologies. We should therefore be careful when we describe the pathophysiology and provide mechanistic evidence to support them rather than simple associative findings.

We hope this book may offer new insights to its readers who may better appreciate the various contemporary pathophysiologic approaches that can be incorporated into their clinical management decisions. More importantly, we hope such insights may lead to better individualized treatment approaches for patients suffering from cardio-renal syndrome. Indeed, we would like to dedicate this book to them, who deserve our continued tireless efforts to

advance the field and improve their lives. We have much to learn after a century of progress.

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References

1. Starr I. Our changing viewpoint about congestive failure. Ann Intern Med. 1949;30(1):1–23.
2. Warren JV, Stead EA. Flud dynamics in chronic congestive heart failure: an interpretation of the mechanisms producing the edema, increased plasma volume, and elevated venous pressure in certain patients with prolonged congestive failure. Arch Intern Med. 1944;73(2):138–47.

A Historical Perspective on Evolving Concepts of Cardiorenal Syndrome in Heart Failure

1

Joshua Grant and Hector O. Ventura

Introduction

Cardiorenal syndrome, the clinical process that describes the interaction between the heart and the kidneys, has recently received a great deal of attention from clinical and research standpoints. Patients that have heart and kidney problems are common today in clinical practice and the presence of cardiorenal abnormalities is associated with high morbidity and mortality. The concept of cardiorenal syndrome is however not novel. Thus, it is critical to re-examine efforts of the past. The trials and tribulations of yesterday's clinical investigators are important and give us greater insight into today's practice. In this narrative, we sought to report a historical overview of cardiorenal interactions and thus render homage to those physicians dedicating their work to this subject. Those physicians have paved the way to an era in which the concept, consequences and pathophysiology of cardiorenal syndrome is much better understood.

Ancient History

Egyptian Medicine

The Egyptian civilization utilized the medical papyri as the source of medical knowledge and as a guide for the practice of medicine. The papyri contain

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descriptions of anatomy and function of the human body, instruments utilized by doctors at that time, as well as different diseases and their remedies. The cardiac glosses of the Ebers papyrus comprise the concepts and notions of the Egyptian physicians about the heart and its diseases [1–7]. The urinary tract is mentioned by the Egyptians, not as a system, but by individual parts. Although there is no hieroglyphic word for kidney, words meaning loin, such as 'depet', 'geget', 'geret' and 'gelet' have been related to it. Some authors support the opinion that the Egyptian physicians considered the kidneys to have an important role, because they were left in the body together with the heart giving special significance to these two organs [8, 9]. However, other authors believe that the kidneys were left in because their retroperitoneal location made them unreachable in the normal evisceration that was part of mummification [6, 8]. Egyptian physicians knew that the ureters conducted urine to the bladder. A study has speculated that the Egyptians also knew that the source of urine was the kidneys, however their understanding of this anatomic relationship has not been confirmed. Thus, it is not clear if the Egyptians physicians appreciated not only the anatomy, but also the physiologic role of the kidney [6, 8]. The Ebers papyrus described urine or 'moyt' that was formed in the region of the bladder, by a process similar to purification and was considered a clean fluid. The document describes that "thou art a servant who cometh in vomitus; thou art a noble who cometh in urine", alluding the cleansing function of urine [4, 8]. A possible relationship between the heart and the kidneys can also be found on studies performed on preserved mummies indicating that kidney and heart diseases were not uncommon [6]. In addition, a passage on the Book of the Dead suggests that Egyptians gave a mythological role to the kidneys and the heart, "May naught be against me in the presence of the great god, the lord Amentet. Homage to thee, O my heart. Homage to thee, O my kidneys" [10].

Chinese Medicine

Traditional Chinese Medicine dates back 3000 years. Its principles are based on concepts of Yin and Yang, two opposing qualities that are in a constant state of dynamic balance. According to Chinese medical theory, there are five organs that produce, transform, and store *qi,* the body's vital energy: the lungs, spleen, heart, liver, and kidneys. Disease may occur when the balance of Yin and Yang is altered because of a deficiency or excess of either quality [11]. The relationship between the kidney and the heart is explained by the Five Elements theory: the heart belongs to fire and the kidneys to water. Both have Yin and Yang properties that are closely related. If this functional relationship between Yin and Yang is abnormal, the dynamic equilibrium is disrupted. This morbid condition has been termed as "non-coordination between the heart and the kidney" [11].

Hebrew Culture

The Hebrews believed that the kidneys (reins) were the seat of desire and longing, and the heart was the seat of thought and will, which accounts for them often being coupled in the Bible. They are mentioned in the following passages as the organs examined by God to deliver judgment on humans [12]:

- "..The righteous God trieth the hearts and reins." (Psalm 7:9)
- "But, O Lord of hosts, that judgest righteously, that trieth the reins and the heart, let me see thy vengeance on them: for unto thee have I revealed my cause." (Jeremiah 11:20)
- "… Examine me, O Lord, and prove me; try my reins and my heart." (Psalms 26:2)
- "… I, the Lord, search the heart, I try the reins, even to give every man according to his ways, and according to the fruit of his doings." (Jeremiah 17:10).

Post-classical history

Middle Ages

During the Middle Ages, there was not a clear understanding of the site of the disease that caused fluid overload or dropsy. However, there were several descriptions that attempted to relate the heart and the kidney as plausible underlying mechanism. Aetius of Amida was a Greek-born who atributed dropsy (fluid overload) to hardening of the kidneys [13]. Perhaps the most famous of the Islamic physicians, Avicenna, who was author of the famous medical encyclopedia Canon of Medicine, also held that dropsy appeared in the course of hardening of the kidneys. It is notable that Avicenna tried to differentiate the cause of different dropsies, ascribing some to affections of the liver and others to diseases of the kidney [14, 15]. In the fourteenth century, Gentile da Foligno, a professor and teacher of medicine at the Universities of Bologna, Padua, Siena and Perugia, reported seminal observations on the physiology of the formation of urine [16]. He stated that urine was blood's filtration through the porous tubules of the kidney and is then delivered to the bladder. He also described the relationship between heart disease and the colour and output of urine. He stated that a small volume of urine output in the course of acute fever could indicate heart disease. Oliguria and signs of swelling sometimes signify a bad mixture in the heart. In addition, he also described the relationship between fast pulse rate and urine output [16]. Giovanni Battista Morgagni, professor of Anatomy in Padua, compiled his clinical observations in a series of letters that were incorporated in his landmark treatise "De Sedibus et Causis Morborum per Anatomen Indagatis Libri Quinque" or "The

Seats and Causes of Disease Investigated by Anatomy in Five Books", published in 1761 [17]. Morgagni devoted several letters of the "De Sedibus" to study the clinical pathological correlation of heart diseases and described cases of granular, contracted kidneys, associated with dropsy [18].

Modern History

Several investigators have reported the relation between heart and kidney disease in the nineteenth century. Richard Bright recognized that many patients with renal disease have diffuse vascular disease, kidney disease, and cardiac hypertrophy, more than half a century before a blood pressure measuring device was utilized [19]. He stated "The obvious structural changes in the heart [in patients with shrunken kidneys] have consisted chiefly of hypertrophy with or without valve disease and, what is most striking, out of 52 cases of hypertrophy, no valvular disease whatsoever could be detected in 34… We must look for the cause of this hypertrophy in the fact that the blood, in consequence of degeneration of the kidney, being contaminated by urinary excreta and otherwise deteriorated, is impeded in its transit through the minute arteries throughout the body…" [19]. Bright thus begins to describe a complex pathopyhsiologic interplay between the heart and the kidneys. William Senhouse Kirkes was an English physician whose main interest was in cardiology and vascular disease and he gave the first account of embolism from vegetations in infective endocarditis in 1852 [20]. Three years later, he published a study on apoplexy in Bright's disease, a historical classification for what is nowadays is termed nephritis. Kirkes clearly described the role of raised intra-arterial tension in the causation of arterial disease, a point that had eluded Bright, Johnson, and other contemporaries [21]. He stated: "I believe that the affection of the kidneys is the primary disease. A hypertrophied condition of the left ventricle ... of the various explanations of this pathological fact, the most probable perhaps is that which regards the blood as so far altered from its normal constitution ... as to move with less facility through the systemic capillaries, and thus to require increased pressure, and consequently increased two cases, either the heart or the cerebral vessels were growth of the left ventricle, to effect its transmission." [21] Thus, he remains one of the first physicians to ascribe a principle renal pathology leading to disease of the heart. Ludwig Traube, in 1856, published Ueber den Zusammen hang von Herz und Nieren krankheiten (The Relation Between Cardiac and Renal Diseases), that was directed to the elucidation of the mechanisms responsible for the presence of left ventricular hypertrophy in patients with kidney disease [22]. He stated: "The shrinking of the renal parenchyma has therefore, 2-fold consequences. It will firstly act by decreasing the blood volume, which flows out in a given time from the arterial system into the venous system. It will secondly act by decreasing the amount of liquid, which at the same time is removed from the arterial system as urinary secretion. As a result of both these conditions, particularly because of the latter, as is clear from what has just been stated, the mean pressure of the arterial system must increase. Consequently

again, an increase in resistance is produced, which opposed emptying of the left ventricle" [22]. In addition, in a different publication, Traube credits Senhouse Kirkes [23], when he stated: "It was Senhouse-Kirkes who first proposed the tenet that arteriorenal disease, and the neglect of his contribution, probably sclerosis, is first of all the results of long-lasting high-grade tension of the aortic system. Thus there appeared, I believe, the first allusion to the correct viewpoint, not only on the origin of this affection, but also its pathological significance. We place his contributions within the setting of the development of arteriosclerosis that has the same foundation as the hypertrophy of the left ventricle." [23]

William Stokes from the Irish School of Medicine wrote Diseases of the Heart and the Aorta, published in 1854. This treatise was the result of 20 years of experience and demonstrated Stokes' clinical acumen and intimate familiarity with the literature of cardiology [24]. He wrote: "During these (orthopnea) attacks, the irregularity of the heart and the precordial distress increased, until orthopnea was established. The kidneys acted scantly … on each attack the tumefaction of the liver increased with great rapidity, but this condition as rapidly subsided with the improvement in symptoms. No relief was ever obtained until the action of the kidneys was established; … In this condition of intervals of comparatively good health, while the attack came on once in about every five weeks ... another bad attack supervened in the early part of the autumn, but it yielded to the usual treatment. But this was the last time that the system responded to medicine ... The anasarca increased, and the occurrence of a congestion of both lungs, so great as to cause general dullness and bronchial respiration, was the immediate forerunner of death…" [24]. Here Stokes establishes a clear relationship between the symptoms of volume overload in heart failure and the role of the kidneys in a compensatory corrective response. In addition, Stokes attempt to find an explanation of the patients symptoms: "Although these cases are to be met with every day, especially in private practice, we still observe that physicians differ as to their nature. One holds that the liver is the organ at fault; another that the disease is in the valves of the heart; a third believes that the symptoms are those of hydrothorax, from disease of the kidney; while a fourth sees nothing but misplaced gout. Each of them may be said to be in one sense right, all of them in another sense wrong. That the heart, liver and lung are in fault, in most of the cases, is certain; that the kidney is functionally affected, and the gouty condition present, is commonly true. But we must learn to look fairly at the entire case, and not dwell on its separate phenomena. In a clinical point of view these cases form one of a group of diseases which may be classed as examples of weakness of the heart. For although they differ in the special signs and symptoms, and, above all in their history and accompanying circumstances, yet they agree in exhibiting a diminished force, especially of the ventricles…" [24] This description demonstrates that Stokes correctly characterized the correlation of clinical symptoms with pathologic findings on the syndrome of heart failure. Notably, he identified that the main problem was seated in the heart. In addition, Stokes' clinical-pathologic observations indicate a relation between heart disease "weakness of the heart" and functional abnormalities of the kidneys [25].

Twentieth Century

The term "cardio-renal" was introduced by the English clinician Dr. Thomas Lewis, who described a unique form of paroxysmal dyspnea in the setting of concomitant cardiac and renal dysfunction. He delivered a lecture in 1913 entitled "Paroxysmal Dyspnoea in Cardio–Renal Patients" and attempted to ascribe the etiology of dyspnea to renal or cardiac pathology [26]. He wrote: "We attempt to distinguish the two types of dyspnea after death… When the body is examined the conspicuous lesion is found in the kidney, or it is found in the heart; the morbid anatomist points to one or other organ as the seat of the chief mischief. We come to this standpoint that the clinical or anatomical distinction between cardiac and renal asthma, is no certain one. Asthma occurring in patients who show on the one hand prominent cardiac lesions and on the other hand prominent renal lesions, may or may not be due to a single cause…" Although the relationship between the heart and kidneys is here acknowledged, it is clear that identifying the implicit pathophysiology remains elusive [26]. The following summer, Dr. Alfred Stengel presented his proposal at the American Medical Association Annual Session in Atlantic City, New Jersey, and stated that patients are often encountered with symptoms of both "cardiac weakness" and "renal disease." [27] He wrote: "The clinician encounters many cases, mainly in persons of middle age or older, in which evidences of cardiac weakness and other circulatory disturbances, such as high pressure, are associated with signs of failure of renal function or urinary indications of renal disease. When this combination of symptoms is of such character that the observer cannot readily assign to either the cardiovascular system or to the kidneys, the preponderance of responsibility, the term "cardiorenal disease" is often employed. The term therefore comprises cases of combined cardiovascular and renal disease, without such manifest predominance of either as to justify a prompt determination of the one element as primary and important and the other as secondary and unimportant. Among the pathologic conditions included in the term are 3 important groups: 1) primary valvular or myocardial disease with secondary renal disease; 2) primary arterial or arteriolar disease with secondary renal and myocardial disease; and 3) primary renal disease with secondary myocardial and vascular disease…" [27].

In 1940, Benjamin Gouley from Philadelphia reported the association between myocardial degeneration and uremia [28]. He stated: "A peculiar type of myocardial degeneration appears to be intimately associated with the uremic and pre-uremic states of arteriolar nephrosclerosis and chronic glomerular nephritis. It is found especially in patients who have cardiac failure. The latter may be the outstanding feature of the uremic intoxication…".28] Thus, Gouley identifies a disease process in which the kidneys result in cardiac pathology. Meanwhile in 1947, Langendorf and Pirani reported 27 fatal cases of uremia and described their electrocardiographic, kidneys and heart anatomic changes [29]. They stated: "The average weight of the heart was 466 g, the minimum weight was 300 g, and the maximum weight was 650 g. There was no definite relation between the weight of the heart and the underlying renal disease. High weights were however more consistently found in nephrosclerosis of the arteriolar variety, while approximately normal weights were present in 2 instances of acute ascending pyelonephritis… The myocardium was generally rather pale with a moderate to severe cloudy swelling. The consistency was diminished in only a few

instances and occasionally oedema was present. Old and recent myocardial infarcts were observed in 7 hearts, most frequently in the anterior wall of the left ventricle. Microscopically, the most consistent finding in the myocardium was a moderate to severe interstitial fibrosis, which was present in the hearts of all but 2 patients… In a few instances, the myocardial fibrosis was particularly marked in perivascular location. In others either the outer or the inner third of the left ventricular wall was more severely involved. A diffuse, slight fatty degeneration was noted in many hearts. In only 2 instances however, it did reach a severe degree: both of these patients had a marked anemia. Fat infiltration of the right ventricular wall was present in 8 hearts; the infiltration was rather marked in 3…" [29] The introduction of hemodialysis as treatment renewed the interest in the relationship between cardiac structure and function in patients with end-stage renal disease. Thus, several studies demonstrated that both clinical and echocardiographic disease occur frequently in patients with chronic renal disease and uraemia. Heart failure appeared to be very common and was associated with poor prognosis. Left ventricular systolic dysfunction, hypertrophy and dilation were present by echocardiography and associated with higher mortality [30–32]. Lidner et al., in 1974, demonstrated prospectively that patients on long-term regular hemodialysis not only had a high mortality (56.4% at the end of the 13-year follow-up), but also a higher incidence of cardiovascular disease [32]. Fourteen of 23 deaths were attributed to arteriosclerotic complications such as myocardial infarction (n = 8), strokes (n = 3), and refractory heart failure (n = 3). The authors concluded that that accelerated atherosclerosis was a major risk to long-term survivors on hemodialysis [32]. Other more contemporary studies have confirmed that kidney disease or decreased renal function worsens the prognosis of patients with heart failure [33–36]. More recently, the Framingham Heart Study has demonstrated that levels of natriuretic peptide and urinary albumin-to-creatinine ratio are major predictors of major cardiovascular events [37].

The Present

The definition of cardiorenal syndrome has evolved, but it remains largely descriptive in nature and not necessarily reflecting specific underlying pathophysiologic processes. For example, the Acute Decompensated Heart Failure Registry (ADHERE) defined cardiorenal syndrome clinically as the presence or development of renal dysfunction in patients with heart failure [38]. Bongartz et al. defines cardiorenal syndrome as a pathophysiological condition in which combined cardiac and renal dysfunction amplifies progression of failure of the individual organ to lead to astounding morbidity and mortality in this patient group [39]. More recently, cardiorenal syndrome has been defined as disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other and 5 subtypes of cardiorenal syndrome have been described [40]. It is somewhat remarkable that despite over a century of medical progress, our classification scheme for cardio-renal syndrome has remained largely descriptive of such temporal bi-directional relationships between cardiac and renal dysfunction.

Conclusion

Richard Horton wrote in 1997: "Medicine pays almost exclusive homage to the shock of the new – we place constant emphasis on novelty – this is an era of the instantaneous and the immediate." [41] It seems that medicine's concern with the "new" leaves a little space for history. We do not advocate this point of view, as T.S. Eliot wrote: "the historical sense involves the perception not only of the pastness of the past, but of its presence…" [42] Thus, one cannot appreciate the present separate from the past. The new developed concepts on cardiorenal syndrome and its therapies will be detailed in this book, however, the successes of our present days are rooted in the past and thus a historical overview of the cardiorenal connection is critical to acknowledge not only how far we have come, but also how much we can carry out further in the future.

References

1. Nunn JF. Ancient Egyptian medicine, vol. 6. Norman: University of Oklahoma Press; 1996. p. 113–4.
2. Vargas A, López M, Lillo C, Vargas MJ. The Edwin Smith papyrus in the history of medicine. Rev Med Chil. 2012;140:1357–62.
3. Saba MM, Ventura HO, Saleh M, Mehra MR. Ancient Egyptian medicine and the concept of heart failure. J Card Fail. 2006;12:416–21.
4. Badr MM. The history of urology in ancient Egypt. J Int Ther Notes. 1955;3:43–9.
5. Badr MM. The history of urology in ancient Egypt. Col Surg. 1963;30:404–13.
6. Ruffer MA. Studies of paleopathology of Egypt. Chicago: Verlag, 1973 University of Chicago Press; 1921.
7. Ghalioungui P. The Ebers papyrus: a new English translation, commentaries and glossaries. Cairo: Academy of Scientific Research and Technology; 1987.
8. Shokeir AA, Hussein MI. The urology of pharaonic Egypt. BJU International. 1999;84:755–61.
9. Bongartz LG, Cramer J, Joles JA. Origins of the cardiorenal syndrome and the cardiorenal connection. Chronic Kidney Disease. Available from: http://www.cdn.intechopen.com/pdfs-wm/32307/pdf. Last accessed on 2 Jan 2018.
10. Taylor JH, editor. Ancient Egyptian book of the dead: journey through the afterlife. London: Museum Press; 2010. p. p54.
11. Nei Ching. Yellow emperor's classic of internal medicine. Books 2-9, published between 2698 and 2598 B.C.
12. Greydanus DE, Merrick J. Medical history: some perspectives. New York: Nova Biomedical; 2016. p. 216.
13. Diamandopoulos A. Twelve centuries of nephrological writings in the Graeco-Roman world of the Eastern Mediterranean (from Hippocrates to Aetius Amidanus). Nephrol Dial Transplant. 1999;14(Suppl 2):2–9.
14. Jarcho S. A summary of this story. In: The concept of heart failure. From Avicenna to Albertini. Cambridge: Harvard University Press; 1980. p. 362–3.
15. Ventura HO, Mehra MR. Bloodletting as a cure for dropsy: heart failure down the ages. J Card Fail. 2005;11:247–52.
16. Timio M. Gentile da Foligno, a pioneer of cardionephrology: commentary on Carmina de urinarum iudiciis and De pulsibus. Am J Nephrol. 1999;19:189–92.
17. Ventura HO. Giovanni Battista Morgagni and the foundation of modern medicine. Clin Cardiol. 2000;23:792–4.

18. Morgagni GB. The seats and causes of diseases investigated by anatomy, in five books. Letter XLII, article 17. Page 160 ex typographia Remondiniana, Venice; 1761.
19. Bright R. Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine. Guy's. Hosp Rep. 1836;1:338–400.
20. Cameron JS, Hicks J. High blood pressure and the kidney: the forgotten contribution of William Senhouse Kirkes. Kidney Int. 2000;57:724–34.
21. Kirkes WS. On apoplexy in relation to chronic renal disease. Med Times Gaz. 1855;24:515–7.
22. Traube L. Ueber den Zusammenhang von Herz- und Nierenkrank- heiten gesammelte beitrage zur pathologie und physiologie. Berlin: Nirschwald; 1871. p. 290–353.
23. Traube L. Ein fall von pulsus bigeminus nebst bemerkungen ueber die leberschwellungen bei klappenfehlern und ueber acute leberarophie. Berl Klin Wochenschr. 1872;9:185–8.
24. Stokes W. Disease of the muscular structures of the heart. In: The diseases of the heart and the aorta. 1st ed. Dublin: University Press; 1853. p. 255–98.
25. Ventura HO, Mehra MR. Colles-Stokes contributions to the concept of heart failure. Am J Cardiol. 1998;81:1470–3.
26. Lewis T. A clinical lecture on paroxysmal dyspnoea in cardiorenal patients with special reference to "cardiac" and "uraemic" asthma: delivered at University College Hospital, London, November 12th, 1913. Br Med J. 1913;2:1417–20.
27. Stengel A. Cardiorenal disease: the clinical determination of cardiovascular and renal responsibility, respectively, in its disturbances. J Am Med Assoc. 1914;LXIII:1463–9.
28. Gouley BA. The myocardial degeneration associated with uremia in advanced hypertensive disease and chronic glomerular nephritis. Am J Med Sci. 1940;200:39–49.
29. Langendorf R, Pirani CL. The heart in uremia. Am Heart. 1947;33:282–307.
30. Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis inprolonged maintenance hemodialysis. N Engl J Med. 1974;290:697–701.
31. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int. 1995;47:186–92.
32. Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. Kidney Int. 1995;47:884–90.
33. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med. 2004;351:1285–95.
34. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
35. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000;35:681–9.
36. Forman DE. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004;43:61–7.
37. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med. 2006;355:2631–9.
38. Heywood JT. The cardiorenal syndrome: lessons from the ADHERE database and treatment option. Heart Fail Rev. 2004:195–201.
39. Bongartz LG, Cramer MJ, Braam B. The cardiorenal connection. Hypertension. 2004;43:e14.
40. Ronco C. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J. 2000;31:703–11.
41. Horton R. A manifesto for reading medicine. Lancet. 1997;349:872–4.
42. Eliot TS. Tradition and the individual talent. In: The sacred wood: essays on poetry and criticism. London: Methune; 1920.

Hemodynamic Insights to Cardio-Renal Syndrome: A View Looking Back to See Forward

2

Lynne Warner Stevenson

Recognizing the Role of Renal Function

When digitalis and diuretics were the only therapies for heart failure, patients presented after relatively short duration of disease when obvious decline in kidney function was uncommon except in frank cardiogenic shock. Some early trials in heart failure did not even report renal function. It was 8 years after the initial publication of the Studies of Left Ventricular Dysfunction (SOLVD) trial results that the striking impact of even mild kidney dysfunction on outcomes in both asymptomatic and symptomatic heart failure was first reported [1]. Since then chronic kidney dysfunction has come to be recognized as one of the core predictors of worse outcome at every stage of heart failure, regardless of ejection fraction (EF). In a large community database from Canada including all EF heart failure, median survival after the initial and each subsequent hospitalization for heart failure was decreased by half for patients with a diagnosis of kidney dysfunction [2].

The Pre-renal Concept

After the approval of cyclosporin in 1984, the lure of cardiac transplantation drew increasing numbers of patients with heart failure from the communities where they had been languishing. These patients concentrated at the growing heart failure centers, where they challenged us to relieve their symptoms after they were listed or more often rejected for cardiac transplantation [3]. Heart failure was then traditionally viewed as "forward failure" and "backward failure", with the emphasis on increasing contractility to improve forward failure. The prevalent model of

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congestion was that of an inevitable burden needed to support adequate filling for cardiac output from the dilated failing heart. When creatinine and blood urea nitrogen increased during diuretic therapy to relieve dyspnea and edema, the cause was assumed to be due to excessive reduction of forward cardiac output leading to inadequate renal blood flow, the "pre-renal" concept.

Insight into the hemodynamic aspects of end-stage heart failure resulted from the evaluation for presence and reversibility of pulmonary hypertension during cardiac transplant evaluation. One-time evaluation in the catheterization laboratory did not provide enough information, so pulmonary artery catheters were left in to guide reduction of pulmonary capillary wedge pressures through diuretics and vasodilators [3]. Preceding chronic inhibition of the renin-angiotensin system, decompensation was characterized by marked vasoconstriction as well as volume load [4]. The relative targets and response of diuretics and vasodilators could not be distinguished without invasive hemodynamic monitoring. Investigation to determine the optimum filling pressures, at which stroke volume was maximal, revealed that this was consistently achieved at pulmonary capillary wedge pressures close to 16 mm Hg, often reduced from initial levels of 30 mm Hg or higher [5]. This was generally achieved during infusion of sodium nitroprusside or nitroglycerin titrated to systemic vascular resistance around 1200 dynes-cm-sec^5, during and after which intravenous loop diuretics were titrated to reach the lowest filling pressures possible. The intravenous vasodilators were then weaned slowly during uptitration of hydralazine and nitrates to maintain equivalent loading conditions [6].

This apparent "inverse Starling curve" in the dilated failing heart may reflect multiple factors including better myocardial oxygen supply-demand relationship and decreased interventricular and pericardial constraint. However, the major factor proven was the dramatic reduction of mitral regurgitant flow in favor of forward flow without substantial change in the summed ejection fraction [7]. More recent echocardiographic studies during tailored therapy have tracked the reduction in left ventricular size and effective mitral regurgitant orifice area, frequently with reduction of mitral regurgitant volume by more than 50% [8]. It is of interest that reduction of filling pressures and cardiac volumes alone is sufficient to decrease neurohormonal activation during decompensation [9].

These observations led to distinction between congestion with and without evidence of hypoperfusion [10]. The "warm and wet" profile is treated primarily with diuresis without intervention to increase cardiac output. Fewer than 20% of patients admitted to most centers have a profile of "cold and wet", in which adjunctive therapy with vasodilators or inotropic therapy may be needed to aid diuresis toward the warm and dry profile. The dominance of congestion without hypoperfusion supports the separation of congestion from perfusion, emphasizing that fluid retention in most patients is *not* primarily due to inadequate resting cardiac output. However, the rarity of patients with clinical hypoperfusion without clinical congestion (cold and dry) does support the corollary concept that patients with low cardiac output generally do develop fluid retention.

The transition from an intravenous to an oral regimen was generally accomplished without increases in creatinine or blood urea nitrogen. However, serum

creatinine levels sometimes increased later during the hospital course or after discharge, by which time hemodynamics were no longer known. Increases in diuretic doses during outpatient management were often associated with increases in creatinine and it was surmised that this was a cause-effect relationship. This was further emphasized by observational studies that the use of loop diuretics, and particularly high doses of diuretics, were associated with worse outcomes [11]. Eventually it has become clear that it is the *need* for such doses (diuretic resistance) rather than the doses themselves that are responsible for the association [12].

Renal Implications of Heart Failure with Preserved Ejection Fraction

Before 2-dimensional echocardiography came into standard use, all heart failure had been assumed to be a disease of decreased contractility with low ejection fraction and low cardiac output. The fluid retention was assumed to result from inadequate stimulation of arterial baroreceptors by low output and a resultant increase in neurohormonal reflexes to retain volume.

Recognition grew slowly that heart failure could occur without low ejection fraction [13]. Debate still continues over nomenclature and the relative contributions of intrinsic diastolic and systolic dysfunction, the hemodynamic and echocardiographic criteria, and the role of other co-morbidities associated with heart failure with preserved ejection fraction. The common factors in presentation remain the congestive symptoms and physical evidence of elevated filling pressures and frequent excess of total body volume. This overturned the prevailing concept that impairment of cardiac output was the main stimulus for fluid retention in cardiac disease. As decreases in renal function were observed during hospitalization as often with preserved ejection fraction as with low ejection fraction heart failure [14], this syndrome was further evidence against the model of renal dysfunction in heart failure as due primarily to forward failure.

Retention of excess volume remains the cardinal feature of what has been termed heart failure with preserved ejection fraction. A minority of patients with this diagnosis have consistently normal resting pressures with symptoms and pressure elevations that occur only with exercise. Some patients with the label of heart failure with preserved ejection fraction instead have fluid retention of another primary etiology such as kidney or liver disease, to which the heart is only a bystander. Obesity itself is associated with decreased fluid excretion and increased fluid volumes in which direct cardiac involvement does not always not play the major role [15, 16]. With the heterogeneity of causes for fluid retention in the presence of normal ejection fractions, it is not surprising that the only strategy effective to decrease hospitalizations for this diagnosis has been the use of ambulatory hemodynamic monitoring supervised with algorithms designed to achieve and maintain low pulmonary pressures [17]. This pressure-guided strategy has led to consistent reduction of pulmonary artery pressures without overall decline in renal function.

Reversal of the Impact of Increased Creatinine During Hospitalizations

One of the first systematic reports of the lack of relationship of cardiac output to worsening renal function cited a rate of about 1 in 4 patients with worsening renal function during heart failure hospitalization [18]. This was associated with older age, lower baseline creatinine clearance (although same absolute creatinine levels) higher right atrial pressures, atrial fibrillation, and subsequently with longer length of stay and higher event rate after discharge [18]. This was followed by a report of 1000 patients from 11 academic centers confirming the longer LOS and higher in-hospital mortality [19]. A similar report demonstrated that this association persisted for multiple definitions of worsening renal function [20]. However, both the absolute increases and the proportional increases are more likely to occur in the setting of baseline renal insufficiency, so some of this predictive power reflects the impact of baseline renal insufficiency on prognosis. Interestingly, this is the very cohort in which the infamous 0.3–0.5 mg/dL rise of creatinine was coined as "worsening renal function", based on the cut-off values that balance the sensitivity versus specificity in predicting in-hospital mortality.

A strange reversal occurred around the time of the ESCAPE trial. During this period there was new emphasis on the importance of achieving decongestion during heart failure hospitalization. For example, the goals in the ESCAPE trial empiric arm were resolution of clinical signs and symptoms of congestion [21], as in the subsequent trials of the Heart Failure Network [22–24]. In the matched invasive arm of ESCAPE, diuretics and vasodilators were titrated to approach goals of pulmonary capillary wedge pressure $\leq$ 16 mmHg and right atrial pressure < 8 mmHg while maintaining systolic blood pressure at least 80 mmHg [21]. Renal function was slightly less likely to deteriorate in the hemodynamically guided arm before discharge but this benefit was not sustained in the months after discharge [25]. Furthermore, the change in renal function during hospitalization was no longer found to predict worse outcomes, which were instead better explained by baseline renal function. Subsequent analysis of the degree of decongestion indicated that small creatinine increases in hospital paralleled other indicators of hemoconcentration, which as a marker of more effective decongestion was associated with better outcomes after discharge [26]. This was confirmed in other analyses in both the United States and in Europe, where worsening renal function was found to confer worse prognosis only in the presence of residual congestion at discharge [27]. It is ironic that some studies such as the trial of ultrafiltration versus aggressive diuretic escalation used worsening creatinine as part of the composite endpoint, before the higher priority of decongestion was appreciated [23].

There has been much confusion about the relatively rapid reversal after 2005 from the "ominous" to optimistic view of small increases in creatinine during heart failure hospitalization. The most likely explanation is that uncertainty about the goals of diuresis previously triggered premature discontinuation of diuresis despite residual congestion, if the creatinine increased early during hospitalization [28]. A large group of investigators in the United States and Europe in the meantime reached consensus

together about the proximate causes and goals of heart failure hospitalization [29]. The increasing recognition of the danger of residual congestion has now encouraged clinicians to override the creatinine and push through to resolution of clinical congestion, as captured in the EVEREST and PROTECT congestion scores [27, 30].

Forward and Backward Flow for the Kidney

Forward Failure

Cardiogenic shock clearly threatens the kidneys and the other vital organs. Rapid worsening of kidney and liver function in the setting of hypotension and lactic acidosis warrants rapid triage for aggressive intervention to support cardiac output as appropriate in view of overall health. However, the severity of chronic hypoperfusion can be under-recognized in patients with ambulatory heart failure, and should be carefully assessed clinically upon presentation. Uncertainty regarding right and left filling pressures, systemic and pulmonary vascular resistances is a recommended indication for invasive hemodynamic assessment [31]. However, the finding of low calculated cardiac output during a single measurement is not easy to interpret. The increasing reliance upon room temperature for convenience of thermodilution measurement and assumed oxygen consumption from body weight for "Fick outputs" has diluted the gold standard of measured cardiac output.

Renal blood flow can also be threatened by maldistribution of an adequate cardiac output into regional beds. While obvious in sepsis, maldistribution may be subtle in other settings. The recommended combination of medical therapies for heart failure such as neurohormonal antagonists often leads to low systolic blood pressures as an off-target effect. Renal autoregulation is generally considered to be impaired below a threshold of mean arterial pressure of 80 mg [32], which may even be higher after long-standing hypertension. Inhibitors of the renin-angiotensin system have specific effects also to decrease efferent glomerular tone and glomerular filtration rate. Often speculated, it is not known what degrees of hypotension and progressive renal dysfunction cancel the anticipated benefits of this neurohormonal inhibition in patients with advanced heart failure. In fact, early concerns for broad vasodilator use dwells on this very point. For example, hydralazine is a reliable arterial vasodilator but can also occasionally divert blood flow away from the kidneys. Nesiritide was associated with occasional decrease in kidney function (which was subsequently not seen with more conservative dosing in larger studies), as has also been seen more recently with sacubitril/valsartan. Thus far, it is not clear to what extent these effects relate to vasodilation or excessive natriuresis.

Meanwhile, the hemoglobin content can itself play an important role in kidney function during progressive heart failure beyond hemodynamic derangements. The anemia of chronic disease as well as the iron deficiency seen in heart failure often further impair kidney function. Effective diuresis and improved glomerular filtration rate are frequently seen following transfusions in patients with advanced heart disease and anemia. This "arterial underfilling" concept has been broadly promoted

by nephrologists, and perhaps prompted the tug-of-war between cardiologists and nephrologists regarding the optimal systemic blood pressure ranges that would best maintain renal perfusion.

Backward to the Kidney

The right heart has increasingly been recognized by both nephrologists and heart failure cardiologists as the central hemodynamic factor in the progressive renal dysfunction of chronic heart failure [33, 34]. Elevated right heart pressures are associated with worse outcome for many cardiac conditions, including adult congenital heart disease. Elevation of left heart pressures is closely matched with proportional (but not numerically equal) elevation of right heart pressures in chronic heart failure in 75–80% of patients with heart failure and low ejection fraction [35]. Thus, multivariate models vary with regard to the hierarchy of predictors among the closely-related parameters of pressures in the right atrium, right ventricle at end diastole, pulmonary pressures and left-sided filling pressures. All of these pressures, tricuspid regurgitation, and the measurements of right ventricular volumes and systolic function can be related both to kidney function and overall outcomes in heart failure.

Mounting intra-peritoneal pressure related to systemic venous congestion and ascites may direct compress the kidneys and the renal veins [36]. This concept, however was not entirely new either, as intra-abdominal hypertension can be observed in some postoperative patients with renal compromise, and can be alleviated either by decompression of ileus or by paracentesis if technically feasible. Several factors may promote right heart failure to cause renal dysfunction. These include renal venous hypertension and the backwash of tricuspid regurgitation and elevated intraperitoneal pressures. Malnutrition and inflammatory cascades may also result from the hepato-splanchnic congestion of right heart failure. Once attributed to low hepatic perfusion, impaired nutrition is most tightly associated with elevated right atrial pressures and tricuspid regurgitation [37]. It can also lead to low oncotic pressure with extravascular sequestering of edema fluid. Leak of intestinal antigens contributes to stimulation of inflammatory mediators [38].

The left heart also connects meaningfully with the kidney through systemic neurohormonal connections other than through impairment of forward cardiac output. The natriuretic peptides have multiple effects on renal function that are lost when the heart is totally removed, as in replacement with the total artificial heart [39]. Atrophy of veno-atrial stretch receptors during sustained volume overload as shown in animal models [40] may be responsible for blunted inhibitory sympathetic outflow to the kidney and apparent dependence on atrial distention for maintenance of renal function in some situations.

Left ventricular assist devices (LVAD) offer a novel way to isolate some of the right and left heart contributions to kidney function. Rapid improvement in renal function was noted early after the implantation of mechanical circulatory support devices [41]. Often however, the initial improvement fades and kidney dysfunction again becomes evident within months. There is considerable debate regarding

whether kidney function improved more with the pulsatile assist devices than with the current continuous flow device. Such a difference could reflect both the dependence of the kidneys on pulsatility and on a differential effect of the two modes of left ventricular support on the unsupported right ventricle facing a higher venous return. Certainly, right ventricular function during LVAD support does not improve as much as initially anticipated [42]. Kidney dysfunction is so common in the current era of mechanical circulatory support that the revised INTERMACS definition of right ventricular failure as an adverse event after LVAD includes progressive renal dysfunction as one of the clinical criteria for severity of right ventricular failure [43]. The total artificial heart does not truly restore a normal circulation, as cardiac output and heart rate are higher than normal, hemoglobin is lower, small imbalances of right and left-sided flow affect lung function, and the intrinsic cardiac neurohormonal modulation is absent [39].

Conclusions: From Backward Failure Into Forward Progress

We have journeyed far from the days of "Pre-Renal", through "Cardio-Renal", and now to RV-renal or perhaps the "Veno-Renal" syndrome as the most common single link in the long chain of connections between heart failure and kidney function. Just as we have recognized the dominance of "backward failure" over "forward failure" for the symptoms and prognosis of cardiac disease, we have recognized that the backward flow has limited kidney function more often than lack of forward inflow.

The field of heart failure has long supported the funeral march of inevitable progression. The search continues for the theory of everything that leads the impaired left ventricle from adaptation to failure. New data emerging from ambulatory hemodynamic monitoring suggests that many episodes of pulmonary artery pressure elevation are not mysterious but can be traced to an excess of sodium intake or an interruption in recommended medications. The time course of events after implementation of the pressure-guided management strategy shows a progressive decrease of interventions needed to decrease pulmonary artery pressures and hospitalizations over time in real-world use. There has not yet been sufficient time to see whether this strategy will decrease progression to right heart failure but the amount of decrease in chronic pulmonary pressures has already been associated with decreased mortality [44]. The new options for non-surgical reduction of mitral regurgitation may further diminish the accumulation of congestion over time and interrupt disease progression from left to right heart failure [45]. Once we have been able to remove the congestion that increases myocardial wall stress, it may become possible to truly isolate and interrupt the remaining intrinsic processes in the myocardium and its scaffolding that contribute to progressive failure.

The premise of this chapter is to provide an overview of the various hemodynamic contributors that may lead to cardio-renal syndrome. Identifying and recognizing these factors may help prevent and treat the kidney dysfunction of heart failure, thereby improving the prognosis of heart failure itself. However, we have not made enough progress on the fundamental question of why and when fluid is

first retained by the patient with cardio-renal syndrome. We recognize now that it can occur long before evidence of impaired perfusion, often in patients without symptoms of heart disease, as shown in the classic saline infusion studies before and after ACE inhibitors in asymptomatic patients after myocardial infarction [46]. We know also that fluid retention in turn begets more fluid retention. Once we can uncover the first triggers, perhaps we can learn how to detect and prevent the first fluid retention during asymptomatic dysfunction, long before symptoms of congestion. We can then re-channel our efforts to sustain a new landscape where the heart and kidney function together as when we first came out of the water onto dry land.

References

1. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000;35:681–9.
2. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J. 2007;154:260–6.
3. Stevenson LW, Dracup KA, Tillisch JH. Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. Am J Cardiol. 1989;63:461–4.
4. Drazner MH, Hamilton MA, Fonarow G, Creaser J, Flavell C, Stevenson LW. Relationship between right and left sided filling pressures in 1000 patients with advanced heart failure. J Heart Lung Transplant. 1999;18:1–10.
5. Stevenson LW, Tillisch JH. Maintenance of cardiac output with normal filling pressures in patients with dilated heart failure. Circulation. 1986;74:1303–8.
6. Stevenson LW. Tailored therapy before transplantation for treatment of advanced heart failure: effective use of vasodilators and diuretics. J Heart Lung Transplant. 1991;10:468–76.
7. Stevenson LW, Bellil D, Grover-McKay M, Brunken RC, Schwaiger M, Tillisch JH, Schelbert HR. Effects of afterload reduction (diuretics and vasodilators) on left ventricular volume and mitral regurgitation in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1987;60:654–8.
8. Rosario LB, Stevenson LW, Solomon SD, Lee RT, Reimold SC. The mechanism of decrease in dynamic mitral regurgitation during heart failure treatment: importance of reduction in the regurgitant orifice size. J Am Coll Cardiol. 1998;32:1819–24.
9. Johnson W, Omland T, Hall C, Lucas C, Myking O, Collins C, Pfeffer M, Rouleau J, Stevenson LW. Neurohormonal activation rapidly decreases after intravenous therapy with diuretics and vasodilators for class IV heart failure. J Am Coll Cardiol. 2002;39:1623–9.
10. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 2003;41:1797–801.
11. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E. Diuretic use, progressive heart failure, and death in the Studies of Left Ventricular Dysfunction. J Am Coll Cardiol. 2003;42:705–8.
12. Mielniczuk LM, Tsang SW, Desai AS, Nohria A, Lewis EF, Fang JC, Baughman KL, Stevenson LW, Givertz MM. The association between high-dose diuretics and clinical stability in ambulatory chronic heart failure patients. J Card Fail. 2008;14:388–3938.
13. Cohn JN, Johnson G. Heart failure with normal ejection fraction: the V-HeFT Study. Circulation. 1990;8:II48–53.
14. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004;43:61–7.

15. Licata G, Volpe M, Scagliano R, Rubattu S. Salt-regulating hormones in young normotensive obese subjects. Hypertension. 1994;23:I20–4.
16. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation. 2017;136:6–19.
17. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, Henderson J, Cowart P, Stevenson LW. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail. 2014;7:935–44.
18. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. Am Heart J. 1999;138:285–90.
19. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J. 2004;147:331–8.
20. Gottlieb SS, Abraham W, Butler J, Forman D, Loh E, Massie BM, O'Conner CM, Rich MW, Stevenson LW, Young J, Krumholz HM. The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail. 2002;8:136–41.
21. Investigators TESCAPE. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA. 2005;294:1625–33.
22. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM, Network NHFCR. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805.
23. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E. Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367:2296–304.
24. Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, DeVore AD, Khazanie P, Redfield MM, Goldsmith SR, Bart BA, Anstrom KJ, Felker GM, Hernandez AF, Stevenson LW. Relief and recurrence of Congestion During and After Hospitalization for Acute Heart Failure: Insights From Diuretic Optimization strategy evaluation in acute decompensated heart failure (DOSE-AHF) and cardiorenal rescue study in acute decompensated heart failure (CARESS-HF). Circ Heart Fail. 2015;8:741–8.
25. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the ESCAPE trial. J Am Coll Cardiol. 2008;51:1268–74.
26. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122:265–72.
27. Metra M, Cotter G, Senger S, Edwards C, Cleland JG, Ponikowski P, Cursack GC, Milo O, Teerlink JR, Givertz MM, O'Connor CM, Dittrich HC, Bloomfield DM, Voors AA, Davison BA. Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion: a post hoc analysis of the PROTECT Data. Circ Heart Fail. 2018;11:e004644.
28. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail. 2012;5(1):54–62.
29. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A,

McMurray JJ, Filippatos G. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12:423–33.
30. Ambrosy AP, Pan PS, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in the EVEREST trial. Eur Heart J. 2013;34:835–43.
31. Yancy CW, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchel JE, Peterson PN, Reigel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure. J Am Coll Cardiol. 2013;62:e147–239.
32. Valtin H, Schafer JA. Renal function. Boston: Little, Brown, and Co.; 1995. p. 100–2.
33. Chen C, Lee J, Johnson AE, Mark RG, Celil LA, Danziger J. Right ventricular function, peripheral edema, and acute kidney injury in critical illness. Kidney Int Rep. 2017;2:1059–65.
34. Dini FL, Demmer RT, Simioniuc A, Morrone D, Donati F, Guarini G, Orsini E, Caravelli P, Marzilli M, Colombo PC. Right ventricular dysfunction is associated with chronic kidney disease and predicts survival iln patients with chronic systolic heart failure. Eur J Heart Failure. 2012;14:287–94.
35. Campbell P, Drazner MH, Kato M, Lakdawala N, Palardy M, Nohria A, Stevenson LW. Mis-match of right and left-sided filling pressures in chronic heart failure. J Card Fail. 2011;17:561–8.
36. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53:589–96.
37. Carr JG, Stevenson LW, Walden JA, Heber D. Prevalence and hemodynamic correlates of malnutrition in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1989;63:709–13.
38. Krack A, Sharma R, Figulia HR, Anker SD. The importance of the gastrointestinal system in the pathogenesis of heart failure. Eur Heart J. 2005;22:2368–74.
39. Delgado R, Wadia Y, Kar B, Ethridge W, Zewail A, Pool T, Myers TJ, Scroggins N, Frazier OH. Role of b-type natriuretic peptide and effect of nesiritide after total cardiac replacement. J Heart Lung Transplant. 2005;24:1166–70.
40. Zucker IH, Earle AM, Gilmore JP. Mechanism of adaptation of left atrial stretch receptors in dogs with chronic congestive heart failure. J Clin Invest. 1977;60:323–31.
41. Kirklin JK, Naftel DC, Kormos RL, Pagani FD, Myers SL, Stevenson LW, Givertz MM, Young JB. Quantifying the effect of cardiorenal syndrome on mortality after left ventricular assist device implant. J Heart Lung Transplant. 2013;32:1205–13.
42. Palardy M, Nohria A, Rivero J, Lakdawala N, Campbell P, Kato M, Griffin LM, Smith CM, Couper GS, Stevenson LW, Givertz MM. Right ventricular dysfunction during intensive pharmacologic unloading persists after mechanical unloading. J Card Fail. 2010;16:218–24.
43. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Miller MA, Timothy Baldwin J, Young JB. Sixth INTERMACS annual report: a 10,000-patient database. J Heart Lung Transplant. 2014;33:555–64.
44. Zile MR, Bennett TD, Hajj SE, Kueffer FJ, Baicu CF, Abraham WT, Bourge RC, Stevenson LW. Intracardiac pressures using an implantable HD monitor: relationship to mortality. Circ Heart Fail. 2017;10:pii:003594.
45. Stone GW, Lindenfeld JA, Abraham WT, et al. Transcatheter mitral valve repair in patients with heart failure. New Eng J Med. 2018;379:2307–18.
46. Volpe M, Tritto C, De Luca N, Mele AF, LEmbo G, Rubattu S, Romano M, De Campora P, Enea I, Ricciardelli B. Failure of atrial natriuretic factor to increase with saline load in patients with dilated cardiomyopathy and mild heart failure. J Clin Invest. 1991;88:1481–9.

Part I

Insights from Pathophysiologic Mechanisms

Mechanisms of Cardiorenal Syndrome: From Molecular Pathways to Novel Therapeutics

3

Tomoki Ichiki, Yang Chen, and John C. Burnett Jr

Introduction

A fundamental concept of heart failure (HF) is the importance of a cardiorenal connection in which both organs talk to each other from the perspective of structure and function [1]. Importantly, they communicate not only from a hemodynamic perspective but also from a hormonal one. Under physiological conditions there is a balance between the natriuretic peptide system (NPS), which consists of atrial natriuretic peptide (ANP), B-type NP (BNP) and C-type NP (CNP) of cardiac origin and the renin-angiotensin-aldosterone system (RAAS) which is of renal and adrenal origin. This physiological balance is central to blood pressure and body fluid homeostasis. In HF, there emerges an imbalance in these two systems in which RAAS predominates and contributes to the signs and symptoms of HF while also offsetting the beneficial and compensatory actions of the NPS. Indeed, the most severe extreme of this imbalance in part contributes to what is called the Cardiorenal Syndrome, which broadly can be defined as impaired renal function in the setting of HF, which increases the risk of progressive HF, death and rehospitalization. Indeed, Damman and co-workers in an elegant meta-analysis of 85 clinical studies of renal impairment in human HF reported that worsening renal function was highly prevalent HF, especially in the setting of chronic kidney disease (CKD), and strongly associated with increased mortality [2].

It is well established that there is activation of detrimental molecular pathways in the heart, which contribute to the progression of HF [3]. An unequivocal activator

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of such pathways in Angiotensin II (ANGII), which possesses deleterious actions on multiple molecular pathways, involved with cellular hypertrophy, apoptosis, inflammation and fibrosis. Indeed, the repeated pivotal clinical trials which report the improvement of outcomes in both HF and in CKD with angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) underscore the importance of ANGII in the pathophysiology of cardiorenal disease [4]. Of note, the pivotal HF trial of sacubitril (a neprilysin inhibitor which augments the NPS)/valsartan (an ARB) which reduced hospitalization and death resulted in the approval of this novel HF drug which further supports a protective role for cardiorenal function in HF through interruption of the RAAS and promotion of the NPS [5, 6].

As well established, the kidney plays a key role in HF exemplified by the fact that impaired renal function increases the risk for poor outcomes. Studies support the concept that reduced myocardial pump function with either reduced arterial pressure and/or increased venous pressure impairs renal perfusion and induces sodium and water retention while reducing glomerular filtration rate which may result in congestion and diuretic resistance [7]. What remains incompletely defined unlike in heart are the deleterious molecular pathways activated in HF with worsening renal function. Toward this goal, we investigated such pathways in a large animal model of HF with impaired renal function together with excessive activation of RAAS and co-activation of the RAAS [8].

As expected, our canine HF model was characterized by reduced ejection fraction and blood pressure, elevated PCWP and PAP and marked activation of the circulating NPS and RAAS along with sodium and water retention. As stated above, a hallmark of HF is a progressive decline in renal function, which has been termed the CRS. Indeed, renal impairment in HF and/or acute kidney injury (AKI) is recognized as a powerful independent predictor of outcomes. Notably, our recent findings provided a first attempt to explore gene patterns in both the kidney focusing on a wide range of inflammatory, renal injury, apoptotic and pro-fibrotic genes in response to experimental HF in a large animal model which closely mimics human CRS. Further, as the kidney is the site of initial renin activation, specifically localized to the kidney cortex (KC), there may be a fundamental mechanism of cardiorenal injury through increased circulatory levels of RAAS and modulation of renal gene expression, which would be an important therapeutic target for renal protection.

Employing a strategy, which involved determining gene expression of 179 selected genes, we defined HF-induced gene expression in inflammatory, renal injury, apoptotic, and fibrotic genes in our experimental model [8]. The major finding was demonstration of gene activation in both the KC and kidney medulla (KM) involving these key pathways (Fig. 3.1). Importantly, we also compared changes in the kidney to changes in the heart in which we observed the greatest changes in atrial compared to ventricular myocardium. We also validated at the protein level 4 genes from inflammatory pathways at the protein level, which included MCP-1, IL-6, IL1

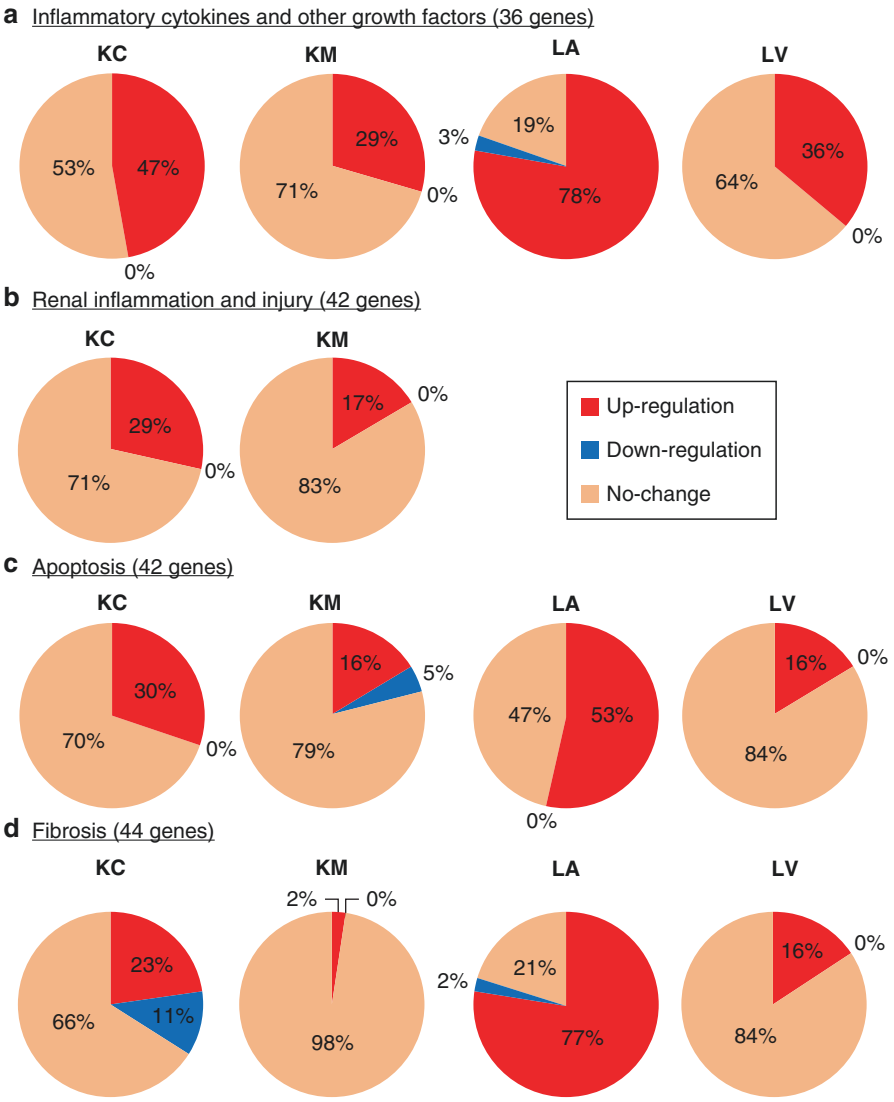

Fig. 3.1 Summary of gene modifications in experimental HF compared to normal kidney and heart by pathway. Each pie graph illustrates the percentage of up-regulated genes (red), down-regulated genes (blue) and un-changed genes (orange) in each organ for inflammatory cytokines and other growth factors (**a**), renal inflammation and injury (**b**), apoptosis (**c**), and fibrosis (**d**). Significantly changed gene compared to normal tissues for each organ ($p < 0.05$) were counted. (Adapted from Ref. [8])

beta and TNF alpha. All demonstrated activation at the protein level although the increases in TNF alpha strongly trended toward an increase but did not achieve significance. We concluded that these activated pathways might play an important role in the initiation of renal injury detected in KC in an animal model, which mimics CRS (Fig. 3.2). Of note, the KM showed fewer gene changes compared to KC, particularly of inflammatory cytokines at the gene and protein levels. These data suggest that the KC becomes injured in an experimental model highly relevant to CRS to KM damage with the same pathways activated sequentially as in the heart, which is in contrast with the prevailing theory of medullary ischemia as a driver in HF. Since there are few studies demonstrating concurrent tissue injury of the KM and KC, our findings are very unique and establish cortical injury, which is more prominent than medullary changes in experimental HF. Regarding mechanism, it is widely thought that only systemic RAAS activation mediates organ injury. However we speculate that in the kidney, intrarenal RAAS play an important role in renal injury and disease progression, particularly in the cortex [9, 10]. In mild HF, the early activation of the NPS is prominent with the RAAS suppressed or only minimally activated [11]. This early activation of NPS during the evolution of HF is associated with preservation of renal function and few if any symptoms of HF. We speculate that the activation of RAAS during the evolution of HF may serve as a mechanism to attenuate the protective properties through stimulation of phosphodiesterases or impairment in NP receptor function offsetting the protective actions of the NPS in multiple cell types of the kidney which is associated with a reduction in the second messenger system of the NPS which is a decrease in urinary excretion and production of cGMP [12].

Taken together our findings and those of others have clinical implications for CRS. Specifically, they lay the foundation for further studies of potential pharmacological interventions targeting these multiple molecular pathways in the kidney, which could limit progressive renal impairment and the CRS including adverse outcomes. The NPS are activated both in the heart and kidneys in our model, along with activation of RAAS, supporting studies where pharmacological interventions such as ACE inhibitor/NEP inhibitor, which co-target the RAAS and NPs, have promising reno-cardiac protection in HF.

Urinary CNP: A Potential Novel Urinary Biomarker for CRS and ADHF Prognosis

CRS in the setting of acute decompensated HF (ADHF) is associated with increased mortality that has provided a need to identify high-risk ADHF patients especially from the perspective of the kidney. Analogous to this concept is the global use of NT-proBNP as a biomarker for myocardial dysfunction in ADHF [13, 14]. To date however, there are less robust renal biomarkers in ADHF as compared to NT-proBNP. Indeed, creatinine-based estimates of glomerular function or urine albumin excretion lack strong prognostic assessment of renal tubular injury, which characterizes CRS.

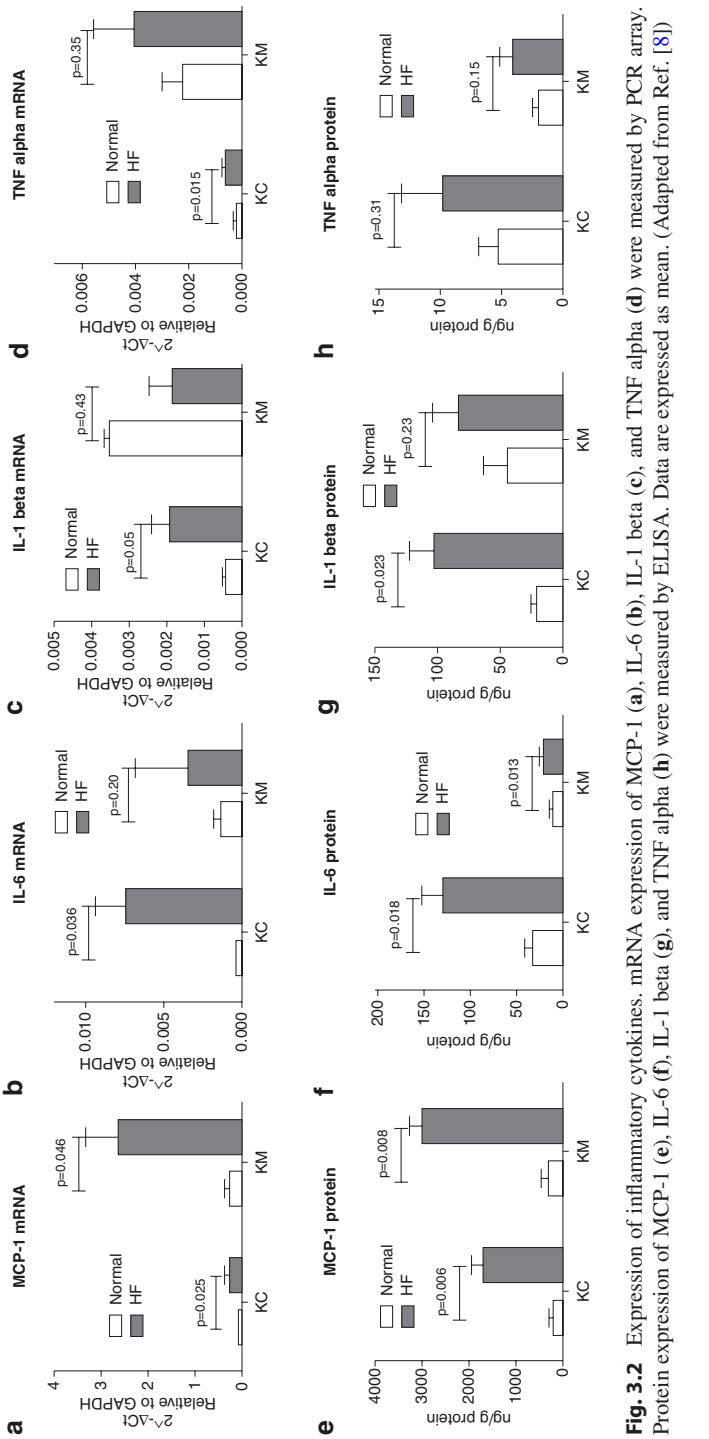

Fig. 3.2 Expression of inflammatory cytokines. mRNA expression of MCP-1 (**a**), IL-6 (**b**), IL-1 beta (**c**), and TNF alpha (**d**) were measured by PCR array. Protein expression of MCP-1 (**e**), IL-6 (**f**), IL-1 beta (**g**), and TNF alpha (**h**) were measured by ELISA. Data are expressed as mean. (Adapted from Ref. [8])

CNP is the renally derived member of the NP family and is produced in the kidney as well as the endothelium and has been localized to renal tubules [15, 16]. CNP is synthesized as a 103 amino acid proCNP hormone that is then processed into NT-proCNP and CNP53 by furin. Additional processing cleaves CNP53 to the biologically active CNP22 and an inactive form NT-proCNP53. While it is known that urinary CNP is increased in HF, the prognostic power of molecular forms of urinary CNP to identify high risk of poor outcomes was important to define. We therefore investigated if urinary NT-proCNP53, which, like NT-proBNP may have a longer half-life and be more resistant to enzymatic degradation, would identify high-risk subjects with ADHF and be more powerful in prognosis in ADHF than contemporary urinary biomarkers of tubular injury such as kidney injury molecule (KIM-1) and neutrophil gelatinaese-associaed lipcalin (NGAL). We also investigated if urinary NT-CNP53 could be of incremental predictive value to plasma NT-proBNP in risk stratification in human ADHF.

Our studies specifically measured 24-hour urinary excretion and plasma concentrations of CNP22, CNP53 and NT-CNP53 in 58 patients with ADHF and 20 normal control subjects without cardiovascular disease [17]. In all ADHF patients, all molecular forms of CNP in the urine were all increased with concentrations significantly greater than plasma levels. In these studies, plasma CNP22 and CNP53 were increased in ADHF patients but without correlation with urinary excretion. As expected, plasma NT-proBNP and urinary KIM-1 were increased in ADHF while urinary NGAL was not increased. Importantly, we defined outcomes at 6 months. Here there was an 86% event free survival for mortality and 59% for all-cause rehospitalization or death. The major finding was that only urinary NT-CNP53 was the only predictor of morality. Further, our study also reported that urinary NT-CNP53 combined with plasma NT-proBNP (a cardiorenal integrated biomarker combination) improved the prediction of adverse outcomes.

We concluded that urinary NT-CNP53 might represent renal biomarker of early renal injury as it is produced in the proximal tubule, its gene expression in the kidney was increased in our animal model of HF and hypoxia and cytokines are stimuli for CNP production [8, 18, 19]. Thus, these recent studies taken together support the clinical use of urinary CNP in ADHF to detect early renal injury and potentially developing CRS. Importantly, urinary NT-CNP53 correlated with outcomes than either NGAL or KIM-1 and improved the prognostic value of plasma NT-proBNP.

CRRL 269: A Novel Designer NP for CRS and AKI

In 1982, Forsmann discovered a renal derived peptide he named Urodilatin (URO) [20]. URO is a 32 amino acid (AA) NP that is of renal origin and processed from proANP within the kidney and contains the 28 AA sequence of ANP, but with 4 additional AAs at the end of the N-terminus. URO has been reported to have greater renal enhancing properties than ANP, through the pGC-A/cGMP pathway [21]. We and others have advanced the concept that URO may function as the renal component of a novel cardiorenal hormonal cGMP mediated system [22].

Advances in peptide engineering have led to discovery and clinical development of novel designer NPs that possess actions, which go beyond the native NPs. Such designer peptides contain unique AA sequences that provide attractive biological properties making them potential innovative peptide therapeutics [23]. One major goal for designer NP therapeutics is the discovery and clinical development of more renal selective and/or potent peptides that possess enhanced natriuretic and diuretic properties with preservation or enhancement of GFR, while retaining RAAS suppressing actions. Optimally, such peptides would also possess less hypotensive properties, which has limited the therapeutic use of NPs such as BNP (i.e., nesiritide).

We therefore recently undertook the design, synthesis and in vitro and in vivo investigation of a novel cardiorenal therapeutic designer NP that we call CRRL269 [24]. Our aim was to engineer an innovative peptide that had more renal enhancing actions compared to BNP (a NP highly resistant to NEP degradation and from the heart) and URO (a renal produced highly NP), but retain RAAS suppressing properties with less hypotension. To achieve this goal we integrated key AA sequences of BNP with key AAs of URO so as to result in a peptide with superior renal pGC-A activation *in vitro* and mediate renal-enhancing properties *in vivo* compared to the two respective native NPs.

We employed solid phase peptide synthesis to produce CRRL269. We defined the ability of CRRL269 to stimulate pGC-A and cGMP in HEK293 cells engineered to overexpress human pGC-A receptors and in primary human renal proximal tubular cells (RPTCs) and human aortic endothelial cells (HAECs) *in vitro*. Recognizing the importance of resistance to NEP degradation, we also defined CRRL269 degradation by NEP. We also compared CRRL269 renal, hemodynamic, and neurohormonal actions to BNP and URO. Lastly, to better understand its less hypotensive properties, we investigated CRRL269 mediated vasorelaxation of canine arterial rings compared to BNP and compared cAMP production in cultured human cardiomyocytes recognizing cAMP as a mediator of positive inotropism in the heart.

Supporting our goal, we found that CRRL269 possessed the most potent cGMP activating properties in HEK293 cells overexpressing human pGC-A receptors compared to BNP and URO supporting its renal selective properties. CRRL269 also generated higher cGMP in RPTCs compared to non-renal endothelial cells. CRRL269 also exerted resistance to NEP although less than BNP. CRRL269 was more diuretic and natriuretic with less blood pressure reduction, in normal dogs compared to BNP or URO. CRRL269 also had aldosterone inhibiting actions and GFR preserving properties. Lastly, CRRL269 generated greater cAMP than BNP *in vitro* and exerted less arterial ring relaxation *ex vivo*. Thus, CRRL269 may represent a potential renal enhancing therapeutic for cardiorenal disease states such as CRS going beyond native pGC-A activators.

These studies, which are highly relevant to CRS therapeutics, underscore that the pGC-A/cGMP pathway is a critical stimulator of water and sodium excretion with increases in GFR [25]. Studies have established that cGMP mediates its renal enhancing actions through cGMP-gated ion channels, which include the amiloride-sensitive cation channel, and through protein kinase G activation [26, 27]. Sodium retention observed with a pGC-A receptor antagonist in canine studies support the

role of pGC-A/cGMP in the renal actions of NPs [28]. The increased cGMP generating properties in renal cells and the trend of higher plasma cGMP production in vivo by CRRL269 support the role of cGMP. During the infusion of CRRL269, URO and BNP, the increase in diuresis was similar with CRRL269 and URO and greater for both compared to BNP. A similar pattern was observed for natriuresis. Importantly however, CRRL269 induced natriuresis and diuresis was more sustained and persistent well into the washout and recovery periods compared to BNP or URO. Renal blood flow increased with all three peptides. Of note, GFR increased with CRRL269 compared to baseline that was also observed at the end of the recovery period, which was more efficacious, that either other peptide. We concluded that the greater maintenance of blood pressure and renal perfusion pressure by CRRL269 might be a central mechanism by which it mediates the greater increase of GFR. Further studies are needed, such as the use of isolated glomeruli, to provide greater insights into the GFR enhancing actions of CRRL269. A key property of pGC-A activation is the inhibition of both renin and aldosterone [29]. The mechanism(s) may involve direct activation of pGC-A in the adrenal gland and in the kidney but also may involve a macula densa mechanism for renin suppression. CRRL269 retained RAAS suppressing properties observed with URO and BNP. Thus, the unique design of CRRL269 possesses favorable renal and adrenal properties beyond native BNP and URO with more sustained natriuresis and diuresis together with GFR enhancing and RAAS suppressing actions.

It is well recognized that NEP is a degrading enzyme for NPs and is highly expressed in the kidney [30]. BNP is known to be highly resistant to NEP degradation. Investigations of URO and ANP have documented that the increased renal actions of URO compared to ANP were also secondary to the greater resistance to NEP [31]. It is reasonable to conclude that CRRL269 retained the resistance to NEP degradation from the core AA sequences of BNP and/or URO. In our study, we reported that CRRL269 possessed improved resistance to NEP compared to URO, but less than BNP, which also may a mechanism that contributes to CRRL269's enhanced renal actions *in vitro* and *in vivo*.

The greater and sustained renal actions of CRRL269 support its potential as a renal therapeutic drug in CRS (Fig. 3.3). Its RAAS suppressing actions with less hypotension than BNP or URO further advances its therapeutic potential. The combination of renal enhancing and RAAS inhibiting properties of CRRL269 renders it a potential drug for CRS as well as AKI. Of note, clinical trials have documented that ANP and BNP infusion mediated sustained renal benefits in patients undergoing cardiac surgery [32, 33]. However, both ANP and BNP resulted in unwanted arterial hypotension. Based on the renal-selective properties *in vitro* and *in vivo* of CRRL269 and less of a blood pressure lowering action compared to BNP or URO, CRRL269 may represent a novel drug for renoprotection in CRS and AKI.

Nesiritide (BNP) was approved for ADHF treatment in 2001 but in the pivotal ASCEND-HF Trial, nesiritide demonstrated no significant additive beneficial effects compared to standard therapy [34]. The lack clinical benefits with nesiritide in ASCEND-HF may be secondary to excessive hypotension, as a reduction in blood pressure may have reduced renal perfusion pressure, thus worsening kidney function and reinforcing the concept that blood pressure preservation is critical

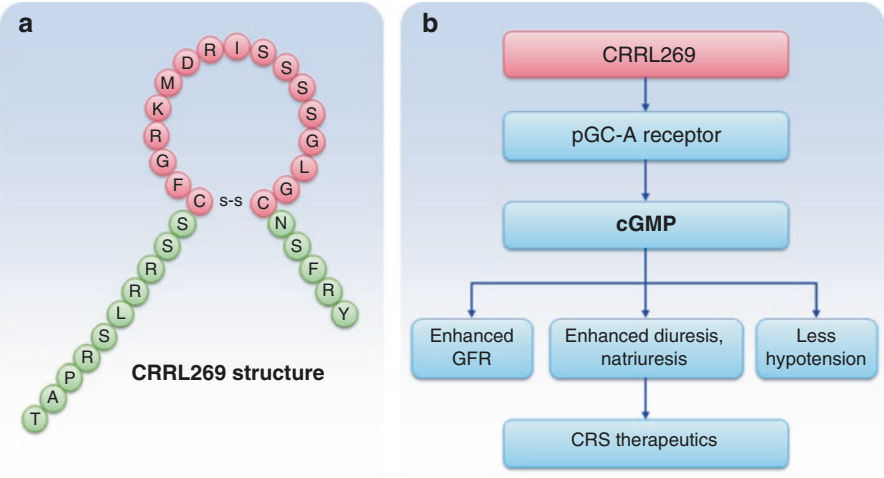

Fig. 3.3 CRRL269 as an enhanced pGC-A activator. (**a**) CRRL269 structure; (**b**) CRRL269 implicated as a potential drug for CRS mediating increased GFR, diuresis and natriuresis with less hypotension than native NPs. (Adapted from Ref. [24])

during HF treatment [35]. The discovery of URO revealed that this renal NP has less BP lowering effects as compared to cardiac derived BNP. However in human AHF, URO (Ularitide) mediated beneficial physiological actions, but short-term treatment did not improve clinical composite end points or reduce long-term cardiovascular mortality which again may have been due to excessive reductions in blood pressure[36]. CRRL269 has enhanced natriuresis and diuresis, which was more sustained than URO or BNP with less blood pressure reductions compared to BNP or URO and retained anti-RAAS properties. These favorable properties suggest that CRRL269 may represent a novel drug for HF and especially CRS.

Writing about designer NPs, Gardner stated intriguing possibilities may exist for designing novel NPs with attractive therapeutic profiles based on the selection and synthesis of specific structural motifs from native NPs[37]. Thus, designer NPs could result in properties that are not available in endogenous NPs. CRRL269 represents a novel designer NP that possesses a more efficacious renal profile compared to URO or BNP which is more natriuretic and diuretic than either BNP or URO which both bind to pGC-A but with less hypotension and possible positive inotropism.

Conclusion

It is important to go beyond looking at the kidney as a black box if advances are to be made in syndromes such as the CRS as well as AKI. Increasing evidence establishes that like the heart in HF there is widespread activation of deleterious molecular pathways related to inflammation, fibrosis, apoptosis and renal injury. A key mediator may be RAAS, which may not only activate such deleterious pathways but may offset the renoprotective actions of the NPs. As we develop novel therapies, such

as the designer peptide CRRL269 whose molecular target is pGC-A/cGMP signaling in the kidney, the renal produced NP CNP (and its molecular form NT-CNP53) may provide the opportunity to detect early renal injury and CRS prompting novel preventive therapies to reduce the burden of CRS.

References

1. Braunwald E. Heart failure. JACC Heart Fail. 2013;1:1–20.
2. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35:455–69.
3. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation. 2005;111:2837–49.
4. Yang T, Xu C. Physiology and pathophysiology of the intrarenal renin-angiotensin system: an update. J Am Soc Nephrol. 2017;28:1040–9.
5. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). Eur J Heart Fail. 2013;15:1062–73.
6. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile M, Andersen K, Arango JL, Arnold JM, Belohlavek J, Bohm M, Boytsov S, Burgess LJ, Cabrera W, Calvo C, Chen CH, Dukat A, Duarte YC, Erglis A, Fu M, Gomez E, Gonzalez-Medina A, Hagege AA, Huang J, Katova T, Kiatchoosakun S, Kim KS, Kozan O, Llamas EB, Martinez F, Merkely B, Mendoza I, Mosterd A, Negrusz-Kawecka M, Peuhkurinen K, Ramires FJ, Refsgaard J, Rosenthal A, Senni M, Sibulo AS Jr, Silva-Cardoso J, Squire IB, Starling RC, Teerlink JR, Vanhaecke J, Vinereanu D, Wong RC. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation. 2015;131:54–61.
7. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53:589–96.
8. Ichiki T, Huntley BK, Harty GJ, Sangaralingham SJ, Burnett JC Jr. Early activation of deleterious molecular pathways in the kidney in experimental heart failure with atrial remodeling. Physiol Rep. 2017;5(9):e13283.
9. Luchner A, Stevens TL, Borgeson DD, Redfield MM, Bailey JE, Sandberg SM, Heublein DM, Burnett JC Jr. Angiotensin II in the evolution of experimental heart failure. Hypertension. 1996;28:472–7.
10. Haneda M, Kikkawa R, Maeda S, Togawa M, Koya D, Horide N, Kajiwara N, Shigeta Y. Dual mechanism of angiotensin II inhibits ANP-induced mesangial cGMP accumulation. Kidney Int. 1991;40:188–94.
11. Stevens TL, Burnett JC Jr, Kinoshita M, Matsuda Y, Redfield MM. A functional role for endogenous atrial natriuretic peptide in a canine model of early left ventricular dysfunction. J Clin Invest. 1995;95:1101–8.
12. Marguiles K, Heublein DM, Perrella M, Burnett JC Jr. ANF-mediated renal cGMP generation in congestive heart failure. Am J Phys. 1991;260:F562–8.
13. McKie PM, Cataliotti A, Huntley BK, Martin FL, Olson TM, Burnett JC Jr. A human atrial natriuretic peptide gene mutation reveals a novel peptide with enhanced blood pressure-lowering, renal-enhancing, and aldosterone-suppressing actions. J Am Coll Cardiol. 2009;54:1024–32.

14. McKie P, Burnett JC Jr. NT-proBNP: the gold standard biomarker in heart failure. J Am Coll Cardiol. 2016;6:2437–9.
15. Mattingly MT, Brandt RR, Heublein DM, Wei CM, Nir A, Burnett JC Jr. Presence of C-type natriuretic peptide in human kidney and urine. Kidney Int. 1994;46:744–7.
16. Dean AD, Greenwald JE. Regulation of C-type natriuretic peptide (CNP) in the kidney. J Am Soc Nephrol. 1993;4(3):436.
17. Zakeri R, Sangaralingham SJ, Sandberg S, Heublein DM, Scott C, Burnett JC Jr. Urinary C-type natriuretic peptide. JACC Heart Fail. 2013;1:170–7.
18. Sangaralingham SJ, Heublein DM, Grande JP, Cataliotti A, Rule AD, McKie PM, Martin FL, Burnett JC Jr. Urinary C-type natriuretic peptide excretion: a potential novel biomarker for renal fibrosis during aging. Am J Physiol Renal Physiol. 2011;301:F943–52.
19. Zakeri R, Burnett JC Jr, Sangaralingham SJ. Urinary C-type natriuretic peptide: an emerging biomarker for heart failure and renal remodeling. Clin Chim Acta. 2015;443C:108–13.
20. Feller SM, Gagelmann M, Forssmann WG. Urodilatin: a newly described member of the ANP family. Trends Pharmacol Sci. 1989;10:93–4.
21. Abassi ZA, Golomb E, Agbaria R, Roller PP, Tate J, Keiser HR. Hydrolysis of iodine labelled urodilatin and ANP by recombinant neutral endopeptidase EC. 3.4.24.11. Br J Pharmacol. 1994;113:204–8.
22. Dean AD, Vehaskari VM, Greenwald JE. Synthesis and localization of C-type natriuretic peptide in mammalian kidney. Am J Physiol. 1994;266:F491–6.
23. Meems LMG, Burnett JC Jr. Innovative therapeutics: Designer natriuretic peptides. JACC Basic Transl Sci. 2016;1:557–67.
24. Chen Y, Harty GJ, Huntley BK, Iyer SR, Heublein DM, Harders GE, Meems L, Pan S, Sangaralingham SJ, Ichiki T, Burnett JC Jr. Crrl269: a novel designer and renal-enhancing pGC-A peptide activator. Am J Physiol Regul Integr Comp Physiol. 2018;314:R407–14.
25. Chen Y, Burnett JC. Particulate guanylyl cyclase a/cgmp signaling pathway in the kidney: physiologic and therapeutic indications. Int J Mol Sci. 2018;19:1006–14.
26. Light DB, Corbin JD, Stanton BA. Dual ion-channel regulation by cyclic GMP and cyclic GMP-dependent protein kinase. Nature. 1990;344:336–9.
27. Scavone C, Scanlon C, McKee M, Nathanson JA. Atrial natriuretic peptide modulates sodium and potassium-activated adenosine triphosphatase through a mechanism involving cyclic GMP and cyclic GMP-dependent protein kinase. J Pharmacol Exp Ther. 1995;272:1036–43.
28. McKie PM, Cataliotti A, Lahr BD, et al. The prognostic value of N-terminal pro-B-typenatriuretic peptide for death and cardiovascular events in healthy normal and stage A/B heart failure subjects. J Am Coll Cardiol. 2010;55:2140–2147, 2010.
29. Sezai A, Hata M, Niino T, Yoshitake I, Unosawa S, Wakui S, Kimura H, Shiono M, Takayama T, Hirayama A. Results of low-dose human atrial natriuretic peptide infusion in nondialysis patients with chronic kidney disease undergoing coronary artery bypass grafting: the NU-HIT (Nihon University working group study of low-dose HANP Infusion Therapy during cardiac surgery) trial for CKD. J Am Coll Cardiol. 2011;58:897–903.
30. Mentzer RM Jr, Oz MC, Sladen RN, Graeve AH, Hebeler RF Jr, Luber JM Jr, Smedira NG. Effects of perioperative nesiritide in patients with left ventricular dysfunction undergoing cardiac surgery:the NAPA Trial. J Am Coll Cardiol. 2007;49:716–26.
31. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalan R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Mendez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365:32–43.
32. Vaduganathan M, Butler J, Pitt B, Gheorghiade M. Contemporary drug development in heart failure: call for hemodynamically neutral therapies. Circ Heart Fail. 2015;8:826–31.

33. Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, Dickstein K, Filippatos G, Holcomb R, Krum H, Maggioni AP, Mebazaa A, Peacock WF, Petrie MC, Ponikowski P, Ruschitzka F, van Veldhuisen DJ, Kowarski LS, Schactman M, Holzmeister J. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med. 2017;376:1956–64.
34. Gardner DG. Designer natriuretic peptides. J Clin Invest. 1993;92:1606–7.
35. Burnett JC Jr, Korinek J. Tumultuous journey of nesiritide. Circulation. 2008;1:6–8.

Pathophysiology of Cardio-Renal Syndrome: Autonomic Mechanisms

4

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Introduction

Heart failure (HF) is a complex clinical syndrome with high morbidity and mortality characterized by signs and symptoms of congestion. The abnormal circulatory hemodynamics resulting from the failing heart invokes a response, in particular, from the autonomic nervous system (ANS) and the kidneys that ultimately leads to a congestive state. This response is initially adaptive and attempts to maintain an adequate cardiac output and blood pressure. However, it becomes chronic and maladaptive in the long term resulting in pathological structural and functional changes in the heart as well as multiple other organs. These changes are especially important in the heart and the kidneys on account of their direct interdependence. The heart depends directly on kidneys for the regulation of salt and water content of the body which is of particular importance in conditions with a congestive state such as HF, since the kidneys are directly dependent upon blood flow and pressure generated by the heart.

Interactions between the heart and the kidneys have been alluded to as early as the nineteenth century [1]. The adverse effects of passive venous congestion on kidney function in dogs was demonstrated by Rowntree et al. in 1913 [2]. In a series of experiments in dogs, Blake et al. demonstrated that even modest elevations of renal venous pressure resulted in significant decreases in sodium and water excretion without any change in renal plasma flow or glomerular filtration rate [3]. These experiments recognized for the first time the importance of venous congestion for the development of renal dysfunction in the setting of a congestive state such as HF. Since then there have been a plethora of studies on cardiorenal interactions particularly in the setting of HF. It is now clear that acute or chronic dysfunction of the

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heart can cause acute or chronic dysfunction of the kidneys and vice versa. These complex and multifaceted interactions were recognized as a syndrome around 2004. Ronco and colleagues described the condition as a distinct entity and suggested the existence of at least 5 conceptual subtypes of the 'Cardiorenal syndrome' [4]. In "Type 1," acute worsening of cardiac function leads to acute kidney injury (AKI). In "Type 2," chronic abnormalities in cardiac function leads to kidney injury or dysfunction [5]. The other subtypes of cardio-renal syndrome refer to the development of cardiac dysfunction in the setting of renal dysfunction or systemic illness. While the classification has been useful in developing an awareness of the various cardiorenal interactions, data to support the distinction based on pathophysiology, treatment, and prognosis are limited [6].

This chapter will focus on cardio-renal syndrome (either acute or chronic) in which HF is the driver of renal dysfunction, with a focus on the autonomic mechanisms affecting the pathophysiology of this syndrome.

Epidemiology

In ambulatory patients with chronic HF, several retrospective analyses of clinical trials demonstrated that even moderate degrees of renal dysfunction are independently associated with increased risk for all-cause mortality [7–9]. In patients with advanced HF, renal dysfunction was a stronger predictor of mortality than Left Ventricular ejection fraction and New York Heart Association class. A more recent meta-analysis of 85 studies involving over 1 million patients with HF, baseline chronic kidney disease (CKD) and/or worsening renal function (WRF) were associated strongly with increased mortality risk [10]. This was particularly true for patients with CKD. The overall prevalence of CKD was 32% while WRF was present in 23% of the patients. The mortality risk for patients with HF and coexisting renal dysfunction was approximately twice that of those without evidence of renal dysfunction, a risk independent of the chronicity or phenotype of HF. Only studies that provided a detailed description of the definition of WRF were included in this meta-analysis, defined by either a decrease in estimated glomerular filtration rate (GFR) or an increase in serum creatinine or cystatin C over time. In hospitalized patients with acute decompensated HF (ADHF), the ADHERE database revealed that at least moderate renal dysfunction (stage III) was seen in 75,382 of 118,465 patients (63.6%) [11]. Only 10.6% of men and 7.5% of women had normal renal function as defined by GFR. In-hospital mortality increased from 1.9% for patients with normal renal function to 7.6% and 6.5% for patients with severe dysfunction (stage IV) and kidney failure (stage V), respectively. Acute cardio-renal syndrome occurs in about 25 to 33% of patients hospitalized for ADHF [12, 13]. It is clear that renal dysfunction is common in patients with HF regardless of the chronicity and it is associated with a 2-fold or greater increase in mortality.

Pathophysiological Mechanisms Implicated in Cardio-Renal Syndrome

The pathophysiological mechanisms attributed to the development of cardio-renal syndrome can be subdivided broadly into hemodynamic and non-hemodynamic factors, although from the description of the cardiorenal connection proposed by Bongartz et al. it would appear impossible to separate the two completely [14]. In this model, the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), nitric oxide-reactive oxygen species (NO-ROS) imbalance and inflammation are 'cardiorenal connectors' that interact synergistically contributing to cardiac and renal functional derangement.

Hemodynamic Factors

Historically, the development of renal dysfunction in patients with HF has been attributed to the inability of the failing heart to develop sufficient forward flow or intravascular volume depletion on account of aggressive diuresis, resulting in renal hypoperfusion and a decrease in GFR. However, in a landmark study of patients with moderate to severe HF, Ljungman and colleagues demonstrated that although the renal blood flow (RBF) decreased as the cardiac output decreased, this was accompanied by a compensatory increase in filtration fraction such that GFR remained relatively stable except in patients with severely impaired cardiac output. GFR became flow dependent only in patients with the most advanced stage of HF who had exhausted the renal autoregulatory capacity [15].

In recent years, a reappraisal of the relationship between venous congestion and decreased GFR has led to a shift in focus for the causes of renal dysfunction in the setting of HF. Decrease in urinary flow in the presence of venous congestion had been observed as early as 1861 [16]. There has been convincing evidence to support the association between increased central venous pressure (CVP) or venous congestion and reduced GFR independent of reduction in RBF [17, 18]. In the chronic setting, a significant association has been shown between increasing CVP and impairment in renal function [19]. In the setting of ADHF Mullens and colleagues demonstrated that central venous congestion was the most important hemodynamic determinant of WRF [18]. Multiple hypotheses have been proposed to explain venous congestion induced renal dysfunction. They include renal venules distorting distal tubules, and increased renal interstitial pressure on account of elevated central venous pressures causing tubular collapse and progressive decline in GFR [16, 20]. Yet the pathophysiology of venous congestion-induced renal dysfunction remains incompletely understood, and the relationship between CVP and WRF is not without controversy, and appears more complicated than previously thought [21]. For example Uthoff and colleagues reported that although ADHF patients with low systolic blood pressure (SBP) and high CVP had lower GFR, CVP seemed to have

no effect on GFR in patients with normal to high SBP [22]. In another report by Dupont and colleagues, blood pressure decrease, rather than alterations in cardiac output or central venous pressure, was associated with changes in serum creatinine during treatment of ADHF [23]. Improvement in renal function was less related to changes in right atrial (RA) pressures and cardiac output than previously thought.

Despite the recent focus on venous congestion and renal dysfunction, on account of the tight coupling between the RBF and GFR, RBF remains the most important determinant of GFR in HF [6]. Although renal autoregulation can increase filtration fraction (within limits), very low RBF can result in low GFR. The relative contribution of venous congestion in these circumstances is thought to be marginal at best.

Non-hemodynamic Factors

"Nonhemodynamic factors" influence GFR primarily through changes in intrarenal hemodynamics. Activation of nonhemodynamic factors can in turn worsen cardiorenal hemodynamics and a vicious cycle develops through the cardiorenal connection [14].

Renin-Angiotensin-Aldosterone System (RAAS) RAAS activation is a common feature in HF, particularly in patients with HF with reduced ejection fraction (HFrEF). Angiotensin II (ANG II) promotes renal fibrosis, directly affects GFR, induces hypo-responsiveness to natriuretic peptide and mediates sympathetic nervous system (SNS) activation which in turn has deleterious effects on the kidneys [24, 25]. Through nicotinamide adenine dinucleotide phosphate (reduced) oxidase activation, ANG II promotes the formation of ROS, which can cause intrarenal injury, in particular in the proximal tubules [26, 27]. Chronic RAAS activation can damage the structure and function of both the heart and kidney.

Sympathetic Nervous System SNS activation is a common feature in both heart failure and renal failure. Converse and colleagues first reported the connection between chronic renal failure and SNS activation [28]. Such activation, regardless of the source, results in adverse consequences to the heart as well as the kidneys. It also is associated with formation of ROS, renal tubular injury, and activation of RAAS [14]. Prolonged SNS activation can promote ROS-mediated growth on the walls of intrarenal blood vessels and cause inflammation by norepinephrine-mediated cytokine production from the liver [14, 29, 30].

Inflammation and Nitric Oxide-ROS Imbalance Studies in a canine model of HF by Ichiki and colleagues have demonstrated up-regulation of genes related to inflammation, renal inflammation and injury, apoptosis and fibrosis within the kidney even in early stage HF [31]. These investigators found that there was also vacuolization of the distal tubules consistent with mild renal injury. NO has several salutary effects

in multiple organ systems. In the kidney, it is involved in vasodilation, natriuresis, and desensitization of tubuloglomerular feedback mechanisms [14, 32]. It also inhibits several components of atherogenesis and smooth muscle cell proliferation. In renal dysfunction there is a relative deficiency of NO and the balance between NO and ROS is shifted in favor of ROS.

Abdominal Congestion and Redistribution Abdominal congestion that includes splanchnic venous and interstitial congestion has been implicated in the development of cardio-renal syndrome [33]. Fallick and colleagues have proposed that increased neurohormonal activation can result in redistribution of the splanchnic venous reservoir leading to an increase in effective circulatory volume and thereby venous congestion in the absence of a net increase in total body weight or volume [34]. This helps to explain the phenomenon of circulatory congestion in the absence of increased weight, which is the case in most patients presenting with ADHF.

There is cross talk between the cardiorenal connectors, viz. RAAS, SNS, Inflammation, NO-ROS balance and, hemodynamic control involving the extracellular fluid volume (ECFV), cardiac output (CO), and mean arterial pressure. This is particularly true with RAAS and SNS.

Autonomic Nervous System (ANS) in HF

HF is characterized by hemodynamic abnormalities that result in neurohormonal activation and autonomic imbalance. In particular, there is increased sympathetic activity and a withdrawal of parasympathetic activity [35, 36]. These changes can have profound effects on cardiac as well as renal structure and function. Evidence-based therapies for HF mitigate the effects of these neurohormonal changes and are now standard of care for patients with reduced LVEF. However, much less well studied are the therapies that augment parasympathetic activity and also address autonomic dysregulation in ADHF [37, 38]. As important as they are, the focus in this chapter will be the autonomic mechanism involving cardio-renal syndrome and, in particular, neural control of the kidney that may impact the maladaptive autonomic imbalance driving HF.

Innervation of the Kidney

Efferent sympathetic nerve fibers reach the renal vasculature, tubules, juxtaglomerular cells, and the renal pelvic wall to innervate the kidney. These nerves derive from the para and pre-vertebral ganglia (neuraxis) and enter the hilus of the kidney along the renal artery and vein. In contrast to the widespread distribution of sympathetic nerve fibers, the majority of the afferent renal sensory nerves are found in the renal pelvis [39], where they proceed from the kidney along the spinal cord toward

the dorsal root ganglia. Eventually, interneurons that synapse with the afferent renal nerves project to sites within the central nervous system associated with cardiovascular regulation, including nucleus tractus solitarius, rostral ventrolateral medulla, subfornical organ, and paraventricular nucleus of hypothalamus [40]. Evidence also exists for a monosynaptic projection of the afferent renal nerves to areas within the brainstem [41]. Electrical stimulation of the renal afferent nerves has been shown to activate neurons in the rostral ventricular lateral medulla and supraoptic nucleus leading to increased urinary sodium excretion by the contralateral kidney, providing functional evidence for central integration of the afferent renal nerve signals [42]. Additionally, using immunohistochemical detection of the protein Fos (a marker for neuronal activation), Goodwill and colleagues demonstrated that the renal pelvic administration of hypertonic NaCl resulted in the activation of numerous CNS sites in the forebrain and brainstem [43].

Many of the sympathetic nerve fibers are in close contact with the sensory nerves in the renal pelvis. Furthermore, sympathetic nerves and the sensory nerves are separate fibers that often are intertwined [44]. The majority of renal nerves are unmyelinated. There is no direct evidence of parasympathetic innervation of the kidney [45], and studies in animal models have failed to demonstrate any connection between the kidney and the vagal nuclei [46]. However, using tissue derived from patients undergoing autopsy, van Amsterdam and colleagues determined that sympathetic, parasympathetic and afferent nerves exist in the vicinity of the renal artery [47]. The nerves were closer to the artery in the more distal segments, and parasympathetic fibers were closer to the lumen than sympathetic or afferent fibers. While this information is useful to ensure complete renal denervation (RDN), the significance of the finding pertaining to parasympathetic nerves is unclear. Sakakura and colleagues reported that the density of peri-arterial renal sympathetic nerve fibers is lower in distal segments and dorsal locations, but as reported by Amsterdam they were closer to the lumen in more distal segments [48, 49]. They found a clear predominance of efferent nerve fibers, with decreasing prevalence of afferent nerves from proximal to distal peri-arterial and renal parenchyma. Afferent nerves dominate in the renal pelvis [50].

Efferent sympathetic nerves also reach the renin-containing granular cells of the juxtaglomerular apparatus, the renal tubular epithelial cell basement membrane, and the renal pelvic wall [44, 45, 51]. Efferent renal nerves are post-ganglionic fibers, and the majority of them are adrenergic with norepinephrine varicosities at the nerve terminals. In the vasculature and renal tubules, increasing efferent renal sympathetic nerve activity (RSNA) reduces RBF and urinary sodium excretion via α1-adrenoceptor activation. In the juxtaglomerular cells, increases in RSNA result in increased renin secretion by activation of β1-adrenoceptors. These are the primary mechanisms whereby RSNA plays a critical role in the homeostatic regulation of sodium and water balance.

Two classes of renal sensory nerves have been identified: Mechanosensory and chemosensitive. Mechanosensory nerves respond to stretch of renal tissue in the pelvis and/or interstitium. Chemosensitive nerves respond to renal ischemia and/or changes in the chemical environment surrounding the nerve endings [52, 53]. Two

classes of chemosensitive fibers have been described in the kidney. R1 chemosensitive nerve fibers, which have no basal activity and are activated by renal ischemia, and R2 chemosensitive nerve fibers, which are active both tonically and by changes in the chemical composition of the urine [54].

Renal Sympathetic Nerve Activity

Animal studies have demonstrated that small increases in RSNA augment renin secretion without altering either RBF or tubular reabsorption of sodium. With further increases of RSNA, renin secretion continues to increase and urinary sodium excretion begins to decrease. Reduction in RBF requires much higher levels of RSNA suggesting that RBF is not modulated by changes in renal sympathetic nerve activity within the physiological range [45, 52].

The primary neurotransmitter released by the renal sympathetic nerves is norepinephrine. Stimulation of the renal efferent nerves increases renal venous outflow of norepinephrine, and surgical removal of the renal nerves results in >90% decrease in renal tissue norepinephrine content [55, 56]. Neuropeptide Y (NPY) and ATP are co-released from renal efferent nerve terminals during increases in RSNA [52]. Studies in isolated rat and mouse models have demonstrated that ATP contributes to vasoconstrictor responses from renal sympathetic nerve stimulation at relatively low frequencies [57, 58]. ATP may also contribute to neurally-induced sodium reabsorption [59]. Release of NPY requires high intensity renal nerve stimulation and, as such, the physiologic impact of NPY in the kidney is unclear [45]. Of note, ANG II facilitates neurotransmission, and stimulation of ANG II Type I (AT1) receptors on pre-synaptic nerve terminals enhances norepinephrine release [24, 45]. In addition to the classic RAAS pathway, there is also intrarenal production of ANG II which plays a paracrine role in the kidney [60]. There is selective local regulation of intrarenal ANG II [61, 62]. Inappropriate activation of intrarenal ANG II can lead to the development of hypertension and renal injury [63, 64]. Treatment with angiotensin converting enzyme inhibitors (ACEI) results in decreases in both plasma as well as intrarenal ANG II levels [60, 65].

Afferent Renal Nerve Activity (ARNA)

While a great deal of attention has been paid to the role of efferent renal nerves in cardiovascular and renal dysfunction, the ability of the afferent renal nerves to modulate central reflexes and sympathetic outflow makes it a potential target for therapeutic intervention in HF and cardio-renal syndrome.

The primary sensory neurotransmitters in afferent renal nerves are Substance P and Calcitonin gene-related peptide (CGRP). Substance P is produced in the neural cell bodies in the dorsal root ganglia and transported along the afferent nerves to peripheral nerve endings where it is stored in vesicles for release in response to stimuli [45]. CGRP is co-localized with Substance P in the renal pelvic sensory

nerves and is released in response to the same stimuli that release Substance P [45, 66]. While Substance P plays an important role in the activation of renal sensory nerves, the role of CGRP in this regard is unclear. CGRP receptor blockade does not reduce the responsiveness of afferent neural nerves to various stimuli. It appears that CGRP delays the catabolism of Substance P and prolongs the effects of neurally-released Substance P [67].

Several mechanisms contribute to the release of Substance P from renal pelvic sensory nerves. Bradykinin is an activator of sensory nerve fibers [68]. Bradykinin 2 receptor antagonists reduce the ARNA responses to increases in renal pelvic pressure [69]. The action of bradykinin appears to depend on the route of administration. Renal pelvic administration results in release of Substance P, increased ARNA, and decreased RSNA without altering mean arterial pressure [45, 69, 70]. On the other hand, intrarenal administration of bradykinin into the cortico-medullary border results in increases in RSNA, and infusion of bradykinin into the renal artery results in increased activation of neurosecretory vasopressin cells [71, 72]. Whether this is related to a differential response between the mechanosensory nerves and the chemosensitive nerves with one resulting in an inhibitory response and the other an excitatory response respectively is unclear. Prostaglandins have been shown to increase the responsiveness of sensory nerve fibers [73, 74]. The kidney, and in particular the renal medulla, has active prostaglandin-producing tissue [75]. ANG II reduces the responsiveness of renal afferent sensory nerves by suppressing the Prostaglandin E2 (PGE2) mediated release of Substance P [76].

Renorenal Reflex in Heart Failure

Increases in RSNA result in increases in ARNA [44]. In physiologic states there is a reciprocal relationship between ARNA and RSNA whereby increases in ARNA will result in decreased RSNA via the activation of reno-renal reflexes and thus maintain a low level of RSNA [45]. Thus, ARNA activation produces a sympathoinhibitory response. Pathological conditions such as hypertension and HF are characterized by impairment of sympathoinhibitory renorenal reflexes and, in the case of renal injury or disease, a shift to excitatory renorenal reflexes leading to increased RSNA (Fig. 4.1) [28, 45, 77]. This appears to initiate a vicious cycle in which increased RSNA increases ARNA leading to further increases in RSNA, with central activation of sympathetic outflow contributing to the sympathoexcitatory state and profound structural and functional changes involving the heart, kidney, and other organs. The impairment in inhibitory renorenal reflexes has been attributed at least in part to increased endogenous ANG II present in many of these pathological conditions [78, 79]. Additionally, in HF, impairment of arterial and cardiopulmonary baroreflexes contribute to increased RSNA [80, 81]. Evidence for sympathoexcitatory reflexes originating in diseased or injured kidneys comes by way of studies in rats and humans. Recordati et al. demonstrated that stimulation of R1 and R2 chemoreceptors in rats resulted in excitatory renorenal reflexes that were present whether the spinal cord was intact or transected at the T6 level, suggesting that the excitatory chemoreceptor reflexes were integrated at a spinal level [82]. In

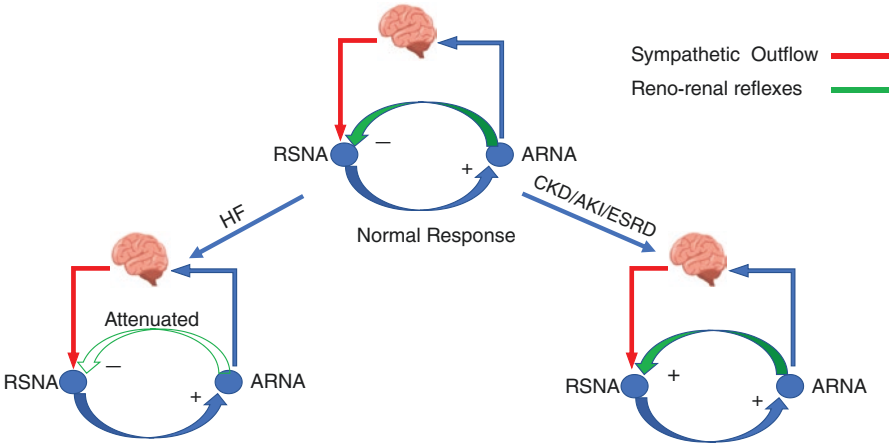

Fig. 4.1 Changes in the Reno-renal reflex in HF and kidney disease. Schematic diagram illustrating the different pathways integrating afferent renal nerve activity that affect renal sympathetic nerve activity. Normally, activation of reno-renal reflexes result in sympatho-inhibitory responses. In HF the reno-renal reflexes are impaired, with the attenuated signal resulting in increased RSNA. In states with renal injury or disease, reno-renal reflexes become excitatory. Abbreviations: ARNA Afferent Renal Nerve Activity, RSNA Renal Sympathetic Nerve Activity

patients on hemodialysis, arterial blood pressure, vascular resistance, and muscle sympathetic nerve activity are significantly lower in patients with bilateral nephrectomy compared to patients with intact kidneys [28]. The investigators attributed this finding to chemosensitive afferent nerve stimulation that in turn led to reflex activation of efferent sympathetic nerve discharge. They were uncertain about the chemical mediator stimulating the renal afferent nerves, and attributed it to uremic toxins or other chemical substances present in the uremic milieu. Hausberg and colleagues confirmed and further extended these findings by comparing muscle sympathetic nerve activity in renal transplant patients with and without their native kidneys as well as a cohort of hemodialysis patients referred for renal transplantation [77]. Muscle sympathetic nerve activity did not differ significantly between the hemodialysis patients and patients after renal transplantation with their native kidneys, despite correction of uremia in the latter arguing against uremia-related toxins as the cause of sympathoexcitatory reflexes originating in the diseased kidneys. Of note, there was a significant decrease in muscle sympathetic nerve activity in patients who had undergone bilateral nephrectomy. These and other animal studies provide strong evidence for excitatory ARNA in diseased kidneys having an excitatory effect on the sympathetic nervous system [83].

Clinical Implications

There is evidence for the integration of afferent nerve signals from a number of sources including the kidneys, the carotid sinus, and cardiac nerves, in areas of the brain involved in cardiovascular control and sympathetic outflow [40, 84–87].

These interactions appear to ultimately determine overall sympathetic tone and extracellular fluid volume status. As a result, the kidney, with its extensive afferent sensory and efferent sympathetic innervation, can be a source as well as the target of sympathetic overactivation in HF [50, 88, 89]. Interventions to abort or mitigate the effects of impaired or excitatory afferent renal nerve signals present in HF, in particular with concurrent renal injury or disease, have the potential to change the course of cardio-renal syndrome and HF. Beta adrenoreceptor blockers, ACE inhibitors, and angiotensin receptor blockers are already part of the armamentarium of interventions available to address the consequences of sympathetic overactivation and increased levels of ANG II. One intervention that has garnered a great deal of interest in supplementing the currently available interventions is RDN. The focus thus far has been on renal sympathetic denervation to reduce sympathetic outflow to the kidney [90, 91]. Surgical RDN in animal models with HF have demonstrated enhanced renal sodium excretion as well as improvement in cardiac structure and function [92–96]. Afferent RDN in rats with chronic kidney failure has demonstrated that the ARNA in the diseased kidneys may contribute to an increase in central sympathetic outflow [83]. Based on the available evidence in disease states such as HF that exhibit exaggerated sympathoexcitatory reflexes, perhaps greater attention to afferent RDN should be made [88, 97, 98].

The development over the past decade of catheter-based endovascular RDN with proven overall safety has made this less invasive percutaneous technique a more acceptable intervention in patients with HF [99, 100]. Currently there are limited data from trials in humans pertaining to RDN in HF. In patients with HF and concurrent renal dysfunction, 12 month outcomes from the Simplicity HF feasibility study demonstrated statistically significant reductions in N-terminal pro-B-type natriuretic peptide and 120 minute glucose tolerance test following RDN [101]. There were no serious adverse events in this study that used a single-electrode catheter system. However, no significant changes in left ventricular ejection fraction or 6-minute walk test were noted. The REACH-pilot study that evaluated the effects of catheter based RDN in patients with reduced ejection fraction HF demonstrated that catheter based RDN was safe [102].

The development of newer multielectrode catheters to provide effective bilateral RDN with histologically verified renal sympathetic denervation, and possibly concomitant afferent renal denervation, have the potential to for benefit in clinical practice. In a porcine model of HF, use of such a catheter resulted in significant improvement in cardiac function as well as well as a decrease in the renal and myocardial norepinephrine gradients, likely as a result of ablation involving both efferent as well as afferent renal nerves [98]. Whether these results can be replicated in human trials and would hold up to result in clinical benefit over the longer term is yet to be seen. There are several factors that may play a role in the long-term efficacy of complete RDN. Perhaps the most significant of them is the potential for renal nerves to reinnervate. Renal sympathetic nerves clearly reinnervate following denervation or transplantation, with the time course for reinnervation varying depending on the organism – weeks in rats, months in dogs, and months to years in humans [50, 103]. Studies in rats have demonstrated that renal afferent

nerves reinnervate in a time course similar to sympathetic nerve reinnervation [104]. A more recent study in sheep demonstrated complete anatomical and functional reinnervation of afferent and efferent renal nerves by 11 months following endovascular RDN [105]. Data on afferent renal nerve reinnervation in humans is currently lacking. Another factor that may limit efficacy of RDN is the apparent supersensitivity to vasoconstrictor effects of norepinephrine noted in rats following RDN, transplantation or neonatal sympathectomy [106, 107]. There may be other mechanisms responsible for the lack of benefit in the human trials completed thus far. Long-term follow up results from ongoing human trials evaluating the safety and efficacy of RDN in HF may inform how this intervention can be used in the future.

Conclusions

A large body of evidence, mainly from animal studies, points to the integration of ARNA in areas of the brain involved in cardiovascular control and sympathetic outflow. The changes in ARNA that occur in disease states, with a shift from an inhibitory to less inhibitory—or even an excitatory response—can have a profound effect not only on central sympathetic outflow but also on renorenal reflexes. These changes may contribute to the development and maintenance of cardio-renal syndrome and also to the sympathetic activation present in HF. Available evidence suggests that in the setting of renal disease, chemosensitive nerves contribute significantly to excitatory ARNA. Human data following nephrectomy appear to confirm this finding. Therefore, RDN has the potential to attenuate or abrogate the maladaptive responses in HF, though awaits definitive testing in long-term outcome studies in humans.

References

1. Moxon W. Case of extreme granular degeneration of the kidneys, without hypertrophy of the heart. Br Med J. 1872;1(598):637–8.
2. Rowntree LG. The effects of experimental chronic passive congestion on renal function. Arch Intern Med. 1913;XI(2):121.
3. Blake WD, Wégria R, Keating RP, Ward HP. Effect of increased renal venous pressure on renal function. Am J Physiol. 1949;157(1):1–13.
4. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52(19):1527–39.
5. Ronco C, Bellasi A, Di Lullo L. Cardiorenal syndrome: an overview. Adv Chronic Kidney Dis. 2018;25(5):382–90.
6. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J. 2015;36(23):1437–44.
7. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000;35(3):681–9.
8. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006;113(5):671–8.

9. Mahon NG, Blackstone EH, Francis GS, Starling RC, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. J Am Coll Cardiol. 2002;40(6):1106–13.
10. Damman K, Valente MA, Voors AA, O'connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2013;35(7):455–69.
11. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J, et al. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail. 2007;13(6):422–30.
12. Bagshaw SM, Cruz DN, Aspromonte N, Daliento L, Ronco F, Sheinfeld G, et al. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference: Oxford University Press; 2010.
13. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol. 2012;60(12):1031–42.
14. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: 'Guyton revisited'. Eur Heart J. 2004;26(1):11–7.
15. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Drugs. 1990;39(4):10–21.
16. Winton FR. The influence of venous pressure on the isolated mammalian kidney. J Physiol. 1931;72(1):49–61.
17. Damman K, Navis G, Smilde TD, Voors AA, van der Bij W, van Veldhuisen DJ, et al. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. Eur J Heart Fail. 2007;9(9):872–8.
18. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(7):589–96.
19. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009;53(7):582–8.
20. Braam B, Cupples WA, Joles JA, Gaillard C. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. Heart Fail Rev. 2012;17(2):161–75.
21. Testani JM, Damman K. Venous congestion and renal function in heart failure… it's complicated. Eur J Heart Fail. 2013;15(6):599–601.
22. Uthoff H, Breidthardt T, Klima T, Aschwanden M, Arenja N, Socrates T, et al. Central venous pressure and impaired renal function in patients with acute heart failure. Eur J Heart Fail. 2011;13(4):432–9.
23. Dupont M, Mullens W, Finucan M, Taylor DO, Starling RC, Tang WW. Determinants of dynamic changes in serum creatinine in acute decompensated heart failure: the importance of blood pressure reduction during treatment. Eur J Heart Fail. 2013;15(4):433–40.
24. Dibona GF. Nervous kidney: interaction between renal sympathetic nerves and the renin-angiotensin system in the control of renal function. Hypertension. 2000;36(6):1083–8.
25. Charloux A, Piquard F, Doutreleau S, Brandenberger G, Geny B. Mechanisms of renal hyporesponsiveness to ANP in heart failure. Eur J Clin Investig. 2003;33(9):769–78.
26. Giam B, Kaye DM, Rajapakse NW. Role of renal oxidative stress in the pathogenesis of the cardiorenal syndrome. Heart Lung Circ. 2016;25(8):874–80.
27. Iwata K, Matsuno K, Murata A, Zhu K, Fukui H, Ikuta K, et al. Up-regulation of NOX1/NADPH oxidase following drug-induced myocardial injury promotes cardiac dysfunction and fibrosis. Free Radic Biol Med. 2018;120:277–88.
28. Converse RL Jr, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med. 1992;327(27):1912–8.
29. Bleeke T, Zhang H, Madamanchi N, Patterson C, Faber JE. Catecholamine-induced vascular wall growth is dependent on generation of reactive oxygen species. Circ Res. 2004;94(1):37–45.

30. Liao J, Keiser JA, Scales WE, Kunkel SL, Kluger MJ. Role of epinephrine in TNF and IL-6 production from isolated perfused rat liver. Am J Physiol. 1995;268(4):R896–901.
31. Ichiki T, Huntley BK, Harty GJ, Sangaralingham SJ, Burnett JC. Early activation of deleterious molecular pathways in the kidney in experimental heart failure with atrial remodeling. Physiol Rep. 2017;5(9):e13283.
32. Braam B. Renal endothelial and macula densa NOS: integrated response to changes in extracellular fluid volume. Am J Physiol. 1999;276(6):R1551–61.
33. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WHW, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol. 2013;62(6):485–95.
34. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail. 2011;4(5):669–75.
35. Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. Eur Heart J. 2015;36(30):1974–82.
36. Florea VG, Cohn JN. The autonomic nervous system and heart failure. Circ Res. 2014;114(11):1815–26.
37. Dunlap ME, Bhardwaj A, Hauptman PJ. Autonomic modulation in heart failure: ready for prime time? Curr Cardiol Rep. 2015;17(11):103.
38. Bhardwaj A, Dunlap ME. Autonomic dysregulation as a therapeutic target for acute HF. Curr Treat Options Cardiovasc Med. 2015;17(10):43.
39. Marfurt CF, Echtenkamp SF. Sensory innervation of the rat kidney and ureter as revealed by the anterograde transport of wheat germ agglutinin-horseradish peroxidase (WGA-HRP) from dorsal root ganglia. J Comp Neurol. 1991;311(3):389–404.
40. Solano-Flores LP, Rosas-Arellano MP, Ciriello J. Fos induction in central structures after afferent renal nerve stimulation. Brain Res. 1997;753(1):102–19.
41. Wyss JM, Donovan MK. A direct projection from the kidney to the brainstem. Brain Res. 1984;298(1):130–4.
42. Nishi EE, Martins BS, Milanez MI, Lopes NR, de Melo JF Jr, Pontes RB, et al. Stimulation of renal afferent fibers leads to activation of catecholaminergic and non-catecholaminergic neurons in the medulla oblongata. Auton Neurosci. 2017;204:48–56.
43. Goodwill VS, Terrill C, Hopewood I, Loewy AD, Knuepfer MM. CNS sites activated by renal pelvic epithelial sodium channels (ENaCs) in response to hypertonic saline in awake rats. Auton Neurosci. 2017;204:35–47.
44. Kopp UC, Cicha MZ, Smith LA, Mulder J, Hokfelt T. Renal sympathetic nerve activity modulates afferent renal nerve activity by PGE2-dependent activation of α1-and α2-adrenoceptors on renal sensory nerve fibers. Am J Physiol. 2007;293(4):R1561–72.
45. Kopp UC. Neural control of renal function. In: Colloquium Series on Integrated Systems Physiology: From Molecule to Function to Disease. San Rafael: Morgan & Claypool Life Sciences; 2018. p. 1–106.
46. Norvell JE, Anderson JM. Assessment of possible parasympathetic innervation of the kidney. J Auton Nerv Syst. 1983;8(3):291–4.
47. van Amsterdam WA, Blankestijn PJ, Goldschmeding R, Bleys RL. The morphological substrate for renal denervation: nerve distribution patterns and parasympathetic nerves. A post-mortem histological study. Ann Anat-Anat Anz. 2016;204:71–9.
48. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. J Am Coll Cardiol. 2014;64(7):635–43.
49. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Kolodgie F, et al. Anatomical distribution of human renal sympathetic nerves: pathologic study. J Am Coll Cardiol. 2014;63(12. Supplement):A2151.
50. Kopp UC. Role of renal sensory nerves in physiological and pathophysiological conditions. Am J Physiol. 2014;308(2):R79–95.
51. Barajas L, Müller J. The innervation of the juxtaglomerular apparatus and surrounding tubules: a quantitative analysis by serial section electron microscopy. J Ultrastruct Res. 1973;43(1–2):107–32.

52. Dibona GF, Kopp UC. Neural control of renal function. Physiol Rev. 1997;77(1):75–197.
53. Stella A, Zanchetti A. Functional role of renal afferents. Physiol Rev. 1991;71(3):659–82.
54. Recordati G, Moss NG, Genovesi S, Rogenes P. Renal chemoreceptors. J Auton Nerv Syst. 1981;3(2–4):237–51.
55. DiBona GF, Sawin LL. Renal nerves in renal adaptation to dietary sodium restriction. Am J Physiol. 1983;245(3):F322–8.
56. Kopp U, Bradley T, Hjemdahl P. Renal venous outflow and urinary excretion of norepinephrine, epinephrine, and dopamine during graded renal nerve stimulation. Am J Physiol. 1983;244(1):E52–60.
57. Schwartz DD, Malik KU. Renal periarterial nerve stimulation-induced vasoconstriction at low frequencies is primarily due to release of a purinergic transmitter in the rat. J Pharmacol Exp Ther. 1989;250(3):764–71.
58. Vonend O, Okonek A, Stegbauer J, Habbel S, Quack I, Rump LC. Renovascular effects of sympathetic cotransmitters ATP and NPY are age-dependent in spontaneoulsy hypertensive rats. Cardiovasc Res. 2005;66(2):345–52.
59. Loesch A, Unwin R, Gandhi V, Burnstock G. Sympathetic nerve varicosities in close apposition to basolateral membranes of collecting duct epithelial cells of rat kidney. Nephron Physiol. 2009;113(3):p15–21.
60. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev. 2007;59(3):251–87.
61. Navar LG, Nishiyama A. Intrarenal formation of angiotensin II. In: The renin-angiotensin system and progression of renal diseases. Basel: Karger Publishers; 2001. p. 1–15.
62. Navar LG, Nishiyama A. Why are angiotensin concentrations so high in the kidney? Curr Opin Nephrol Hypertens. 2004;13(1):107–15.
63. Navar LG, Kobori H, Prieto-Carrasquero M. Intrarenal angiotensin II and hypertension. Curr Hypertens Rep. 2003;5(2):135–43.
64. Navar LG. The role of the kidneys in hypertension. J Clin Hypertens. 2005;7(9):542–9.
65. Imig JD, Navar GL, Zou L-X, O'Reilly KC, Allen PL, Kaysen JH, et al. Renal endosomes contain angiotensin peptides, converting enzyme, and AT1A receptors. Am J Physiol. 1999;277(2):F303–11.
66. Kopp UC, Cicha MZ, Smith LA, Hökfelt T. Nitric oxide modulates renal sensory nerve fibers by mechanisms related to substance P receptor activation. Am J Physiol. 2001;281(1):R279–90.
67. Gontijo JR, Smith LA, Kopp UC. CGRP activates renal pelvic substance P receptors by retarding substance P metabolism. Hypertension. 1999;33(1):493–8.
68. Geppetti P. Sensory neuropeptide release by bradykinin: mechanisms and pathophysiological implications. Regul Pept. 1993;47(1):1–23.
69. Kopp UC, Farley DM, Cicha MZ, Smith LA. Activation of renal mechanosensitive neurons involves bradykinin, protein kinase C, PGE2, and substance P. Am J Physiol. 2000;278(4):R937–46.
70. Kopp UC, Farley DM, Smith LA. Bradykinin-mediated activation of renal sensory neurons due to prostaglandin-dependent release of substance P. Am J Physiol. 1997;272(6):R2009–16.
71. Barry EF, Johns EJ. Intrarenal bradykinin elicits reno-renal reflex sympatho-excitation and renal nerve-dependent fluid retention. Acta Physiol. 2015;213(3):731–9.
72. Day TA, Ciriello J. Effects of renal receptor activation on neurosecretory vasopressin cells. Am J Physiol. 1987;253(2):R234–41.
73. Kopp UC, Cicha MZ, Smith LA. PGE2 increases release of substance P from renal sensory nerves by activating the cAMP-PKA transduction cascade. Am J Physiol. 2002;282(6):R1618–27.
74. Nicol GD, Cui M. Enhancement by prostaglandin E2 of bradykinin activation of embryonic rat sensory neurones. J Physiol. 1994;480(3):485–92.
75. Bonvalet JP, Pradelles P, Farman N. Segmental synthesis and actions of prostaglandins along the nephron. Am J Physiol. 1987;253(3):F377–87.
76. Kopp UC, Cicha MZ, Smith LA. Endogenous angiotensin modulates PGE2-mediated release of substance P from renal mechanosensory nerve fibers. Am J Physiol. 2002;282(1):R19–30.

77. Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, Kisters K, et al. Sympathetic nerve activity in end-stage renal disease. Circulation. 2002;106(15):1974–9.
78. DiBona GF, Jones SY, Sawin LL. Effect of endogenous angiotensin II on renal nerve activity and its arterial baroreflex regulation. Am J Physiol. 1996;271(2):R361–7.
79. Kopp UC, Cicha MZ, Smith LA. Impaired responsiveness of renal mechanosensory nerves in heart failure: role of endogenous angiotensin. Am J Physiol. 2003;284(1):R116–24.
80. Dibner-Dunlap ME, Thames MD. Baroreflex control of renal sympathetic nerve activity is preserved in heart failure despite reduced arterial baroreceptor sensitivity. Circ Res. 1989;65(6):1526–35.
81. Dibner-Dunlap ME, Thames M. Control of sympathetic nerve activity by vagal mechanoreflexes is blunted in heart failure. Circulation. 1992;86(6):1929–34.
82. Recordati G, Genovesi S, Cerati D. Renorenal reflexes in the rat elicited upon stimulation of renal chemoreceptors. J Auton Nerv Syst. 1982;6(2):127–42.
83. Campese VM, Kogosov E, Koss M. Renal afferent denervation prevents the progression of renal disease in the renal ablation model of chronic renal failure in the rat. Am J Kidney Dis. 1995;26(5):861–5.
84. Felder RB. Excitatory and inhibitory interactions among renal a cardiovascular afferent nerves in dorsomedial medulla. Am J Physiol. 1986;250(4):R580–8.
85. Calaresu FR, Ciriello J. Renal afferent nerves affect discharge rate of medullary and hypothalamic single units in the cat. J Auton Nerv Syst. 1981;3(2–4):311–20.
86. Coote JH. A role for the paraventricular nucleus of the hypothalamus in the autonomic control of heart and kidney. Exp Physiol. 2005;90(2):169–73.
87. Xu B, Zheng H, Liu X, Patel KP. Activation of afferent renal nerves modulates RVLM-projecting PVN neurons. Am J Physiol. 2015;308(9):H1103–11.
88. Booth LC, May CN, Yao ST. The role of the renal afferent and efferent nerve fibers in heart failure. Front Physiol. 2015;6. [cited 2019 Jan 7]. Available from: https://doi.org/10.3389/fphys.2015.00270.
89. Zheng H, Patel KP. Integration of renal sensory afferents at the level of the paraventricular nucleus dictating sympathetic outflow. Auton Neurosci. 2017;204:57–64.
90. Tang WW, Dunlap ME. Reconsidering renal sympathetic denervation for heart failure. JACC: Basic Transl Sci. 2017;2:282–4.
91. Sobotka PA, Krum H, Böhm M, Francis DP, Schlaich MP. The role of renal denervation in the treatment of heart failure. Curr Cardiol Rep. 2012;14(3):285–92.
92. Nozawa T, Igawa A, Fujii N, Kato B, Yoshida N, Asanoi H, et al. Effects of long-term renal sympathetic denervation on heart failure after myocardial infarction in rats. Heart Vessel. 2002;16(2):51–6.
93. Hu J, Li Y, Cheng W, Yang Z, Wang F, Lv P, et al. A comparison of the efficacy of surgical renal denervation and pharmacologic therapies in post-myocardial infarction heart failure. PLoS One. 2014;9(5):e96996.
94. Hu J, Yan Y, Zhou Q, Ji M, Niu C, Hou Y, et al. Effects of renal denervation on the development of post-myocardial infarction heart failure and cardiac autonomic nervous system in rats. Int J Cardiol. 2014;172(3):e414–6.
95. Li Z-Z, Jiang H, Chen D, Liu Q, Geng J, Guo J-Q, et al. Renal sympathetic denervation improves cardiac dysfunction in rats with chronic pressure overload. Physiol Res. 2015;64(5):653–62.
96. Liu Q, Zhang Q, Wang K, Wang S, Lu D, Li Z, et al. Renal denervation findings on cardiac and renal fibrosis in rats with isoproterenol induced cardiomyopathy. Sci Rep. 2015;5:18582.
97. Sobotka PA, Mahfoud F, Schlaich MP, Hoppe UC, Böhm M, Krum H. Sympatho-renal axis in chronic disease. Clin Res Cardiol. 2011;100(12):1049–57.
98. Liao S-Y, Zhen Z, Liu Y, Au K-W, Lai W-H, Tsang A, et al. Improvement of myocardial function following catheter-based renal denervation in heart failure. JACC Basic Transl Sci. 2017;2(3):270–81.
99. Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H, et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. Eur Heart J. 2014;35(26):1752–9.

100. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393–401.
101. Hopper I, Gronda E, Hoppe UC, Rundqvist B, Marwick TH, Shetty S, et al. Sympathetic response and outcomes following renal denervation in patients with chronic heart failure: 12-month outcomes from the SYMPLICITY HF Feasibility Study. J Card Fail. 2017;23(9):702–7.
102. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, et al. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. Int J Cardiol. 2013;162(3):189–92.
103. Gazdar AF, Dammin GJ. Neural degeneration and regeneration in human renal transplants. N Engl J Med. 1970;283(5):222–4.
104. Mulder J, Hökfelt T, Knuepfer MM, Kopp UC. Renal sensory and sympathetic nerves reinnervate the kidney in a similar time-dependent fashion after renal denervation in rats. Am J Physiol. 2013;304(8):R675–82.
105. Booth LC, Nishi EE, Yao ST, Ramchandra R, Lambert GW, Schlaich MP, et al. Reinnervation of renal afferent and efferent nerves at 5.5 and 11 months after catheter-based radiofrequency renal denervation in sheep. Hypertension. 2015;65(2):393–400.
106. Grisk O. Renal denervation and hypertension-The need to investigate unintended effects and neural control of the human kidney. Auton Neurosci. 2017;204:119–25.
107. Kline RL, Mercer PF. Functional reinnervation and development of supersensitivity to NE after renal denervation in rats. Am J Physiol. 1980;238(5):R353–8.

Insights on Diuretic Therapy from Clinical and Pharmacologic Perspectives

5

David H. Ellison and Shweta Bansal

Introduction

Diuretics are among the most commonly prescribed drugs for cardiorenal disorders; while effective, such patients are at substantial risk for complications, making it especially important to understand and appreciate diuretic pharmacokinetics and pharmacodynamics. Although the available diuretic drugs possess distinctive pharmacokinetic and pharmacodynamic properties that affect both response and potential for adverse effects, many clinicians use them in a stereotyped manner, reducing effectiveness and potentially increasing side effects (common diuretic side effects are listed in Table 5.1). Diuretics have many uses, but this chapter will focus on clinical use of diuretics to treat extracellular fluid (ECF) volume expansion in the setting of cardiorenal syndrome, taking their pharmacology into consideration.

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Table 5.1 Common side effects of diuretics

Loop diuretics
Hypersensitivity reactions
Extracellular fluid volume depletion
Hypokalemic alkalosis
Hypomagnesemia*
Ototoxicity
Distal convoluted tubule diuretics
Hypersensitivity reactions
Hyponatremia
Hypokalemic alkalosis
hyperglycemia/diabetes
hyperuricemia/gout
Hypomagnesemia
Hypokalemia and prerenal azotemia, when combined with loop diuretics
Potassium sparing diuretics
Hypersensitivity
Hyperkalemia
Metabolic acidosis
Azotemia
Gynecomastia, vaginal bleeding (spironolactone)

May be secondary to underlying disease [75]
* hypomagnesemia is less common with loop diuretics than with distal convoluted tubule diuretics

Classification and Mechanisms of Action

Diuretic drugs are typically classified first according to their predominant site of action along the nephron and second by the mechanism by which they inhibit transport (Fig. 5.1). The sulfonamide-based loop diuretics furosemide, bumetanide, and torsemide act from the lumen to inhibit the Na-K-2Cl cotransporter (*NKCC2* encoded by *SLC12A1*) along the thick ascending limb and at the macula densa. Ethacrynic acid is a non-sulfonamide-based loop diuretic. It is used primarily for patients who are truly allergic to the sulfonamide-based drugs, as it appears to have greater toxicity and is more difficult to use. As organic anions, loop diuretics bind within the translocation pocket on the transport protein by interacting with the chloride-binding site (2). Because they are larger than chloride, they are not transported through the pocket, and thereby inhibit the transporter. Distal convoluted tubule diuretics (thiazides and thiazide-like drugs) are also organic anions that act in much the same manner, but bind to the thiazide-sensitive NaCl cotransporter (NCC, encoded by *SLC12A3*) along the distal convoluted tubule (Fig. 5.1). This mechanism of action accounts for a key aspect of loop and distal convoluted tubule diuretic action; both classes of drug exert their effect from within the lumen of the tubule.

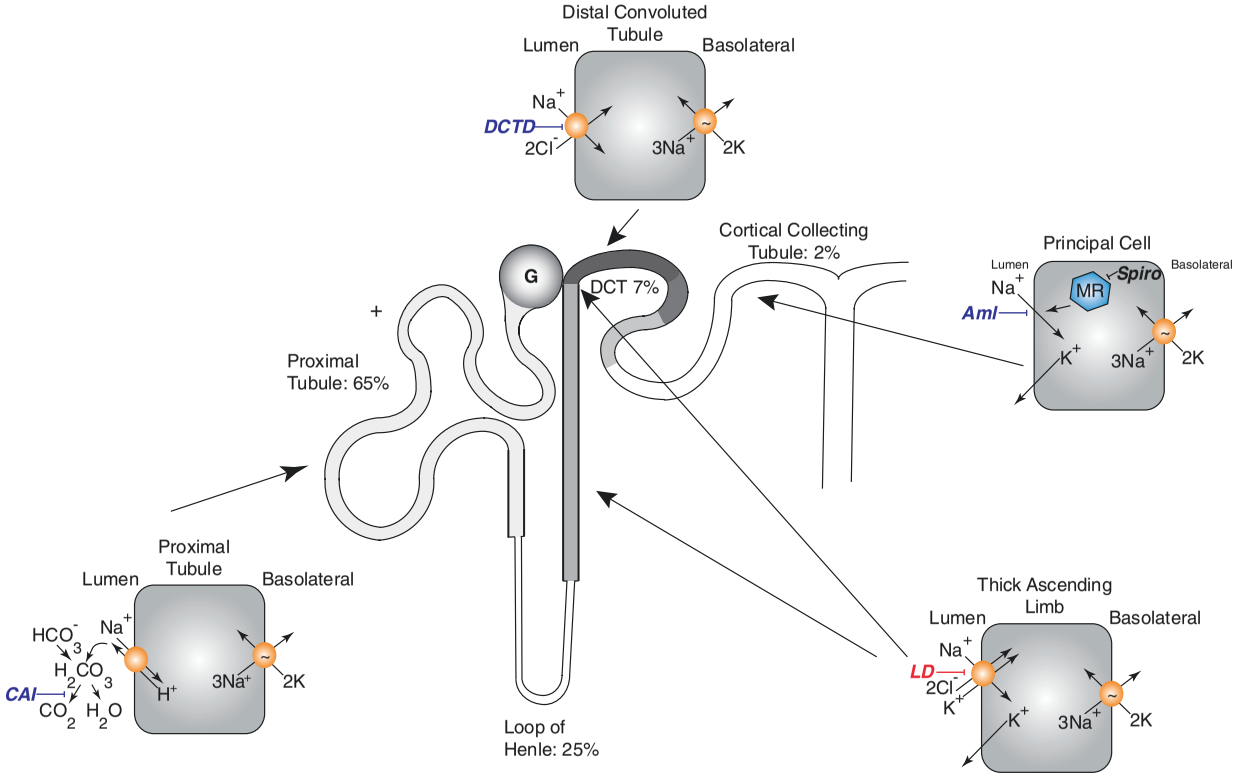

Fig. 5.1 Diagram of nephron showing sites of sodium reabsorption and diuretic action along the nephron. CAI carbonic anhydrase inhibitors, DCTD distal convoluted tubule diuretic, Aml amiloride (also triamterene), LD loop diuretics, MR mineralocorticoid receptors in the CD are blocked by spironolactone and eplerenone action (note that these steroid antagonists act within the cell). Percentages show approximate percentage of sodium reabsorption by associated segment. The translocation pocket for ions and diuretic binding of the Na-K-2Cl cotransporter is shared [73, 74]

There are 2 major classes of potassium-sparing diuretics, which act along the aldosterone-sensitive distal nephron. The first includes drugs that block apical sodium channels (amiloride and triamterene), whereas the second includes drugs that antagonize mineralocorticoid receptors (spironolactone, eplerenone). A new non-steroidal mineralocorticoid blocker, finerenone, which is structurally unrelated to the others, is currently in phase III clinical trials. The mineralocorticoid blockers act within cells and do not require secretion into the tubular lumen.

Bioavailability of Diuretics Determining the Dose and Frequency of Administration

The normal metabolism of loop diuretics is depicted in simplified form in Fig. 5.2a. Furosemide, bumetanide, and torsemide are absorbed relatively quickly after oral administration (see Fig. 5.2b), reaching peak concentrations within 0.5–2 hours [1, 2]; when administered intravenously (IV), their effects are nearly instantaneous. The oral bioavailability of bumetanide and torsemide typically exceeds 80%, whereas that of furosemide is highly variable and substantially lower, at approximately 50% (see Table 5.2) [3]. Although the half-life of furosemide is short, its duration of action is longer when administered orally, as its gastrointestinal absorption may be slower than its elimination half-life. This is a phenomenon called *absorption-limited kinetics* [1] and may explain the mnemonic that oral furosemide "lasts 6 hours" [4]. This is not the case for bumetanide and torsemide, where oral absorption is rapid and consistent [5].

Based on oral bioavailability, when a patient is switched from an intravenous to oral loop diuretic, the dose of bumetanide or torsemide should be maintained, whereas the dose of furosemide should be doubled [5]; in practice, however, and as discussed further below, other factors affect diuretic efficacy and a fixed intravenous/oral conversion cannot be given [6]. Gastrointestinal absorption of thiazide and other potassium sparing diuretics is fairly rapid and predictable, and oral bioavailability ranges from 65% to 90%.

The loop diuretics have steep dose response curves. This property is often neglected in clinical practice but is crucial to optimal use. Figure 5.2c shows a a schematic of a typical natriuretic response plotted versus the logarithm of the plasma diuretic concentration. Inspection reveals that there is little diuretic or natriuretic effect when the plasma concentration is low. Once the concentration exceeds a certain level, often called the diuretic threshold, the response increases, and even small further increases caused substantially increased sodium excretion. Although such relations are typically plotted as the logarithm of the diuretic concentration or dose, clinicians do not typically think in logarithmic terms. This underlies the reasoning behind the common recommendation to double the dose, if no response

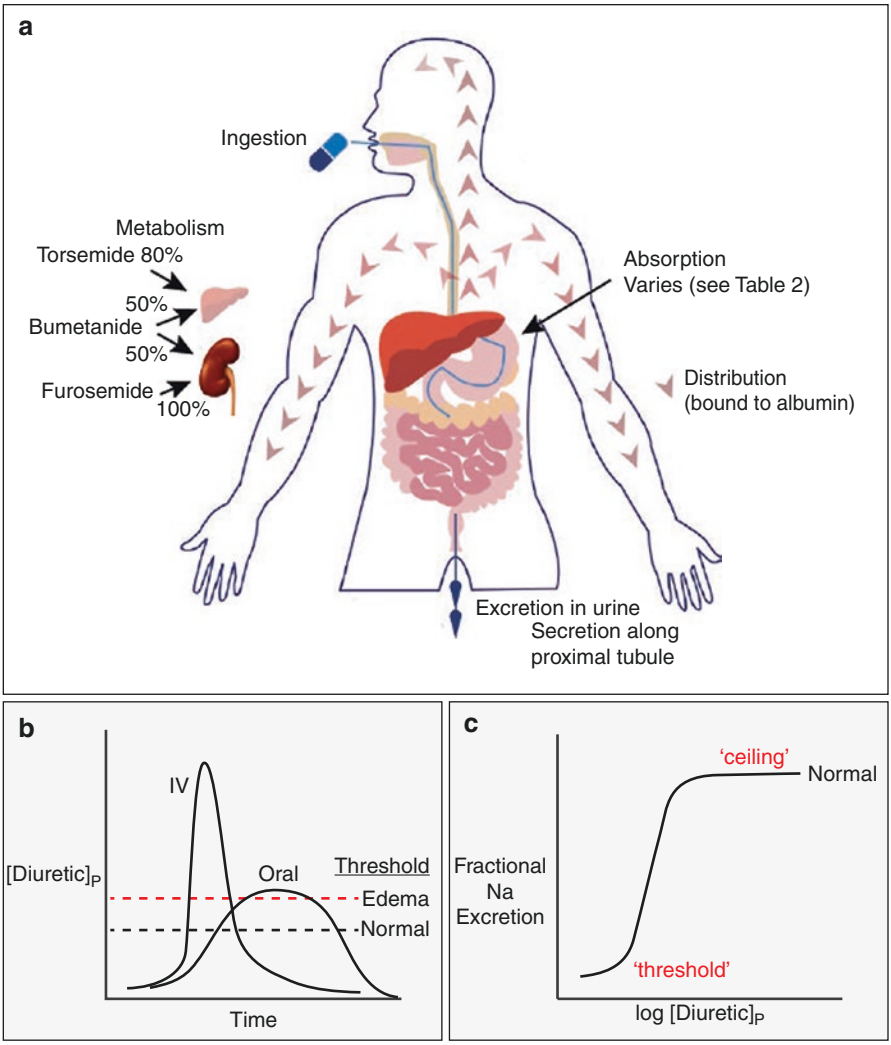

Fig. 5.2 (a) shows features of **a**bsorption, **d**istribution, **m**etabolism, and **e**xcretion (so-called ADME of drugs). (**b**) compares the plasma diuretic concentration as a function of time following oral or intravenous diuretic administration. The dashed lines show natriuretic thresholds in normal individuals and in those with edema. Note that the primary determinant of natriuresis is the time above the threshold, indicating why route of administration has different effects in stable patients and in those with severe edema. In a normal individual, an oral dose may be effective, whereas it may not be in edema, despite retained bioavailability. (**c**) Classic dose response curve, plotted versus the logarithm of the plasma concentration. Note the threshold for natriuresis and the maximal level, often called the ceiling. (Figure adapted from Ref. [74])

Table 5.2 Pharmacokinetics of commonly used diuretics

Diuretic	Oral bioavailability, %	Elimination half-life, hours			
		Normal	CKD	Cirrhotic ascites	Heart failure
Furosemide	50 (10–100)	1.5–2	2.8	2.5	2.7
Bumetanide	80–100	1	1.6	2.3	1.3
Torsemide	68–100	3–4	4–5	8	6
Hydrochlorothiazide	55–77	6–15	Prolonged		
Chlorthalidone	61–72	40–60	Prolonged		
Metolazone	70–90[a]	14–20	Prolonged		
Amiloride	~50[&]	6–26	100	Not changed	
Spironolactone	>90	1.5*	**		

Adapted from Ref. [76]
[#]Absorption may be decreased in heart failure
[&]Decreased by food
*Active metabolites of spironolactone have half-lives of >15 hours
**Active metabolites accumulate in CKD

is obtained to the first dose. Although the dose response looks steep, when plotted logarithmically, it is less so when plotted in a linear manner, and a small increase will often be ineffective. At higher concentrations, a plateau or *ceiling* is reached, with progressively higher plasma concentrations failing to elicit more natriuresis. Although this fact has been used to invoke the concept of *ceiling doses* of loop diuretics, we will argue that increasing a diuretic dose above this ceiling often elicits more natriuresis, owing to pharmacokinetic considerations (see below).

As should be evident from these plots, a diuretic dose must exceed the threshold to be effective; yet the failure to give a dose that exceeds the threshold is one of the most common errors in diuretic usage. The problem is that the *threshold* is not easily estimated in an individual, especially an individual with cardiorenal syndrome. While nearly all healthy individuals will respond to 20 mg of oral furosemide (or its equivalent), patients with conditions that predispose to ECF volume expansion and edema need higher doses, since these conditions alter both the pharmacokinetics and pharmacodynamics of diuretics as discussed below. It is little wonder that an empirically selected dose may be ineffective. Below, we will provide broad generalizations about dose adjustments for individuals within a variety of settings. Yet adherence to algorithms may lead to diuretic failure. Instead, it is often best to approach a patient as an *n of 1 trial*. Start with a dose consistent with the clinical guidelines (more aggressive for acute edema, more conservative for more chronic processes) and then adjust the dose according to the response.

Although low bioavailability is a concern with furosemide, a larger problem may be its inconsistent bioavailability. Furosemide absorption varies from day to day in an individual, and between individuals [7, 8]. Absorption is also affected

by food consumption, unlike that of bumetanide or torsemide [9, 10], although the clinical significance of this effect has been doubted [1]. The more consistent bioavailability of torsemide, compared with furosemide, and its relatively longer half-life, have suggested that it may be a superior loop diuretic, as suggested by 2 small clinical trials [11–14]. A recent non-randomized post-hoc analysis of the large Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) has suggested that patients with heart failure discharged on torsemide have lower mortality [15]. In contrast, the bioequivalent doses of 2 loop diuretics given in a double-blind randomized crossover trial, failed to demonstrate superiority of torsemide with respect to natriuresis or 24-h ambulatory blood pressure control in chronic kidney disease (CKD) patients [16]. The compelling differences in pharmacokinetics suggest that torsemide might be superior clinically, but this needs to be tested in sufficiently powered and rigorous trials. ToRsemide compArisoN With furoSemide FORManagement of Heart Failure (TRANSFORM-HF) is a large-scale, pragmatic, randomized, unblinded clinical effectiveness study comparing torsemide versus furosemide as treatment for heart failure. The study is sponsored by National Heart, Lung, and Blood Institute (NHLBI), actively recruiting patients and expected to be complete by 2022 (NCT 03296813).

Gastrointestinal absorption can be slowed, especially during exacerbations of heart failure, although again, this problem is worst with furosemide [17]. Even though total bioavailability is typically maintained in these situations, natriuresis may be impaired when absorption is slowed, especially given a concomitant increase in natriuretic threshold, as diagramed in Fig. 5.2b. As an example, the areas under the curves for arbitrary intravenous and 2× oral furosemide doses may be similar, but the differences in shapes of those curves may lead to a diuretic being effective when given intravenously, but not orally. As the diuretic threshold is higher in cardiorenal syndrome, this difference may be especially relevant in this situation. This is likely to explain the common observation that intravenous doses of loop diuretics, which achieve higher peak levels, may be effective when oral doses lose their efficacy, especially if the natriuretic threshold is increased. Not surprisingly, heart failure exacerbation requiring IV diuretics remains one of the major reasons for visits to emergency department and outpatient clinics, and for hospital admissions. In this context, development of subcutaneous (SC) furosemide has garnered increasing optimism as a safe and effective outpatient alternative to the traditional hospital-based IV diuretic strategy. Recently, 2 proof-of-concept studies have demonstrated similar urine output with a pH-neutral formulation of SC furosemide compared to IV furosemide in outpatients presenting with decompensated heart failure [18]; and longer duration at therapeutic plasma levels and more urine output compared to oral furosemide [19]. Subcutaneous administration of buffered furosemide was well tolerated with no evidence of any drug-induced skin reactions. The possibility of delivering an *IV equivalent* diuretic agent at home, if proved efficacious in larger trials, could be transformative for HF care delivery.

Volumes of Distribution, Metabolism and Half-lives

Loop diuretics are organic anions that circulate tightly bound to albumin (>95%). Thus, their volumes of distribution are low, except during extreme hypoalbuminemia [20]. This has suggested that severe hypoalbuminemia might impair diuretic effectiveness, owing to impaired delivery to the kidney, and that albumin administration might enhance natriuresis. This conjecture was supported in an early proof-of-concept study [20], but subsequent larger studies have produced mixed results. A relatively recent meta-analysis concluded that the existing data, albeit of poor quality, suggest transient effects of modest clinical significance for co-administration of albumin with furosemide in hypoalbuminemic patients [21]. One concern about the more recent studies, many of which have been negative, is that most have only enrolled patients whose serum albumin concentrations exceeded 2 g/dL. Owing to physiological plausibility and anecdotal experience, most experts would still consider adding albumin infusion for refractory patients who are severely hypoalbuminemic. Yet, extreme caution should be used when treating patients with cardiorenal syndrome, as their extracellular fluid volume is typically expanded substantially; as albumin infusions expand the extracellular fluid volume, they should be avoided in most patients with cardiorenal syndrome.

Approximately 50% of an administered furosemide dose is excreted unchanged into the urine. The remainder appears to be eliminated by glucuronidation, predominantly also in the kidney. Torsemide and bumetanide are eliminated both by hepatic processes and urinary excretion, although hepatic metabolism may predominate, especially for torsemide [22]. The differences in metabolic fate mean that the half-life of furosemide is prolonged in kidney failure, where both excretion by the kidney and kidney-mediated glucuronidation are slowed. In contrast, the half-lives of torsemide and bumetanide tend to be preserved in patients with kidney dysfunction [23]. While the ratio of equipotent doses of furosemide to bumetanide is 40:1 in normal individuals, that ratio declines as kidney disfunction worsens [24]. Although this *apparent increase in furosemide potency* may seem beneficial, it also likely increases the toxic potential of furosemide when it is used in very high doses. Deafness and tinnitus from loop diuretics appear to result primarily from high serum concentrations, which inhibit a Na-K-2Cl isoform (NKCC1, encoded by *SLC12A2*). This transport protein, which is different from that reabsorbs salt in the kidney, is expressed by the stria vascularis and participates in secretion of K^+-rich endolymph [25, 26]. Although this complication was seen more frequently in the past when very large bolus doses of loop diuretics were employed to forestall dialysis [27], one relatively recent meta-analysis of furosemide use for patients with acute kidney injury, suggested that the odds ratio for hearing loss was >3 when high dose furosemide was used; it should be noted, however, that the doses cited in that analysis (1–3 grams daily) exceeded those currently recommended [28]. The tendency of bolus infusion to lead to high peak furosemide concentrations is one reason that many investigators recommend continuous infusions instead [29].

Although loop diuretics are small molecules, they typically undergo little glomerular filtration. As they exert their actions by binding to transport proteins along

the luminal membrane of thick ascending limb cells, to gain access to the tubular fluid and therefore to their sites of activity, they must be secreted. This is likely true for all three loop diuretics, although some data suggest that bumetanide is also delivered into the tubule lumen by filtration [30]. However, most evidence still suggests that bumetanide gains entry primarily via secretion [31]. Peritubular uptake by cells along the proximal tubule is mediated by the organic anion transporters OAT1 and OAT3, whereas the apically located multidrug resistance-associated protein 4 (Mrp-4) appears to mediate at least a portion of secretion into the tubular fluid. Mice lacking OAT1, OAT3 or Mrp-4 are resistant to loop and thiazide diuretics illustrating the functional importance of diuretic secretion for diuretic effectiveness [30, 32].

Impact of Drugs and Chronic Kidney Disease on the Effectiveness of Diuretics

While human mutations in OAT1 have not been described, drugs other than diuretics as well as endogenous toxins also bind to the OATs, thereby competing with diuretics for secretion into the proximal tubule [30]. Non-steroidal anti-inflammatory drugs inhibit diuretic secretion and alter diuretic responsiveness, and because of their frequent use, are an important cause of heart failure exacerbations [33]. Yet other classes of drugs, including antihypertensives,antibiotics and antivirals may also interact with these transporters and cause resistance [34]. Endogenous metabolites also compete for diuretic secretion, including indoxyl sulfate, carboxy-methyl-propyl-furanpropionate, p-cresol sulfate, and kynurenate, all of which accumulate when kidney function is poor [35]. In all of these situations, the natriuretic dose-response curve is shifted to the right (Fig. 5.3a).

There are additional reasons that patients with poor kidney function are resistant to loop diuretics. Metabolic acidosis, which is frequently observed in uremia, depolarizes the membrane potential of proximal tubule cells [36] which also decreases organic anion secretion, an effect that may explain why diuretic secretion is enhanced by alkalosis [37]. In addition to a shift in the dose-response curve, patients with poor kidney function and those taking non-steroidal anti-inflammatory drugs (NSAIDs) have a downward shift of the ceiling natriuresis, when expressed as absolute sodium excretion (rather than fractional). The mechanism for resistance attributable to NSAIDs is complex. Loop diuretic inhibition of NaCl reabsorption at the macula densa stimulates both renin secretion and prostaglandin production, the latter predominantly via cyclooxygenase-2 (COX-2) [38]. When this happens, prostaglandin E2 feeds back on tubules, contributing to the resulting natriuresis by inhibiting NaCl transport along the thick ascending limb and collecting duct [39, 40]. NSAIDs block this prostaglandin-mediated natriuresis. When used chronically, NSAIDs increase the abundance and activity of NKCC2 along the thick ascending limb [41]. Additionally, loop diuretics inhibit the second transporter isoform, NKCC1, mentioned above, which, in addition to being expressed in the ear, is also expressed by vascular smooth muscle cells; loop diuretics contribute to vasodilation of the glomerular afferent arteriole by blocking this transporter [42], thus helping

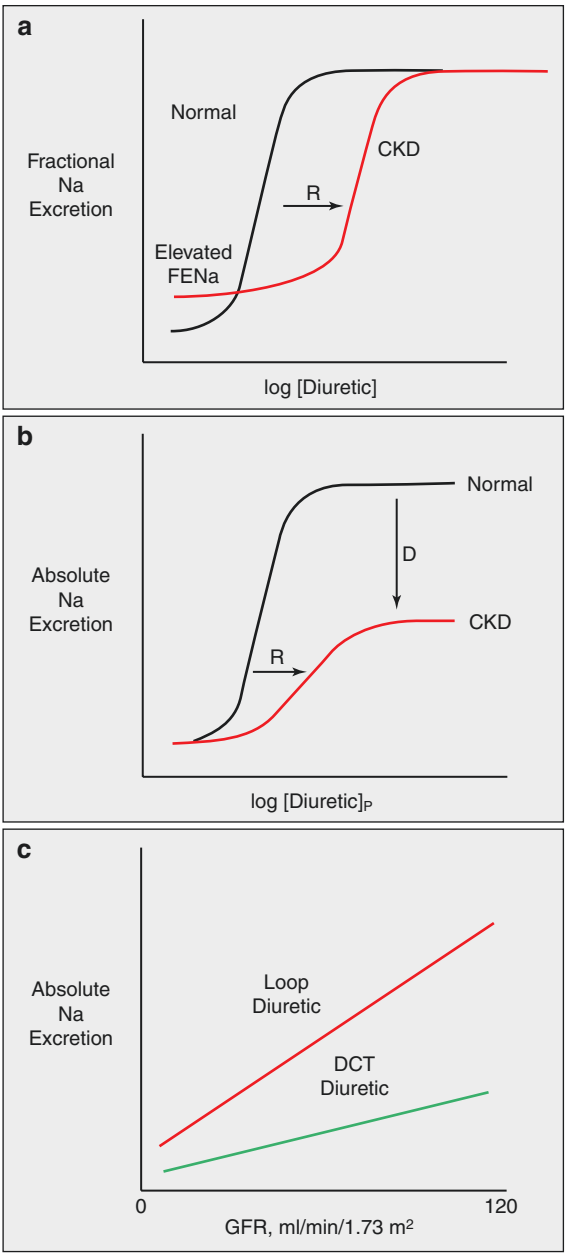

Fig. 5.3 (**a**) effects of chronic kidney disease on diuretic actions. Note that, in CKD, baseline fractional sodium excretion is high, to maintain absolute rates of sodium excretion equal to intake. There is a shift in the dose response curve to the right (R), primarily owing to impaired diuretic secretion, but no change in the ceiling effect. (**b**) shows the same relationship plotted versus absolute rates of sodium excretion. The same rightward shift is evident, but the ceiling is lower, owing to the GFR reduction. (**c**) compares effects of loop diuretics and distal convoluted tubule diuretics on absolute sodium excretion, given a retained effect on fractional excretion. (Figure adapted from Ref. [74])

to maintain glomerular filtration rate despite a lower ECF volume. Again, this compensatory adaptation is largely dependent on prostaglandin production and can be blocked by NSAIDs. The clinical impact of these effects is evident in the association between recent use of NSAIDs and risk for hospitalization in patients with heart failure [33]. In fact, in the setting of loop diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, the addition of a third class of drug that alters intrarenal hemodynamics such as NSAIDs, is associated with acute kidney injury [43].

Intrinsic kidney dysfunction also impairs the natriuretic response to diuretics through a different mechanism (Fig. 5.3b). It is frequently noted that the maximal natriuretic capacity of loop diuretics is maintained in the setting of chronic kidney disease, when natriuresis is measured as a fraction of filtered load (FE_{Na}). Yet the maximal natriuretic effect of these diuretics, when measured as the more clinically relevant absolute rate, is markedly reduced. This is because, as glomerular filtration rate and filtered sodium load decrease, kidneys suppress sodium reabsorption by the remaining tubules to keep sodium excretion equal to dietary salt intake. This suppression occurs in part along the thick ascending limb, so that even when a diuretic reaches the segment and inhibits the transporter, its net effect is reduced. Thus, NSAIDs and CKD cause diuretic resistance both by shifting the diuretic dose response curve to the right (which can be overcome by higher doses) and by reducing maximal natriuresis (which cannot overcome by higher doses, compare Fig. 5.3a, b).

Loop diuretics are characterized by relatively short half-lives (see Table 5.2). Thus, the initial natriuresis typically wanes within 3–6 hours, so that a single daily dose leaves some 16–21 hours per day for the kidneys to compensate for the diuretic-induced salt and water losses (Fig. 5.4). For individuals in steady state, the phenomenon of *post-diuretic NaCl retention* defines the fact that urinary NaCl excretion declines below the baseline when the diuretic effect wears off. This is typically true until another dose of diuretic is administered [44]. It should be noted however that while this relationship applies to patients who are at steady state (and thereby excreting their daily intake of salt), it is altered in patients with decompensated edema, such as many patients with cardiorenal syndrome, who may present during a period of a positive NaCl balance, with urinary NaCl very low, even without diuretic administration. In this case, any increase in urinary NaCl excretion will be beneficial.

Regardless of these differences, the net NaCl loss from a diuretic typically results from a short period of natriuresis and a longer period of anti-natriuresis. This accounts for the usual recommendation to use loop diuretics twice daily. Clearly, from inspection of the half-lives, this imperative is most important when using furosemide and bumetanide and least so with torsemide. As noted above, when CKD progresses, the half-life of furosemide is prolonged, increasing its apparent relative potency versus bumetanide. Even when administered twice daily, however, long inter-natriuretic periods limit drug effectiveness; this is most important when dietary NaCl intake is high, as NaCl retention by the kidneys will lead to more positive NaCl balance.

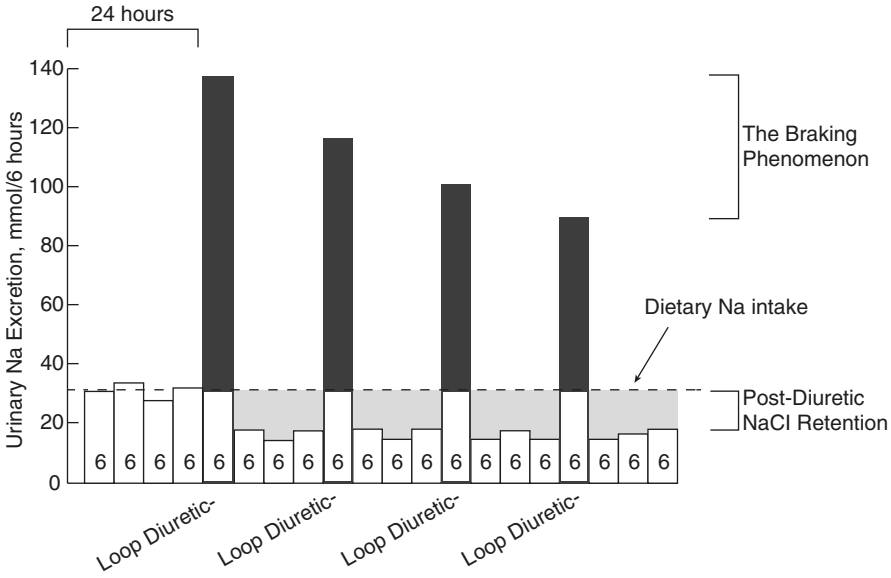

Fig. 5.4 Schematic effect of a loop diuretic on urinary NaCl excretion. Figure shows dietary NaCl intake (dashed line), which equals excretion before diuretic administration. A loop diuretic increases NaCl excretion for approximately 6 hours, after which urinary excretion declines below baseline (post-diuretic NaCl retention). After several doses, the magnitude of each natriuretic diuretic effect declines (the 'braking phenomenon'). (Data adapted from Ref. [54])

One strategy to address half-life issues, at least for hospitalized patients, is to infuse loop diuretics continuously. While the advantages of this approach over high-dose bolus treatment remain contentious [45], the physiological basis for this approach is appealing, and recent stepped care guidelines regarding treatment of acute decompensated heart failure (ADHF) (see below), recommend continuous infusions [46]. Along these lines, an investigational extended release formulation of torsemide that delivers torsemide to the circulation during 8–12 hours was reported recently to double salt and water losses in normal volunteers after a single dose, without increasing potassium excretion [47]. If such a formulation, which should avoid some of the obvious pharmacokinetic limitations of short-acting loop diuretics, works as well in patients with heart failure, it may change the standard approach to treatment.

After oral use, diuresis begins within 2 hours with hydrochlorothiazide and amiloride. Plasma half-life of hydrochlorothiazide averages 10 hours and amiloride ranges from 6–9 hours in subjects with normal renal function. These are prolonged in renal failure as both the drugs are mainly eliminated via the kidneys in unchanged form. On the other hand, spironolactone gets rapidly metabolized into its active metabolites; half-lives of these metabolites can last up to 18 hours. Due to mechanism of action involving genomic effect, the onset of action of spironolactone is prolonged. All these 3 drugs allow once daily dosing because of their long half-lives.

Using Diuretics Effectively to Treat Extracellular Fluid Volume Expansion

When diuretics are initiated to treat edema, whether in a patient with normal or abnormal kidney function, it is essential to confirm that the dose provides a concentration in the tubule lumen that exceeds the threshold (Fig. 5.1). That this threshold has been reached can be detected by most ambulatory patients, who should notice an increase in urine volume within 2–4 hours of an oral dose. A discrepancy between diuresis and weight loss in outpatients suggests that excessive NaCl consumption is limiting efficacy. In such cases, measuring 24-hours urine Na^+ excretion, with urinary creatinine excretion assessed to confirm collection adequacy, may confirm excessive NaCl intake, although single urine collections may not give fully accurate results [48]. Many patients with cardiorenal syndrome are hospitalized; there, a dose reaching the threshold should lead to an increase in urine volume should be evident during the 6 hours that follow it. Based on the relationship of plasma diuretic concentration and time shown in Fig. 5.2b, diuresis should occur more promptly following an intravenous dose. This difference may be especially pronounced if furosemide is the diuretic chosen. If an effect is not observed during this period, it is customary to double the dose, for example from 20 to 40 mg of furosemide or from 80 to 160 mg of furosemide, a recommendation predicated on the dose response curve shown above. The dose is then escalated to a maximal safe level, as discussed below. Although loop diuretics are typically administered twice daily, there is no reason to introduce a second daily dose if the first dose does not exceed the threshold. Once a threshold has been reached, however, most patients will require 2 daily doses.

Although dose recommendations for loop diuretics have been published based on pharmacokinetic and pharmacodynamic considerations [22] or expert consensus [49], a few more specific dose ranges have been tested in clinical trials. For ADHF, Felker and colleagues compared 2.5 times the home daily dose versus 1 times the home daily dose, given intravenously. Although differences in the primary outcome were not observed, several prespecified secondary outcomes, such as weight loss and area under the curve for dyspnea, favored the higher dose; importantly, negative consequences of the higher dose were not observed. This and other recent trials, including those for patients with cardiorenal syndrome, aimed for 3–5 liters of diuresis per day for initial treatment [46], rates that are more aggressive than often targeted. These studies emphasize that, for hospitalized patients, an aggressive approach to diuresis is often safe, as well as effective. Prior observational trials suggesting that higher diuretic doses were associated with worse patient survival, therefore, likely reflected confounding by indication [50]. In fact, post-hoc analyses of large trials suggest that those who experience a moderate increase in creatinine (worsening kidney function) may actually have better prognosis than those who do not [51, 52].

The net or therapeutic natriuretic response to a diuretic is determined by the difference between the sodium excreted in the urine and the sodium consumed. Although increasing a diuretic dose above the ceiling does not increase the maximal *minute-natriuresis* (the maximal rate of NaCl excretion per given time, see Fig. 5.2c), it often increases the net natriuresis by prolonging the period during

which the diuretic concentration exceeds the threshold (see Fig. 5.2a). This is one reason that current guidelines for heart failure may recommend doses that exceed ceiling doses and are multiples of prior or home doses [44].

Braking Phenomenon or Loop Diuretic Resistance

In both normal individuals and in patients with ECF volume expansion, there is a linear relationship between ECF volume and sodium excretion ($U_{Na}V$), elegantly elucidated by Walser [53]. This is similar to, but distinct from the pressure natriuresis, which describes the relationship between mean arterial pressure and $U_{Na}V$. Diuretics are recommended universally to treat symptomatic ECF volume expansion and therapeutic success is considered to be reduction in the ECF volume, and as importantly, symptoms and signs. This invariably requires initial sodium and water losses, induced by diuretic doses that exceed the threshold (Fig. 5.4). Yet the situation changes as initial treatment moves toward successful chronic treatment. At any therapeutically active dose, natriuresis wanes as extracellular fluid declines, an effect often called the *braking phenomenon* [54]. This means that, at steady state, the individual returns to NaCl balance during which urinary NaCl excretion is equal to dietary NaCl intake once again. This occurs, however, at a lower ECF volume than prior to treatment. Functionally, chronic diuretic treatment shifts the relationship between ECF volume and $U_{Na}V$ to the left (see Fig. 5.4), thereby permitting NaCl excretion rates to again equal intake, albeit with lower ECF volume. It should be noted, however, that although daily NaCl excretion normalizes, the pattern of salt and water loss remains more episodic, so that a patient may complain that the diuretic regimen is increasing urine output.

While the braking phenomenon is adaptive once ECF volume has been reduced successfully, it is maladaptive when it occurs in the setting of persistent ECF volume expansion. Many factors resulting from a decrease in ECF volume, such as stimulation of renal nerves and activation of the renin-angiotensin system, likely contribute to braking [55, 56], but it is now recognized that adaptive structural changes in segments other than the thick ascending limb also contribute importantly [57, 58]. Remodeling of the distal nephron occurs [59] leading to hypertrophy and hyperplasia, especially of distal segments. This results from increased salt delivery [60], increased angiotensin II [61] and aldosterone concentrations [62], and changes in potassium balance [63]. The consequences of remodeling are that distal tubules increase their transport capacity substantially; for this reason, more of the NaCl that escapes the loop of Henle is reabsorbed distally, and net natriuresis is reduced.

Approaches to Overcome the Braking Phenomenon

Adding a thiazide or thiazide-like drug will help to treat, and may even prevent, this type of adaptation and restore diuretic efficacy. Most commonly, especially in patients with advanced kidney dysfunction, metolazone is chosen as the agent

added to the loop diuretic regimen, although other thiazides may be equally effective [64]. Interestingly, at least three factors may contribute to the beneficial effects of adding a diuretic that acts in the distal convoluted tubule. First, by blocking transport along the distal tubule, where tubule remodeling has led to enhanced transport capacity, the potency of these normally relatively weak thiazide-type diuretics will be increased [65]. Second, when oral metolazone or chlorthalidone is used in this situation, its longer half-life (approximately 14 and 50 hours [66] may attenuate post-diuretic NaCl retention and overcome one of the key limitations of the loop diuretics. Third, thiazide diuretics may mitigate distal nephron remodeling itslf and thereby prevent or reverse a key contributing feature (NCC) [67]. Nevertheless, a key hazard of this approach is the potential for enhanced side effects, especially hypokalemia [68]. As a decrease in plasma potassium concentration is now recognized as the dominant factor that activates NCC [69], the resulting metabolic changes may counteract the beneficial effect of adding a second class of diuretic. In this situation, using a mineralocorticoid receptor antagonist, or when already in use, increasing the dose can be an alternative. The potassium sparing effect, long duration of action and alleviation of distal nephron remodeling via inhibition of aldosterone [62] has the advantage of increasing natriuresis while maintaining potassium balance. In earlier studies, addition of high-dose spironolactone resulted in significant natriuresis without hyperkalemia in patients with heart failure and resistance to loop diuretics [70]. However, the recent Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial using high-dose spironolactone (100 mg/day) added to standard of care in ADHF patients; failed to improve the primary outcome of reduction in NT-proBNP and congestion scores [71]. One shortcoming of this trial was that it randomized all heart failure patients, instead of only those who found to have loop-diuretic resistant ADHF. One of the major causes for ADHF admissions is improper use of loop diuretic either because of lack of affordability or inadequate doses for the disease state. ATHENA-HF trial randomized all these subjects to the intervention or control arm without considering the underlying cause of decompensation. Thus, it is possible that the majority of these subjects would respond to the usual care without any additional benefit of high-dose spironolactone; if this is true, the ATHENA-HF trial may not have been powered to capture the diuretic resistant population. In a recent study of patients with loop-diuretic resistant ADHF, the addition of high dose spironolactone (100–200 mg/day) resulted in significant weight loss, increased urine output and symptoms relief. This decongestion was not associated with worsening renal function or hyperkalemia (Bansal, Abstract, Kidney Week 2018).

Addition of an aldosterone antagonist is an attractive option in hospitalized patients admitted with ADHF and loop diuretic resistance; however, this approach may lead to complications patients with heart failure in outpatient setting and advanced CKD. Addition of aldosterone antagonists may work well in patients with persistent ECF expansion in steady state by overcoming the braking phenomenon. However, patients may not be in steady state, as the dietary NaCl changes frequently and doses of loop diuretic may need to be adjusted. In the absence of those adjustments, these patients are prone for acute kidney injury from either rapid diuresis

(when the rate of diuresis is higher than rate of shift of fluid from interstitium to intravascular space) or overdiuresis. Hyperkalemia as a complication of AKI can be disproportionate to the degree of AKI due to potassium-sparing effect of spironolactone and can be difficult to manage given the long half-lives of its active metabolites, which are further prolonged in renal insufficiency, heart failure and cirrhosis patients. For the similar reasons, use of spironolactone is not recommended in patients with advance renal insufficiency with braking phenomenon.

Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) is an ongoing trial to assess the safety and efficacy of loop and thiazide diuretic combination in patients with ADHF in comparison with a loop diuretic regimen alone. The CLOROTIC trial should answer the safety concerns of hypokalemia with this approach. High-dose aldosterone antagonists in combination with loop diuretics should not be prescribed in outpatient setting or advanced CKD unless close monitoring is available to adjust the dose of diuretics and follow serum chemistry.

Evidence-based Diuretic Dosing for Extracellular Fluid Volume Expansion

While recommendations for loop diuretic dosing have traditionally been based on their pharmacology, some more recent studies of ADHF have focused on patient-centered outcomes. The Diuretic Optimization Strategies Evaluation trial in Acute Heart Failure (DOSE-AHF) trial compared high and low doses of loop diuretics for ADHF and showed that the higher dose (2.5× the home daily dose) is well tolerated and effective. One concern about aggressive diuretic approaches in this situation is worsening kidney function, which was used as a harm signal in this study. Yet worsening kidney function in this trial, as indicated by a rise in creatinine, was found in a post-hoc analysis to be associated with better, rather than worse, prognosis [51]. When adequate diuresis does not occur, a stepped care approach, shown in Table 5.3, has been recommended [46]. While not compared directly with other approaches, this approach was employed successfully in randomized trials and proved at least as effective as invasive techniques, such as ultrafiltration [72].

Comparison of Three Loop Diuretics

Table 5.2 shows the differences in pharmacokinetics of various diuretics. It is a common practice to switch from one loop diuretic to another one in both inpatient and outpatient setting when adequate responses are not achieved. Taking the pharmacology into consideration, switch from oral furosemide to either oral bumetanide or torsemide is logical given wide variation in bioavailability of oral furosemide administration. However, there are no definitive clinical studies comparing the effectiveness of different loop diuretics in heart failure patients; thus, results of TRANSFORM-HF trial will be valuable (see above). Until then, many experts prefer torsemide rather than furosemide or bumetanide in managing heart

Table 5.3 Stepped pharmacological care algorithm for heart failure

Level	Current daily furosemide* dose	Bolus	Infusion rate	Metolazone (oral)
1	≤80 mg	40 mg	5 mg/hour	0
2	81–160 mg	80 mg	10 mg/hour	5 mg daily
3	161–240 mg	80 mg	20 mg/hour	5 mg twice daily
4	≥240 mg	80 mg	30 mg/hour	5 mg twice daily

Adapted from Refs. [46, 72]. The full algorithm provided in the references includes additional considerations for vasodilator, inotropic, or mechanical therapy for patients who fail to respond within 48 hours

*Diuretic equivalents: 40 mg furosemide is considered equivalent to 1 mg bumetanide 20 mg torsemide

failure patients in the outpatient setting, given the convenience of once a day dosing and avoidance of nocturia as seen with furosemide or bumetanide if the second dose is administered late in the day. On the contrary, these pharmacokinetic differences have less impact when using diuretics IV, since the bioavailability is similar of the IV preparations. Rather, a stepped-up approach is recommended to achieve the threshold for the particular diuretic to be effective.

Summary

Diuretic drugs, agents that target solute transport along the nephron, are used commonly in individuals with cardiorenal syndrome. Each has a unique pharmacokinetic profile, but such differences may not receive sufficient consideration when the drugs are used therapeutically. Recent large clinical trials now provide an evidence base for diuretic treatment of ADHF. Yet, even when such evidence is available, a deep understanding of diuretic pharmacokinetics and pharmacodynamics enhances the clinical approach to diuresis. A formal collaboration between cardiologists and nephrologists can bridge gaps in knowledge to augment the goal of decongestion. As the drugs have substantial ability to ameliorate breathlessness and edema, the goal of optimizing their use should improve patient-focused clinical outcomes. The development of diuretic drugs has been one of the greatest accomplishments of scientific medicine; the persistence of disorders of extracellular fluid volume into the twenty-first century, means that these drugs will continue to play central roles in medical practice for the foreseeable future.

References

1. Hammarlund MM, Paalzow LK, Odlind B. Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis. Eur J Clin Pharmacol. 1984;26:197–207.
2. Brater DC, Day B, Burdette A, Anderson S. Bumetanide and furosemide in heart failure. Kidney Int. 1984;26:183–9.
3. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. Am J Physiol Renal Physiol. 2003;284:F11–21.

4. Huang X, Dorhout Mees E, Vos P, Hamza S, Braam B. Everything we always wanted to know about furosemide but were afraid to ask. Am J Physiol Renal Physiol. 2016;310:F958–71.
5. Brater DC. Diuretic pharmacokinetics and pharmacodynamics. In: Seldin DW, Giebisch G, editors. Diuretic Agents: Clinical Physiology and Pharmacology. San Diego: Academic Press; 1997. p. 189–208.
6. Brater DC. Pharmacodynamic considerations in the use of diuretics. Ann Rev Pharmacol Toxicol. 1983;23:45–62.
7. Murray MD, Haag KM, Black PK, Hall SD, Brater DC. Variable furosemide absorption and poor predictability of response in elderly patients. Pharmacotherapy. 1997;17:98–106.
8. Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. Clin Pharmacol Ther. 1995;57:601–9.
9. McCrindle JL, Li Kam Wa TC, Barron W, Prescott LF. Effect of food on the absorption of frusemide and bumetanide in man. Br J Clin Pharmacol. 1996;42:743–6.
10. Kramer WG. Effect of Food on the Pharmacokinetics and Pharmacodynamics of Torsemide. Am J Ther. 1995;2:499–503.
11. Murray MD, Ferguson JA, Bennett SJ, Adams LD, Forrhofer MM, Minick SM, Tierny WM, Brater DC. Fewer hospitalizations for heart failure by using a completely and predictably absorbed lood diuretic. J Gen Intern Med. 1998;13:18.
12. Murray MD, Deer MM, Ferguson JA, Dexter PR, Bennett SJ, Perkins SM, Smith FE, Lane KA, Adams LD, Tierney WM, Brater DC. Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. Am J Med. 2001;111:513–20.
13. Bikdeli B, Strait KM, Dharmarajan K, Partovian C, Coca SG, Kim N, Li SX, Testani JM, Khan U, Krumholz HM. Dominance of furosemide for loop diuretic therapy in heart failure: time to revisit the alternatives? J Am Coll Cardiol. 2013;61:1549–50.
14. DiNicolantonio JJ. Should torsemide be the loop diuretic of choice in systolic heart failure? Futur Cardiol. 2012;8:707–28.
15. Mentz RJ, Hasselblad V, DeVore AD, Metra M, Voors AA, Armstrong PW, Ezekowitz JA, Tang WH, Schulte PJ, Anstrom KJ, Hernandez AF, Velazquez EJ, O'Connor CM. Torsemide Versus Furosemide in Patients With Acute Heart Failure (from the ASCEND-HF Trial). Am J Cardiol. 2016;117:404–11.
16. Vasavada N, Saha C, Agarwal R. A double-blind randomized crossover trial of two loop diuretics in chronic kidney disease. Kidney Int. 2003;64:632–40.
17. Vasko MR, Brown-Cartwright D, Knochel JP, Nixon JV, Brater DC. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med. 1985;102:314–8.
18. Gilotra NA, Princewill O, Marino B, Okwuosa IS, Chasler J, Almansa J, Cummings A, Rhodes P, Chambers J, Cuomo K, Russell SD. Efficacy of Intravenous Furosemide Versus a Novel, pH-Neutral Furosemide Formulation Administered Subcutaneously in Outpatients With Worsening Heart Failure. JACC Heart Failure. 2018;6:65–70.
19. Sica DA, Muntendam P, Myers RL, Ter Maaten JM, Sale ME, de Boer RA, Pitt B. Subcutaneous furosemide in heart failure: pharmacokinetic characteristics of a newly buffered solution. JACC Basic Transl Sci. 2018;3:25–34.
20. Inoue M, Okajima K, Itoh K, Ando Y, Watanabe N, Yasaka T, Nagase S, Morino Y. Mechanism of furosemide resistance in analbuminemic rats and hypoalbuminemic patients. Kidney Int. 1987;32:198–203.
21. Kitsios GD, Mascari P, Ettunsi R, Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. J Crit Care. 2014;29:253–9.
22. Brater DC. Diuretic therapy. N Engl J Med. 1998;339:387–95.
23. Brater DC. Disposition and response to bumetanide and furosemide. Am J Cardiol. 1986;57:20A–5A.
24. Voelker JR, Cartwright-Brown D, Anderson S, Leinfelder J, Sica DA, Kokko JP, Brater DC. Comparison of loop diuretics in patients with chronic renal insufficiency. Kidney Int. 1987;32:572–8.

25. Delpire E, Lu J, England R, Dull C, Thorne T. Deafness and imbalance associated with inactivation of the secretory Na-K-2Cl co-transporter. Nat Genet. 1999;22:192–5.
26. Flagella M, Clarke LL, Miller ML, Erway LC, Giannella RA, Andringa A, Gawenis LR, Kramer J, Duffy JJ, Doetschman T, Lorenz JN, Yamoah EN, Cardell EL, Shull GE. Mice lacking the basolateral Na-K-2Cl cotransporter have impaired epithelial chloride secretion and are profoundly deaf. J Biol Chem. 1999;274:26946–55.
27. Dormans TP, Van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol. 1996;28:376–82.
28. Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ. 2006;333:420.
29. Keller F, Hann A. Clinical pharmacodynamics: principles of drug response and alterations in kidney disease. Clin J Am Soc Nephrol. 2018;13:1413–20.
30. Nigam SK, Wu W, Bush KT, Hoenig MP, Blantz RC, Bhatnagar V. Handling of drugs, metabolites, and uremic toxins by kidney proximal tubule drug transporters. Clin J Am Soc Nephrol. 2015;10:2039–49.
31. Lau HS, Shih LJ, Smith DE. Effect of probenecid on the dose-response relationship of bumetanide at steady state. J Pharmacol Exp Ther. 1983;227:51–4.
32. Vallon V, Rieg T, Ahn SY, Wu W, Eraly SA, Nigam SK. Overlapping in vitro and in vivo specificities of the organic anion transporters OAT1 and OAT3 for loop and thiazide diuretics. Am J Physiol Renal Physiol. 2008;294:F867–73.
33. Heerdink ER, Leufkens HG, Herrings RMC, Ottervanger JP, Stricker BHC, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med. 1998;158:1108–12.
34. Burckhardt G. Drug transport by organic anion transporters (OATs). Pharmacol Ther. 2012;136:106–30.
35. Wu W, Bush KT, Nigam SK. Key role for the organic anion transporters, OAT1 and OAT3, in the in vivo handling of uremic toxins and solutes. Sci Rep. 2017;7:4939.
36. Cemerikic D, Wilcox CS, Giebisch G. Intracellular potential and K+ activity in rat kidney proximal tubular cells in acidosis and K+ depletion. J Membr Biol. 1982;69:159–65.
37. Loon NR, Wilcox CS. Mild metabolic alkalosis impairs the natriuretic response to bumetanide in normal human subjects. Clin Sci. 1998;94:287–92.
38. Mann B, Hartner A, Jensen BL, Kammerl M, Kramer BK, Kurtz A. Furosemide stimulates macula densa cyclooxygenase-2 expression in rats. Kidney Int. 2001;59:62–8.
39. Stokes JB. Effects of prostaglandin E2 on chloride transport across the rabbit thick ascending limb of Henle. J Clin Invest. 1979;64:495–502.
40. Hebert RL, Jacobson HR, Breyer MD. Prostaglandin E2 inhibits sodium transport in rabbit cortical collecting duct by increasing intracellular calcium. J Clin Invest. 1991;87:1992–8.
41. Fernandez-Llama P, Ecelbarger CA, Ware JA, Andrews P, Lee AJ, Turner R, Nielsen S, Knepper MA. Cyclooxygenase inhibitors increase Na-K-2Cl cotransporter abundance in thick ascending limb of Henle's loop. Am J Phys. 1999;277:F219–26.
42. Oppermann M, Hansen PB, Castrop H, Schnermann J. Vasodilatation of afferent arterioles and paradoxical increase of renal vascular resistance by furosemide in mice. Am J Physiol Renal Physiol. 2007;293:F279–87.
43. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ. 2013;346:e8525.
44. Ellison DH, Felker GM. Diuretic treatment in heart failure. N Engl J Med. 2017;377:1964–75.
45. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev. 2005;CD003178.
46. Grodin JL, Stevens SR, de Las Fuentes L, Kiernan M, Birati EY, Gupta D, Bart BA, Felker GM, Chen HH, Butler J, Davila-Roman VG, Margulies KB, Hernandez AF, Anstrom KJ, Tang WH. Intensification of medication therapy for cardiorenal syndrome in acute decompensated heart failure. J Card Fail. 2016;22:26–32.

47. Shah S, Pitt B, Brater DC, Feig PU, Shen W, Khwaja FS, Wilcox CS. Sodium and fluid excretion with torsemide in healthy subjects is limited by the short duration of diuretic action. J Am Heart Assoc. 2017;6:e006135.
48. Titze J. Estimating salt intake in humans: not so easy! Am J Clin Nutr. 2017;105:1253–4.
49. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128:1810–52.
50. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J. 2004;147:331–8.
51. Brisco MA, Zile MR, Hanberg JS, Wilson FP, Parikh CR, Coca SG, Tang WH, Testani JM. Relevance of changes in serum creatinine during a heart failure trial of decongestive strategies: insights from the DOSE trial. J Card Fail. 2016;22:753–60.
52. Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, Felker GM, Hernandez AF, O'Connor CM, Sabbisetti VS, Bonventre JV, Wilson FP, Coca SG, Testani JM. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. Circulation. 2018;137:2016–28.
53. Walser M. Phenomenological analysis of renal regulation of sodium and potassium balance. Kidney Int. 1985;27:837–41.
54. Wilcox CS, Mitch WE, Kelly RA, Skorecki K, Meyer TW, Friedman PA, Souney PF. Response of the kidney to furosemide: I. Effects of salt intake and renal compensation. J Lab Clin Med. 1983;102:450–8.
55. Wilcox CS, Guzman NJ, Mitch WE, Kelly RA, Maroni BJ, Souney PF, Rayment CM, Braun L, Colucci R, Loon NR. Na+,K+ and BP homeostasis in man during furosemide: effects of prozosin and captopril. Kidney Int. 1987;31:135–41.
56. Kelly RA, Wilcox CS, Mitch WE, Meyer TW, Souney PF, Rayment CM, Friedman PA, Swartz SL. Response of the kidney to furosemide. II. Effect of captopril on sodium balance. Kidney Int. 1983;24:233–9.
57. Loon NR, Wilcox CS, Unwin RJ. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. Kidney Int. 1989;36:682–9.
58. Rao VS, Planavsky N, Hanberg JS, Ahmad T, Brisco-Bacik MA, Wilson FP, Jacoby D, Chen M, Tang WHW, Cherney DZI, Ellison DH, Testani JM. Compensatory distal reabsorption drives diuretic resistance in human heart failure. J Am Soc Nephrol. 2017;28:3414–24.
59. Subramanya AR, Ellison DH. Distal convoluted tubule. Clin J Am Soc Nephrol. 2014;9:2147–63.
60. Yang YS, Xie J, Yang SS, Lin SH, Huang CL. Differential roles of WNK4 in regulation of NCC in vivo. Am J Physiol Renal Physiol. 2018;314:F999–F1007.
61. Castaneda-Bueno M, Gamba G. Mechanisms of sodium-chloride cotransporter modulation by angiotensin II. Curr Opin Nephrol Hypertens. 2012;21:516–22.
62. Abdallah JG, Schrier RW, Edelstein C, Jennings SD, Wyse B, Ellison DH. Loop diuretic infusion increases thiazide-sensitive Na(+)/Cl(−)-cotransporter abundance: role of aldosterone. J Am Soc Nephrol. 2001;12:1335–41.
63. Saritas T, Puelles VG, Su XT, McCormick JA, Welling PA, Ellison DH. Optical clearing in the kidney reveals potassium-mediated tubule remodeling. Cell Rep. 2018;25:2668–2675 e2663.
64. Fliser D, Schröter M, Neubeck M, Ritz E. Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. Kidney Int. 1994;46:482–8.
65. Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med. 1991;114:886–94.
66. Kountz DS, Goldman A, Mikhail J, Ezer M. Chlorthalidone: the forgotten diuretic. Postgrad Med. 2012;124:60–6.

67. Grimm PR, Taneja TK, Liu J, Coleman R, Chen YY, Delpire E, Wade JB, Welling PA. SPAK isoforms and OSR1 regulate sodium-chloride co-transporters in a nephron-specific manner. J Biol Chem. 2012;287:37673–90.
68. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56:1527–34.
69. Terker AS, Zhang C, McCormick JA, Lazelle RA, Zhang C, Meermeier NP, Siler DA, Park HJ, Fu Y, Cohen DM, Weinstein AM, Wang WH, Yang CL, Ellison DH. Potassium modulates electrolyte balance and blood pressure through effects on distal cell voltage and chloride. Cell Metab. 2015;21:39–50.
70. Eng M, Bansal S. Use of natriuretic-doses of spironolactone for treatment of loop diuretic resistant acute decompensated heart failure. Int J Cardiol. 2014;170:e68–9.
71. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, Mann DL, Margulies KB, McNulty SE, Mentz RJ, Redfield MM, Tang WHW, Whellan DJ, Shah M, Desvigne-Nickens P, Hernandez AF, Braunwald E, National Heart Lung and Blood Institute Heart Failure, Clinical Research Network. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. JAMA Cardiol. 2017;2:950–8.
72. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367:2296–304.
73. Somasekharan S, Tanis J, Forbush B. Loop diuretic and ion binding residues revealed by scanning mutagenesis of transmembrane helix 3 (TM3) of the Na-K-Cl Cotransporter (NKCC1). J Biol Chem. 2012;287:17308–17.
74. Ellison DH. Clinical pharmacology in diuretic use. Clin J Am Soc Nephrol. 2019:CJN.09630818.
75. Milionis HJ, Alexandrides GE, Liberopoulos EN, Bairaktari ET, Goudevenos J, Elisaf MS. Hypomagnesemia and concurrent acid-base and electrolyte abnormalities in patients with congestive heart failure. Eur J Heart Fail. 2002;4:167–73.
76. Karim A. Spironolactone: disposition, metabolism, pharmacodynamics and bioavailability. Drug Metab Rev. 1978;8:151–88.

Part II

Case-Based Discussions

A Patient with Progressive Renal Insufficiency in Chronic Heart Failure with Reduced Ejection Fraction

6

Kevin Damman

Case Vignette

Mr. Y is a 72 y/o man with an ischemic cardiomyopathy after suffering an anterior myocardial infarction at the age of 68 years. He is currently residing in New York Heart Association functional class II. His past medical record is also notable for poorly controlled diabetes with microvascular complications of retinopathy and nephropathy. Serum creatinine levels were normal at the time of his myocardial infarction, but have increased gradually up till 2.47 mg/dL now (estimated glomerular filtration rate 25 mL/min/1.73 m^2). Mr. Y is taking aspirin, atorvastatin, metformin, insulin in a basal-bolus scheme, lisinopril 20 mg daily, carvedilol 25 mg twice daily, and eplerenone 50 mg daily. Serum potassium levels are slightly elevated at 5.2 mmol/L without other electrolyte disturbances. Blood pressure is well controlled at 132/58 mmHg. The electrocardiogram of Mr. Y shows a left bundle branch block with QRS width equal to 148 ms. On his latest echocardiography, left ventricular ejection fraction was 30%.

Chapter Key Points

- Incidence and prognostic impact of chronic kidney disease (CKD) in heart failure with reduced ejection fraction (HFrEF)
- Use of evidence-based medications for HFrEF in patients with CKD
- Device therapy in HFrEF and CKD
- Reno-protective strategies in HFrEF

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Brief Discussion of the Case

The first thing that should come to mind in any clinician treating patients similar to the case presented here, is whether this patient is in stable condition. To do so, a detailed anamnesis, followed by physical examination and if necessary follow up diagnostic tests are warranted to do so. It is imperative to identify unstable patients before the clinical course is detrimental to such an extent only limited treatment options remain. If the patient is stable, this gives the clinician time to evaluate the patient closely, possibly seeing the patient in the outpatient clinic several times, and perhaps discuss this patients treatment with other physicians, consulting specialists and of course the patient and his caregivers. Fortunately, the gentleman in this case seems to be in reasonable shape, as he is in NYHA functional class II heart failure (HF). This means there is time to evaluate the current status, get a detailed picture of the medical situation, and decide on a treatment plan based on patients condition, laboratory and other diagnostic and functional test, as well as taking into consideration current HF guidelines [1–3].

This patient is suffering from HF with reduced ejection fraction (HFREF), probably caused by the (large) myocardial infarction 4 years ago. Immediately, a clinician familiar with the syndrome of HF will recognize that there is no available cure, which means all treatment options available are focused on improving quality of life, including extending length of life, as well as keeping the patient out of hospital [2]. When assessing such a patient with HFREF, it is important to evaluate whether any comorbidities exist that might further impair long term outcomes or increase the risk of decompensation, hospitalization or dying [4]. Furthermore, some comorbidities may interfere with treatment options. Certainly, the presence of comorbidities that by itself confer a substantial mortality risk (which could surpass the mortality risk of HF), could mean certain HF treatments should not be embarked on.

In general comorbidities that should interest a HF physician include among others: Diabetes Mellitus, Pulmonary Disease (including chronic obstructive pulmonary disease (COPD)), Coronary Artery Disease, Atrial Fibrillation, Cerebrovascular disease, Depression and perhaps most importantly for the current case: renal insufficiency [4–7].

Renal Function in HFREF

Why is renal function so important in HF? First, it is the organ that is in the end responsible for the maladaptive salt and water retention in response to neurohormonal activation when cardiac dysfunction (whatever is the cause) develops [8]. Second, because it is exactly there where evidence based treatments in HFREF exert their action (among other places). Thirdly, whatever the cause of renal dysfunction in HF, it is one of the strongest predictors of clinical outcome (and therefore risk marker) in HF [6, 9]. At the end of the twentieth century, this detrimental association between lower creatinine clearance and mortality was formally recognized in retrospective analyses from both SOLVD and PRIME II studies, sparking up more research in the field on why renal dysfunction was so important in HF [10, 11]. Ultimately, this culminated in a large study based meta-analysis, including over one

million cases, where having chronic kidney disease (CKD) at baseline was associated with a more than two-fold mortality risk [6]. This risk was, surprisingly, similar in acute and chronic HF. These findings by itself should be sufficient reason to evaluate renal function closely in patients with HFREF.

Pathophysiology of Renal Insufficiency in Heart Failure

Even though we largely think we understand the importance of renal dysfunction in HFREF patients, the pathophysiology is still under debate (Fig. 6.1 shows most common concepts) [8, 12, 13]. However, we now know from small mechanistic studies that a reduction in cardiac output and increase in central venous pressure

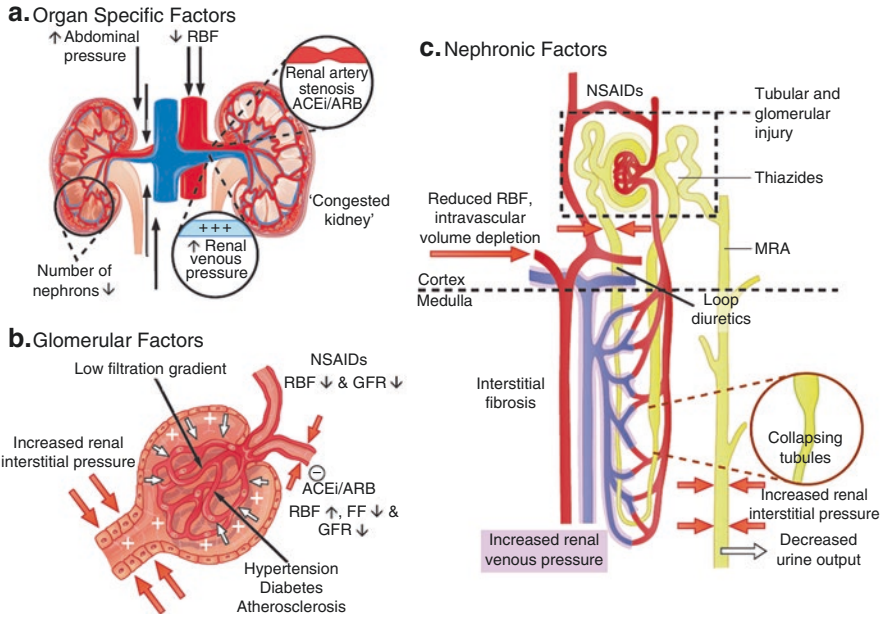

Fig. 6.1 Overview of the pathophysiology of renal insufficiency in HFREF. (**a**) Organ-specific factors: Reduction in RBF and increased (renal) venous pressure, resulting in increased renal interstitial pressure (directly opposing filtration in Bowmans capsule (**b**)). Glomerular factors: Renal autoregulation preserves GFR, a process inhibited by RAAS inhibitors causing (pseudo) worsening renal function. Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis, thereby impairing prostaglandin associated increase/dependent renal blood flow. Concomitant diseases have direct, but differential effect on glomerular filtration, glomerular integrity and podocyte function, as well as autoregulation. (**c**) Nephronic factors: the combination of increased interstitial pressure, reduced arterial perfusion, concomitant disease and therapies can cause tubular and glomerular injury. Increased renal interstitial pressure causes collapsing of renal tubules, thereby lowering GFR, and eventually leading to decreased urine output, sodium retention, and congestion. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor: ARB, angiotensin II receptor blocker: FF, filtration fraction: GFR, glomerular filtration rate: MRA, mineralocorticoid receptor antagonist: NSAIDs, non-steroidal anti-inflammatory drugs: RAAS, renin–angiotensin–aldosterone system: RBF, renal blood flow. (From Damman et al. [21])

directly transmit to the kidney [14–17]. This means that in HFREF patients, with and without renin angiotensin aldosterone system (RAAS) blockade, there is a direct and strong relationship between renal blood flow and glomerular filtration rate (GFR) [14, 16]. When HF advances, and besides left sided filling pressures, also right sided pressures, especially central venous pressure start to rise and overt congestion develops, this also has it effects on renal function [18]. Importantly, high central venous pressure (directly transmits to renal venous pressure) contributes to a reduced GFR in two important ways. First it decreases the pressure gradient over de kidney (and glomerulus), thereby decreasing renal blood flow (this is an indirect way). Second, increased central and renal venous pressure leads to renal interstitial hypertension (high intracapsular pressure) [19–21]. On the long term this accelerates fibrosis and intrarenal damage, but on the short term it means pressure in the renal parenchymal tissues are high, resulting in collapsing of tubules, reducing the flow of ultrafiltrate from Bowman's capsule to the collecting duct, which means lower filtration [22]. There are also signs that by itself, high renal venous pressure further promotes salt and water retention. It is therefore essential to get a feeling of congestive status of the HFREF patient with renal dysfunction to understand the cause of CKD in the individual patient (Tables 6.1, 6.2, and 6.3).

In the current case, this patient does have a strikingly reduced estimated GFR (25 mL/min/1.73 m^2), more than might be expected from his age, creatinine and severity of HF. In such a situation, it is important to re-evaluate findings and medical history to understand the disproportional low eGFR. It could be that the hemodynamic status of the patient is more compromised than can be seen with minimal

Table 6.1 Important considerations when approaching a HFREF patient with renal dysfunction

Current situation: Hemodynamics
Is the patient stable? If not, this should be the first treatment goal.
Excessive congestion? Evidence of edema?
Hypo or hypertensive?
Predisposing conditions that can cause (more than expected) renal impairment
Diabetes mellitus
Atherosclerosis
Hypertension
Background therapy
Any medical therapy that can compromise renal function?
Any medical therapy that is renally cleared?
What about HF therapy: what is the current type and dose of evidence based HF therapy, especially RAAS inhibitors?
Use of (loop) diuretics?
Dynamics in renal function
What was the course of eGFR/serum creatinine in the past weeks/months?
What was the most likely reason for the change?
Any indication of organ damage? What about albuminuria (especially in hypertensives, diabetics)
Any indication of adverse events linked to renal dysfunction?
Hyperkaleamia
Gout like symptoms
Muscle cramps

Abbreviations: eGFR: estimated Glomerular Filtration Rate, HF: Heart Failure, HFREF: Heart failure with reduced ejection fraction, RAAS: Renin Angiotensin Aldosterone System

Table 6.2 Hyperkalaemia

Hyperkalaemia is a frequent condition that occurs in patients with heart failure and concomitant renal dysfunction. Normally, hyperkaleamia is defined as a potassium above 5.0 mmol/L. Up to 25–30% of chronic HFREF patients may develop at some stage hyperkaleamia, which may be due to underlying conditions, such as renal dysfunction, or can occur after initiation and/or uptitration of evidence based heart failure therapies. It is therefore a very important disorder that prohibits sometimes the uptitration of RAAS-inhibitor therapy, and in specific mineralocorticoid receptor antagonists (MRA's) that are known to elevate potassium levels. Some obvious causes of hyperkaleamia such as inadequate blood draw, use of potassium supplements or metabolic disorders should always be considered and excluded. Then, as with the current patient is the case, if no other causes can be identified, care should be taken to re-evaluate potassium levels regularly. If any further increase is observed, either MRA (or other RAAS inhibitor) should be downtitrated, or if the patient is congested, loop diuretics can be initiated, which are known to reduce serum potassium levels.
Novel treatments to specifically lower potassium levels to allow further uptitration of evidence based therapies are now being evaluated but have not found their way to clinical practice yet.

Table 6.3 Worsening renal function

Changes in filtration rate occur all the time in patients with HFREF, and even with daily determination of serum creatinine it is difficult to establish true alterations in GFR. Improvements in serum creatinine and GFR will hardly alert any clinician, while certain increases in creatinine will quickly alarm many HF specialists. From epidemiological data, any increase in serum creatinine, whatever the cause, was associated with worse clinical outcomes. However, the magnitude of this excess risk (which can be minimal to substantial) depends entirely on the circumstances during which this increase developed. If the clinical status of a patient improves, but serum creatinine increases, this normally is not associated with worse outcomes. It should prompt re-evaluation after some time, but would not necessarily need any action to be taken. Similarly any modest increase in serum creatinine after RAAS-inhibitor initiation or uptitration should be expected and accepted, even in patients with already compromised kidney function. Only very large (and unexpectedly large) increases in serum creatinine should alarm the HF specialist to reduce or even stop these life saving drugs. Always check whether other factors could have been responsible for the deterioration in renal function, such as over the counter NSAIDs, antibiotics, loop diuretics, or clinical deterioration. If the patient remained stable, re-challenge with a RAAS inhibitor should be considered, possibly in lower dosages and a slower uptitration regime. In difficult cases, a consultation by nephrologist should be considered.

examination and anamnesis. If this is suspected, care should be taken to get objective evidence of to support this. More importantly, not only HF induces a decline in renal function, also many comorbidities exert detrimental effects, some of which contribute to the development of HF as well. Particularly, atherosclerosis, hypertension and diabetes mellitus are associated with worse renal function and more renal function decline in non HF populations, and all are associated with the development of HF by themselves [23, 24]. What this actually means is that in some patients, before the development of (overt) HF, renal function is often already compromised [25]. In the current case, this patient was already suffering from poorly controlled diabetes with end organ damage (retinopathy and nephropathy) probably long before HF occurred after the myocardial infarction. Although this did not translate in to an elevated serum creatinine level when the infarction occurred, diabetes can cause accelerated decline in renal function, cause glomerulosclerosis and tubular injury, as well as causing nephron loss [26]. Diabetic patients are also known to have renal hyperfiltration

where filtration fraction (GFR divided by renal blood flow) actually increases; which is thought to be a sign of renal compensation, but also a sign of renal end organ damage [27]. This might have been the case with the current patient when serum creatinine was still normal at the time of the coronary event. Although hyperfiltration normally doesn't occur in hypertension, this condition is also associated with accelerated decline in renal function and loss of nephrons [28]. It is also a major risk factor for HF, either directly or through promoting cardiovascular events [29]. Controlling blood pressure and optimizing diabetic regulation are therefore important treatment targets in patients at risk of HF, but also in HF patients themselves, since this might be associated with favourable renal outcomes. Although this has not been shown in an evidence based manner, it is unlikely that pathophysiological processes associated with early renal function decline in patients without (or before) HF are either halted, attenuated or even reversed when overt HF develops. Therefore, from a renal perspective, taking care of blood pressure and especially diabetic control, should be part of the treatment of HFREF patients with renal insufficiency.

Treatment of HFREF Patients with Renal Insufficiency

Besides diagnosing, controlling and treating comorbidities in HFREF, the primary focus of the treatment of HFREF patients – also in those with important renal insufficiency- should be initiation, uptitration and continuation of evidence based therapies as much as possible according to most recent HF guidelines [1–3]. As is the case for any HFREF patient, a patient with mild to moderate renal insufficiency (CKD stage 1–3, eGFR >30 mL/min/1.73 m^2) should be treated with guideline recommended HF treatment (Fig. 6.2) [30]. The classes of drugs to consider in these patients include Angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), Angiotensin receptor blocker neprilysin inhibitors (ARNI), beta-blockers and mineralocorticoid receptor antagonists (MRA), which all have a class I recommendation in clinical HF guidelines [2, 3]. ACEi and ARBs are often withheld in patients with modest to moderate (and severe) renal insufficiency in HF because of the perceived risk of worsening of renal function and hyperkaleamia [30]. In randomized clinical trials, where only patients were included with eGFR >30 ml/min/1.73m^2 (so CKD stage 1 to 3b, but not stage 4 or 5 (dialysis)), there was no significant interaction between baseline CKD and the treatment effect of either ACEi or ARB. This means that the beneficial effects were maintained when baseline eGFR was lower. Since the absolute risk in these high risk patients was higher, this also meant that with similar relative risk reduction, the absolute risk reduction in these patients was actually greater [30]. However, this was offset by more frequent occurrence of hyperkaleamia and other adverse events, indicating that close monitoring of renal function and electrolytes is warranted, especially when renal function at baseline is already compromised. Similar results were found in post hoc analyses of both RALES and EMPHASIS-HF, showing that MRA therapy was beneficial also in patients with moderate renal insufficiency [31, 32]. The perceived risk of worsening renal function with RAAS inhibitors is actually

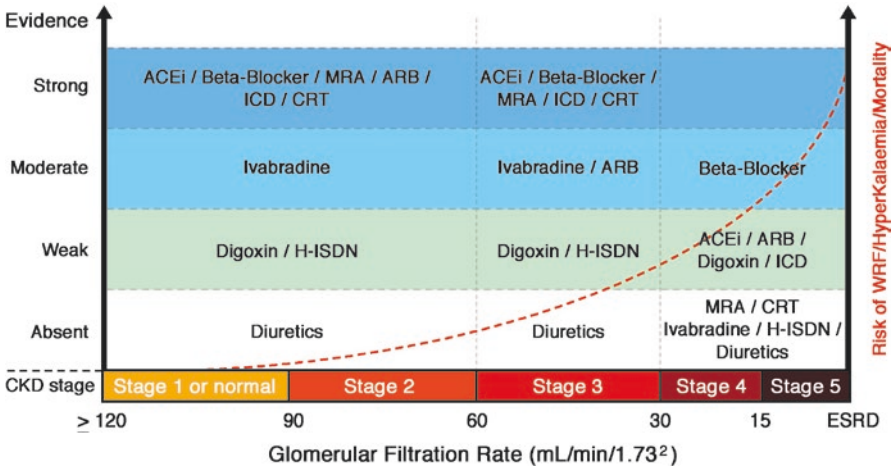

Fig. 6.2 Evidence of guideline recommended treatments in HFREF according to CKD stages. Angiotensin blocker neprilysin inhibitor (ARNI) shows the same evidence as for ACEi, although only in one study. Abbreviations: ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, CKD: Chronic kidney disease, CRT: cardiac resynchronization therapy, ESRD: End stage renal disease, GFR: glomerular filtration rate, H-ISDN: hydralazine and isosorbide-dinitrate, ICD: implantable cardioverter-defibrillator, MRA: mineralocorticoid receptor antagonist, RAAS: renin angiotensin aldosterone system. (From Damman et al. [30])

true but should be seen in a different context [21]. As a response to a reduction in renal perfusion pressure, efferent vasoconstriction occurs in the kidney, which results in a stable GFR (at the cost of neurohormonal activation). With RAAS inhibition by ACEi, ARB and MRA's, this efferent vasoconstriction is (partly) attenuated, which directly results in improvement of renal perfusion, but decline in GFR (and therefore lower FF) [14]. This decline in GFR called worsening renal function is seen in all studies with RAASi in HF [33]. However, when worsening renal function occurs in the setting of starting or uptitration of RAAS inhibitors, there is no associated detrimental effect on clinical outcome. Some increase in serum creatinine (or decrease in eGFR) should therefore be accepted, which could be up to 3 mg/dL or more than 50% increase in eGFR. Very large or steep increases in serum creatinine should always prompt more investigating and temporary halting the RAAS inhibitor, and in any circumstance, renal function and electrolytes should be checked regularly. The one exception within the group of RAAS inhibitors with regards to change in renal function is sacubitril/valsartan (ARNI). Compared with enalapril, sacubitril/valsartan resulted in a less pronounced decline in eGFR over time, while improving prognosis, even in patients with moderate CKD [34].

In some situations, as is the case with the present patient, renal function could decline below the threshold of eGFR <30 ml/min/1.73 m^2, either because of or despite starting treatment with RAAS inhibitors. It is imperative to try to keep patients on these life saving drugs, even though renal function is poor. Although we do not know whether discontinuation of these drug in these situation do any

harm (or good), it is also very unlikely that the benefit of these therapies suddenly stops in patients with baseline eGFR <30 mL/min/1.73m^2 [30]. However, what we do know is that more side effects such as hypotension occur, and the risk of hyperkaleamia rises [32]. With close monitoring and a case by case treatment plan, it is often possible to keep these patients on their evidence based therapies. Whether to pursue further uptitration (i.e. the present patient is treated with lisinopril 20 mg OD which could be uptitrated further) should also be decided on an individual basis. For instance, if a drop in eGFR was caused by the introduction of the ACEi, further uptitration might not be reasonable. On the other hand, if eGFR has remained stable over some period of time, and blood pressure permits, under close monitoring of vital signs and potassium, uptitration could be considered. In the circumstance this particular patient was RAAS inhibitor naïve and had the same laboratory results, a similar approach can be followed; use small dose steps, adjust according to changes in renal function and electrolytes and monitor vitals. For Beta-blocker therapy, although also in these trials patients with eGFR <30 ml/min/1.73 m^2 were mostly excluded, there is even more consensus to treat HFREF patients with moderate/severe renal insufficiency according to general guidelines [30]. The reason is that there is no (detrimental) effect of beta-blocker therapy on renal function in HFREF patients, and the effect of the drugs were at least as strong (possibly stronger) in patients with more severe CKD stages. Whether or not other medical therapies such as digoxin, ivabradine, hydralazine or nitrates may be used in patients with moderate renal insufficiency has been extensively reviewed [30].

Device Therapy in HFREF Patients with Renal Insufficiency

After a HFREF patient with renal insufficiency has been treated with optimal medical therapy (highest tolerated dose), the question arises whether there is also an indication for device therapy [1, 3]. As is the case for medical treatment, large trials on implantable cardioverter defibrillator (ICD) treatment have excluded patients with severe renal dysfunction. But it is probable that the beneficial effect ICD therapy as observed in the entire HFREF population persists when renal dysfunction worsens. These patients might also be at increased risk of sudden death, especially given electrolyte abnormalities such as hyperkaleamia, and lower dosage of prescribed evidence based therapies [30]. Of course, whether or not an ICD should be implanted is not only dependent of cardiac status, but also of age, frailty, non cardiac life expectancy, comorbidities and patients preference.

Whereas all above mentioned treatment option should only be considered because of mortality or morbidity benefit (and not particularly for their benefit on renal function), this might not be the case for cardiac resynchronization therapy (CRT). The patient in the current case has a widened QRS complex (148 ms), with left bundle branch block morphology, which makes CRT a good option when on stable, high dose evidence based treatment (IIa B recommendation) [1]. This therapy is associated with improved long term outcomes in this patient category,

including those with CKD stage 3 a/b, and it is plausible that it also improves outcome in patients with more severe stages of CKD (i.e. stage 4), although these were not included in the large trials. More importantly there is some evidence that CRT therapy may improve cardiac output and thereby improve renal perfusion, increasing GFR [35]. This might not be a direct reason to implant such a device, given also the risk of peri and post procedural complications, one of which could be contrast-induced nephropathy, but it at least suggests that renal impairment by itself should not be a reason not to implant a CRT in these patients.

Finally, HF patients who have severe renal dysfunction often have advanced HF. In selected patients, left ventricular assist devices (LVAD) implantation may be an option, either as bridge to transplant or as destination therapy. Conceptually, LVAD implantation will result in improvement of hemodynamics and most often result in improved renal function [36, 37]. However, there is increased risk of peri and direct posteroperative worsening of renal function on top of a compromised renal function already. The risk of dialysis is therefore real, but difficult to establish individually. Probably, renal impairment by itself (to some extent), should not be a reason not to implant a LVAD.

Renoprotective Strategies in Chronic HFREF

Certainly, no trial has been designed with the specific intent of improving renal function, although the Evaluation of Losartan in the Elderly Study (ELITE) specifically aimed to reduce the risk of worsening renal function [38]. However, losartan was similar to captopril with respect to renal function, but showed lower mortality risk, which was then not confirmed in ELITE II [39]. Renal dysfunction or worsening renal function has been part of most randomized clinical trials as adverse events. However the interpretation of these adverse events, especially in RAAS-inhibitor placebo controlled trials is difficult. In most if not all RAAS-inhibitor trials, the active compound was associated with more frequent renal adverse events [30]. However, we also know that despite this, mortality benefit was maintained suggesting that striving for improved or stable renal function when RAAS-inhibitor therapy is started or uptitrated really doesn't necessarily translate into better outcomes [33]. Diuretics (mainly loop diuretics) have not been studied in a randomized, placebo controlled manner, but their use is advocated when congestion is present in any HF patient. From a renal perspective, diuretics probably have beneficial but also unwanted effects in HF. They improve and reduce (renal) venous congestion, thereby improving renal perfusion and reducing renal interstitial pressure. This may lead to improved renal function opening up the possibility for uptitration of evidence based treatments. On the other hand, reports suggest that long term use of (high dose loop) diuretics may be associated with worse (renal) outcomes, and even alterations on a nephron level [40–42]. However, it is extremely difficult to establish whether these associations are causative, considering confounding by indication where sicker patients are prescribed more (often) diuretics. The general consensus is however to prescribe a HFREF patients with as much diuretics as possible to

achieve and maintain euvolemia, and as little diuretics as possible to preserve renal function and prevent common side effects such as gout like symptoms, cramps and intravascular depletion. By using a standardized approach, clinicians may be able to improve renal function (by altering dosing of ACEi, Diuretics, switching to clopidogrel), which might be especially useful in the frail, elderly population where also orthostatic hypotension and frequent multiple comorbidities are present [43]. Finally, it is important to prevent the use of certain (combination of) drugs to prevent (or treat) renal function decline. For instance, the use non-steroidal anti-inflammatory drugs (NSAIDs) should be minimized as their combination with RAAS-inhibitors can cause significant renal dysfunction. Combination therapy of ACEi and ARBs (or ARNI/Direct Renin inhibitors) is not advised, given the higher incidence of worsening renal function and hyperkaleamia, without robust evidence of improved outcomes. In any circumstance, frequent determination of renal function (serum creatinine, estimated GFR) and associated electrolytes (sodium, potassium, blood urea nitrogen) is indicated in any patients with HFREF, especially those who have changes in renal function, are unstable and/or are uptitrated with RAAS-inhibitors.

Conclusion

As the pivotal organ that induces the maladaptive salt and water retention in HF and is the target for therapy for most of our evidence based treatments, the kidney can never receive too much attention from HF clinicians. Although (severe) renal dysfunction in chronic HFREF should prompt concerns, it should not be a reason to withhold evidence based treatments. In any patient with chronic HFREF with renal dysfunction it is important to regularly monitor renal function and electrolytes, and to put effort into keeping or starting patients on these life saving therapies.

References

1. WRITING COMMITTEE MEMBERS, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):e240–327.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017;23(8):628–51.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200.
4. van Deursen VM, Damman K, van der Meer P, Wijkstra PJ, Luijckx GJ, van Beek A, et al. Co-morbidities in heart failure. Heart Fail Rev. 2014;19(2):163–72.

5. Kajimoto K, Sato N, Takano T, investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Relationship of renal insufficiency and clinical features or comorbidities with clinical outcome in patients hospitalised for acute heart failure syndromes. Eur Heart J Acute Cardiovasc Care. 2017;6(8):697–708.
6. Damman K, Valente MA, Voors AA, O'Connor CM, Van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35(1522-9645; 0195-668; 7):455–69.
7. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol. 2014;64(21):2281–93.
8. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J. 2015;36(23):1437–44.
9. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol. 2006;47(1558-3597; 0735-1097; 10):1987–96.
10. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000;35(0735-1097; 0735-1097; 3):681–9.
11. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, De ZD, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000;102(1524-4539; 0009-7322; 2):203–10.
12. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52(1558-3597; 19):1527–39.
13. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: 'Guyton revisited'. Eur Heart J. 2005;26(0195-668; 0195-668; 1):11–7.
14. Smilde TD, Damman K, van der Harst P, Navis G, Daan Westenbrink B, Voors AA, et al. Differential associations between renal function and "modifiable" risk factors in patients with chronic heart failure. Clin Res Cardiol. 2009;98(1861-0692; 2):121–9.
15. Damman K, van Deursen VM, Navis G, Voors AA, Van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009;53(1558-3597; 0735-1097; 7):582–8.
16. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. Drugs. 1990;39 Suppl 4(0012-6667; 0012-6667):10–21.
17. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(1558-3597; 7):589–96.
18. Damman K, Navis G, Smilde TD, Voors AA, van der Bij W, van Veldhuisen DJ, et al. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. Eur J Heart Fail. 2007;9(1388-9842; 9):872–8.
19. Burnett JC Jr, Knox FG. Renal interstitial pressure and sodium excretion during renal vein constriction. Am J Physiol. 1980;238(0002-9513; 0002-9513; 4):F279–82.
20. Fiksen-Olsen MJ, Strick DM, Hawley H, Romero JC. Renal effects of angiotensin II inhibition during increases in renal venous pressure. Hypertension. 1992;19(0194-911; 2):137–41.
21. Damman K, Tang WH, Testani JM, McMurray JJ. Terminology and definition of changes renal function in heart failure. Eur Heart J. 2014;35(48):3413–6.
22. Verbrugge FH, Dupont M, Steels P, Grieten L, Swennen Q, Tang WH, et al. The kidney in congestive heart failure: 'are natriuresis, sodium, and diuretics really the good, the bad and the ugly?'. Eur J Heart Fail. 2014;16(2):133–42.
23. Halbesma N, Brantsma AH, Bakker SJ, Jansen DF, Stolk RP, De ZD, et al. Gender differences in predictors of the decline of renal function in the general population. Kidney Int. 2008;74(1523-1755; 0085-2538; 4):505–12.

24. James MT, Grams ME, Woodward M, Elley CR, Green JA, Wheeler DC, et al. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. Am J Kidney Dis. 2015;66(4):602–12.
25. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.
26. Anders HJ, Huber TB, Isermann B, Schiffer M. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. Nat Rev Nephrol. 2018;14(6):361–77.
27. Tonneijck L, Muskiet MH, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. J Am Soc Nephrol. 2017;28(4):1023–39.
28. Hoy WE, Hughson MD, Bertram JF, Douglas-Denton R, Amann K. Nephron number, hypertension, renal disease, and renal failure. J Am Soc Nephrol. 2005;16(9):2557–64.
29. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996;275(20):1557–62.
30. Damman K, Tang WH, Felker GM, Lassus J, Zannad F, Krum H, et al. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. J Am Coll Cardiol. 2014;63(1558-3597; 0735-1097; 9):853–71.
31. Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, et al. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). J Am Coll Cardiol. 2012;60(1558-3597; 0735-1097; 20):2082–9.
32. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, et al. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Circ Heart Fail. 2014;7(1):51–8.
33. Clark H, Krum H, Hopper I. Worsening renal function during renin-angiotensin-aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. Eur J Heart Fail. 2014;16(1879-0844; 1388-9842; 1):41–8.
34. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. JACC Heart Fail. 2018;6(6):489–98.
35. Boerrigter G, Costello-Boerrigter LC, Abraham WT, Sutton MG, Heublein DM, Kruger KM, et al. Cardiac resynchronization therapy improves renal function in human heart failure with reduced glomerular filtration rate. J Card Fail. 2008;14(1532-8414; 7):539–46.
36. Brisco MA, Kimmel SE, Coca SG, Putt ME, Jessup M, Tang WW, et al. Prevalence and prognostic importance of changes in renal function after mechanical circulatory support. Circ Heart Fail. 2014;7(1):68–75.
37. Hasin T, Topilsky Y, Schirger JA, Li Z, Zhao Y, Boilson BA, et al. Changes in renal function after implantation of continuous-flow left ventricular assist devices. J Am Coll Cardiol. 2012;59(1):26–36.
38. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet. 1997;349(9054):747–52.
39. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000;355(9215):1582–7.

40. Damman K, Kjekshus J, Wikstrand J, Cleland JG, Komajda M, Wedel H, et al. Loop diuretics, renal function and clinical outcome in patients with heart failure and reduced ejection fraction. Eur J Heart Fail. 2016;18(3):328–36.
41. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol. 2003;42(0735-1097; 0735-1097; 4):705–8.
42. Ellison DH, Felker GM. Diuretic treatment in heart failure. N Engl J Med. 2017;377(20):1964–75.
43. de Silva R, Nikitin NP, Witte KK, Rigby AS, Loh H, Nicholson A, et al. Effects of applying a standardised management algorithm for moderate to severe renal dysfunction in patients with chronic stable heart failure. Eur J Heart Fail. 2007;9(4):415–23.

A Patient with Chronic Kidney Disease and Heart Failure with Preserved

7

Zubair Shah and James C. Fang

Case Vignette

A 61-year-old woman presents to the emergency department because of severe dyspnea. Her symptoms began gradually 4 weeks ago; she has noted increasing leg swelling and the inability to sleep supine. She has noted increasing difficulty controlling her blood pressure. Her history is notable for longstanding obesity, glucose intolerance, hypertension, and chronic renal insufficiency. Her current medications include atorvastatin, ramipril/hydrochlorothiazide 5/12.5 mg twice daily, amlodipine 10 mg daily and moxonidine 0.4 mg daily. On exam, she is dyspneic and sitting upright. Height 5′2″, weight 250 pounds, blood pressure 186/112 mmHg, heart rate 114 bpm, oxygen saturation 92%. Venous pressure difficult to discern, lungs with bibasilar rales, heart sounds distant but tachycardic, abdomen obese and distended, clear 1+ bilateral lower extremity edema with venous stasis changes, warm to touch. The electrocardiogram shows sinus tachycardia 114 bpm and left ventricular hypertrophy. Chest X-ray shows cardiomegaly and small bilateral pleural effusions. Hemoglobin 9.8 g/dL, potassium 5.9 mmol/L. sodium 132 mg/dL, glucose 210 mg/dL, BUN 35 mg/dL, Cr 2.5 mg/dL. Five years ago, her serum Cr was 1.0 mg/dL.

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Chapter Key Points

- Incidence of heart failure with preserved ejection fraction (HFpEF) in patients with chronic kidney disease (CKD) is increasing
- Important comorbidities common to both HF and CKD mediate cardiac and renal disease progression (e.g. cardiometabolic syndrome tension)
- Close followup and aggressive treatment of common comorbidities is essential
- Treatment options in HFpEF and CKD are currently limited

Brief Discussion of the Case

This case illustrates a common presentation for volume overload in a patient with HFpEF. Multiple comorbidities are present, including obesity, diabetes, hypertension, and chronic renal insufficiency which all contribute to a cardiometabolic profile common to HFpEF. The consequent systemic inflammation, oxidative stress, and endothelial dysfunction affect the cardiovascular system to produce myocardial and vascular stiffness as well as cardiac fibrosis; other organ systems are similarly affected.

In the case of the kidney, progression of the renal insufficiency is typical leading to inability of the kidney to maintain salt and water homeostasis. Salt and water avidity may be further stimulated by dynamic and heterogeneous degrees of neurohormonal activation. In obese patients (due to the limitations of the physical exam), unrecognized vascular distension may also lead to further vascular dysfunction.

Epidemiology of HFpEF and CKD

Chronic kidney disease and HFpEF are common and increasing. The worldwide prevalence of CKD is 8–16% (generally defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/m^2) [1]. CKD is also a well-known independent cardiovascular risk factor [2, 3] and even mild to moderate decreases in eGFR translate into worse cardiovascular outcomes [3–6]. CKD acts as a risk multiplier, accelerating the development of cardiovascular disease and increasing the cardiovascular mortality 10–20 times compared to age- and gender-matched controls [2–6]. Cardiovascular disease accounts for 50% of deaths in CKD patients [7–10]. Furthermore, CKD patients on renal replacement therapies are more likely to die from cardiovascular causes than from renal failure itself [7–10].

The prevalence of HFpEF has also increased over the past few decades and now accounts for 54% of all patients with clinical heart failure [11, 12]. Importantly, the coexistence of CKD and HFpEF is very common, with numerous studies suggesting that more than half of HFpEF patients have CKD [4, 5, 13–17]. Furthermore, studies have shown that up to 40% and 17% of HFpEF patients show worsening of renal function (WRF) during hospitalization and after 1 year of follow-up, respectively [4, 14,

15]. Several underlying risk factors have been postulated for this predisposition. Patients with HFpEF are typically older and frequently have hypertension and diabetes [11]. As a result, they may have significant pre-existing intrinsic renal disease and hence are at higher risk for progression of renal disease. Moreover, renal dysfunction in HFpEF may also be a marker of more advanced systemic vascular disease or a reflection of metabolic syndrome.

Comorbidities are common to CKD and HFpEF and 30% of patients with HFpEF die of non-cardiac causes, as compared with 17% of patients with heart failure with reduced ejection fraction (HFrEF) [18–20]. This is likely a reflection of the comorbidity burden on mortality rates. It has long been recognized that heart failure and renal dysfunction are a lethal combination; this amplification of mortality in heart failure by CKD may be more pronounced in HFpEF relative to HFrEF [21, 22]. Several studies have shown a deleterious impact of decreased baseline eGFR on the in-hospital and long-term mortality in HFpEF [13, 16–18, 22]. A meta-analysis of 16 studies has revealed an annual mortality of 42% among HFpEF patients with any degree of renal impairment [22]. Rasinaru, et al. in a prospective study revealed that renal impairment at the time of admission for HFpEF was associated with a significant increase in the adjusted risk of 7-year mortality (35% for all-cause death and 42% for death from cardiovascular causes). Additionally, HFpEF patients with impaired baseline renal function who developed WRF during the hospitalization had an extremely high 7-year mortality risk. In contrast, the occurrence of WRF from admission to discharge did not appear to increase the long-term mortality risk in HFpEF patients with normal baseline renal function [17].

Pathophysiology of Renal Impairment in HFpEF

Which condition, CKD or HFpEF, comes first is unclear. Some observational reports imply that renal impairment is the pathogenic process leading to HFpEF, as some degree of renal dysfunction has preceded the development of HFpEF in these studies. Data from the Prevention of Renal and Vascular End-stage Disease (PREVEND) trial and Atherosclerosis Risk in Communities (ARIC) study noted that the presence of renal impairment doubled the risk of new-onset HFpEF [23–26]. Other observations have suggested that CKD is independently associated with findings common in HFpEF, such as greater left ventricular (LV) mass and impaired cardiac mechanics (more impaired diastolic relaxation, worse left atrial strain, LV longitudinal strain, and RV free wall strain) [27–29]. However, HFpEF and its associated comorbidities may, themselves, lead to CKD through changes to glomerular or tubular function.

Perhaps most likely is a simultaneous insult to both organs from the inflammatory, oxidant, and metabolic insults of multiple comorbidities, e.g. metabolic syndrome. In this paradigm, the impact of these insults on the heart or kidneys relative to one another would likely be variable in any given patient. It should be appreciated that the vascular tree as an organ would also be a casualty of such a hostile milieu and the subsequent vascular dysfunction would be anticipated to exacerbate the injury to both organs through abnormal vascular coupling and endothelial dysfunction.

Regardless of the order of the insults, the interplay between CKD and HFpEF is almost certainly bidirectional and results in a vicious cycle, often referred to as the cardiorenal syndrome (CRS) [30–32]. Mechanistic studies have revealed that injury to kidneys or the myocardium results in adaptive responses that may influence the other organ and exacerbate disease progression [33]. Some authors have suggested that it may be more appropriate to acknowledge the primacy of the renal dysfunction (e.g. renocardiac syndrome), which would refer to development of cardiac failure and cardiac complications in patients with CKD [33].

The cardiorenal axis is mediated by several mechanisms including hemodynamic, neurohumoral, oxidant, inflammatory and metabolic factors (Fig. 7.1 and Table 7.1) [30]. A central hemodynamic finding in HFpEF and CKD is water and sodium retention resulting in cardiac and renal congestion; in some, but not all, impaired organ perfusion can also be found. Renal inability to maintain sodium and fluid balance seem to be a proximal event contributing to the development of HFpEF [34]. Sodium and volume overload ultimately lead to renal and cardiovascular dysfunction in a vicious cycle, likely mediated by vascular distension and consequent endothelial dysfunction. For example, a high-salt diet intake in animal models results in hypertension, LV hypertrophy, and cardiac fibrosis, as well as proteinuria, glomerulosclerosis, and renal inflammation. Renal impairment also predisposes to salt-sensitive hypertension, which is common in the elderly with HFpEF [35].

Neurohumoral mechanisms drive salt and water avidity in HFrEF and consist of activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic

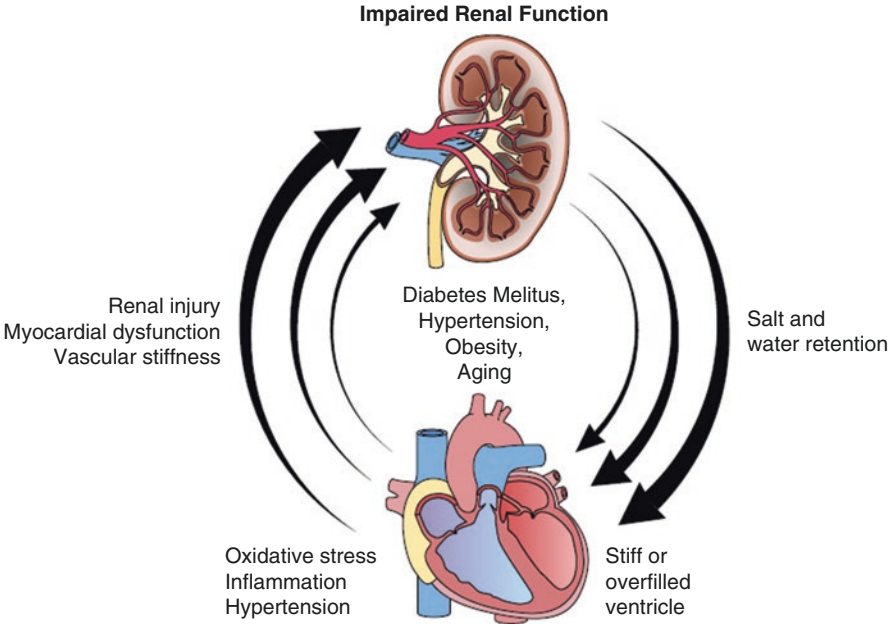

Fig. 7.1 Mechanisms of impaired renal function in heart failure with preserved ejection fraction

Table 7.1 Pathophysiologic mechanisms of cardiorenal interactions

Traditional cardiovascular risk factors	Smoking Obesity Hypertension Diabetes Dyslipidaemia
Neurohumoral factors	Sympathetic nervous system Renin-angiotensin-aldosterone system
Inflammation-mediated pathways	Endothelial dysfunction Immune-mediated damage Oxidative stress Coagulation imbalance
Hemodynamic factors	Ventriculo-arterial uncoupling Elevated central venous pressure Sodium and water retention Hypertension
Other factors	Natriuretic peptides Anemia Uremic solute retention Calcium and phosphate abnormality Electrolyte and acid-base imbalances

nervous system (SNS) [36, 37]. Although both systems are presumed to be operational in HFpEF, there is only modest evidence to support this hypothesis [22, 38].

Chronic inflammation plays an especially important role in CKD and likely leads to the promotion and progression of HFpEF. Many factors contribute to the induction and maintenance of chronic inflammation in CKD, such as SNS activation, oxidative stress, venous congestion, uremic toxins, obesity, and diabetes, as well as nutritional, environmental and genetic factors. Increased inflammation and oxidative stress lead to fibrosis and remodeling in both organs, as well as endothelial dysfunction [36, 37]. High levels of reactive oxygen species (ROS) induce several molecules, such as transforming growth factor (TGF)-β, nuclear factor (NF)-kB and galectin-3, which are involved in inflammation and interstitial fibrosis though upregulation and proliferation of fibroblasts and production of procollagen [36, 37]. Many other conditions common to the patient with CKD, such as Anemia, metabolic changes, hyperphosphatemia, insulin resistance, hyper-homocysteinemia and dyslipidemia may also play important roles in myocardial dysfunction characteristic of HFpEF [3, 30, 35, 39].

Comorbidities in HFpEF and CKD

The term "cardio-metabolic syndrome" describes the clustering of several cardiovascular and renal risk factors, including type 2 diabetes, central obesity, hypertension, and dyslipidemia. Approximately 34% of the adult US population have cardio-metabolic syndrome, which significantly increases the risk for both HFpEF and CKD [40].

The prevalence of diastolic dysfunction in the patients with cardio-metabolic syndrome is reported to be significantly higher compared with the general population [41, 42]. However, the progressive transition into clinical HFpEF remains to be fully studied. Cardiac insulin resistance and impaired insulin signaling are the main molecular mechanisms leading to diastolic dysfunction and clinical HFpEF in patients with CMS [43]. In the early stage, altered substrate use, endothelium-related dysregulation of myocardial perfusion and impaired calcium handling leads to decreased myocardial ATP generation; the consequent repetitive intermittent energy supply and demand mismatch results in diastolic dysfunction. The progression to remodeling processes include myocellular hypertrophy, altered titin, collagen and fibrosis metabolism, accumulation of triglycerides, and advanced glycemic end-products. The subsequent activation of the RAAS and SNS leads to further myocardial cell damage, contractile dysfunction and clinical HFpEF [44, 45].

Numerous studies have also confirmed CMS as an independent risk factor for the development of CKD. Multiple abnormalities that can lead to kidney injury have been identified in CMS patients including insulin resistance, compensatory hyperinsulinemia, inappropriate activation of the RAAS and increased oxidative stress, endoplasmic reticulum stress, coagulability, and impaired fibrinolysis. The combined effects of these conditions in the kidney lead to pressure natriuresis, glomerular hypertension, endothelial dysfunction, and vasoconstriction, as well as matrix proliferation and expansion, which culminate in clinical CKD [46].

Diabetes

Diabetes is a leading cause of CKD and end-stage renal disease; about 50% of patients with diabetes will develop CKD [47, 48]. The prevalence of heart failure in patients with diabetes is high (27–50%) and mostly of the HFpEF phenotype [49, 50]. The rising prevalence of diabetes in young individuals and increasing longevity characterize the changes in the epidemiology of CKD and HFpEF in the United States and worldwide [51].

Diabetes has been shown to be an independent predictor of adverse outcomes in HFpEF patients. Analyses of the Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial showed that HFpEF patients with diabetes had more signs of congestion, worse quality of life, and a higher risk of cardiovascular mortality and hospitalization [52]. Similarly, in the Candesartan in Heart failure – Assessment of mortality and Morbidity (CHARM) study, diabetes was associated with an adjusted two-fold increase in cardiovascular death or hospitalization for heart failure and a 80% increase in the hazard of all-cause mortality [53]. The Digital Intervention Group (DIG) trial enrolled patients with a left ventricular ejection fraction >45% and showed that patients with diabetes had an adjusted hazard of 1.68 for heart failure death or hospitalization [54]. An ancillary study of the Phosphodiesterase-5 Inhibition to Improve Clinical Status and

Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX) trial showed that apart from a worse clinical presentation, more frequent hospitalizations and less exercise capacity, HFpEF patients with diabetes had more LV hypertrophy and greater LV stiffness [55].

Evidence indicates that the cardio-renal interaction is aggravated by diabetes and this combination is sometimes referred as a "triple threat" [56]. Recently, an analysis of the National Health and Nutrition Examination Survey (NHANES) data revealed that the prevalence of primary renal failure that progressively leads to cardiac dysfunction was significantly higher among individuals with diabetes as compared to those without diabetes after controlling for medical and demographic risk factors [56]. Furthermore, studies have shown the presence of diabetes as an independent risk factor for WRF among HFpEF patients during hospitalization and after 1 year follow up period [13].

Anemia

Anemia is more frequent in HFpEF patients than in HFrEF patients [57–60] and is a common complication of CKD. In the Get with The Guidelines Registry, there was an association between higher ejection fraction and increased prevalence of Anemia [60]. These findings were confirmed in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (*OPTIMIZE-HF*) registry and CHARM studies [61, 62]. Several studies have shown Anemia as an independent predictor of mortality in HFpEF [18, 63–65]. Persistent Anemia has also been associated with ventricular hypertrophy and myocyte dysfunction, as well as activation of the RAAS, renal vasoconstriction and diminished eGFR [64–66]. Recently, a post-hoc analysis of the Treatment Of Preserved Cardiac function heart failure with an *Aldosterone* Antagonist (*TOPCAT*) study revealed Anemia as an independent predictor of hyperkalemia among HFpEF patients that received spironolactone [67]. The combination of HFpEF, CKD, Anemia, and/or iron deficiency is associated with the progression of CKD and HFpEF and an unfavorable prognosis [3, 68, 69]. Analysis of a large Medicare database did note that the relative risk of death at 2 years was increased by a factor of 1.6 in anemic patients with HFpEF who also had CKD [70].

Several studies have shown CKD as one of the strongest predictors of Anemia in HFpEF patients [64, 71–73]. Inadequate production of erythropoietin has been suggested as one of the main mechanisms of Anemia in the patients with HFpEF with concomitant CKD [73, 74]. Also, 50–70% of HFpEF patients have iron deficiency, which is exacerbated by CKD [9, 66, 72, 75, 76]. Chronic inflammation in HFpEF and CKD may also lead to functional iron deficiency, erythropoietin resistance and bone marrow unresponsiveness to erythropoietin due to intrinsic bone marrow defects [77–79]. Low vitamin D levels are common in CKD patients, and associated with the development of myocardial dysfunction, heart failure, and sudden cardiac death [80–83].

Heart Failure Assessment in a Patient with CKD

Interpretation of various cardiovascular biomarkers in the presence of CKD is complicated by the near ubiquitous presence of concomitant cardiovascular disease. However, heart failure biomarkers such as B-type natriuretic peptide (BNP), N-terminal of the prohormone of BNP (NT-proBNP) and troponin T (TnT) appear to have good predictive value for cardiovascular outcomes in patients with CKD [84–86]. Elevated TnT and NT-proBNP levels correlate with hypervolemia and identify a subgroup of asymptomatic CKD patients with increased cardiovascular mortality [84, 87–90]. A detailed baseline echocardiographic assessment with focus on parameters of diastolic dysfunction should therefore be obtained.

Renal tubular biomarkers are available primarily for research purposes, and have not been generally incorporated into clinical practice. Urinary N-acetyl glucosaminidase (NAG), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) may reflect tubular injury that may not be apparent from assessments of blood urea nitrogen (BUN), eGFR, or sodium excretion. NGAL seems to play an important role in limiting oxidative damage in acute kidney injury and CKD, and it represents the earliest kidney biomarker of ischemic damage. KIM-1 is a transmembrane glycoprotein, normally undetected in urinary samples, that can be found in the urine after an ischemic or nephrotoxic insult to proximal tubular cells; urinary KIM-1 levels seem to be highly specific for acute tubular necrosis. Such biomarkers may have diagnostic and prognostic value for cardiovascular outcomes in CKD patients [91, 92].

Treatment Options in HFpEF and CKD

Medical management of patients with concomitant cardiac and renal dysfunction remains challenging as there are no consensus approaches to the management of HFpEF or the cardiorenal syndrome (Table 7.2).

Preventative Measures

Primary prevention cannot be overemphasized for both renal and cardiac disease as they share common risk factors. Aggressive and early treatment of comorbidities, such as hypertension, diabetes, and lipids with lifestyle changes and pharmacologic therapies form the cornerstone of prevention. Although there is evidence that inhibition of a stimulated RAAS by angiotensin II receptor blockers (ARB) in CKD patients has cardioprotective effects, the specific impact of such agents on preventing HFpEF in CKD is not clear [93–96].

Clinical trial evidence suggests that drugs that impact sodium excretion reduce incident HFpEF among CKD patents. In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the diuretic chlorthalidone, was associated with less incident HFpEF over time in comparison with lisinopril,

Table 7.2 Management of heart failure patients with preserved ejection fraction and chronic kidney disease

Initial assessment	Collaborative relationship between cardiologist and nephrologist A detailed patient history and physical examination Baseline electrocardiogram and echocardiogram Renal ultrasound Urinalysis Consider renal biomarkers
Preventive measures	Blood pressure, cholesterol and glucose management Physical activity Smoking cessation
Treatment options	Diuretics to achieve euvolemia in patients with volume overload Strong consideration to mineralocorticoid receptor antagonists Consider sacubitril/valsartan Consider pulmonary artery pressure–guided management Statins according to current guidelines Comorbidity management

amlodipine, or doxazosin [97]. It also is notable that spironolactone, a diuretic, lowered the risk of the secondary end-point of heart failure hospitalizations (predominantly attributable to volume overload) in the landmark HFpEF trial, TOPCAT [98].

Dyslipidemia represents another fundamental target to achieve in managing cardiovascular complications in CKD patients. The Study of Heart and Renal Protection (SHARP) represents the largest study of statin therapy in CKD patients and has demonstrated a significant benefit of the combination simvastatin/ezetimibe on major atherosclerotic events, although all-cause mortality was unaffected [99].

Treatment of the complications of CKD may also impact on the development of heart failure, although data for HFpEF in particular are not clear. Cinacalcet is a calcimimetic that is used to treat hypercalcemia and hyperparathyroidism. In the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, a reduction in the number of first heart failure episodes was reported in the cinacalcet group [103]. Hyperphosphatemia, through FGF-23, may also be operational in predisposing CKD patients to heart failure. Di Lullo et al. found that treating pre-dialysis patients with sevelamer hydrochloride, a calcium-free phosphate binder, reduced cardiac valve calcifications and attenuated the decline in kidney function [104]. Gut-derived uremic toxins, such as indoxyl sulphate, a metabolite of dietary tryptophan, may also contribute to vascular stiffness in heart failure; oral charcoal has been used to decrease indoxyl sulphate levels and decrease cardiovascular complications in animal models.

Treatment of the cardiometabolic syndrome may be instrumental in preventing the consequences (e.g. HFpEF) of diabetes, CKD, and obesity. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (*EMPA-REG OUTCOME*) and *Canagliflozin* Cardiovascular Assessment Study (CANVAS) have revealed a marked reduction in deaths from cardiovascular causes, heart failure hospitalizations, and deaths from any cause when empagliflozin and canagliflozin, respectively, were added to the standard care of patients with diabetes [105, 106]. Similar findings were observed in Comparative Effectiveness of Cardiovascular

Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) study [107]. Multiple planned and ongoing trials are testing the hypothesis that this class of diabetes agents can be used to treat patients with established HFpEF or HFrEF.

Treatment Options in the Patients with Cardiorenal Syndrome

Treatment of Volume Overload

For the patients presenting with volume overload and not requiring dialysis, diuretics should be used for relief of symptoms. The dose should be adjusted according to the patient's body weight, symptoms, and electrolyte status. Intermittent use of a thiazide-like diuretic such as metolazone, administered before the dose of a loop diuretic, may be helpful in outpatients with volume overload that is refractory to higher doses of loop diuretics. A careful monitoring is required because of the risk of hypokalaemia, hyponatremia, and WRF. Persistent diuretic resistance may result from impaired diuretic absorption, necessitating intravenous administration of loop diuretics. In the light of the TOPCAT trial, strong consideration should be given to mineralocorticoid receptor antagonists if the eGFR and serum potassium levels are acceptable (e.g. serum creatinine <2.5 mg/dL and serum potassium level <5.0 mmol/L). In cases of diuretic-refractory volume overload, dialysis may be required for relief of patient symptoms. Lowering of extremely elevated central venous pressures (e.g., >15 mmHg) with direct volume removal may in fact improve renal function to the point that dialysis can be discontinued in favor of traditional diuretic management.

Treatment of Hypertension

Hypertension may exacerbate heart failure and predispose patients to other adverse outcomes. The 2017 Joint National Committee recommend target blood pressures of less than 130/80 mmHg in persons with CKD. In those with stage 3 or higher CKD or stage 1 or 2 CKD with albuminuria (>300 mg/day), treatment with an angiotensin-converting enzyme inhibitor is reasonable to slow progression of kidney disease. An angiotensin receptor blocker is reasonable if an angiotensin-converting enzyme inhibitor is not tolerated [108]. The choice of additional agents to achieve blood pressure control should be guided by the presence of coexisting conditions, the patient's ability to receive the agent without adverse effects, and the effect of the agent on blood pressure.

Treatment of Comorbidities

Patients should be treated with statins according to the usual criteria. Patients with coronary artery disease should receive medical therapies according to current

guidelines. Atrial fibrillation should be managed according to current guidelines, which recommend rate control and anticoagulation initially; a trial of rhythm control should be considered if symptoms persist despite adequate rate control [109]. Parenteral iron therapy in iron-deficient HFpEF patients improves symptoms, exercise tolerance, quality of life and reduces readmissions [110]. Observational studies, including a propensity-score–matched analysis and a large meta-analysis have shown lower mortality among patients with HFpEF who have received statins [100–102].

Pulmonary Artery Pressure-Guided Management

In a subgroup analysis from the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial, pulmonary artery pressure–guided management in patients with heart failure showed to reduce hospitalizations for both HFrEF and HFpEF. However, the effect of remote monitoring strategies in the patients with CKD and HFpEF needs to be further explored [111].

Targeting Natriuresis in HFpEF

Modulation of the natriuretic peptide system in patients with HFpEF is appealing. The natriuretic peptide activity appears to be relevant in both HFpEF and HFrEF; elevated BNP levels predict adverse clinical outcomes in both groups of patients [112]. In addition, data suggests that the natriuretic peptide system may also modulate cardiomyocyte stiffness and resting passive tension [113].

Neprilysin Inhibition

Neprilysin is responsible for the breakdown of multiple endogenous vasoactive peptides including bradykinin, natriuretic peptides, and adrenomedullin. The Prospective comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection fraction (PARAMOUNT) study provides phase 2 clinical trial data for the use of sacubitril/valsartan in HFpEF patients. The sacubitril/valsartan group demonstrated a greater decline in NT-proBNP levels, greater improvement in left atrial volumes, no increase in clinical adverse events, and lower levels of high-sensitivity troponin. Furthermore, treatment with sacubitril/valsartan as compared to valsartan resulted in significantly less decline in eGFR and fewer episodes of elevated creatinine or serum potassium [114–116]. In aggregate, these data suggest that ARNIs could potentially slow the progression of CKD, lower NT-proBNP and decrease left atrial volume in HFpEF. The Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) trial is the subsequent ongoing phase 3 trial of sacubitril/valsartan use in HFpEF. It is

aimed to compare the rate of cardiovascular death and heart failure hospitalizations among subjects with New York Heart Association functional class II–IV HFpEF with an ejection fraction ≥45% who are treated with sacubitril/valsartan versus valsartan.

Sodium-Glucose Transporter-2 Inhibitors

The role of sodium-glucose transporter-2 (SGLT-2) inhibitors is also being explored in a number of HFpEF trials, which include patients with and without diabetes. Dapagliflozin in Type 2 Diabetes or Pre-diabetes, and Preserved Ejection Fraction Heart Failure (PRESERVED-HF) is assessing the role of dapagliflozin in lowering NT-proBNP levels in HFpEF without diabetes and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER-HF) is testing the hypothesis that dapagliflozin will lower clinically relevant outcomes and is powered for cardiovascular mortality and heart failure hospitalizations as a primary end-point.

Treatment Pearls for the Case Vignette

The cornerstone of management is the prevention of insidious salt and water overload, e.g. avoidance of TZDs, NSAIDs, and other agents that may stimulate volume overload. Ambulatory hemodynamic monitoring (e.g. CARDIOMEMS) may also be useful in this regard. The use of SGLT2i should also be considered in light of their known natriuretic effects, ability to slow renal insufficiency, and the observed reduction in HF events in randomized trials. Spironolactone has also been associated with a reduction in HF hospitalizations, which may reflect its pleiotropic cardiovascular effects as well as its diuretic action. Weight loss, exercise, and dietary management should be addressed as well.

References

1. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63:713–35.
2. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–81.
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
4. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004;43:61–7.
5. Smith GL, Lichtman JH, Bracken MB, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol. 2006;47:1987–96.

6. Garg AX, Clark WF, Haynes RB, House AA. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. Kidney Int. 2002;61:1486–94.
7. Sarnak MJ. Cardiovascular complications in chronic kidney disease. Am J Kidney Dis. 2003;41:11–7.
8. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154–69.
9. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. Circulation. 2007;116:85–97.
10. Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006;17:2034–47.
11. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med. 2016;375:1868–77.
12. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol. 2004;43:317–27.
13. Casado J, Montero M, Formiga F, et al. Clinical characteristics and prognostic influence of renal dysfunction in heart failure patients with preserved ejection fraction. Eur J Intern Med. 2013;24:677–83.
14. Klein L, Massie BM, Leimberger JD, et al. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). Circ Heart Fail. 2008;1:25–33.
15. Krumholz HM, Chen YT, Vaccarino V, et al. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. Am J Cardiol. 2000;85:1110–3.
16. McAlister FA, Ezekowitz J, Tarantini L, et al. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. Circ Heart Fail. 2012;5:309–14.
17. Rusinaru D, Buiciuc O, Houpe D, Tribouilloy C. Renal function and long-term survival after hospital discharge in heart failure with preserved ejection fraction. Int J Cardiol. 2011;147:278–82.
18. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol. 2012;59:998–1005.
19. Curtis JP, Sokol SI, Wang Y, et al. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol. 2003;42:736–42.
20. Lee DS, Gona P, Albano I, et al. A systematic assessment of causes of death after heart failure onset in the community: impact of age at death, time period, and left ventricular systolic dysfunction. Circ Heart Fail. 2011;4:36–43.
21. Ahmed A, Young JB, Love TE, Levesque R, Pitt B. A propensity-matched study of the effects of chronic diuretic therapy on mortality and hospitalization in older adults with heart failure. Int J Cardiol. 2008;125:246–53.
22. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35:455–69.
23. Agarwal SK, Chambless LE, Ballantyne CM, et al. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. Circ Heart Fail. 2012;5:422–9.
24. Smink PA, Lambers Heerspink HJ, Gansevoort RT, et al. Albuminuria, estimated GFR, traditional risk factors, and incident cardiovascular disease: the PREVEND (Prevention of Renal and Vascular Endstage Disease) study. Am J Kidney Dis. 2012;60:804–11.
25. Kottgen A, Russell SD, Loehr LR, et al. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. J Am Soc Nephrol. 2007;18:1307–15.

26. Brouwers FP, de Boer RA, van der Harst P, et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. Eur Heart J. 2013;34:1424–31.
27. Fink HA, Ishani A, Taylor BC, et al. Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: a systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline. Ann Intern Med. 2012;156:570–81.
28. Kim MK, Kim B, Lee JY, et al. Tissue Doppler-derived E/e' ratio as a parameter for assessing diastolic heart failure and as a predictor of mortality in patients with chronic kidney disease. Korean J Intern Med. 2013;28:35–44.
29. Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. Am J Kidney Dis. 1996;27:347–54.
30. Shiba N, Shimokawa H. Chronic kidney disease and heart failure – Bidirectional close link and common therapeutic goal. J Cardiol. 2011;57:8–17.
31. Ronco C. The cardiorenal syndrome: basis and common ground for a multidisciplinary patient-oriented therapy. Cardiorenal Med. 2011;1:3–4.
32. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. Intensive Care Med. 2008;34:957–62.
33. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52:1527–39.
34. Hung SC, Lai YS, Kuo KL, Tarng DC. Volume overload and adverse outcomes in chronic kidney disease: clinical observational and animal studies. J Am Heart Assoc. 2015;4.
35. Hall JE. Renal dysfunction, rather than nonrenal vascular dysfunction, mediates salt-induced hypertension. Circulation. 2016;133:894–906.
36. Fu Q, Cao L, Li H, Wang B, Li Z. Cardiorenal syndrome: pathophysiological mechanism, preclinical models, novel contributors and potential therapies. Chin Med J. 2014;127:3011–8.
37. Jonsson S, Agic MB, Narfstrom F, Melville JM, Hultstrom M. Renal neurohormonal regulation in heart failure decompensation. Am J Physiol Regul Integr Comp Physiol. 2014;307:R493–7.
38. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA. 2002;288:2144–50.
39. Collins AJ. Cardiovascular mortality in end-stage renal disease. Am J Med Sci. 2003;325:163–7.
40. Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med. 2004;140:167–74.
41. von Bibra H, Paulus WJ, St John Sutton M, Leclerque C, Schuster T, Schumm-Draeger PM. Quantification of diastolic dysfunction via the age dependence of diastolic function – impact of insulin resistance with and without type 2 diabetes. Int J Cardiol. 2015;182:368–74.
42. Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. J Am Coll Cardiol. 2014;63:407–16.
43. Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. J Am Coll Cardiol. 2008;51:93–102.
44. Fontes-Carvalho R, Ladeiras-Lopes R, Bettencourt P, Leite-Moreira A, Azevedo A. Diastolic dysfunction in the diabetic continuum: association with insulin resistance, metabolic syndrome and type 2 diabetes. Cardiovasc Diabetol. 2015;14:4.
45. Phan TT, Abozguia K, Nallur Shivu G, et al. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. J Am Coll Cardiol. 2009;54:402–9.
46. El-Atat FA, Stas SN, McFarlane SI, Sowers JR. The relationship between hyperinsulinemia, hypertension and progressive renal disease. J Am Soc Nephrol. 2004;15:2816–27.
47. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet. 2012;380:1662–73.

48. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med. 1999;341:1127–33.
49. Boonman-de Winter LJ, Rutten FH, Cramer MJ, et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. Diabetologia. 2012;55:2154–62.
50. Roberts AW, Clark AL, Witte KK. Review article: left ventricular dysfunction and heart failure in metabolic syndrome and diabetes without overt coronary artery disease – do we need to screen our patients? Diab Vasc Dis Res. 2009;6:153–63.
51. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol. 2016;12:73–81.
52. Kristensen SL, Mogensen UM, Jhund PS, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve trial (Irbesartan in heart failure with preserved ejection fraction). Circulation. 2017;135:724–35.
53. MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J. 2008;29:1377–85.
54. Aguilar D, Deswal A, Ramasubbu K, Mann DL, Bozkurt B. Comparison of patients with heart failure and preserved left ventricular ejection fraction among those with versus without diabetes mellitus. Am J Cardiol. 2010;105:373–7.
55. Lindman BR, Davila-Roman VG, Mann DL, et al. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. J Am Coll Cardiol. 2014;64:541–9.
56. Banerjee S, Panas R. Diabetes and cardiorenal syndrome: understanding the "Triple Threat". Hell J Cardiol. 2017;58:342–7.
57. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251–9.
58. Yancy CW, Lopatin M, Stevenson LW, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol. 2006;47:76–84.
59. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50:768–77.
60. Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012;126:65–75.
61. Young JB, Abraham WT, Albert NM, et al. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). Am J Cardiol. 2008;101:223–30.
62. O'Meara E, Clayton T, McEntegart MB, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation. 2006;113:986–94.
63. Felker GM, Shaw LK, Stough WG, O'Connor CM. Anemia in patients with heart failure and preserved systolic function. Am Heart J. 2006;151:457–62.
64. Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004;110:149–54.
65. Anand IS, Chandrashekhar Y, Wander GS, Chawla LS. Endothelium-derived relaxing factor is important in mediating the high output state in chronic severe anemia. J Am Coll Cardiol. 1995;25:1402–7.
66. Scrutinio D, Passantino A, Santoro D, Catanzaro R. The cardiorenal Anemia syndrome in systolic heart failure: prevalence, clinical correlates, and long-term survival. Eur J Heart Fail. 2011;13:61–7.

67. Desai AS, Liu J, Pfeffer MA, et al. Incident hyperkalemia, hypokalemia, and clinical outcomes during spironolactone treatment of heart failure with preserved ejection fraction: analysis of the TOPCAT trial. J Card Fail. 2018;24:313–20.
68. Go AS, Yang J, Ackerson LM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation. 2006;113:2713–23.
69. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;38:955–62.
70. Herzog CA, Muster HA, Li S, Collins AJ. Impact of congestive heart failure, chronic kidney disease, and anemia on survival in the Medicare population. J Card Fail. 2004;10:467–72.
71. Anand IS, Kuskowski MA, Rector TS, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation. 2005;112:1121–7.
72. von Haehling S, van Veldhuisen DJ, Roughton M, et al. Anemia among patients with heart failure and preserved or reduced ejection fraction: results from the SENIORS study. Eur J Heart Fail. 2011;13:656–63.
73. Westenbrink BD, Visser FW, Voors AA, et al. Anemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. Eur Heart J. 2007;28:166–71.
74. Jensen JD, Eiskjaer H, Bagger JP, Pedersen EB. Elevated level of erythropoietin in congestive heart failure relationship to renal perfusion and plasma renin. J Intern Med. 1993;233:125–30.
75. Nanas JN, Matsouka C, Karageorgopoulos D, et al. Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol. 2006;48:2485–9.
76. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol. 2000;35:1737–44.
77. Westenbrink BD, Voors AA, de Boer RA, et al. Bone marrow dysfunction in chronic heart failure patients. Eur J Heart Fail. 2010;12:676–84.
78. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005;352:1011–23.
79. Thomas C, Thomas L. Anemia of chronic disease: pathophysiology and laboratory diagnosis. Lab Hematol. 2005;11:14–23.
80. Drechsler C, Pilz S, Obermayer-Pietsch B, et al. Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. Eur Heart J. 2010;31:2253–61.
81. Mehrotra R, Kermah DA, Salusky IB, et al. Chronic kidney disease, hypovitaminosis D, and mortality in the United States. Kidney Int. 2009;76:977–83.
82. Ravani P, Malberti F, Tripepi G, et al. Vitamin D levels and patient outcome in chronic kidney disease. Kidney Int. 2009;75:88–95.
83. Wang AY, Lam CW, Sanderson JE, et al. Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. Am J Clin Nutr. 2008;87:1631–8.
84. Satyan S, Light RP, Agarwal R. Relationships of N-terminal pro-B-natriuretic peptide and cardiac troponin T to left ventricular mass and function and mortality in asymptomatic hemodialysis patients. Am J Kidney Dis. 2007;50:1009–19.
85. Voroneanu L, Siriopol D, Nistor I, et al. Superior predictive value for NTproBNP compared with high sensitivity cTnT in dialysis patients: a pilot prospective observational study. Kidney Blood Press Res. 2014;39:636–47.
86. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol. 2007;50:2357–68.
87. DeFilippi CR, Fink JC, Nass CM, Chen H, Christenson R. N-terminal pro-B-type natriuretic peptide for predicting coronary disease and left ventricular hypertrophy in asymptomatic CKD not requiring dialysis. Am J Kidney Dis. 2005;46:35–44.

88. Wang AY, Lam CW, Yu CM, et al. N-terminal pro-brain natriuretic peptide: an independent risk predictor of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic peritoneal dialysis patients. J Am Soc Nephrol. 2007;18:321–30.
89. Dierkes J, Domrose U, Westphal S, et al. Cardiac troponin T predicts mortality in patients with end-stage renal disease. Circulation. 2000;102:1964–9.
90. Mallamaci F, Zoccali C, Parlongo S, et al. Troponin is related to left ventricular mass and predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis. 2002;40:68–75.
91. Yndestad A, Landro L, Ueland T, et al. Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. Eur Heart J. 2009;30:1229–36.
92. Zografos T, Haliassos A, Korovesis S, Giazitzoglou E, Voridis E, Katritsis D. Association of neutrophil gelatinase-associated lipocalin with the severity of coronary artery disease. Am J Cardiol. 2009;104:917–20.
93. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–9.
94. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851–60.
95. Lesogor A, Cohn JN, Latini R, et al. Interaction between baseline and early worsening of renal function and efficacy of renin-angiotensin-aldosterone system blockade in patients with heart failure: insights from the Val-HeFT study. Eur J Heart Fail. 2013;15:1236–44.
96. Schmieder RE, Delles C, Mimran A, Fauvel JP, Ruilope LM. Impact of telmisartan versus ramipril on renal endothelial function in patients with hypertension and type 2 diabetes. Diabetes Care. 2007;30:1351–6.
97. Davis BR, Kostis JB, Simpson LM, et al. Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Circulation. 2008;118:2259–67.
98. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383–92.
99. Haynes R, Lewis D, Emberson J, et al. Effects of lowering LDL cholesterol on progression of kidney disease. J Am Soc Nephrol. 2014;25:1825–33.
100. Alehagen U, Benson L, Edner M, Dahlstrom U, Lund LH. Association between use of statins and mortality in patients with heart failure and ejection fraction of >/=50. Circ Heart Fail. 2015;8:862–70.
101. Fukuta H, Goto T, Wakami K, Ohte N. The effect of statins on mortality in heart failure with preserved ejection fraction: a meta-analysis of propensity score analyses. Int J Cardiol. 2016;214:301–6.
102. Liu G, Zheng XX, Xu YL, Ru J, Hui RT, Huang XH. Meta-analysis of the effect of statins on mortality in patients with preserved ejection fraction. Am J Cardiol. 2014;113:1198–204.
103. Investigators ET, Chertow GM, Block GA, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012;367:2482–94.
104. Di Lullo L, Floccari F, Santoboni A, et al. Progression of cardiac valve calcification and decline of renal function in CKD patients. J Nephrol. 2013;26:739–44.
105. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.
106. Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:2099.
107. Kosiborod M, Lam CSP, Kohsaka S, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. J Am Coll Cardiol. 2018;71:2628–39.
108. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and

management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017.
109. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014;130:e199–267.
110. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361:2436–48.
111. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011;377:658–66.
112. Grewal J, McKelvie RS, Persson H, et al. Usefulness of N-terminal pro-brain natriuretic Peptide and brain natriuretic peptide to predict cardiovascular outcomes in patients with heart failure and preserved left ventricular ejection fraction. Am J Cardiol. 2008;102:733–7.
113. van Heerebeek L, Hamdani N, Falcao-Pires I, et al. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. Circulation. 2012;126:830–9.
114. Jhund PS, Claggett B, Packer M, et al. Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial. Eur J Heart Fail. 2014;16:671–7.
115. Jhund PS, Claggett BL, Voors AA, et al. Elevation in high-sensitivity troponin T in heart failure and preserved ejection fraction and influence of treatment with the angiotensin receptor neprilysin inhibitor LCZ696. Circ Heart Fail. 2014;7:953–9.
116. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380:1387–95.

Heart Failure in a Patient with End-Stage Kidney Disease on Renal Replacement Therapy

8

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Case Vignette

Mrs. X is a 76 year-old lady with type 2 diabetes, diabetic retinopathy, and nephropathy that has progressed to end-stage renal disease (ESRD) for which she has been in chronic ambulatory hemodialysis for 14 years. Over the last month, she suffered from persistent volume overload with progressive dyspnea with New York Heart Association functional class III. She has been experiencing frequent episodes of intradialytic hypotension (IDH) during her regular dialysis sessions that required holding dialysis and reducing blood pressure lowering medications like amlodipine. An echocardiography demonstrates diastolic dysfunction and high normal left ventricular end-diastolic dimensions with moderate left ventricular hypertrophy and a preserved left ventricular ejection fraction (LVEF) of 64%. Mitral inflow shows restrictive filling and moderate-to-severe pulmonary hypertension (PH) estimated by tricuspid valve insufficiency signal. Laboratory values are notable for a hemoglobin level of 8.7 g/dL, parathyroid hormone level of 167 ng/L, and 1,25-OH vitamin D level of 8.7 pmol/L.

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Chapter Key Points

- Incidence and predictors of reno-cardiac syndrome in patients with ESRD
- Diagnostic work-up for heart failure (HF) in an ESRD patient on dialysis
- Assessment of cardiac stressors associated with hemodialysis
- Approach to metabolic derangements in patients with HF on dialysis (anemia, calcium/phosphate metabolism, metabolic acidosis)

Brief Discussion of the Case

This case describes a common sequela of ESRD. Because she has had dialysis for a long period of time, excessive shunting from arterio-venous fistula may have led to high-output HF in this case. Therefore, the most common cause in this scenario is the progressive cardiac and vascular remodeling leading to reduced so-called "effective circulating volume," which is manifested via the development of stiffer ventricles and vasculature, both with lower capacitance to propel blood volume. Meanwhile, volume overload alone promotes left ventricular hypertrophy (LVH) [1]. Especially salient is the progressive LVH without significant increase in ventricular volumes, leading to relative underfilling due to a reduced stroke volume. This is coupled with calcification and fibrosis in both myocardium and vessel walls leading to an overall "non-compliant" cardiovascular system and inadequate perfusion on demand despite a preserved LVEF.

Hemodialysis itself imposes significant cardiovascular stress with large intravascular volume shifts, which promotes cardiac remodeling, left ventricular hypertrophy and diastolic dysfunction, and development of HF as seen in this patient. Unable to support systemic perfusion, blood pressure falls, and myocardial ischemia may even ensue. Besides hemodynamic challenges, many metabolic derangements further contribute to HF. Uremia activates fibroblasts, leading to fibrosis and stiffening of the myocardium, which ultimately impair diastolic filling as shown in this patient's echocardiogram [2]. As the endocrine functions of the kidney are also impaired, erythropoietin production and vitamin D activation are compromised, leading to anemia and hyperparathyroidism respectively. Anemia decreases the viscosity of the blood, promoting endothelial dysfunction [3–5]. Anemia also decreases myocardial oxygen delivery, promoting a chronic state of cardiac ischemia. With decreased vitamin D levels and electrolyte reabsorption derangement, renal failure causes a state of hyperphosphatemia, hypercalcemia and hyperparathyroidism, which promotes calcification of blood vessels [6]. Calcification decreases vasculature compliance, increasing afterload, which further promotes left ventricular hypertrophy. In addition to calcium disturbances, ESRD also causes metabolic acidosis, which decreases cardiac contractility as hydrogen is exchanged for calcium at the myocardial cell membrane [7]. In this section, we will review the physiologic impact of dialysis in patients with HF and discuss its management.

Epidemiology and Risk Factors

The majority of deaths among ESRD patients are due to cardiovascular disease (CVD) [8]. Though the connection between the kidney and heart may seem obvious, there are many factors that cause accelerated cardiovascular pathology in the setting of renal failure (Fig. 8.1). ESRD patients may exhibit so-called "reverse epidemiology" when it comes to traditional CVD risk factors. Specifically, obesity, hypercholesterolemia, and hypertension appear to be paradoxically protective features against CVD in the ESRD population. However, it is also clear that concomitant traditional cardiovascular risk factors contribute to disease progression, with parallel hemodynamic and metabolic derangements that promote significant cardiovascular compromise, including the thrice weekly "stress sessions" of hemodialysis in which significant intravascular volumes are being shifted for purposes of extracorporeal solute exchange.

Despite continued advancements in understanding and managing CVD and ESRD, we simply do not fully understand the intersection of these often co-morbid diseases [9]. We have recognized for some time LVH is prevalent in ESRD patients on hemodialysis. Predictors of HF in the ESRD population include primarily co-morbidities of CVD: history of ischemic heart disease, LVH, diabetes mellitus, age >60 years, heightened inflammation (defined as elevated C-reactive protein), and >1 year on dialysis [10, 11]. However, some may be promoted in the setting of dialysis.

Although dialysis reduces fluid overload, it also induces significant hemodynamic stress, inflammation, and endothelial dysfunction. Cardiovascular event incidence is high in the first few weeks after hemodialysis initiation [12] and repeated treatment promotes physiologic changes that may inadvertently contribute to the accelerated decay of cardiac function. Indeed, heart failure with preserved ejection fraction (HFpEF) is the more prevalent subtype in hemodialysis patients, [13, 14] and age, female sex, body mass index, blood pressure, and dialysis modality are predictive of HFpEF [13].

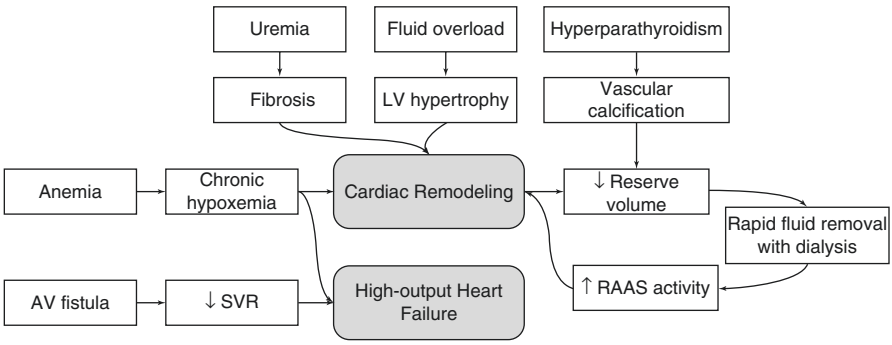

Fig. 8.1 Accelerated cardiovascular pathology in the setting of renal failure

Cardiovascular Stressors of Hemodialysis

Pathophysiologic Considerations

During intermittent hemodialysis, non-physiological fluid removal imposes hemodynamic stress on the already maladaptive cardiovascular system in uremic patients. As a result of impaired filling due to uremic cardiomyopathy and vascular calcification, reserve volume in the intravascular compartment is reduced. With rapid removal of fluid from the intravascular compartment, IDH occurs commonly, and is a well-established predictor of mortality [15]. Rapid volume contraction also activates the baroreceptor-mediated reflex arc, further increasing neurohormonal activation, a well-described contributor to HF pathophysiology [16, 17]. The combination of intradialytic hypotension and left ventricular hypertrophy creates a vicious cycle for further myocardial damage during dialysis (Fig. 8.2).

During dialysis, oxygen delivery to the subendocardium is compromised due to both decreased supply (decreased blood volume, pre-existing anemia) and increased demand (neurohormonal activation, continuous ultrafiltration). In addition, left ventricular hypertrophy and uremic cardiomyopathy contribute to compression of the coronary vasculature during systole [18]. Hemodialysis-induced regional wall motion abnormalities occur in over 25% of patients and are an independent risk factor for increased mortality [19]. Patients often develop myocardial stunning during dialysis and this injury often remains subclinical, particularly in patients with diabetic neuropathy [19, 20]. However, direct demonstration that such observations indeed correspond to the oxygen tension at the myocyte level have not been consistently shown in humans, even though such postulated pathophysiology is highly plausible.

Extrinsic stressors not accounted for in non-dialysis individuals may also play a role. For example, dialysis also imposes thermal stress with relatively large volume infusion and exchange of dialysates, and an increase in core temperature can be observed during a typical session [21]. Heat accumulation is related to decline in blood volume, which can lead to paradoxical reflex vasodilation. Especially in those

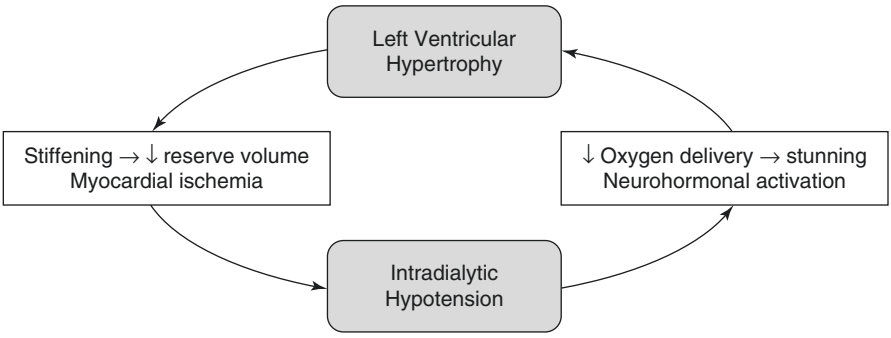

Fig. 8.2 Vicious cycle for myocardial damage during dialysis

with large ultrafiltration requirements, this vasodilation may prevent maintenance of blood pressure. Cooling of the dialysate has been shown to decrease the incidence of IDH compared to isothermic dialysis, in which there is no change in core temperature, and thermoneutral dialysis in which there is no energy added or removed from the patient [22].

Dialysis also imposes inflammatory stress, most notably due to biomaterial contact. Current dialyzer membranes, optimized for pore size manipulation and permeability, are hydrophobic and provide ample surface area for protein deposition, which promotes deposition of IgG, C3, and fibrinogen, promoting complement activation and coagulation [23]. Complement activation has been shown to occur in the first 30 minutes of HD sessions and leads to proinflammatory changes in cytokine transcription profiles [23, 24]. Heparin can inhibit complement, however, this effect is not seen in the doses typically prescribed during dialysis [23]. Inflammatory markers, including C-reactive protein (CRP), have been independently associated with HD-induced regional left ventricular systolic dysfunction [19]. The mechanistic link between inflammation and CVD is not clear and involves significant crosstalk between inflammation, thrombosis, and vascular dysfunction pathways [25]. Surface-modified hydrophilic membranes which have lower protein-adsorptive properties are available but not commonly used [23, 26].

Evaluation of Congestive HF in ESRD

Renal Evaluation in ESRD with HF

Dialysis modality and timing can impact the severity of dialysis-induced cardiovascular dysfunction. Interestingly, long-term development of LVH is more common and more severe in peritoneal dialysis (PD) patients, while hemodialysis (HD) patients may have more acute issues with effective blood pressure control. Standard intermittent hemodialysis is typically three sessions per week lasting 4–6 hours. In patients with persistent symptoms, often times a re-evaluation of their "dry weight" targets is necessary with changes in cardiovascular physiology. This can be accomplished by assessment of hemodynamics to determine if intracardiac filling pressures are adequately controlled (as a surrogate of volume overload). Prolonging duration of dialysis with slower fluid removal rates and more frequent sessions may reduce cardiovascular stress and improve survival. A benefit in a composite outcome of death, LV mass, and quality of life was associated with intensive hemodialysis in the Frequent Hemodialysis Network (FHN) Daily trial [27]. Meanwhile, online hemodiafiltration also showed improved survival over high-flux hemodialysis in the ESHOL (Estudio de Supervivencia de Hemodiafiltración On-Line) study [28]. Alternatively, home dialysis may also achieve the same duration and fluid removal goals, and has gained some traction for patients capable of performing it at home.

Dialysis access also directly or indirectly contributes to cardiovascular dysfunction. An arteriovenous fistula (AVF) is the most common route of vascular access

for chronic hemodialysis patients due to high blood flow rate, patency, and low infection risk. Upon creation of the direct shunt from arterial to venous circulation, systemic vascular resistance is decreased. In compensation, renin angiotensin aldosterone and sympathetic systems are activated, ultimately increasing cardiac output. Neurohormonal activation promotes cardiac remodeling and further left ventricular hypertrophy. Congruently, patients with AVF closure show a decrease in both eccentric and concentric hypertrophy [29]. Patients with underlying heart disease may not be able to sustain compensatory mechanisms and cardiac remodeling requirements, making them more susceptible to developing HF with a patent AVF. In the setting of high AVF blood flow, some patients can develop symptomatic high-output HF, defined by symptoms of HF in the presence of an elevated cardiac index ($\geq$3 L/min^2) and low systemic vascular resistance [30]. This can be demonstrated during right heart catheterization, in which temporary compression of AVF by a blood pressure cuff can acutely reverse these hemodynamic abnormalities and indicate the need to surgically revise the AVF. In a small randomized study, ligation of the hemodialysis AVF in stable post–renal transplant patients improves LV remodeling and also reduces NT-proBNP at 6 months [31].

Cardiovascular Evaluation in ESRD with HF

Clinicians should actively monitor signs and symptoms of HF in all ESRD patients, which is the most challenging aspect of making the diagnosis since many of the clinical presentation of HF and ESRD are similar (shortness of breath, fatigue, edema, exercise intolerance). All ESRD patients at risk of congestive HF should have baseline echocardiographic assessment at dry weight. This is a challenge upon itself since body composition changes over time and so does the evolution of "dry weight" that is hard to determine at the bedside. Although no specific guideline recommendations are available, it is reasonable for symptomatic patients with LVEF >35% to have serial transthoracic echocardiography for monitoring annually, while those with LVEF $\leq$35% should repeat every 3–6 months until stabilized if correctable abnormalities are present especially when there are treatment changes with medical optimization [32]. Echocardiography is mainly a monitoring and diagnostic tool, and not a treatment modality.

Over time with volume overload in a similar manner to left-sided valve diseases or HFpEF, left-sided HF progresses to right-sided HF as increased pressures are transmitted to the pulmonary circuit. Persistent PH promotes pathological changes in the vasculature, including intimal thickening, smooth muscle cell hypertrophy, and development of irreversible plexiform lesions. Fluid overload between dialysis sessions can also cause progressive PH. Beyond the above-mentioned indications of right heart catheterization for assessing volume status and determining excessive shunting from AVF, hemodynamic evaluation is often helpful to determine the severity of PH and determinination of adequate cardiac compensation and balance between left- and right-sided pressures and the need for pharmacologic interventions or changes in dialysis modalities or goals.

Interestingly, the goals of dialysis have remained largely unchanged over the decades, which are focused on reducing solutes rather than other uremic toxins or maintaining optimal vascular function. Future studies are warranted to determine the optimal targets and choices of dialysis modalities and dialysate management.

Medical Management of Congestive HF in ESRD

Heart Failure Disease Management

Managing congestive HF in the ESRD population follows the same general principles as in the rest of the population, however, there is a paucity of data supporting clinical decisions. In HFpEF, evidence is even more limited but generally the goal is management of contributing conditions. The primary targets are adequate volume and afterload reduction. Dialysis remains a mainstay for acute decompensation from a volume management perspective (many patients on dialysis are oliguric or even anuric). In the long-term, salt restriction, beta blockers, and angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) can be used as treatment when there is adequate blood pressure support. In the context of HFrEF, addition of ARB like telmisartan to standard therapies significantly reduces all-cause mortality, cardiovascular death, and HF hospital stays in hemodialysis patients, however, this has not been shown in HFpEF [33]. ARB therapy can reduce the risk of HF in ESRD patients but ACE-I is generally preferred [34]. Interestingly, there have been suggestions that pre-dialysis patients with Stage 4 CKD may also benefit from ACE-I [35].

On the other hand, beta-blockers mitigate deleterious effects of neurohormonal activation, with carvedilol, which is poorly dialyzed, specifically showing significant benefit in ESRD patients [36]. Large-scale clinical trials using beta-blockers have been attempted, but recruitment and blood pressure tolerability have been challenging [37, 38]. Meanwhile in small studies, spironolactone has been shown to reduce blood pressure, aortic calcification, and mortality [39, 40]. The use of mineralocorticoid receptor antagonists (MRA) remains controversial and randomized controlled-trials are ongoing (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial [ALCHEMIST], ClinicalTrials.gov NCT01848639). It is noted that the combination of ACE-I, ARB, and an MRA should be avoided due to concern for hyperkalemia.

Associated conditions include atrial fibrillation, hyperlipidemia, and myocardial ischemia. The patient should be assessed for comorbid atrial fibrillation, which is common in HFpEF, with an EKG. Restoration and maintenance of sinus rhythm is preferred but rate control can be targeted when this cannot be achieved. Carvedilol, which shows significant benefit in ESRD patients, would be a reasonable first-line option although there might be higher risk of hypotension [37, 38]. Though used in HFrEF patients, digoxin use in HFpEF patients with AF at a mean follow-up of 37 months had no effect on all-cause or cause-specific mortality or all-cause or

cardiovascular hospitalization [41]. Additionally, digoxin use in dialysis patients has been associated with increased mortality, particularly if predialysis serum potassium levels are low [42].

Coronary Atherosclerotic Disease Management

Statins appeared to have no incremental benefit in preventing major adverse cardiac events in the ESRD population as addressed in the 4-D, AURORA, and SHARP trials, though continuation of previously prescribed statin therapy according to latest clinical guidelines is appropriate [43–46]. In ESRD patients with coronary artery disease, antithrombotic agents are often prescribed with little evidence to guide decision-making, and with increased complications since ESRD patients have acquired intrinsic platelet abnormalities. Specifically, ESRD patients have reduced serotonin content and impaired ADP release, and are simultaneously at increased risk of bleeding and in a prothrombotic state with "nontraditional" risk factors for thrombosis, such as hyperhomocysteinemia, endothelial dysfunction, inflammation, and malnutrition [47, 48].

Assessment of coronary artery disease is difficult in the ESRD population due to complications from comorbid conditions, such as diabetic neuropathy. However, revascularization by percutaneous coronary intervention (PCI) should be pursued if indicated. Low-dose aspirin use in ESRD patients is of unproven cardiovascular benefit and no clinical trials have addressed its utility. Observational studies inherently present confounding by indication but have reported increased mortality risk in hemodialysis patients on aspirin. Overall, usage is likely safe, provider-dependent, and may be discussed with the patient [49–51]. Meanwhile, the Arterial Revascularization Therapies Study (ARTS) showed that in patients with CKD, there was no significant difference in operative death, myocardial infarction, and stroke for those treated by either coronary artery bypass grafting (CABG) or PCI, while CABG was associated with a lower risk for repeat revascularization [52]. For patients with Stage IV chronic kidney disease, CABG was associated with a decreased mortality rate compared to PCI, even though there may be higher mortality rates for the first 3 months in patients who underwent CABG compared to PCI [53]. The ASCERT study showed that the estimated mortality rate in the general population who underwent CABG was 3.2%, 6.4%, 8.1%, and 23.3% at 30 days, 180 days, 1 year, and 3 years, respectively [53]. Predictors for late cardiac events include advanced age (>63 years), diabetes, and peripheral artery disease, whereas, predictors for late death include diabetes and LVEF <40% [54].

Anemia and Metabolic Management

To mitigate chronic myocardial ischemia, anemia can be managed using Erythropoietin-Stimulating Agents (ESA), which effectively increase hemoglobin levels. However, higher doses of ESA and higher hematocrit management goals

have failed to show survival benefit in multiple RCTs; secondary analyses of these trials has implicated high ESA dose or resistance, rather than higher hemoglobin levels, as the cause [55–57]. Erythropoietin-stimulating agents are also associated with a higher risk of thrombotic events, mediated through a multifaceted mechanism of polycythemia/hyperviscosity syndrome, thrombocytosis, platelet hyperactivity, and activation of blood coagulation [58].

Both hyperphosphatemia and hyperparathyroidism promote vascular calcification in ESRD patients; the goal of management is to treat hyperphosphatemia, maintain normocalcemia, and treat vitamin D deficiency. Phosphate binders, calcimimetics, and vitamin D analogs can be used. Both ergocalciferol and cholecalciferol are effective in treating vitamin D deficiency. Metabolic acidosis can be managed using sodium bicarbonate. Dialysate content can also be manipulated to control electrolyte balance and affect survival. A dialysate potassium of <2 mEq/L has been associated with an increased risk of sudden cardiac death and a lower serum-to-dialysate calcium gradient may be advisable in patients with cardiorenal syndrome [59].

Device Therapy for HF and ESRD

ESRD patients are generally managed medically due to higher rates of complications, however, implantable cardioverter defibrillator (ICD) therapy may be considered in patients with cardiomyopathy as primary prevention of sudden cardiac death. The benefits and risks of ICD should be discussed with patients with LVEF consistently <35% despite medical therapy. Compared with estimates in HFrEF, the rates of sudden cardiac death in HFpEF are lower [60]. However, ESRD patients, who inherently have higher arrhythmic risk, may benefit from ICD therapy. In patients with mild to moderate CKD, ICD implantation regardless of indication reduces mortality, however, this benefit is balanced with a higher procedural risk in patients with more advanced renal failure [61]. Meanwhile, for those with CKD eligible for cardiac resynchronization therapy, they should be considered as they provide incremental benefits compared to ICD alone [62].

Renal Transplantation Candidacy and Considerations

Patients with HF are often not referred for renal transplantation for a wide range of reasons. However, renal transplantation has been shown to improve left ventricular mass and function [63, 64]. Prolonged dialysis is associated with a decrease in the beneficial effect of transplantation, thus renal transplantation should be considered early in patients at risk of, or already diagnosed with congestive HF. There is currently no consensus on the minimum LVEF for renal transplantation, and it is important to reassess eligibility after optimizing medical therapy.

Combined heart-kidney transplants have outcomes similar to those with primary heart transplantation, though these cases are highly selective and uncommon. About a decade ago, a risk score was constructed from the United Network for Organ

Sharing (UNOS) data that identified risk factors associated with worse survival benefit included: (1) a history of peripheral arterial disease (4 points); (2) recipient age >65 years (3.5 points); (3) non-ischemic cause of heart failure (2 points); (4) bridge to transplantation with use of a ventricular assist device (2 points); and dialysis dependency (2.5 points) [65]. They observed in patients with eGFR less than 33 mL/min undergoing heart trasnplant with low-risk (total score <4), there was a significant survival benefit of combined heart-kidney transplant compared to heart transplant alone. Newer analysis also extended such benefits to those at high risk of developing post-transplant dialysis dependence or in older individuals [66, 67].

Treatment Pearls for the Case Vignette

This patient's echocardiogram supports a diagnosis of HFpEF with diastolic dysfunction and PH. The history of worsening symptoms suggests chronic progression, which is common in ESRD patients. High-output failure due to AVF is of lower probability in this case due to the chronicity of dialysis, although it needs to be ruled out if accompanied by acute changes in the AVF itself. In this patient with PH, prevention of progression to right-sided HF should be prioritized. A right heart catheterization would be necessary to determine the degree of elevated pulmonary pressures and their reversibility, as well as the severity of uremic cardiomyopathy. The challenge of medication intolerance due to reducing perfusion pressures is a common challenge, and there are various means including holding drug doses before/after dialysis session or changing to shorter acting drugs with lower propensity of hypotension. In this case with HFpEF, the need to maintain neurohormonal antagonists is less certain. If feasible, switching to frequent hemodialysis may likely provide benefit in improving left ventricular mass and survival. As discussed, the FHN found benefit in a composite outcome of death, LV mass, and quality of life with intensive hemodialysis [27]. Hemodiafiltration has also shown a trend towards improved survival over standard hemodialysis [28]. Home dialysis is another option, but the cost and logistic inconvenience of daily home dialysis may be a barrier for some patients. The patient's advanced age and the diagnosis of HFpEF precluded any meaningful indications or considerations of invasive device therapies or transplantation options, although evaluation of underlying ischemic causes that leads to such changes in clinical presentation may be warranted.

References

1. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int. 1995;47:186–92.
2. Gross ML, Ritz E. Hypertrophy and fibrosis in the cardiomyopathy of uremia – beyond coronary heart disease. Semin Dial. 2008;21:308–18.
3. Eckardt KU. Anaemia in end-stage renal disease: pathophysiological considerations. Nephrol Dial Transplant. 2001;16(Suppl 7):2–8.

4. Malyszko J. Mechanism of endothelial dysfunction in chronic kidney disease. Clin Chim Acta. 2010;411:1412–20.
5. Boulanger CM, Amabile N, Guérin AP, Pannier B, Leroyer AS, Mallat CN, Tedgui A, London GM. In vivo shear stress determines circulating levels of endothelial microparticles in end-stage renal disease. Hypertension. 2007;49:902–8.
6. Jablonski KL, Chonchol M. Vascular calcification in end-stage renal disease. Hemodial Int. 2013;17(Suppl 1):S17–21.
7. Orchard CH, Kentish JC. Effects of changes of pH on the contractile function of cardiac muscle. Am J Phys. 1990;258:C967–81.
8. United States Renal Data System. 2018 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD 2018.
9. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int. 2003;63:793–808.
10. Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. Kidney Int. 1995;47:884–90.
11. Wang AY. Prognostic value of C-reactive protein for heart disease in dialysis patients. Curr Opin Investig Drugs. 2005;6:879–86.
12. Eckardt KU, Gillespie IA, Kronenberg F, Richards S, Stenvinkel P, Anker SD, Wheeler DC, de Francisco AL, Marcelli D, Froissart M, Floege J, ARO Steering Committee. High cardiovascular event rates occur within the first weeks of starting hemodialysis. Kidney Int. 2015;88:1117–25.
13. Antlanger M, Aschauer S, Kopecky C, Hecking M, Kovarik JJ, Werzowa J, Mascherbauer J, Genser B, Säemann MD, Bonderman D. Heart failure with preserved and reduced ejection fraction in hemodialysis patients: prevalence, disease prediction and prognosis. Kidney Blood Press Res. 2017;42:165–76.
14. Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2013;10:401–10.
15. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009;4:914–20.
16. Mentz RJ, O'Connor CM. Pathophysiology and clinical evaluation of acute heart failure. Nat Rev Cardiol. 2016;13:28–35.
17. Lymperopoulos A, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: pathophysiology and therapy. Circ Res. 2013;113:739–53.
18. Edwards NC, et al. Defining the natural history of uremic cardiomyopathy in chronic kidney disease: the role of cardiovascular magnetic resonance. JACC Cardiovasc Imaging. 2014;7:703–14.
19. Assa S, Hummel YM, Voors AA, Kuipers J, Westerhuis R, de Jong PE, Franssen CF. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors, and prognostic significance. Clin J Am Soc Nephrol. 2012;7:1615–23.
20. Koch M, Gradaus F, Schoebel FC, Leschke M, Grabensee B. Relevance of conventional cardiovascular risk factors for the prediction of coronary artery disease in diabetic patients on renal replacement therapy. Nephrol Dial Transplant. 1997;12:1187–91.
21. Kooman JP, Katzarski K, van der Sande FM, Leunissen KM, Kotanko P. Hemodialysis: a model for extreme physiology in a vulnerable patient population. Semin Dial. 2018;31:500–6.
22. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. Nephrol Dial Transplant. 2006;21:1883–98.
23. Ekdahl KN, Soveri I, Hilborn J, Fellström B, Nilsson B. Cardiovascular disease in haemodialysis: role of the intravascular innate immune system. Nat Rev Nephrol. 2017;13:285–96.
24. Friedrich B, Alexander D, Janessa A, Häring HU, Lang F, Risler T, Friedrich B, et al. Acute effects of hemodialysis on cytokine transcription profiles: evidence for C-reactive protein-dependency of mediator induction. Kidney Int. 2006;70:2124–30.

25. Golia E, Limongelli G, Natale F, Fimiani F, Maddaloni V, Pariggiano I, Bianchi R, Crisci M, D'Acierno L, Giordano R, Di Palma G, Conte M, Golino P, Russo MG, Calabrò R, Calabrò P. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Curr Atheroscler Rep. 2014;16:435.
26. Bonomini M, Pavone B, Sirolli V, Del Buono F, Di Cesare M, Del Boccio P, Amoroso L, Di Ilio C, Sacchetta P, Federici G, Urbani A. Proteomics characterization of protein adsorption onto hemodialysis membranes. J Proteome Res. 2006;5:2666–74.
27. FHN Trial Group, et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010;363:2287–300.
28. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A, ESHOL Study Group. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
29. Movilli E, Viola BF, Brunori G, Gaggia P, Camerini C, Zubani R, Berlinghieri N, Cancarini G. Long-term effects of arteriovenous fistula closure on echocardiographic functional and structural findings in hemodialysis patients: a prospective study. Am J Kidney Dis. 2010;55:682–9.
30. MacRae JM, Dipchand C, Oliver M, Moist L, Yilmaz S, Lok C, Leung K, Clark E, Hiremath S, Kappel J, Kiaii M, Luscombe R, Miller LM, Canadian Society of Nephrology Vascular Access Work Group. Arteriovenous access: infection, neuropathy, and other complications. Can J Kidney Health Dis. 2016;3:2054358116669127.
31. Stokes MB, Rajwani A, Rao NN, McDonald SP, Coates T, Teo KS, Worthley MI. Cardiac remodeling following ligation of arteriovenous fistula in stable renal transplant recipients: a randomised controlled study. AHA Scientific Sessions 2018 Late Breaking Clinical Trial.
32. Bhatti NK, Karimi Galougahi K, Paz Y, Nazif T, Moses JW, Leon MB, Stone GW, Kirtane AJ, Karmpaliotis D, Bokhari S, Hardy MA, Dube G, Mohan S, Ratner LE, Cohen DJ, Ali ZA. Diagnosis and management of cardiovascular disease in advanced and end-stage renal disease. J Am Heart Assoc. 2016;5:e003648.
33. Cice G, Di Benedetto A, D'Isa S, D'Andrea A, Marcelli D, Gatti E, Calabrò R. Effects of telmisartan added to Angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled trial. J Am Coll Cardiol. 2010;56:1701–8.
34. Liu Y, Ma X, Zheng J, Jia J, Yan T. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on cardiovascular events and residual renal function in dialysis patients: a meta-analysis of randomised controlled trials. BMC Nephrol. 2017;18:206.
35. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, Jiang JP, Liang M, Wang GB, Liu ZR, Geng RW. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med. 2006;354:131–40.
36. Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, Russo PE, Golino P, Calabrò R. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol. 2003;41:1438–44.
37. Roberts MA, Pilmore HL, Ierino FL, Badve SV, Cass A, Garg AX, Isbel NM, Krum H, Pascoe EM, Perkovic V, Scaria A, Tonkin AM, Vergara LA, Hawley CM, BLOCADE Study Collaborative Group. The β-blocker to lower cardiovascular dialysis events (BLOCADE) feasibility study: a randomized controlled trial. Am J Kidney Dis. 2016;67:902–11.
38. Assimon MM, Brookhart MA, Fine JP, Heiss G, Layton JB, Flythe JE. A comparative study of carvedilol versus metoprolol initiation and 1-year mortality among individuals receiving maintenance hemodialysis. Am J Kidney Dis. 2018;72:337–48.
39. Bomback AS. Mineralocorticoid receptor antagonists in end-stage renal disease: efficacy and safety. Blood Purif. 2016;41:166–70.
40. Shroff GR, Herzog CA. β-blockers in dialysis patients: a nephrocardiology perspective. J Am Soc Nephrol. 2015;26:774–6.
41. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation. 2006;114:397–403.

42. Chan KE, Lazarus JM, Hakim RM. Digoxin associates with mortality in ESRD. J Am Soc Nephrol. 2010;21:1550–9.
43. Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int. 2014;85:1303–9.
44. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E, German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238–48.
45. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F, AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360:1395–407.
46. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R, SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377:2181–92.
47. Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial. 2006;19:317–22.
48. Casserly LF, Dember LM. Thrombosis in end-stage renal disease. Semin Dial. 2003;16:245–56.
49. Ethier J, Bragg-Gresham JL, Piera L, Akizawa T, Asano Y, Mason N, Gillespie BW, Young EW. Aspirin prescription and outcomes in hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2007;50:602–11.
50. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Anticoagulant and antiplatelet usage associates with mortality among hemodialysis patients. J Am Soc Nephrol. 2009;20:872–81.
51. Hiremath S, Holden RM, Fergusson D, Zimmerman DL. Antiplatelet medications in hemodialysis patients: a systematic review of bleeding rates. Clin J Am Soc Nephrol. 2009;4:1347–55.
52. Ix JH, Mercado N, Shlipak MG, et al. Association of chronic kidney disease with clinical outcomes after coronary revascularization: the Arterial Revascularization Therapies Study (ARTS). Am Heart J. 2005;149:512–9.
53. Charytan DM, Yang SS, McGurk S, et al. Long and short-term outcomes following coronary artery bypass grafting in patients with and without chronic kidney disease. Nephrol Dial Transplant. 2010;25:3654–63.
54. Shahian DM, O'Brien SM, Sheng S, et al. Predictors of long-term survival after coronary artery bypass grafting surgery: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (the ASCERT study). Circulation. 2012;125:1491–500.
55. Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis. Am J Kidney Dis. 2013;61:44–56.
56. Solomon SD, Uno H, Lewis EF, Eckardt KU, Lin J, Burdmann EA, de Zeeuw D, Ivanovich P, Levey AS, Parfrey P, Remuzzi G, Singh AK, Toto R, Huang F, Rossert J, McMurray JJ, Pfeffer MA. Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Investigators. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010;363:1146–55.
57. Szczech LA, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, Patel UD, Singh AK. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. Kidney Int. 2008;74:791–8.

58. Lippi G, Franchini M, Favaloro EJ. Thrombotic complications of erythropoiesis-stimulating agents. Semin Thromb Hemost. 2010;36:537–49.
59. Thornley-brown D, Saha M. Dialysate content and risk of sudden cardiac death. Curr Opin Nephrol Hypertens. 2015;24:557–62.
60. Vaduganathan M, Patel RB, Michel A, Shah SJ, Senni M, Gheorghiade M, Butler J. Mode of death in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2017;69:556–69.
61. Fu L, Zhou Q, Zhu W, Lin H, Ding Y, Shen Y, Hu J, Hong K. Do implantable cardioverter defibrillators reduce mortality in patients with chronic kidney disease at all stages? Int Heart J. 2017;58:371–7.
62. Friedman DJ, Singh JP, Curtis JP, Tang WH, Bao H, Spatz ES, Hernandez AF, Patel UD, Al-Khatib SM. Comparative effectiveness of CRT-D versus defibrillator alone in HF patients with moderate-to-severe chronic kidney disease. J Am Coll Cardiol. 2015;66:2618–29.
63. Wali RK, Wang GS, Gottlieb SS, Bellumkonda L, Hansalia R, Ramos E, Drachenberg C, Papadimitriou J, Brisco MA, Blahut S, Fink JC, Fisher ML, Bartlett ST, Weir MR. Effect of kidney transplantation on left ventricular systolic dysfunction and congestive heart failure in patients with end-stage renal disease. J Am Coll Cardiol. 2005;45:1051–60.
64. Hawwa N, Shrestha K, Hammadah M, Yeo PSD, Fatica R, Tang WH. Reverse remodeling and prognosis following kidney transplantation in contemporary patients with cardiac dysfunction. J Am Coll Cardiol. 2015;20(66):1779–87.
65. Russo MJ, Rana A, Chen JM, Hong KN, Gelijns A, Moskowitz A, Widmann WD, Ratner L, Naka Y, Hardy MA. Pretransplantation patient characteristics and survival following combined heart and kidney transplantation: an analysis of the United Network for Organ Sharing Database. Arch Surg. 2009;144:241–6.
66. Kilic A, Grimm JC, Whitman GJ, Shah AS, Mandal K, Conte JV, Sciortino CM. The survival benefit of simultaneous heart-kidney transplantation extends beyond dialysis-dependent patients. Ann Thorac Surg. 2015;99:1321–7.
67. Reich H, Dimbil S, Levine R, Megna D, Mersola S, Patel J, Kittleson M, Czer L, Kobashigawa J, Esmailian F. Dual-organ transplantation in older recipients: outcomes after heart-kidney transplant versus isolated heart transplant in patients aged ≥65 years. Interact Cardiovasc Thorac Surg. 2019;28:45–51.

Diuretic Resistance and Chronic Heart Failure

9

Alice Ravera, Jozine M. ter Maaten, and Marco Metra

Case Vignette

Dr. Z's patient is Mrs. X, a 78 y/o women with stage IV chronic kidney disease (serum creatinine 2.03 mg/dL – estimated glomerular filtration rate 23 mL/min/1.73m^2) and a recent (<3 months) hospital admission due to heart failure. Mrs. X comes into the office complaining from exertional dyspnea and lower leg edema. He is on furosemide 75 mg daily, administered as 3 25 mg tablets in the morning, bisoprolol 2.5 mg daily and ramipril 2.5 mg daily. After examining Mrs. X, Dr. Z decides that the presence of volume overload warrants treatment further diuretic treatment. He wonders whether to admit the patient for intravenous administration and reflects on the optimal dose to be given.

Chapter Key Points

- Volume overload and congestion are detected at a relatively late stage based on clinical signs and symptoms alone
- Loop diuretic resistance develops during chronic treatment through hypertrophy and hyperfunction of areas of the nephron where loop diuretics are not active and neurohormonal activation
- Increased loop diuretic doses and combined administration of diuretics with different sites of action my be used to overcome loop diuretic resistance
- Novel outpatient strategies may become available (e.g. subcutaneous furosemide)
- Administration of the lowest effective loop diuretics doses may prevent resistance

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Brief Discussion of the Case

The clinical vignette presents the case of Mrs. X, a 78 year old woman with a recent hospitalization for heart failure (HF) in the past 3 months and with stage IV chronic kidney disease (CKD), complaining about leg edema and exertional dyspnea during an ambulatory visit in the outpatient clinic. The preliminary information about the recent admission for HF already allows the clinician to classify her into a subset of patients at higher risk of mortality and hospitalization [1–3]. Retrospective analyses of randomized trials and observational studies show that the mortality and readmission rates are higher in the first months after discharge and decrease, approximately in an exponential way, thereafter, though remaining higher than in ambulatory patients even in the long-term [4, 5]. Failure to normalize ventricular filling pressures and persistence of subclinical congestion at discharge are among the main causes of the increased risk of readmission early after discharge [2]. Chronic kidney disease (CKD) increases the patient's risk of diuretic resistance and congestion and contributes to the poor prognosis of the ambulatory HF patients [6]. When the attending resident visited the patient at the outpatient clinic, she had already developed overt signs and symptoms of congestion, despite the ongoing diuretic therapy. The presence of fluid retention despite diuretic treatment is classified as diuretic resistance [7]. Given the signs and symptoms of volume overload, intensification of diuretic treatment is recommended. The presence of peripheral edema despite ongoing oral furosemide administration, generally requires intravenous diuretic treatment with either the same dose or a higher dose compared to the one that the patient was receiving [8].

Volume Overload: Clinical and Subclinical Congestion

Volume overload and/or lung congestion caused by fluid redistribution are the main causes of symptoms and admissions to hospital of HF patients. The relative value of these two mechanisms causes different clinical phenotypes of acute heart failure, independent whether the patients have reduced or normal ejection fraction [9–11]. Diuretic treatment is recommended in patients with signs and/or symptoms of congestion to improve symptoms and reduce the risk of HF hospitalization [8, 12, 13].

Clinical signs of congestion are associated with an increased risk of death and HF hospitalization in patients with congestive HF [14]. However, when compared with direct measurement of cardiac filling pressures with right heart catheterization, physical signs of congestion as jugular venous distention (JVD), orthopnea, pulmonary rales, lower extremity edema, left ventricular third heart sound, and hepatojugular reflux showed limited sensitivity in identifying congestion [15]. A modified composite congestion score (CCS), obtained by summing the individual scores for orthopnea, JVD, and pedal edema may be helpful to quantify residual congestion although it has limited sensitivity [16]. Thus, despite a careful physical examination and the use of congestion scores, there is still a subset of patients that have fluid overload below the threshold of clinical detection [15, 17]. The detection of signs of increased cardiac filling pressures has a major prognostic value independently from the presence of clinical symptoms and signs [18, 19].

Use of Cardiac Biomarkers to Detect Congestion

As clinical signs have poor accuracy, measurement of natriuretic peptides (NP), namely B-type natriuretic peptide (BNP) and amino-terminal pro–B-type natriuretic peptide (NT-proBNP), is recommended not only for the diagnosis but also for the prognostic evaluation of HF patients [20]. However, their value to guide treatment is not demonstrated. The recent GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study, the largest trial testing this hypothesis, enrolled 894 HFrEF patients with a recent HF hospitalization and NT-proBNP >1000 ng/L, randomized 1:1 to NP guided therapy or standard treatment. The study was terminated early for futility and no difference was found in cardiovascular mortality or any of the secondary endpoints between the two treatment strategies [21], with higher healthcare costs in the NT-proBNP guided arm [22]. Similar results were obtained in the PRIMAII trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?), enrolling 431 patients with acute HF [23]. Similar medical treatment in the control and the natriuretic peptides guided therapy arm seem as the main cause of lack of any significant difference. It is possible that measurement of natriuretic peptides may be of greater value when performed in less selected patients' populations. The HF Outpatient Monitoring Evaluation (HOME) study on patients with HFrEF and a recent HF hospitalization suggested that daily home BNP measurements could predict emerging clinical deterioration in patients with HF. However, this study was terminated early for slow enrolment [24]. Other biomarkers have been proposed to guide HF therapy, namely ST-2, galectin-3, adrenomedullin (ADM), carbohydrate antigen-125 (CA-125) and soluble CD146, although we lack of evidence regarding their clinical usefulness [8, 12, 25].

Another promising method to identify subclinical congestion, easily applicable, is point-of-care echography with lung and inferior vena cava (IVC) ultrasound [26, 27]. Both can readily assess volume status and are sensitive to rapid changes in response to HF therapy [12]. Ongoing studies will assess the efficacy of such methods to guide therapy in congestive HF (NCT03613779, NCT03262571).

Comprehensive echocardiography with evaluation of myocardial structure and function and estimation of pulmonary artery pressures (PAP) and left ventricular filling pressures is also used to evaluate lung congestion. Multiparametric algorithms are proposed to estimate left ventricular filling pressure with additive value, when compared to tissue Doppler alone [28, 29]. In addition, pulmonary arterial pressure monitor (PAPM) is an implantable device providing real time measurements of PAP. The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF Patients (CHAMPION) trial showed morbidity and mortality benefit of this remote monitoring strategy in patients with advanced CHF with either HFrEF or HFpEF [30, 31].

Strategies to treat congestion in HF patients are generally not based on randomized clinical trials evidence but rather on small studies and practical recommendations. However, current evidence suggest the value of periodic assessments of congestion based on clinical examination as well as laboratory and/or imaging techniques. Monitoring [8, 32],

Diuretic Resistance in Chronic Heart Failure. Definition and Prevalence

Diuretic resistance in HF is defined as a failure of diuretics to control salt and water retention despite being used in appropriate doses [7, 8, 33]. Several metrics have been used to quantify diuretic response in clinical studies, namely natriuresis, net fluid loss, weight loss, urine output, fractional sodium excretion and urinary sodium/furosemide concentration. Then, to define diuretic resistance, diuretic response must be related to the diuretic dose administered. Examples are persistent congestion despite adequate and escalating doses of diuretic >80 mg of furosemide per day, failure to excrete at least 90 mmol of sodium within 72 hours of a 160 mg oral furosemide dose given twice daily [7, 33]. In retrospective analyses of multicenter trials, diuretic response was measured as the ratio between the change in body weight and the furosemide dose administered and was independently related with mortality at 180 days, mortality and HF rehospitalizations and HF rehospitalizations alone, in one trial, and with death and HF rehospitalizations but not mortality alone in another study [34, 35]. Although it is difficult to quantify in the chronic setting given the complexity of its measurement, diuretic resistance may occur in one third of chronic HF patients, with higher prevalence among those with concomitant chronic kidney disease.

Diuretic Resistance in Chronic Heart Failure. Mechanisms

The pathophysiology of diuretic resistance is multifactorial and single or multiple contributors can cause it in each patient [7, 8, 36].

Compliance and Concomitant Medications

Poor adherence to prescribed medication or concomitant prescription of nephrotoxic drugs (i.e. non-steroidal anti-inflammatory drugs, some antibiotics) can cause kidney injury and diuretic resistance.

Altered Diuretic Pharmacokinetics and Dynamics

Oral loop diuretics are absorbed in the bowel, then circulate in the bloodstream bound to plasma proteins, and after being both filtered by the glomerulus (smallest part) and actively secreted by the organic anion transporter and the multidrug resistance-associated protein 4 in the proximal tubule (largest part), they act on the sodium-chloride-potassium co-transporter (NKCC2) on the luminal side of the thick ascending limb of the loop of Henle [7, 37]. In congested patients, bowel edema can reduce absorption of orally administrated diuretics, causing lower peak plasma

concentration, especially if in case of concomitant food intake. Hypoalbuminemia reduces the amount of bound loop diuretics available for tubular secretion and concomitant albuminuria may bind diuretics on the luminal side of the loop of Henle, thus inhibiting their action. Furthermore, acidosis and uremia cause competitive secretion of organic acids by the proximal tubules' transporters, thus reducing the amount of secreted loop diuretics. Reduced glomerular filtration rate (GFR) in patients with concomitant CKD can further modify loop diuretic pharmacokinetics and dynamics [7, 8].

Hemodynamic Factors

Decreased renal blood flow in patients with low-output HF syndromes, or excessively rapid diuresis with slow fluid recruitment from interstitium to the intravascular compartment may cause a decrease in diuretic response. Namely, renal hypoperfusion increase the fraction of filtered plasma at the glomerular level with more concentrated blood into the efferent arteriole and the peritubular capillaries. The consequent increase in the peritubular osmotic pressure promotes an increase in proximal tubular sodium reabsorption that reduces the distal delivery of sodium and hence loop diuretic efficacy [33]. Moreover, ascites and abdominal congestion cause an increase in intra-abdominal pressure with an increase in renal interstial pressure that further impairs kidney function [38].

Neurohormonal Activation

NKCC2 inhibition by loop diuretics causes reduced chloride concentration in the macula densa cells, ultimately causing renin secretion that further potentiates the renin-angiotensin–aldosterone system (RAAS) activity, already enhanced in HF patients. This mechanism contributes to the *post-diuretic sodium retention*, namely increased sodium and water retention in between diuretic administrations, and the *braking phenomenon*, a decrease in the natriuresis produced by the same amount of loop diuretic over time [33, 36].

Nephron Adaptation to Diuretic Treatment

The chronic increase in distal delivery of sodium and chloride in patients on long-term loop diuretic treatment, especially at high doses, causes hypertrophy and hyperplasia of distal convoluted tubule cells, principal cells, and intercalated cells with increased activity of the thiazide-sensitive sodium chloride cotransporter, the epithelial sodium channel, and the chloride–bicarbonate exchanger pendrin [7, 33, 36, 37, 39]. These changes, named nephron remodeling [36], cause the increased reabsorptive capacity of the distal nephron and are the main cause of diuretic resistance in chronic HF patients.

Diuretic Resistance in Chronic Heart Failure. Management

Based on the above-mentioned mechanisms, several strategies are adopted to overcome diuretic resistance and restore appropriate diuresis.

Multiple Administrations and Patient's Position

In case of inappropriate diuretic response, an increase in the diuretic dose is warranted, especially when concomitant kidney dysfunction is present [8, 36]. Splicing a single daily diuretic dose in multiple administrations may be a complimentary strategy to prevent post-diuretic sodium increased reabsorption, the so-called braking phenomenon [36]. Evening diuretic doses or lying after diuretic administration, a method to increase renal perfusion and reduce sympathetic activation, may further improve diuretic response [40]. Excessively rapid diuresis should be avoided, as an adequate circulatory volume is essential to maintain renal perfusion and diuresis.

Changes in the Loop Diuretic Molecule

Furosemide, bumetanide, torasemide and azosemide are all loop diuretics targeting NKCC2, but with different pharmacologic profile (Table 9.1) [6, 7, 36, 41, 42]. It is common practice to use furosemide as first-line loop diuretic. However, choosing a loop diuretic with a longer half-life may reduce post-diuretic reabsorption phenomenon. Additionally, in hypoalbuminemic patients, switching to diuretics that can circulate bound to plasma globulins, such as bumetanide, may increase the diuretic response [7]. Torsemide and bumetanide have a larger and less variable oral bioavailability, compared with furosemide, and may, thus, provide better diuresis when furosemide is poorly absorbed [8].

It has been suggested that torsemide may have favorable effects on outcomes compared with furosemide due to its anti-fibrotic and antialdosterone effects [41]. Some analyses of previous trials showed promising results [43, 44]. Data are, however, not conclusive [45]. A randomized clinical trial with an innovative pragmatic design comparing furosemide with torsemide in patients with HF is ongoing (ClinicalTrials.gov Identifier: NCT03296813) [8].

Route of Administration

When patients develop congestion despite chronic oral loop diuretic therapy, it is standard procedure to shift to intravenous administration. This eliminates the effect of gut malabsorption due to gut edema and congestion. Therapy may be started administering intravenously the same dose that the patient was receiving orally, low dose regimen in the Diuretic Optimization Strategies Evaluation (DOSE) trial [46]. Alternatively, 1.5 times or higher doses may be administered intravenously, high

Table 9.1 Pharmacologic features of diuretics for treatment of congestion in CHF

		Loop diuretics				Thiazide-like diuretics				MRAs (diuretic dose)			
	Acetazolamide	Furosemide	Bumetanide	Torasemide	Azosemide[a]	Metolazone	Hydrochlorothiazide	Chlortalidone	Chlorothiazide	Spironolactone	Eplerenone	Potassium canrenoate	Amiloride
Site of action	Proximal tubule	Thick ascending limb of loop of Henle				Early distal tubule				Late distal tubule			Late distal tubule
Route of administration	Oral iv	Oral sc[a] iv	Oral iv	Oral	Oral iv	Oral	Oral	Oral	Oral iv	Oral	Oral	Oral iv	Oral
Daily dose Range, mg	250–1500	25–2000	0.5–15	5–300	20–80	2.5–20	6.25–400	25–200	500–1000	25–400	25–100	25–400	5–20
Half-life, hours	2.4–5.4	1.5–2.8	1–1.6	3–6	2–3	6–20	6–15	45–60	0.7–2	0.2[b]	3–6	16.5	6–9
Half-life affected by low GFR	↑	↑	↑	↑	–	–	↑	↑	↑	–	–	–	↑
Oral bioavailability	Variable	10–100%	80–100%	80–100%	20%	40–65%	65–75%	–	9–56%	90%	69%	–	30–90%
Absorption affected by food	No	↓	↓	No	↓	No	↑	↑	–	↑	–	–	No
Protein binding	Albumin	Albumin	Albumin, globulins	Albumin	Albumin, globulins	RBC, albumin	Albumin, globulins	Albumin	Albumin, globulins	Albumin, globulins	Albumin, globulins	–	–
Potency, FENa%	3–5%	20–25%			–	5–8%				2–3%			2–3%

Based on Refs. [7, 8, 33, 36, 41, 42]

iv intravenous, *FENa%* fraction of sodium excreted in the urine, as a percentage of the sodium filtered by the kidney, *GFR* glomerular filtration rate, *MRA* mineralocorticoid receptor antagonist, *RBC* red blood cells, *sc* subcutaneous

[a]Investigational drug/formulation

[b]Canrenone is active metabolite

dose regimen in DOSE trial. No difference in outcomes between the two dosing regimens was shown in the DOSE trial. The high dose regimen was associated with a tendency to a greater symptoms' relief, a larger body weight decrease and fluid loss and a greater likelihood to develop worsening renal function [46].

Intravenous loop diuretic treatment is generally done in a hospital setting. However, the practice of short-term intravenous administration of furosemide in specialized outpatient units is cost-effective and more and more often used [47, 48]. Short-stay unit treatment for <24 hours is compared with standard hospitalization in an ongoing randomized trial (NCT03302910).

A novel subcutaneous furosemide formulation was recently developed. First studies in healthy volunteers and a first phase II trial on CHF patients with refractory congestion showed a remarkable increase in furosemide bioavailability compared with oral formulation, and similar safety, length of action and efficacy as intravenous furosemide in HF patients [49].

Combining Different Diuretics: Sequential Nephron Blockade

When the previous strategies fail to achieve adequate diuresis, nephron remodeling with hyperfunction and hypertrophy of the nephron distally to the ascending branch of the loop of Henle is the most likely mechanism [36, 37, 39]. Thiazide-like diuretics and metolazone promote sodium excretion in the distal tubule and thus counteract the distal tubular hypertrophy that impairs loop diuretic response. A stepped pharmacologic approach with the combination of these drugs on top of loop diuretic treatment is now indicated for the treatment of diuretic resistance [7, 36, 50]. Caution is, however, needed above all when administered on a long-term basis and with frequent, e.g. daily, administrations for the increased risk of hypokaliemia, hyponatremia, worsening renal function and even mortality [51]. Although based on retrospective analysis of existing database, these data made the Authors suggest that a strategy of increasing loop diuretics doses may be preferred to the early combination of thiazide-like diuretics in patients with decompensated HF resistant to standard doses of loop diuretics [51].

Mineralocorticoid receptor antagonists (MRA), administered at relatively high doses, e.g. spironolactone 100 mg, can promote natriuresis and prevent potassium loss associated with loop diuretic therapy, acting on the distal convoluted tubule. Properly powered studies have, however, failed to show a beneficial effect on outcomes of their administration to patients with acute HF [8, 52].

Vasopressin receptor antagonists exert inhibition of aquaporin 2, the receptor responsible for free water reabsorption in the collecting duct. They may be particularly effective in hyponatremic patients [53]. Results of randomized trials have, however, been failed to show beneficial effects on outcomes despite larger body weight reduction and fluid loss with these agents versus placebo [54, 55].

Acetazolamide inhibits carbonic anhydrase in the proximal tubule thus favoring sodium bicarbonate excretion at this level. The increased delivery of sodium to the loop of Henle provides the substrate for loop diuretic action without

compromising renal ability to excrete diluted urine [56]. Moreover, it downregulates pendrin expression in the distal tubule, one mechanism of nephron remodeling and diuretic resistance [8, 36]. Small studies suggested the efficacy of acetazolamide added to furosemide in patients with diuretic resistance. The ongoing randomized Acetazolamide in Decompensated Heart Failure With Volume OveRload (ADVOR) trial is testing the hypothesis that the addition of acetazolamide to standard therapy may improve decongestion and outcomes in patients with acute HF [8, 57].

Sodium-glucose cotransporter 2 (SGLT2) is located in the early proximal tubule and is the major mechanism of renal glucose reabsorption. In addition it also cause reabsorption of about 5% of the filtered sodium. SGLT2 inhibitors can therefore cause glycosuria, osmotic diuresis and natriuresis. Empaglifozin, dapaglifozin and canaglifozin have reduced HF hospitalizations in large randomized controlled trials where they were administered to diabetic patients at high risk of cardiovascular events. Ongoing studies are evaluating their role in patients with established HF with or without diabetes [58, 59].

Sodium Restriction

Conflicting results exist about the optimal amount of sodium to be included in the HF patients' diet [60]. Sodium restriction showed some benefit in stable HF patients (NYHA class II-III) in the Study of Dietary Intervention Under 100 mmol in Heart Failure (SODIUM-HF) [61]. Because of lack of evidence, current ESC hf guidelines recommend to avoid excessive sodium intake (>6 g of salt/die, equal to 100 mmol of sodium, no class recommendation), while strict sodium restriction is not recommended, to date [12].

Other Therapies

Patients with advanced HF who do not respond to increased loop diuretic doses and/or to combination therapy with thiazide-like diuretics may need intravenous inotropic treatment in order to improve renal perfusion and reduce systemic venous congestion. This is still considered palliative therapy as no benefit on patients' outcomes have been shown [12, 13]. However, an improvement in diuretic response may be observed I individual cases. Similarly, low dose dopamine infusion or nesiritide infusion, also proposed to selectively improve renal function have failed to show benefit in properly designed randomized trials [62] but may be of help in individual cases. At a late stage, patients may need ultrafiltration or continuous venous-venous hemofiltration, peritoneal dialysis or hemodialysis as renal replacement therapies. Ultrafiltration has been tested also at an earlier stage as alternative to high dose loop diuretic therapy but no indication to this treatment can be done based on current data. The Peripheral Ultrafiltration for the REIief From Congestion in Heart Failure (PURE-HF) trial (NCT03161158) is evaluating whether tailored, peripheral

veno–venous ultrafiltration added to low-dose diuretics can decrease cardiovascular mortality and HF hospitalization at 90 days after randomization compared to usual care in patients with acute HF and fluid overload [8].

Treatment Pearls for the Case Vignette

The patient in the case vignette showed signs and symptoms of fluid overload, despite the ongoing diuretic therapy. The attending resident should therefore interview the patient about her symptoms, measure her vital signs (blood pressure, heart rate and O_2 saturation) and perform a careful physical examination looking for signs of congestion and precipitating factors of the acute decompensation (e.g. new onset/recurrence of atrial fibrillation, infection, coronary artery disease, poor blood pressure control, non-compliance to prescribed medications) [12, 13]. Blood sample collection for blood cell count, creatinine, electrolytes and natriuretic peptides measurement, and spot urine analysis may provide further useful information to establish the best treatment plan. Echocardiography and possibly lung ultrasound should also be performed [32]. It may detect treatable causes of decompensation, e.g. acute mitral regurgitation, pulmonary embolism, pericardial effusion. Second, it allows categorization of the patients into the low, mid-range and preserved ejection fraction categories with only those with a low ejection fraction having evidence based therapies. Third, echocardiography allows the detection of LV diastolic dysfunction as well as signs of increased intraventricular pressure, pulmonary artery pressure, inferior vena cava dilation and collpsability… Lung ultrasound allows the detection of lung comets.

Given the additional information provided on the patient from the case vignette, i.e. stage IV CKD and a recent hospitalization for HF, it might be prudent to hospitalize this patient to start intravenous diuretic treatment and monitor laboratory exams, such as serum creatinine and electrolytes, and possibly reassess the patient for echocardiographic signs of congestion.

On the other hand, if patient's symptoms are not severely limiting the patient with no signs of hypoperfusion and no treatable precipitating factor, an attempt to manage the patient in the outpatient setting can be made and oral diuretic dose can be doubled. Alternatively, intravenous loop diuretics may be administered in the outpatients clinic and the patient should be reassessed in the following days. With close follow-up visits.

References

1. Fudim M, O'Connor CM, Dunning A, Ambrosy AP, Armstrong PW, Coles A, Ezekowitz JA, Greene SJ, Metra M, Starling RC, Voors AA, Hernandez AF, Michael Felker G, Mentz RJ. Aetiology, timing and clinical predictors of early vs. late readmission following index hospitalization for acute heart failure: insights from ASCEND-HF. Eur J Heart Fail. 2018;20:304–14.
2. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. Nat Rev Cardiol. 2015;12:220–9.

3. Platz E, Jhund PS, Claggett BL, Pfeffer MA, Swedberg K, Granger CB, Yusuf S, Solomon SD, McMurray JJ. Prevalence and prognostic importance of precipitating factors leading to heart failure hospitalization: recurrent hospitalizations and mortality. Eur J Heart Fail. 2018;20:295–303.
4. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA, Candesartan in Heart failure: Assessment of Reduction in M and Morbidity I. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation. 2007;116:1482–7.
5. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlstrom U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A, Heart Failure Association of the European Society of C. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail. 2016;18:613–25.
6. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J. 2015;36:1437–44.
7. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol. 2015;12:184–92.
8. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;21:137–55.
9. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure – re-distribution and other mechanisms beyond fluid accumulation. Eur J Heart Fail. 2008;10:165–9.
10. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM Jr, Abraham WT, Smart FW, Stevenson LW, Kueffer FJ, Bourge RC. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation. 2008;118:1433–41.
11. Van Aelst LNL, Arrigo M, Placido R, Akiyama E, Girerd N, Zannad F, Manivet P, Rossignol P, Badoz M, Sadoune M, Launay JM, Gayat E, Lam CSP, Cohen-Solal A, Mebazaa A, Seronde MF. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. Eur J Heart Fail. 2018;20(4):738–47.
12. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M and Document R. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18:891–975.
13. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. American College of Cardiology F and American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147–239.
14. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med. 2001;345:574–81.
15. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes

A, McMurray JJ, Filippatos G, European Society of C and European Society of Intensive Care M. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12:423–33.
16. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC Jr, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M, Investigators ET. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J. 2013;34:835–43.
17. Chakko S, Woska D, Martinez H, de Marchena E, Futterman L, Kessler KM, Myerberg RJ. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. Am J Med. 1991;90:353–9.
18. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation. 2007;116:1549–54.
19. Dovancescu S, Pellicori P, Mabote T, Torabi A, Clark AL, Cleland JGF. The effects of short-term omission of daily medication on the pathophysiology of heart failure. Eur J Heart Fail. 2017;19:643–9.
20. Maisel AS, Duran JM, Wettersten N. Natriuretic peptides in heart failure: atrial and B-type natriuretic peptides. Heart Fail Clin. 2018;14:13–25.
21. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL Jr, Mark DB, Pina IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2017;318:713–20.
22. Mark DB, Cowper PA, Anstrom KJ, Sheng S, Daniels MR, Knight JD, Baloch KN, Davidson-Ray L, Fiuzat M, Januzzi JL Jr, Whellan DJ, Pina IL, Ezekowitz JA, Adams KF, Cooper LS, O'Connor CM, Felker GM. Economic and quality-of-life outcomes of natriuretic peptide-guided therapy for heart failure. J Am Coll Cardiol. 2018;72:2551–62.
23. Stienen S, Salah K, Moons AH, Bakx AL, van Pol P, Kortz RAM, Ferreira JP, Marques I, Schroeder-Tanka JM, Keijer JT, Bayes-Genis A, Tijssen JGP, Pinto YM, Kok WE. NT-proBNP (N-terminal pro-B-type natriuretic peptide)-guided therapy in acute decompensated heart failure: PRIMA II randomized controlled trial (can NT-ProBNP-guided therapy during hospital admission for acute decompensated heart failure reduce mortality and readmissions?). Circulation. 2018;137:1671–83.
24. McDonald K, Troughton R, Dahlstrom U, Dargie H, Krum H, van der Meer P, McDonagh T, Atherton JJ, Kupfer K, San George RC, Richards M, Doughty R. Daily home BNP monitoring in heart failure for prediction of impending clinical deterioration: results from the HOME HF study. Eur J Heart Fail. 2018;20:474–80.
25. D'Elia E, Iacovoni A, Vaduganathan M, Lorini FL, Perlini S, Senni M. Neprilysin inhibition in heart failure: mechanisms and substrates beyond modulating natriuretic peptides. Eur J Heart Fail. 2017;19:710–7.
26. Pellicori P, Carubelli V, Zhang J, Castiello T, Sherwi N, Clark AL, Cleland JG. IVC diameter in patients with chronic heart failure: relationships and prognostic significance. JACC Cardiovasc Imaging. 2013;6:16–28.
27. Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. Eur J Heart Fail. 2017;19:1154–63.
28. Andersen OS, Smiseth OA, Dokainish H, Abudiab MM, Schutt RC, Kumar A, Sato K, Harb S, Gude E, Remme EW, Andreassen AK, Ha JW, Xu J, Klein AL, Nagueh SF. Estimating left ventricular filling pressure by echocardiography. J Am Coll Cardiol. 2017;69:1937–48.
29. Nagueh SF. Non-invasive assessment of left ventricular filling pressure. Eur J Heart Fail. 2018;20:38–48.

30. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, Henderson J, Cowart P, Stevenson LW. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail. 2014;7:935–44.
31. Givertz MM, Stevenson LW, Costanzo MR, Bourge RC, Bauman JG, Ginn G, Abraham WT, Investigators CT. Pulmonary artery pressure-guided management of patients with heart failure and reduced ejection fraction. J Am Coll Cardiol. 2017;70:1875–86.
32. Harjola VP, Parissis J, Brunner-La Rocca HP, Celutkiene J, Chioncel O, Collins SP, De Backer D, Filippatos GS, Gayat E, Hill L, Lainscak M, Lassus J, Masip J, Mebazaa A, Miro O, Mortara A, Mueller C, Mullens W, Nieminen MS, Rudiger A, Ruschitzka F, Seferovic PM, Sionis A, Vieillard-Baron A, Weinstein JM, de Boer RA, Crespo-Leiro MG, Piepoli M, Riley JP. Comprehensive in-hospital monitoring in acute heart failure: applications for clinical practice and future directions for research. A statement from the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2018;20:1081–99.
33. Verbrugge FH. Editor's Choice-Diuretic resistance in acute heart failure. Eur Heart J Acute Cardiovasc Care. 2018;7:379–89.
34. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. Eur Heart J. 2014;35:1284–93.
35. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G, Greenberg BH, Pang PS, Levin B, Hua TA, Severin T, Ponikowski P, Metra M, Investigators R-A. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome – an analysis from RELAX-AHF. Eur J Heart Fail. 2014;16:1230–40.
36. Ellison DH, Felker GM. Diuretic treatment in heart failure. N Engl J Med. 2017;377:1964–75.
37. Ter Maaten JM, Rao VS, Hanberg JS, Perry Wilson F, Bellumkonda L, Assefa M, Sam Broughton J, D'Ambrosi J, Wilson Tang WH, Damman K, Voors AA, Ellison DH, Testani JM. Renal tubular resistance is the primary driver for loop diuretic resistance in acute heart failure. Eur J Heart Fail. 2017;19:1014–22.
38. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WH, Mullens W. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol. 2013;62:485–95.
39. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology. 2001;96:132–43.
40. Galiwango PJ, McReynolds A, Ivanov J, Chan CT, Floras JS. Activity with ambulation attenuates diuretic responsiveness in chronic heart failure. J Card Fail. 2011;17:797–803.
41. Wargo KA, Banta WM. A comprehensive review of the loop diuretics: should furosemide be first line? Ann Pharmacother. 2009;43:1836–47.
42. Masuyama T, Tsujino T, Origasa H, Yamamoto K, Akasaka T, Hirano Y, Ohte N, Daimon T, Nakatani S, Ito H. Superiority of long-acting to short-acting loop diuretics in the treatment of congestive heart failure. Circ J. 2012;76:833–42.
43. Mentz RJ, Hasselblad V, DeVore AD, Metra M, Voors AA, Armstrong PW, Ezekowitz JA, Tang WH, Schulte PJ, Anstrom KJ, Hernandez AF, Velazquez EJ, O'Connor CM. Torsemide versus furosemide in patients with acute heart failure (from the ASCEND-HF trial). Am J Cardiol. 2016;117:404–11.
44. Greene SJ, Mentz RJ. Potential advantages of torsemide in patients with heart failure: more than just a 'water pill'. Eur J Heart Fail. 2018;20:471–3.
45. Trippel TD, Van Linthout S, Westermann D, Lindhorst R, Sandek A, Ernst S, Bobenko A, Kasner M, Spillmann F, Gonzalez A, Lopez B, Ravassa S, Pieske B, Paulus WJ, Diez J, Edelmann F, Tschope C. Investigating a biomarker-driven approach to target collagen turnover in diabetic heart failure with preserved ejection fraction patients. Effect of torasemide versus furosemide on serum C-terminal propeptide of procollagen type I (DROP-PIP trial). Eur J Heart Fail. 2018;20:460–70.

46. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM, Network NHFCR. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805.
47. Buckley LF, Seoane-Vazquez E, Cheng JW, Aldemerdash A, Cooper IM, Matta L, Medina DS, Mehra MR, Navarro-Velez K, Shea EL, Weintraub JR, Stevenson LW, Desai AS. Comparison of ambulatory, high-dose, intravenous diuretic therapy to standard hospitalization and diuretic therapy for treatment of acute decompensated heart failure. Am J Cardiol. 2016;118:1350–5.
48. Buckley LF, Carter DM, Matta L, Cheng JW, Stevens C, Belenkiy RM, Burpee LJ, Young MA, Weiffenbach CS, Smallwood JA, Stevenson LW, Desai AS. Intravenous diuretic therapy for the management of heart failure and volume overload in a multidisciplinary outpatient unit. JACC Heart Fail. 2016;4:1–8.
49. Gilotra NA, Princewill O, Marino B, Okwuosa IS, Chasler J, Almansa J, Cummings A, Rhodes P, Chambers J, Cuomo K, Russell SD. Efficacy of intravenous furosemide versus a novel, pH-neutral furosemide formulation administered subcutaneously in outpatients with worsening heart failure. JACC Heart Fail. 2018;6:65–70.
50. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56:1527–34.
51. Brisco-Bacik MA, Ter Maaten JM, Houser SR, Vedage NA, Rao V, Ahmad T, Wilson FP, Testani JM. Outcomes associated with a strategy of adjuvant metolazone or high-dose loop diuretics in acute decompensated heart failure: a propensity analysis. J Am Heart Assoc. 2018;7:e009149.
52. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, Mann DL, Margulies KB, McNulty SE, Mentz RJ, Redfield MM, Tang WHW, Whellan DJ, Shah M, Desvigne-Nickens P, Hernandez AF, Braunwald E, National Heart L and Blood Institute Heart Failure Clinical Research N. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. JAMA Cardiol. 2017;2:950–8.
53. Pose A, Almenar L, Gavira JJ, Lopez-Granados A, Blasco T, Delgado J, Aramburu O, Rodriguez A, Manzano L, Manito N. Benefit of tolvaptan in the management of hyponatraemia in patients with diuretic-refractory congestive heart failure: the SEMI-SEC project. ESC Heart Fail. 2017;4:130–7.
54. Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, Haught WH, Wagoner L, Gupta D, Patten R, Gordon P, Korr K, Fileccia R, Pressler SJ, Gregory D, Wedge P, Dowling D, Romeling M, Konstam JM, Massaro JM, Udelson JE, Secret of Chf Investigators C and Committee M. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. J Am Coll Cardiol. 2017;69:1409–19.
55. Felker GM, Mentz RJ, Cole RT, Adams KF, Egnaczyk GF, Fiuzat M, Patel CB, Echols M, Khouri MG, Tauras JM, Gupta D, Monds P, Roberts R, O'Connor CM. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. J Am Coll Cardiol. 2017;69:1399–406.
56. Verbrugge FH, Mullens W, Tang WH. Management of cardio-renal syndrome and diuretic resistance. Curr Treat Options Cardiovasc Med. 2016;18:11.
57. Mullens W, Verbrugge FH, Nijst P, Martens P, Tartaglia K, Theunissen E, Bruckers L, Droogne W, Troisfontaines P, Damman K, Lassus J, Mebazaa A, Filippatos G, Ruschitzka F, Dupont M. Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. Eur J Heart Fail. 2018;20:1591–600.
58. Butler J, Hamo CE, Filippatos G, Pocock SJ, Bernstein RA, Brueckmann M, Cheung AK, George JT, Green JB, Januzzi JL, Kaul S, Lam CSP, Lip GYH, Marx N, McCullough PA, Mehta CR, Ponikowski P, Rosenstock J, Sattar N, Salsali A, Scirica BM, Shah SJ, Tsutsui H, Verma S, Wanner C, Woerle HJ, Zannad F, Anker SD, Program ET. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. Eur J Heart Fail. 2017;19:1390–400.

59. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. Circulation. 2017;136:1643–58.
60. Ravera A, Carubelli V, Sciatti E, Bonadei I, Gorga E, Cani D, Vizzardi E, Metra M, Lombardi C. Nutrition and cardiovascular disease: finding the perfect recipe for cardiovascular health. Nutrients. 2016;8.
61. Colin-Ramirez E, McAlister FA, Zheng Y, Sharma S, Armstrong PW, Ezekowitz JA. The long-term effects of dietary sodium restriction on clinical outcomes in patients with heart failure. The SODIUM-HF (Study of Dietary Intervention Under 100 mmol in Heart Failure): a pilot study. Am Heart J. 2015;169:274–281 e1.
62. Chen HH, Redfield MM. Dopamine vs nesiritide for acute heart failure with renal dysfunction – reply. JAMA. 2014;311:1565–6.

Worsening Renal Function in a Patient with Acute Heart Failure and Volume Overload

10

Ely Gracia, Javed Butler, and Sandeep K. Mallipattu

Case Vignette

Mr. Y is a 73 year old man who has been admitted for decompensated heart failure with reduced ejection fraction for 6 days. During the course of his hospitalization, he lost 6 kg. Net fluid balance is negative 5200 mL and currently he has only trace pedal edema and no orthopnea. Serum creatinine has increased slightly, from 1.26 mg/dL at admission to 1.43 mg/dL currently. During the same time window, the hematocrit has increased from 37% to 41%. Medications during the past 24 hours include lisinopril 20 mg once daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg once daily, aspirin, rosuvastatin and chlorthalidone 50 mg (started on the third day of the admission for emerging diuretic resistance) as well as 80 mg furosemide twice daily. Heart rate is 78 bpm and blood pressure is 108/69 mmHg when Mr. Y is sitting on the edge of his bed. Is Mr. Y ready for discharge?

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Chapter Key Points

- Pharmacokinetics of loop diuretics in acute heart failure
- Pharmacodynamics of loop diuretics in acute heart failure
- Impact of renal function on dosing strategies of loop diuretics to treat volume overload in acute heart failure
- Incidence and risk factors for worsening renal function and electrolyte disturbances in acute heart failure
- Prognostic impact of worsening renal function in acute heart failure, and relationship between worsening renal function and volume overload
- Treatment strategies when a rise in serum creatinine is observed during decongestive treatment in acute heart failure with a focus on renal preservation

Brief Discussion of the Case

Our patient, Mr. Y, was admitted because of an exacerbation of acute heart failure (AHF) and treated with furosemide. During the hospitalization, clinical decongestion was achieved, which is reflected by the resolution of symptoms, weight loss and a negative fluid balance, while remaining hemodynamically stable. However, Mr. Y also demonstrates laboratory marker changes significant for subclinical decongestion, including a rise in serum creatinine (Cr) and hematocrit. In addition to decongestion, the patient is also managed on optimal medications for heart failure with reduced ejection fraction (HFrEF). Based on the above presentation, the patient was determined to be stable for discharge from the hospital with close outpatient follow-up at a heart failure clinic.

Introduction

As one of the most common diagnoses responsible for hospital admissions in patients over the age of 65 years, heart failure accounts for up to one million hospital admissions annually and is associated with high rates of mortality [1–3]. Heart failure is a spectrum disease with transitions between a stable, chronic state and acute decompensations. Acute heart failure (AHF) exacerbations are attributed to fluid retention and overall congestion, and contribute to symptom severity and overall outcomes [4]. Given the inciting factor being overt congestion, the goal of management revolves around diuresis, with loop diuretics being the modality of choice [5]. Although the mechanism of action with loop diuretics is clear, there are currently limited guidelines for the use of loop diuretics in the management of AHF [6] and their potential benefits in improving overall mortality remain debatable.

Pharmacokinetics of Loop Diuretics in Acute Heart Failure

The ability to achieve appropriate decongestion with loop diuretics is dependent on various factors including adequate dosing, bioavailability, and half-life of each medication. The rate of drug delivery and response to loop diuretics is based on a sigmoidal-shaped dose-response curve that sits between both threshold and plateau concentrations [7, 8]. The goal in dosing is to achieve a sufficient concentration that will exceed the threshold (minimally effective dose) concentration. Due to the unique properties of each drug as well as the patient-specific response, tailoring and titrating the dose individually is required for optimization [9]. This *optimal dose* represents the maximally effective dose of diuretic capable of completely blocking sodium reabsorption at the level of the thick ascending limb within the Loop of Henle and varies amongst both choice of diuretic and patients, essentially a *ceiling threshold* to achieve [8, 9]. Previous literature indicates that the ceiling threshold represents the dosage at which a maximal response is elicited and a level that is not to be exceeded [9]. Conversely, a more recent review suggests that increasing the diuretic dose above the ceiling threshold causes further natriuresis by extending the time period at which the plasma diuretic concentration exceeds the natriuresis threshold [7].

Amongst the loop diuretics, furosemide has the most variable and limited bioavailability with an average bioavailability of 50% and ranging from as low as 10–90% [7]. The absorption of furosemide is unpredictable and affected by numerous factors including route of medication, absorption rates and presence of gastric contents. Intravenous furosemide is two times as potent as oral formulations in patients with preserved renal function, allowing for prolonged periods of time at which the peak plasma concentration surpasses the natriuresis threshold and promotes diuresis [7]. The increased intestinal edema and reduced intestinal blood flow often seen in congestive heart failure reduces absorption rates via a reduction in the overall peak plasma concentration, thus keeping plasma concentrations below the natriuresis threshold. As with edema, intake of oral furosemide along with enteral feed alters the rate of absorption via prolongation of gastric emptying times, which affect peak concentration and time to peak concentration, as well as buffering gastric contents via alkalization of normally acidic gastric fluids beyond the optimal pH for diuretic absorption [7, 8]. When compared to furosemide, torsemide and bumetanide both exhibit improved and less variable bioavailability (80–100%)(9) without the hindrance of absorption-limiting kinetics [7].

Amongst the three oral loop diuretics, torsemide has the longest half-life in heart failure patients (6 hours) compared to furosemide (2.7 hours) and bumetanide (1.3 hours) [9]. The significance of this relates to typical dosing schedules of diuretics and inadequate amounts of diuretics at the site of action, which generally lead to periods of post-diuretic sodium retention and a *braking phenomenon*. Post-diuretic sodium retention is a compensatory mechanism in place to equilibrate sodium levels following periods of elevated diuretic-induced sodium losses [10]. During this period, patients are vulnerable for rapid retention of dietary sodium that can potentially nullify the natriuresis previously achieved, which stresses the importance of

maintaining a negative sodium balance [7]. Another post-diuretic adaption is activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) leading to nephron remodeling, which prevents long-term extracellular volume contraction after periods of aggressive diuresis and can potentially lead to diuretic resistance in a persistently congested patient [7, 10]. These findings suggest the need to limit once a day dosing of diuretics as well as an evaluation of appropriate dosing schedules to prevent diuretic resistance.

Pharmacodynamics of Loop Diuretics in Acute Heart Failure

The pharmacodynamics of loop diuretics revolve around blockade of sodium chloride reabsorption at the level of the loop of Henle. Loop diuretics bind directly to the translocation pocket located on the extracellular surface of the sodium-potassium-chloride-cotransporter (NKCC), which is an electroneutral transporter mediating inward movement of ions across membranes, and blockade prevents ion transport [11]. There are two isoforms of the NKCC cotransporters, NKCC1 and NKCC2, with the renal-specific isoform, NKCC2, being located on the apical surface of the thick ascending limb along the loop of Henle and the ubiquitous isoform, NKCC1, located throughout the body including in the ear [7, 12]. Both isoforms are inhibited by loop diuretics. However, blockade of the NKCC2 cotransporter on the thick ascending limb, which is responsible for the reabsorption of up to 25% of filtered sodium and chloride, leads to natriuresis of extracellular volume [7]. NKCC2 blockade at the level of the epithelial cells of the macula densa can contribute to fluctuations in glomerular filtration due to imbalances in increased renin secretion as well as inhibition of the tubuloglomerular feedback [7–12]. Specifically, this activity at the level of the macula densa has opposing forces on glomerular filtration, with renin secretion leading to increased angiotensin II activation and decreased filtration rates while inhibition of tubuloglomerular feedback preserves filtration rates [13]. In addition to the action at the level of the nephron, loop diuretics also have a direct impact on systemic hemodynamics. These properties are dose-dependent and are responsible for the activation of RAAS, via renin secretion, and vasodilation of renal vasculature secondary to inhibition of the NKCC1 [14].

Impact of Renal Function on Dosing Strategies of Loop Diuretics to Treat Volume Overload in Acute Heart Failure

Elevated serum creatinine is a frequently encountered complication in the management of AHF and has commonly been used as a surrogate endpoint in many of the heart failure trials, with its high association with poor outcomes [15]. High-dose loop diuretics, which are often necessary for achieving a decongested state, have been associated with a higher incidence of elevated serum creatinine and poor outcomes, which has led to their judicious use [7, 16–18]. Gottlieb et al. showed that the use of intravenous furosemide in a volume overloaded state induces a significant

reduction in glomerular filtration rate (GFR) by 25% [19] and this demographic was predisposed to developing acute kidney injury (AKI) [20]. However, the association between worsening renal function (WRF), defined as an increase of >0.3 mg/dL in Cr, and poor outcomes has been linked to baseline CKD, sparing patients with normal or mildly impaired renal function [15, 17]. More recently, studies have called into question the validity of Cr to act as a uniform marker for predicting prognosis, given that each patient has a unique response of the GFR to changes in central venous pressure [21–24].

Many strategies exist regarding dosing of loop diuretics in an AHF exacerbation. The Diuretic Optimization Strategies Evaluation (DOSE) trial, which compared high-dosage to low-dosage administration, as well as continuous infusion versus a bolus delivery, found that there was no significant difference between approaches of delivery or dosage amounts [25]. There was however a non-statistically significant trend toward better symptomatic improvement in high- versus low-dosage strategies and higher rates of AKI in the continuous administration arm [25]. A subsequent study further investigated continuous infusions compared to a bolus approach and also observed that continuous infusion was associated with increased rate of AKI despite improvements in B-type natriuretic peptide (BNP) and increased urine output [26].

Incidence and Risk Factors for Acute Kidney Injury in Acute Heart Failure

The majority of heart failure patients have some degree of renal impairment and this population is predisposed to an increased relative risk of mortality of up to 50% compared to patients with normal renal function [27]. More than 40% of patients with chronic heart failure have a GFR <60 mL/min/1.73m^2, which meets the criteria for CKD stage 3 [28]. An analysis of the Acute Decompensated Heart Registry (ADHERE) database revealed that at least moderate renal dysfunction was present in 63.6% of patients admitted with AHF [29, 30].

Patients with more severe degrees of renal impairment have a further compounded risk of prolonged hospitalization and risk of death in the immediate post-discharge period [31]. Additionally, patients with existing CKD who experience a severe AKI during hospitalization are at a high risk for progressing to end-stage renal disease (ESRD) within 30 days of discharge (49% compared to 1.9% of CKD patients without AKI) [32]. Diabetes is another strong risk factors for the development of CKD, with 35% of diabetics having developed baseline kidney dysfunction [33]. Hospitalization places these patients at higher risks for developing AKI while inpatient and 30% will experience a subsequent episode of AKI after discharge [34].

AKI during AHF treatment can vary based on numerous factors and its incidence ranges from 20% to 70%. It has been associated with poor outcome, including prolonged hospitalizations, readmissions and increased mortality [15, 17, 18]. Given the poor outcomes associated with reduced GFR, certain risk factors for elevations

in Cr have been identified. These include decreased renal blood flow, increased renal venous congestion via increased central venous pressure, and increased abdominal pressure [22, 35–37].

Prognostic Impact of Worsening Renal Function in Acute Heart Failure and Relationship Between Elevations in Serum Creatinine and Volume Overload

Due to its association with poor outcomes, elevated Cr levels have been commonly used as an end-point in many AHF trials [15, 27, 38, 39]. However, more recent studies call into question the validity of Cr as a surrogate for prognosis and rather place a greater emphasis on the individual's baseline renal function as the key determinant of prognosis (Fig. 10.1) [22, 40, 41]. In a post-hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE), Beta-blocker Evaluation of Survival Trial (BEST), and Studies of Left Ventricular Dysfunction (SOLVD) trials,

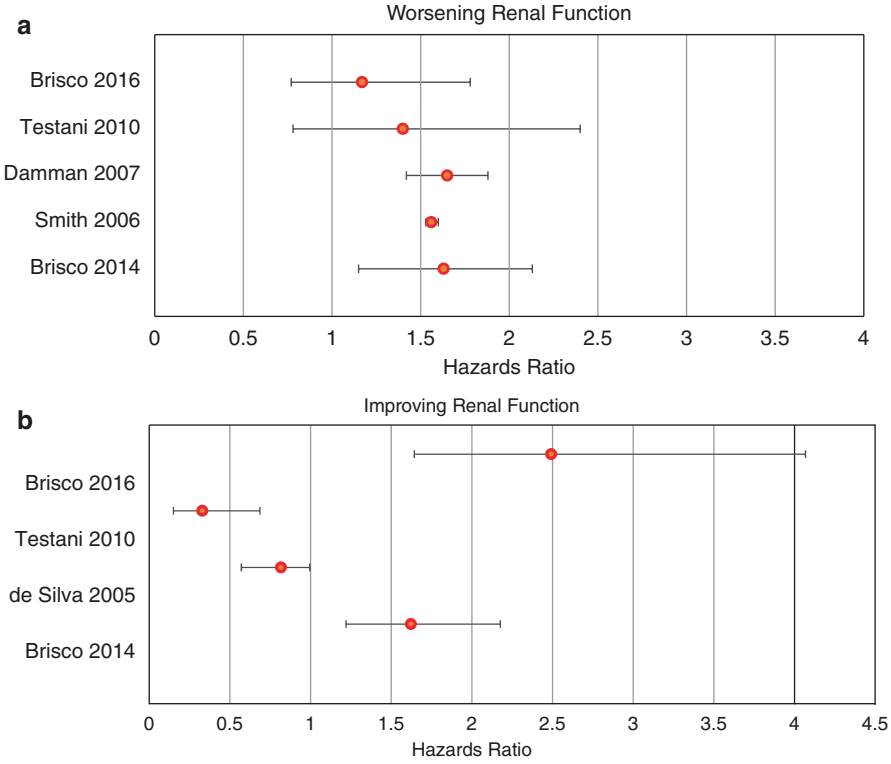

Fig. 10.1 Forrest plots of worsening versus improved renal function, defined as a change in serum creatinine >0.3 mg/dL. The graph demonstrates the wide range of hazard ratios, both statistically significant and insignificant, which has led to the questioning of serum creatinine's use as a valid surrogate marker for outcomes. (**a**) Hazard ratios in the setting of elevated serum creatinine. (**b**) Hazard ratios in the setting of decreasing serum creatinine

isolated elevations in Cr failed to carry any prognostic significance [42]. However, when elevations in Cr occur alongside spikes in blood urea nitrogen (BUN), there was a significantly higher mortality (HR = 1.59, 95% CI 1.34–1.88, $p < 0.0001$) compared to patients with stable BUN (HR = 0.71, 95% CI 0.49–0.96, $p = 0.042$) [43].

In contrast, elevations in Cr in the setting of hemoconcentration, which often occurs with more aggressive diuretic regimens, have been shown to lead to a substantially lower risk of mortality, owing to greater fluid and weight loss, greater reduction in right atrial and pulmonary arterial wedge pressures [40]. Similarly, when occurring in the setting of aggressive diuresis or during the introduction of RAAS blockade, there was a paradoxical association between rising Cr and improved outcomes [15]. Thus, Cr may not be a reliable prognosticating tool, and may lead to the exclusion of many beneficial AHF therapies (Fig. 10.1a, b, Table 10.1) [41].

Table 10.1 Hazard of all-cause mortality with worsening versus improving renal function in heart failure

Group	Year	Ref #	Study	HR, 95%CI
Worsening renal function				
Brisco et al.	2016	15	Post-hoc analysis of the DOSE trial with 301 acute heart failure patients	1.17 (0.77–1.78)
Testani et al.	2010	40	Post-hoc analysis of the ESCAPE trial with 433 heart failure patients with ejection fraction <30% and elevated creatinine levels	1.40 (0.78–2.40)
Damman et al.	2007	38	Meta-analysis of 18,634 heart failure patients with worsening renal function	1.65 (1.42–1.88)
Smith et al.	2006	27	Meta-analysis of 80,098 hospitalized and non-hospitalized heart failure patients with renal impairment	1.56 (1.53–1.60)
Brisco et al.	2014	39	Post-hoc analysis of the INTERMACS registry with 3363 patients on mechanical support for heart failure with renal function followed up to 1 year post device implantation	1.63 (1.15–2.13)
Improving renal function				
Brisco et al.	2016	15	Post-hoc analysis of the DOSE trial with 301 acute heart failure patients	2.52 (1.57–4.03)
Testani et al.	2010	40	Post-hoc analysis of the ESCAPE trial with 433 heart failure patients with ejection fraction <30% and elevated creatinine levels	0.38 (0.18–0.78)
de Silva et al.	2006	24	Observational prospective study of 1216 heart failure patients	0.80 (0.60–1.00)
Brisco et al.	2014	39	Post-hoc analysis of the INTERMACS registry with 3363 patients on mechanical support for heart failure with renal function followed up to 1 year post device implantation	1.64 (1.19–2.26)

Abbreviations: *CI* confidence interval, *Ref* reference, *DOSE* Diuretic Optimization Strategies Evaluation, *ESCAPE* Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; *HR* hazard ratio, *INTERMACS* Interagency Registry for Mechanically Assisted Circulatory Support

Table 10.2 Novel biomarkers for detection of renal injury

Markers of acute kidney injury	Function	AUC, 95%CI
Insulin-like growth factor-binding protein 7 (IGFBP7)	Inducer of G_1 cell cycle arrest	0.77 (0.71–0.82)
Tissue inhibitor of metalloproteinase-2 (TIMP-2)	Inducer of G_1 cell cycle arrest	0.75 (0.70–0.80)
Neutrophil gelatinase-associated lipocalin (NGAL)	Synthesized in renal tubular tissue and upregulated during kidney injury	0.66 (0.60–0.71)
Kidney injury molecule-1(KIM-1)	Transmembrane protein, upregulated during proximal tubular injury	0.66 (0.61–0.72)
Interleukin-18(IL-18)	Cytokine and mediator of renal ischemia-reperfusion injury	0.65 (0.60–0.71)

The univariate area under the receiver-operating characteristics curve was based on RIFLE I or F occurring between 12–36 hours after sample collection
AUC area under the curve, *CI* confidence interval

Alternative Markers of Renal Function in Heart Failure

Due to the inability of Cr alone to accurately predict renal injury in the setting of AHF, several alternative markers of renal injury have been proposed that identify renal injury sooner and more reliably. Elevated levels of specific urinary markers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin-18 (IL-18), have been shown to correlate with renal injury and impairment in natriuresis and diuresis in patients with acute HF but did not necessarily predict AKI or persistent renal impairment [44]. In the ROSE (Renal Optimization Strategies Evaluation) sub-study, urinary levels of NGAL, NAG (N-acetyl-β-d-glucosaminidase) and KIM-1 did not track with changes of either Cr or cystatin C [45]. Furthermore, WRF and rise in tubular injury biomarkers following aggressive diuresis was associated with a paradoxical trend toward improved outcomes [45]. Meanwhile, newer renal function biomarkers, such as insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase-2 (TIMP-2), have demonstrated a higher overall sensitivity and ability to differentiate between AKI and non-AKI conditions including CKD, when compared with NGAL or KIM-1, even though in this critical care study population only 17% patients have HF (Table 10.2) [46].

Treatment Strategies When a Rise in Serum Creatinine Is Observed During Diuresis in Acute Heart Failure with a Focus on Renal Preservation

The pathogenesis of AHF centers around congestion, which ultimately leads to organ dysfunction via persistently elevated central venous pressures and hypoperfusion of the kidneys [47]. During severely decompensated AHF, markedly reduced renal blood flow and extremely elevated renal vascular resistance generates a drop

in GFR without a compensatory activation of the RAAS that preserves perfusion to vital organs including the brain and heart via an increase in filtration fraction [48].

The current treatment of AHF with diuretics, which acts to reduce arterial volumes, predisposes patients with more severe heart failure exacerbations to elevations in Cr levels [48]. In order to address the issue of reduced intravascular volumes leading to elevations in Cr, several small studies have looked at the combination of hypertonic saline with high-dose loop diuretics to augment decongestion and its effects on mortality and readmissions rates. In a small, single-blinded study involving 107 patients with refractory congestive heart failure, the use of hypertonic saline along with high-dose loop diuretics was associated with lower mortality (45.3% versus 87% in conventional treatment), which was attributed to the instantaneous mobilization of fluids into the intravascular space via the increased oncotic pressure of hypertonic saline [49]. This combination of hypertonic saline with high-dose loop diuretics lead to an overall reduction in atrial natriuretic peptide, B-type natriuretic peptide, and immune-inflammatory markers and achieved more rapid weight reduction and reduced hospitalization duration and 30-day readmission rates [50–52].

Another potential adjunct may be the use of serelaxin in the prevention of WRF. By acting as a vasodilator, serelaxin reduces end-organ damage by improving renovascular blood flow during AHF exacerbations, which may work to prevent diuretic-induced WRF [53]. Additionally, there is a rationale for the supplementation of thiamine to a patient on prolonged diuretic use. Loop diuretics, specifically furosemide, lead to increased urinary excretion of thiamine [54]. Thiamine supplementation was associated with an improvement in left ventricular ejection fraction, which translated into improved cardiac function and urine output [55].

In patients with AHF and WRF, renal adjuvant therapy with the use of low-dose dopamine has been used to augment decongestion while preserving renal perfusion during diuresis, leading to more electrolyte homeostasis, reduced hospital lengths of stay and decreased rates of 30-day readmissions [56, 57]. However, in a large, multicenter, randomized study looking at a population with CKD, it was shown that the addition of low-dose dopamine to diuretic therapy did not lead to enhanced decongestion nor improvement in renal function when compared to isolated diuretic therapy [58].

Inappropriately elevated levels of arginine-vasopressin during AHF lead to increased water retention, contributing to both congestive symptoms and electrolyte abnormalities. Tolvaptan, a V2 receptor antagonist, blocks the antidiuretic effects of this hormone and leads to improved fluid excretion and improved renal function [59, 60]. Although useful in achieving additional diuresis, the use of tolvaptan was not associated improved long-term mortality benefits nor heart failure-related morbidity [60].

Diabetes is associated with a substantial risk for the development of renal disease [33, 61]. Inhibition of the sodium glucose transporter-2 (SGLT-2) promotes fluid excretion via blockage of glucose reabsorption in the proximal tubules and promoting glycosuria [62]. In addition to aiding with glucose control and body weight, treatment with SGLT-2 inhibitors was associated with a lower risk of hospitalization

for heart failure, progression of albuminuria, and loss of kidney function compared to placebo groups as well as a significant reduction in death from cardiovascular causes, non-fatal myocardial infarctions, and non-fatal strokes (HR 0.86, 95%CI 0.75–0.97) [63].

An additional method for achieving diuresis in the setting of worsening Cr levels is to augment diuresis through the blockade of aldosterone via mineralocorticoid receptor antagonists. Via competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted tubules and collecting ducts, spironolactone increases sodium and free water excretion while retaining potassium. However when compared to placebo, upfront high-dose spironolactone (100 mg daily for 96 hours) for patients with acute HF was well tolerated but did not improve change in NT-proBNP levels, clinical congestion score, dyspnea assessment, net urine output, or net weight change [64].

Treatment Pearls for the Case Vignette

Loop diuretics remain the cornerstone of therapy for the management of AHF, with their appropriate use, as in the case vignette, leading to resolution of symptoms as well as achieving clinical and subclinical decongestion. Commonly, AHF patients develop elevations in Cr as a consequence of diuretic use, which has led to cautious use of this vital therapy. Numerous studies have shown however that the poor outcomes associated with WRF are actually attributable to baseline kidney dysfunction, with higher incidences and poor outcomes associated with more severe CKD. Given this fact, the use of Cr as a marker of prognosis in AHF may not be accurate without taking into account the overall clinical picture, specifically whether or not WRF is taking place in the setting of appropriate decongestion. Therefore, we are confident Mr. Y is ready for discharge.

References

1. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. J Am Coll Cardiol. 2013;61(4):391–403.
2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019; CIR0000000000000659.
3. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. JAMA. 2004;292(3):344–50.

4. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G, European Society of Cardiology; European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12(5):423–33.
5. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev. 2012;(2):CD003838.
6. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362–425.
7. Ellison DH, Felker GM. Diuretic treatment in heart failure. N Engl J Med. 2017;377(20): 1964–75.
8. Sica DA. Pharmacotherapy in congestive heart failure: drug absorption in the management of congestive heart failure: loop diuretics. Congest Heart Fail. 2003;9(5):287–92.
9. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. Am J Physiol Renal Physiol. 2003;284(1):F11–21.
10. Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med. 1991;114(10):886–94.
11. Somasekharan S, Tanis J, Forbush B. Loop diuretic and ion-binding residues revealed by scanning mutagenesis of transmembrane helix 3 (TM3) of Na-K-Cl cotransporter (NKCC1). J Biol Chem. 2012;287(21):17308–17.
12. Orlov SN, Koltsova SV, Kapilevich LV, Gusakova SV, Dulin NO. NKCC1 and NKCC2: the pathogenetic role of cation-chloride cotransporters in hypertension. Genes Dis. 2015;2(2):186–96.
13. Bell PD, Lapointe JY, Peti-Peterdi J. Macula densa cell signaling. Annu Rev Physiol. 2003;65:481–500.
14. Oppermann M, Hansen PB, Castrop H, Schnermann J. Vasodilatation of afferent arterioles and paradoxical increase of renal vascular resistance by furosemide in mice. Am J Physiol Renal Physiol. 2007;293(1):F279–87.
15. Brisco MA, Zile MR, Hanberg JS, Wilson FP, Parikh CR, Coca SG, Tang WH, Testani JM. Relevance of changes in serum creatinine during a heart failure trial of decongestive strategies: insights from the DOSE trial. J Card Fail. 2016;22(10):753–60.
16. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail. 2007;9(10):1064–9.
17. Palazzuoli A, Ruocco G, Ronco C, McCullough PA. Loop diuretics in acute heart failure: beyond the decongestive relief for the kidney. Crit Care. 2015;19:296.
18. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35(7):455–69.
19. Gottlieb SS, Skettino SL, Wolff A, Beckman E, Fisher ML, Freudenberger R, Gladwell T, Marshall J, Cines M, Bennett D, Liittschwager EB. Effects of BG9719 (CVT-124), an A1-adenosine receptor antagonist, and furosemide on glomerular filtration rate and natriuresis in patients with congestive heart failure. J Am Coll Cardiol. 2000;35(1):56–9.
20. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Dei CL. Worsening renal function in

patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail. 2008;10(2):188–95.
21. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail. 2011;4(6):685–91.
22. Damman K, Ng Kam Chuen MJ, MacFadyen RJ, Lip GY, Gaze D, Collinson PO, Hillege HL, van Oeveren W, Voors AA, van Veldhuisen DJ. Volume status and diuretic therapy in systolic heart failure and the detection of early abnormalities in renal and tubular function. J Am Coll Cardiol. 2011;57(22):2233–41.
23. Metra M, Cotter G, Senger S, Edwards C, Cleland JG, Ponikowski P, Cursack GC, Milo O, Teerlink JR, Givertz MM, O'Connor CM, Dittrich HC, Bloomfield DM, Voors AA, Davison BA. Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion: a post hoc analysis of the PROTECT data. Circ Heart Fail. 2018;11(5):e004644.
24. de Silva R, Nikitin NP, Witte KK, Rigby AS, Goode K, Bhandari S, Clark AL, Cleland JG. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. Eur Heart J. 2006;27(5):569–81.
25. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM, NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797–805.
26. Palazzuoli A, Pellegrini M, Ruocco G, Martini G, Franci B, Campagna MS, Gilleman M, Nuti R, McCullough PA, Ronco C. Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial. Crit Care. 2014;18(3):R134.
27. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol. 2006;47(10):1987–96.
28. Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. The cardiorenal syndrome in heart failure. Prog Cardiovasc Dis. 2011;54(2):144–53.
29. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP, ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209–16.
30. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J, ADHERE Scientific Advisory Committee and Investigators. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail. 2007;13(6):422–30.
31. Klein L, Massie BM, Leimberger JD, O'Connor CM, Piña IL, Adams KF Jr, Califf RM, Gheorghiade M, OPTIME-CHF Investigators. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). Circ Heart Fail. 2008;1(1):25–33.
32. Hsu CY, Chertow GM, McCulloch CE, Fan D, Ordonez JD, Go AS. Nonrecovery of kidney function and death after acute on chronic renal failure. Clin J Am Soc Nephrol. 2009;4(5):891–8.
33. Collins AJ, Foley RN, Herzog C, Chavers B, Gilbertson D, Ishani A, Kasiske B, Liu J, Mau LW, McBean M, Murray A, St Peter W, Guo H, Li Q, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest

B, Constantini E, Everson S, Eggers P, Agodoa L. United States renal data system 2008 annual data report. Am J Kidney Dis. 2009;53(1 Suppl):S1–374.
34. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. Clin J Am Soc Nephrol. 2011;6(11):2567–72.
35. Mullens W, Abrahams Z, Francis GS, Taylor DO, Starling RC, Tang WH. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. J Card Fail. 2008;14(6):508–14.
36. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(7):589–96.
37. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009;53(7):582–8.
38. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail. 2007;13(8):599–608.
39. Brisco MA, Kimmel SE, Coca SG, Putt ME, Jessup M, Tang WH, Parikh CR, Testani JM. Prevalence and prognostic importance of changes in renal function after mechanical circulatory support. Circ Heart Fail. 2014;7(1):68–75.
40. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122(3):265–72.
41. Greene SJ, Gheorghiade M, Vaduganathan M, Ambrosy AP, Mentz RJ, Subacius H, Maggioni AP, Nodari S, Konstam MA, Butler J, Filippatos G, EVEREST Trial investigators. Haemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Eur J Heart Fail. 2013;15(12):1401–11.
42. Testani JM, Coca SG, Shannon RP, Kimmel SE, Cappola TP. Influence of renal dysfunction phenotype on mortality in the setting of cardiac dysfunction: analysis of three randomized controlled trials. Eur J Heart Fail. 2011;13(11):1224–30.
43. Testani JM, Cappola TP, Brensinger CM, Shannon RP, Kimmel SE. Interaction between loop diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. J Am Coll Cardiol. 2011;58(4):375–82.
44. Verbrugge FH, Dupont M, Shao Z, Shrestha K, Singh D, Finucan M, Mullens W, Tang WH. Novel urinary biomarkers in detecting acute kidney injury, persistent renal impairment, and all-cause mortality following decongestive therapy in acute decompensated heart failure. J Card Fail. 2013;19(9):621–8.
45. Ahmad T, Jackson K, Rao VS, Tang WH, Brisco-Bacik MA, Chen HH, Felker GM, Hernandez AF, O'Connor CM, Sabbisetti VS, Bonventre JV, Wilson FP, Coca SG, Testani JM. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. Circulation. 2018;137(19):2016–28.
46. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, Rimmelé T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG, Zacharowski K, Kellum JA. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013;17(1):R25.
47. Merrill AJ. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. J Clin Invest. 1946;25(3):389–400.
48. Ruggenenti P, Remuzzi G. Worsening kidney function in decompensated heart failure: treat the heart, don't mind the kidney. Eur Heart J. 2011;32(20):2476–8.

49. Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, Argano C, Tuttolomondo A, Paterna S. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. Am Heart J. 2003;145(3):459–66.
50. Tuttolomondo A, Pinto A, Di Raimondo D, Corrao S, Di Sciacca R, Scaglione R, Caruso C, Licata G. Changes in natriuretic peptide and cytokine plasma levels in patients with heart failure, after treatment with high dose of furosemide plus hypertonic saline solution (HSS) and after a saline loading. Nutr Metab Cardiovasc Dis. 2011;21(5):372–9.
51. Paterna S, Di Pasquale P, Parrinello G, Fornaciari E, Di Gaudio F, Fasullo S, Giammanco M, Sarullo FM, Licata G. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hypertonic saline solution versus high-dose furosemide alone in refractory congestive heart failure: a double-blind study. J Am Coll Cardiol. 2005;45(12):1997–2003.
52. Paterna S, Di Pasquale P, Parrinello G, Amato P, Cardinale A, Follone G, Giubilato A, Licata G. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. Eur J Heart Fail. 2000;2(3):305–13.
53. Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF Jr, Dorobantu MI, Grinfeld L, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Prescott MF, Edwards C, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin T, Teerlink JR, RELAX-AHF Investigators. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. J Am Coll Cardiol. 2013;61(2):196–206.
54. DiNicolantonio JJ, Niazi AK, Lavie CJ, O'Keefe JH, Ventura HO. Thiamine supplementation for the treatment of heart failure: a review of the literature. Congest Heart Fail. 2013;19(4):214–22.
55. Katta N, Balla S, Alpert MA. Does long-term furosemide therapy cause thiamine deficiency in patients with heart failure? a focused review. Am J Med. 2016;129(7):753 e7–e11.
56. Giamouzis G, Butler J, Starling RC, Karayannis G, Nastas J, Parisis C, Rovithis D, Economou D, Savvatis K, Kirlidis T, Tsaknakis T, Skoularigis J, Westermann D, Tschöpe C, Triposkiadis F. Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. J Card Fail. 2010;16(12):922–30.
57. Aziz EF, Alviar CL, Herzog E, Cordova JP, Bastawrose JH, Pamidimukala CK, et al. Continuous infusion of furosemide combined with low-dose dopamine compared to intermittent boluses in acutely decompensated heart failure is less nephrotoxic and carries a lower readmission at thirty days. Hell J Cardiol. 2011;52(3):227–35.
58. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, Bart BA, Bull DA, Stehlik J, LeWinter MM, Konstam MA, Huggins GS, Rouleau JL, O'Meara E, Tang WH, Starling RC, Butler J, Deswal A, Felker GM, O'Connor CM, Bonita RE, Margulies KB, Cappola TP, Ofili EO, Mann DL, Dávila-Román VG, McNulty SE, Borlaug BA, Velazquez EJ, Lee KL, Shah MR, Hernandez AF, Braunwald E, Redfield MM, NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013;310(23):2533–43.
59. Udelson JE, Smith WB, Hendrix GH, Painchaud CA, Ghazzi M, Thomas I, Ghali JK, Selaru P, Chanoine F, Pressler ML, Konstam MA. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. Circulation. 2001;104(20):2417–23.
60. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007;297(12):1319–31.

61. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, Zhao MH, Lv J, Garg AX, Knight J, Rodgers A, Gallagher M, Kotwal S, Cass A, Perkovic V. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015;385(9981):1975–82.
62. Wright EM. Renal Na(+)-glucose cotransporters. Am J Physiol Renal Physiol. 2001;280(1):F10–8.
63. Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(21):2099.
64. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, Mann DL, Margulies KB, McNulty SE, Mentz RJ, Redfield MM, Tang WHW, Whellan DJ, Shah M, Desvigne-Nickens P, Hernandez AF, Braunwald E, National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. JAMA Cardiol. 2017;2(9):950–8.

Loop Diuretic Resistance in a Patient with Acute Heart Failure

11

Zachary L. Cox and Jeffrey M. Testani

Case Vignette

Mrs. X is a 69 year old woman who has been admitted with acute heart failure. A diagnosis of an idiopathic dilated cardiomyopathy was made 2 years earlier. Currently, left ventricular ejection fraction on transthoracic echocardiography is 32% and maintenance therapy includes furosemide 40 mg twice daily, ramipril 2.5 mg twice daily, carvedilol 6.25 mg twice daily and spironolactone 25 mg daily. Her blood pressure is 137/84 mmHg and her HR is 74 bpm. Her exam reveals good signs of perfusion but her jugular venous pressure is to the angle of the jaw and she has pitting edema to her thighs. Laboratory analysis reveals a serum creatinine of 1.6 mg/dl which is up from her baseline of 1.4 mg/dl. Because of signs and symptoms of volume overload, Mrs. X is treated with intravenous boluses of furosemide. The furosemide dose has been progressively increased from 40 mg twice daily on the first day of the admission to 120 mg twice daily on the third day. However, net weight loss is only 1 kg, despite persistent clinical signs of volume overload. Urine output has decreased from 1750 mL during the first 24 h to 800 mL during the last 24 h.

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Chapter Key Points
- Defining loop diuretic resistance in acute heart failure (HF)
- Mechanisms and classifications of loop diuretic resistance in acute HF
- Prognostic impact of loop diuretic resistance in acute HF
- Dedicated strategies to cope with loop diuretic resistance in acute HF

Brief Discussion of the Case

Mrs. X clearly has diuretic resistance as she is hypervolemic and her rate of diuresis is not satisfactory despite intravenous (IV) diuretic administration six-fold higher than her oral home diuretic regimen (assuming oral bioavailability of 50% for furosemide). Pre-Nephron diuretic resistance is less likely as she is hemodynamically stable. Her renal dysfunction is not severe enough to cause this degree of diuretic refractoriness. The dose-response curve for loop diuretics can be dynamic during the treatment of acute HF and are shifted far to the right in HF. Therefore, loop of Henle diuretic resistance should be the initial treatment target. Her IV loop diuretic regimen should be increased to 200–240 mg IV at least every 8 h to ensure the loop diuretic concentration in the nephron exceed the current diuretic threshold. While Post-Loop of Henle diuretic resistance is the primary mechanism of diuretic resistance, use of combination nephron blockade with thiazides to target distal tubule resistance has been associated with a higher risk of electrolyte abnormalities, kidney dysfunction, and mortality in observational studies. Therefore, we advocate maximizing loop diuretics as the first strategy before pursuit of combination nephron blockade aimed at post-Loop of Henle diuretic resistance. If diuretic efficacy is not restored with the increased loop diuretic regimen, a thiazide such as metolazone 5–20 mg orally daily should be added. Kidney function, serum sodium, serum potassium, and other electrolytes should be monitored at least daily. If the decongestive goals are still not met, an individualized care plan with a HF specialist is required and may include hemodynamic guided medical therapy and/or additional diuretic adjuvants such as high dose potassium sparing diuretics, proximal tubular diuretics such as acetazolamide, or agents such as dopamine continuous infusion.

Defining Diuretic Resistance in Acute Heart Failure

Symptoms of hypervolemia are present in the majority of acute heart failure (AHF) hospitalizations [1, 2]. Intravenous (IV) loop diuretics are the cornerstone of decongestive therapy in AHF, utilized in 80–90% of hospitalizations [2, 3]. Defining diuretic resistance requires subjective analysis of multiple components: (1) presence and magnitude of hypervolemia; (2) *adequacy* of the diuretic regimen; and (3) rate of net negative urine and sodium balance. The difficulty in defining diuretic resistance lies in the interdependent and difficult to measure nature of these

components. Despite the consensus that diuretic resistance is highly prevalent in AHF, no current definition exists. Qualitatively, diuretic resistance is an unsatisfactory rate of diuresis/natriuresis despite an *adequate* diuretic regimen.

Diuretic resistance, by definition, does not consider the presence and magnitude of hypervolemia. Yet, euvolemia must be excluded as the reason for decreased diuresis, since the diuretic response will wane as euvolemia is approached, even if all other parameters remain constant. Measurements of hypervolemia are numerous, each with intrinsic limitations. Limitations of the physical exam include the reliance on the synthesis of multiple exam findings with low sensitivity and specificity for volume assessment [4, 5]. Physical examination performed by specialists only displays a sensitivity of 58% for hypervolemia when compared to a hemodynamically measured standard [6, 7]. Increases in serum bicarbonate, serum creatinine, and blood urea nitrogen (BUN) have diverse, non-volume mediated etiologies including medication effects, hemodynamic changes, and disease progression [8–11]. Because of the limited specificity for volume status [12–14], worsening renal function (WRF) alone is an unreliable marker of euvolemia. Patient-reported dyspnea was not associated with decongestion or euvolemia in the Diuretic Optimization Strategies Evaluation trial in Acute Heart Failure (DOSE-AHF) or the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) populations [15, 16]. Hemodynamic assessment of intravascular volume is the gold standard of euvolemia, although the invasive nature limits its widespread use. Ensuring euvolemia has not been achieved by the best possible methods is an important consideration in defining diuretic resistance.

Diuretic resistance is only contemplated when the loop diuretic regimen is intensive enough that it should yield diuresis, yet the decongestive rate is unsatisfactory. Did you consider the 120 mg of IV furosemide twice daily in the case vignette as adequate? Previous definitions of *high-dose* loop diuretics have included a total daily dose and weight-based threshold [17–19], but these are insufficient alone because they exclude the diuretic response. If the diuretic dose in the case vignette resulted in 8000 mL urine per day, diuretic resistance would not be present. Diuretic efficiency integrates the urine output in context of the loop diuretic dose, expressed as fluid output, weight change, or sodium output per mg of furosemide equivalents [20]. The absence of a set diuretic efficiency threshold is the greatest limitation in the assessment of diuretic resistance. Additionally, diuretic efficiency does not account for other concomitant diuretics. Despite these limitations, diuretic efficiency has significant prognostic implications [20]. An *adequate* diuretic regimen will often be subjective considering the dose, frequency, utilization of other concomitant diuretics, and historical response to diuretics among other factors.

Decongestion rate can be easily assessed during diuresis using weight change and the net difference in volume input and urine output. Yet, these measurements are imprecise in clinical practice due to inaccurate measurements and other influential physiologic factors. Weight change and net urine output have a weak correlation in AHF clinical trials with rigorous measurement [$r = -0.381$ in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) and $r = 0.55$ in DOSE-AHF), highlighting the inaccurate measurement even in the

best of circumstances [16, 21, 22]. Just as the onset of AHF symptoms is often associated with minimal to no weight gain [23, 24], weight loss is an equally poor predictor of euvolemia and decongestive rate [16, 21]. Net urine output without consideration of diuretic dose and frequency or fluid intake is a misleading metric for diuretic resistance. Osmoregulation is often preserved in AHF and thus fluid intake dictates urine output. Most AHF patients ingesting 3 L of water will make approximately 3 L of urine to preserve osmolality. Despite dietary orders to the contrary, fluid intake is poorly regulated during AHF hospitalization and significantly influences urine output. Finally, the composition of the urine, not just the quantity, must be considered. Urine output measures the urine volume but neglects the primary driver of congestive symptoms, sodium. The urinary sodium concentration has wide interpatient variability [25], with 40% of patients excreting <50 mmol sodium within 6 h after an IV loop diuretic dose [26]. While sodium output is a better measure of decongestive rate, it has the same practical limitations as a 24 h urine collection [27, 28].

A quantitative definition of diuretic resistance that will apply to all patients in all circumstances cannot be designed. Spot urinary sodium measurements are a promising approach to measuring diuretic response. By collecting a spot urine sample 1–2 h after the administration of an IV loop diuretic dose, the total sodium excretion over the 6 h working duration of the loop diuretic and the day can be calculated by the following equation:

$$\text{Na output}\ (\text{mmol}) = \text{eGFR} \times (\text{BSA}/1.73) \times (\text{Cr}_{\text{Serum}}/\text{Cr}_{\text{Urine}}) \times 60\ \text{min} \times 2.5\ \text{h} \times (\text{Na}_{\text{Urine}}/1000\ \text{ml})$$

Na = sodium; eGFR = estimated glomerular filtration rate, BSA = body surface area, Cr_{Serum} = serum creatinine; Cr_{Urine} = urine creatinine; h = hours; Na_{Urine} = urinary sodium concentration

Predicted sodium output using this equation has a strong correlation with the measured sodium output ($r = 0.91$, $p < 0.0001$), facilitating early discernment of natriuretic resistance to a diuretic dose [26]. Spot urine sodium is limited as a complete diuretic resistance metric because it does not incorporate diuretic dose. Unlike diuretic efficacy which lacks a threshold value, a predicted sodium output <50–70 mmol/L predicts a positive sodium balance with twice daily IV loop diuretic and is associated with worse heart failure outcomes [26, 29, 30]. By identifying patients with natriuretic resistance within 1–2 h, clinicians can make rapid diuretic titrations to overcome diuretic resistance.

Prognostic Impact of Diuretic Resistance in Acute Heart Failure

The prognostic impact of diuretic resistance varies with the definition of diuretic resistance employed and retains the defining metric's limitations. At the most extreme, diuretic resistance requiring mechanical volume removal denotes a poor prognosis [31]. In the absence of randomized trials comparing therapies for

diuretic resistance, it is unknown whether it is the presence of diuretic resistance itself or the resultant decongestive therapies that confer prognostic value. Loop diuretics increase neurohumoral activation regardless of the volume state, dose, or diuretic response [32, 33]. Initial literature evaluating prognosis focused on the diuretic dose, with an assumption of diuretic resistance. An almost linear association between increasing mortality and increasing IV furosemide daily doses occurred in a multivariate analysis of the ESCAPE [34]. Subsequent analyses adjusted for other covariates to investigate whether high loop diuretic doses were simply a surrogate for severity of illness or a driver of poor outcomes. After applying propensity score matching to balance for illness severity, an analysis of the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) registry found that the association between IV diuretic dose and mortality was no longer present [19]. The DOSE-AHF trial randomized patients to a high or low dose loop diuretic strategy, allowing insight into the relative impact of the beneficial (decongestive) effects of higher diuretic dose and the potential harmful effects (neurohumoral activation) [35]. The DOSE trial found no effect on 60-day death or rehospitalization between those randomized to high or low dose IV diuretics, although the prevalence of diuretic resistance was unknown [36]. Further analyses of the DOSE-AHF trial found a benefit in 60-day outcomes in patients randomized to a high-dose loop diuretic strategy, after adjusting for cumulative dose, but this effect was eliminated after adjusting for the resulting net urine output [35]. Change in renin-angiotensin-aldosterone system (RAAS) biomarkers during diuresis did not differ between the high and low dose groups and were not associated with 60-day outcomes in the DOSE-AHF trial [33]. The potential for dose-related harm from loop diuretics cannot be excluded, although the decongestive benefits of high dose loop diuretics appear to offset potential adverse effects.

Diuretic efficiency, as a proxy of diuretic resistance, has been employed to separate the prognostic effect of decongestive therapy intensity from resistance itself. Using diuretic efficiency above and below the median value, patients in the ESCAPE with low diuretic efficiency had increased mortality (HR 3.57; 95% CI 1.46–8.73; $p = 0.005$), with those exhibiting low diuretic efficiency on high loop diuretic doses having the worst prognosis [20]. Consequently, diuretic resistance is known to confer a worse prognosis when: (1) high dose loop diuretics are required with sustained low diuretic efficiency or (2) resistance prohibits achievement of euvolemia with medical therapy.

Mechanisms of Loop Diuretic Resistance and Mechanism-Based Therapies to Restore Diuretic Efficacy in Acute Heart Failure

Thus far, diuretic resistance has been discussed as a maladaptive process, but there are *beneficial* adaptations to diuretics. A discussion of the frequently used term *diuretic braking* is illustrative in distinguishing maladaptive diuretic

resistance and beneficial adaptation to diuretics. Diuretic braking describes the tachyphylaxis to the same diuretic regimen, but is not an actual mechanism [37]. For example, a patient with a glomerular filtration rate (GFR) of 120 mL/min filters ~1400 g salt a day. If the initial diuretic response excreting 20% of filtered sodium persisted, a continuous loop diuretic infusion would excrete 280 g of salt and 50 L of urine daily. In response to the immediate natriuresis, renal autoregulation and diuretic braking preserve the GFR and provides a safety net allowing loop diuretic therapy. Thus diuretic braking is not only beneficial in these circumstances, but is the primary mechanism by which loop diuretics do not have an unacceptably small therapeutic window. Diuretic braking fails to distinguish between mechanisms of beneficial renal adaptation and maladaptive diuretic resistance. In classifying maladaptive diuretic resistance, a more descriptive nomenclature that describes the mechanism should be employed. Maladaptive diuretic resistance limiting decongestive goals, which may be mechanistically the same as beneficial diuretic braking, can be broadly categorized as pre-nephron diuretic resistance and intra-nephron diuretic resistance (Fig. 11.1). Intra-nephron diuretic resistance can further be divided into pre-loop of Henle diuretic resistance, loop of Henle diuretic resistance, and post-loop of Henle diuretic resistance (Fig. 11.1).

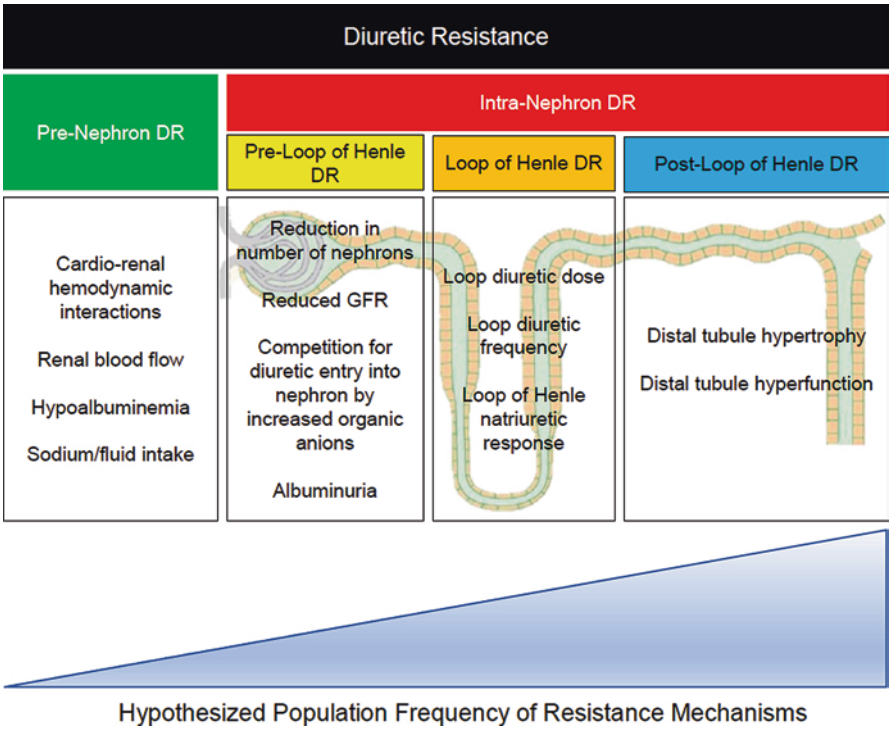

Fig. 11.1 Mechanisms of diuretic resistance

Pre-nephron Diuretic Resistance

Historical literature focusing on pre-nephron and pre-loop of Henle diuretic resistance was performed in healthy subjects or cohorts with hypertension or chronic kidney disease [38–44]. The application of these findings to the AHF patient on modern medical therapies is uncertain. Cardiorenal hemodynamics represent a potential mechanism of pre-nephron diuretic resistance. Poor cardiac output to the kidney was initially believed to be the predominant driver of cardiorenal syndrome and diuretic resistance, but multiple recent analyses have since illustrated that cardiac output is not the primary driver on a population level [13, 14, 45]. Venous congestion, often approximated by elevated right atrial pressure or high intra-abdominal pressure, has been proposed to contribute to diuretic resistance through a reduction in the arterial to venous pressure gradient at the glomerulus. An analysis of the ESCAPE found no difference in baseline right atrial pressure, pulmonary arterial wedge pressure, or cardiac output between patients experiencing high or low diuretic efficiency [20]. Vasodilators such as nesiritide, ularitide, serelaxin, and milrinone failed to augment diuresis by metrics of urine output, IV loop diuretic duration of use, or weight loss in patients with AHF [46–50]. Dopamine at 2 μg/kg/min did not increase urine output compared to placebo in a trial of AHF patients undergoing decongestion with IV loop diuretics [48]. Dopamine trended toward increasing urine volume in those with a baseline systolic blood pressure less than 114 mmHg [48]. Higher diastolic blood pressure predicted greater urine output in the ASCEND-HF trial, although possibly driven by confounding by indication [46]. To the contrary, RAAS antagonism, even in the setting of a blood pressure reduction, may actually improve the natriuretic response to a loop diuretic [51, 52]. Activation of the RAAS varies greatly during decongestion with both diuretics and mechanical volume removal and has unclear associations with diuretic resistance [33, 53]. It remains unclear which patients with lower mean arterial pressures and diuretic resistance should have a temporary cessation in medications that lower blood pressure with initiation of dopamine at 2 μg/kg/min versus those in whom RAAS antagonists should be continued or uptitrated.

Hypoalbuminemia was considered as a pre-nephron diuretic resistance mechanism because all loop diuretics are >90% bound to albumin [54–56]. Hypothesized mechanisms include a reduced intravascular volume available for diuresis and decreased delivery of loop diuretics to the nephron [57]. The majority of literature evaluating the benefit of IV albumin replacement with IV furosemide was performed in nephrotic syndrome or cirrhosis utilizing IV furosemide doses of only 40 mg [41, 58, 59]. A small, retrospective study of patients with a serum albumin <3 g/dL hospitalized for AHF found no difference in net urine output nor diuretic doses needed for diuresis compared to patients with normal serum albumin concentrations [60]. Analysis of the DOSE-AHF and the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-HF) trials found no association between baseline serum albumin concentrations and weight loss ($p = 0.43$), diuretic efficiency ($p = 0.53$), or freedom from congestion ($p = 0.30$) at 72 h [61].

The relationship between sodium and heart failure outcomes is complex [62]. The traditional paradigm teaches that high sodium intake is a driver of pre-nephron diuretic resistance [38, 63]. However, several investigations in AHF populations indicate that a higher sodium intake might be beneficial if a greater net sodium removal is achieved [64]. Hypertonic saline administered with high-dose loop diuretics produced greater urinary sodium excretion, urine volume, and faster achievement of euvolemia than high-dose loop diuretics alone among heart failure patients failing oral combinations of loop and thiazide diuretics [65–67]. However, the quality of data supporting this approach is limited, and it cannot be recommended at this time [68]. Likewise, there is insufficient evidence to recommend any specific dietary sodium limitation for patients with AHF undergoing diuresis [64]. Lastly, non-steroidal anti-inflammatory drugs inhibit renal prostaglandin synthesis leading to a decreased renal blood flow and impaired natriuresis [69, 70].

Pre-loop of Henle Diuretic Resistance

Initially believed to be significant contributors to diuretic resistance from impaired drug delivery to the site of action, renal function and albuminuria are less influential mechanisms of diuretic resistance compared to tubular handling of sodium. In the novel "The House of God", we see renally-based diuretic adjustments taught with "age + BUN = Lasix dose" [71], which contemporary medical pocket resources continue [72]. Proposed diuretic resistance mechanisms of renal dysfunction are listed in Fig. 11.1. Renal dysfunction is a mechanism of pre-loop of Henle diuretic resistance in chronic kidney disease populations, but is less relevant in the contemporary heart failure patient prescribed an adequate diuretic dose. Estimated glomerular filtration rate (eGFR) poorly correlates with net fluid output ($r^2 = 0.0$; $p = 0.35$) and diuretic efficiency ($r^2 = 0.02$; $p < 0.001$) in the ESCAPE [20]. BUN was significantly associated with low diuretic efficiency (OR 1.19 per 10 g/dL increase in BUN; $p = 0.005$) in a multivariate model incorporating eGFR, which could be a result of increased neurohumoral activation and/or competition with loop diuretic entry into the nephron. Similarly, elevated BUN but not reduced eGFR predicted urine output in the ASCEND-HF trial [46]. When evaluating the relative importance of diuretic delivery and renal tubular response, eGFR did not predict 6 h net fluid or net sodium output [73]. Patients with a low eGFR had decreased diuretic delivery to the kidney, with eGFR ($r = 0.58$; $p = 0.001$) and urea clearance ($r = 0.75$; $p = 0.001$) showing strong correlation with urinary diuretic concentration. However, patients with lower eGFR compensated for decreased diuretic concentrations by producing greater fractional excretion of sodium at 6 h. Renal function in heart failure has no impact on the individual nephron's filtrate, but does influence total natriuresis, although at a less significant degree than loop of Henle and post-loop of Henle diuretic resistance. In summary, renal dysfunction is much less of an important mediator of diuretic resistance in AHF than traditional teaching implies.

Albuminuria might contribute to diuretic resistance by binding loop diuretics in the urine as they do in the serum, decreasing the quantity of free drug able to bind

to the $Na^+/K^+/2Cl^-$ symporter [72]. Literature supporting this hypothesis was performed in animal models of nephrotic syndrome [74–76], raising questions of its relevance in AHF. Patients with AHF and either normal albuminuria (45%), microalbuminura (42%), or macroalbuminuria (13%) exhibit very weak correlation between diuretic efficiency and urinary albumin concentrations [77]. Recent analyses in humans with nephrotic syndrome also refute albuminuria as a primary mechanism of diuretic resistance, making it implausible that albuminuria is a significant mechanism of diuretic resistance in AHF patients [78].

Loop of Henle Diuretic Resistance

Loop of Henle diuretic resistance mechanisms are listed in Fig. 11.1. Diuretic resistance from inadequate dose or frequency could be considered pseudo-diuretic resistance, failing the adequate diuretic regimen portion of the diuretic resistance definition. However, 40 mg of furosemide in a normal volunteer will elicit a maximal natriuretic response, providing a low bar for an adequate dose. The loop diuretic's dose-response curve exhibits a sigmoidal pattern along a logarithmic relationship, with a *threshold* and a *ceiling* dose. The diuretic dose and infusion rate primarily determine the concentration in the lumen of the loop of Henle relative to the diuretic threshold. This relationship determines (1) the peak rate of diuresis and (2) the duration of diuresis as time above the threshold (Fig. 11.2a). A dose exceeding the ceiling can still cause a greater diuretic response by maintaining a concentration above the threshold for a longer time (Fig. 11.2b). The ceiling and non-maladaptive adaptation shield against diuretic concentration-related harm, with the exception of potential ototoxicity at infusion rates >4 mg/min or furosemide equivalent bolus doses >500 mg [79, 80]. The scenario depicted in Fig. 11.2b can be advantageous if achieved with low diuretic doses. Diuretic thresholds and therefore the dose needed for diuresis display interpatient and intra-patient variability. When evaluating for loop of Henle diuretic resistance, the natriuretic response to the dose should first be considered. A low or moderate IV bolus dose of loop diuretic that produces less than 500 mL of urine or a spot urine sodium concentration <70 mmol/L at 2 h may result from the situation pictured in Fig. 11.2c. The primary limitation in this scenario is the time above the renal threshold and the dose should be increased to attempt a profile depicted in Fig. 11.2d.

Diuretic dose and frequency are interdependent in loop of Henle diuretic resistance and both must be considered. If a 240 mg furosemide bolus produces 1500 mL of urine over 6 h, euvolemia would doubtfully be achieved if this dose was given once daily despite overcoming the dose-mediated diuretic resistance. Because the half-life of IV loop diuretics is short (~1–2 h), urinary concentrations fall below the diuretic threshold quickly with a duration of action that rarely exceeds 6 h [55, 56]. Typical twice daily dosing may provide diuretic concentration below the diuretic threshold for the majority of the day, allowing compensatory sodium reabsorbtion [37, 81]. Continuous infusions of loop diuretics that maintain the diuretic concentration above the diuretic threshold should be advantageous [82]. The DOSE-AHF

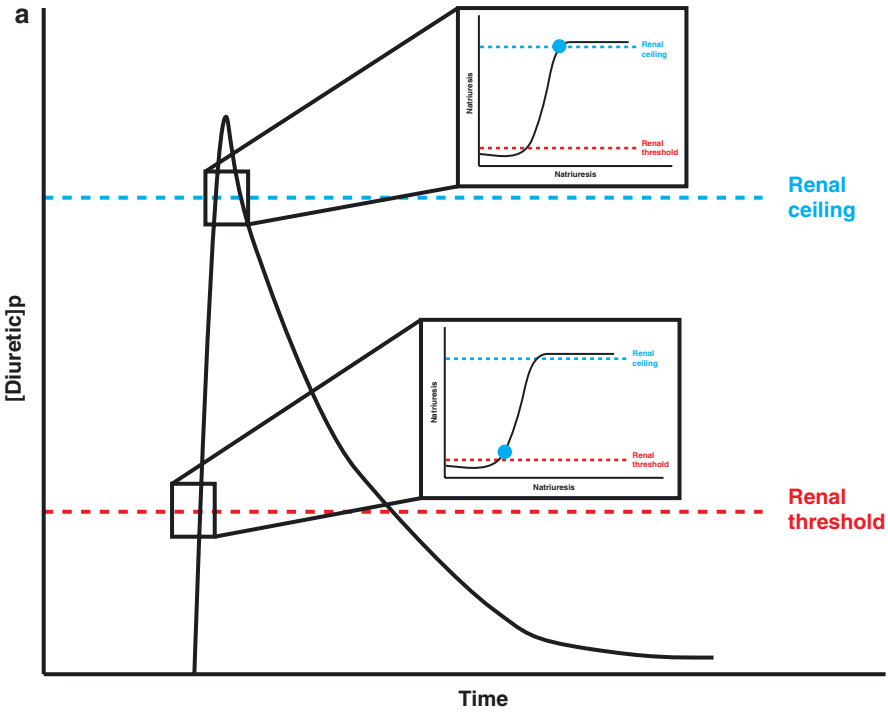

Fig. 11.2 Loop diuretic pharmacokinetics. (**a**) The loop diuretic plasma concentration (y-axis) is plotted over time (x-axis) when given as an intravenous bolus. The Renal Threshold (red dotted line) is the diuretic concentration that must be exceeded to cause diuresis. The Renal Ceiling (blue dotted line) is the diuretic concentration above which no further increases in diuretic response are gained. The two boxes encasing the moment the diuretic concentration crosses the Renal Ceiling and Renal Threshold illustrates the sigmoidal dose-response relationship between the diuretic concentration (x-axis) and the natriuretic response (y-axis), with the blue dot representing the current loop diuretic concentration on this curve. (**b**) The loop diuretic plasma concentration (y-axis) is plotted over time (x-axis) when given as an intravenous bolus. The shaded area illustrates the area of the curve between the Renal Threshold and Renal Ceiling. While no further diuretic action is gained when a dose produces a diuretic concentration exceeding the Renal Ceiling, the total volume of diuresis can be increased as a function of maintaining a loop diuretic plasma concentration above the Renal Threshold for a greater time. (**c**) The loop diuretic plasma concentration (y-axis) is plotted over time (x-axis) when given as an intravenous bolus. The shaded area illustrates the area of the curve above the Renal Threshold. In this scenario, the diuretic response is minimal because of the limited time spent above the Renal Threshold. (**d**) The loop diuretic plasma concentration (y-axis) is plotted over time (x-axis) when given as an intravenous bolus. The shaded area illustrates the area of the curve above the Renal Threshold. By increasing the loop diuretic dose from Fig. 11.2c, the time above the Renal Threshold was increasing, causing a greater diuretic response

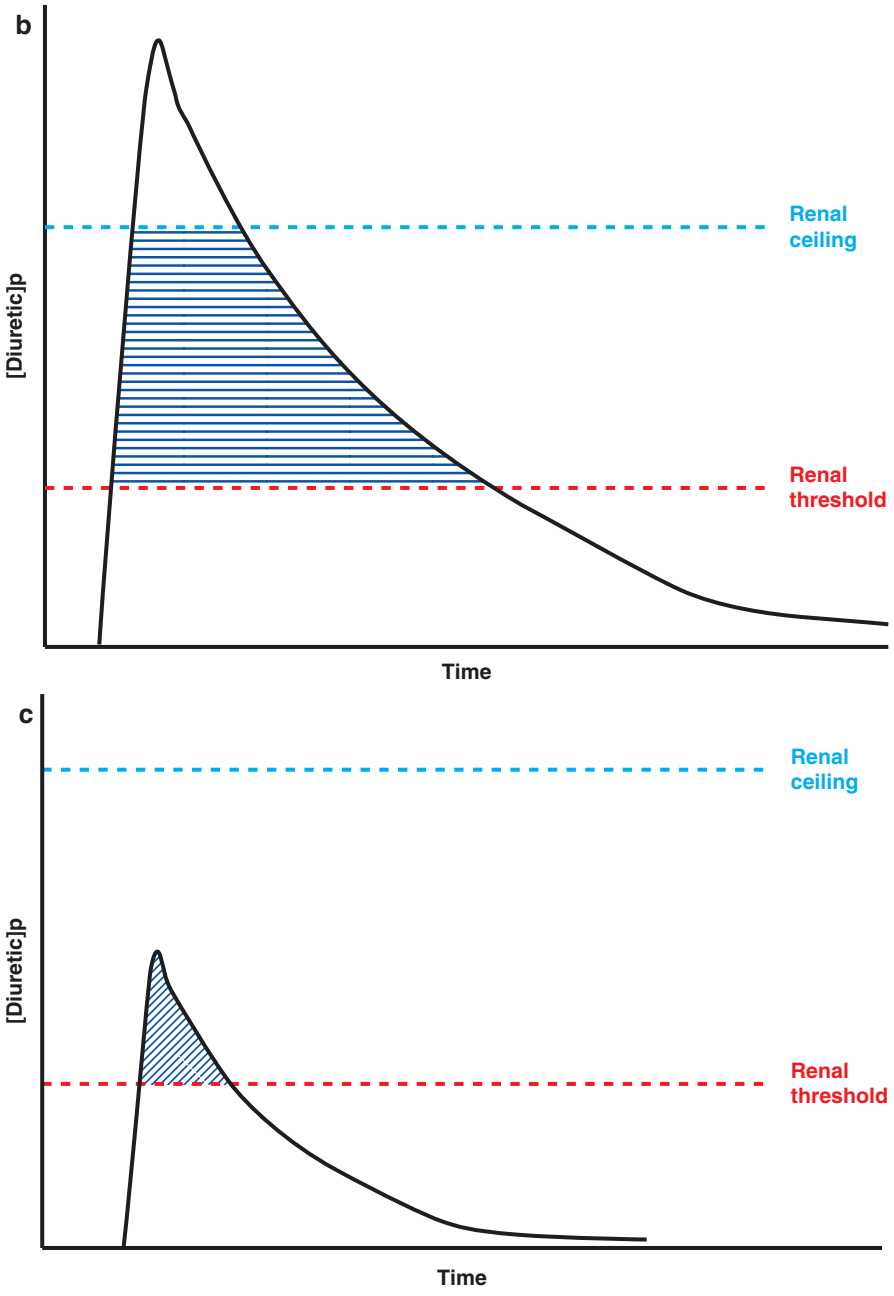

Fig. 11.2 (continued)

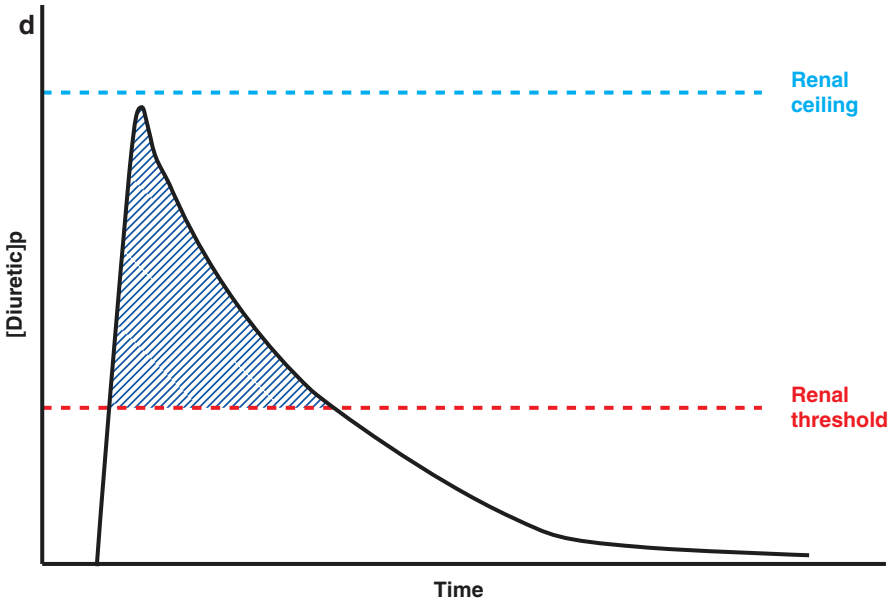

Fig. 11.2 (continued)

trial hypothesized that continuous infusion dosing would be superior to dosing every 12 h [36, 82]. However, no difference was found in symptom improvement, urine output, or weight loss, although the population studied had an unknown prevalence of diuretic resistance. It is unknown why the pharmacokinetic advantage of continuous infusions has not translated into clinical benefits. In patients exhibiting diuretic resistance but with adequate natriuretic response to an IV bolus dose, consideration can be given to the use of IV loop diuretics at greater frequencies to overcome frequency-mediated diuretic resistance, although data proving this theoretical approach is lacking. The major difference between this strategy and the null findings in the DOSE-AHF trial is that more frequent dosing also represents an uptitration of the total diuretic dose given in addition to increased frequency (Fig. 11.3).

Post-loop of Henle Diuretic Resistance

The few contemporary studies in AHF patients indicate that the majority of diuretic resistance is primarily mediated by post-loop of Henle diuretic resistance. Compared to a pre-diuretic baseline, a median dose of IV furosemide 160 mg (40–270 mg) increased the amount of sodium estimated to be leaving the loop of Henle by 12.6 ± 10.8% ($p < 0.001$) [83]. Yet, the fractional excretion of sodium only increased 4.8 ± 3.3%, indicating 66% (25–85%) of the sodium leaving the loop of Henle

underwent distal tubular reabsorption. After controlling for loop of Henle diuretic resistance by using urine diuretic concentration, the increase in sodium leaving the loop of Henle only accounted for 6.4% of the increase in net fractional excretion of sodium. These findings were substantiated in a study administering IV bumetanide to 50 AHF patients which reported that in the majority (71%) diuretic response was related to intra-renal diuretic resistance via renal tubular changes [73]. Continuous loop diuretic exposure results in rapid distal tubular hypertrophy and hyperfunction in animal models [84–86]. Thus, a focus of restoring diuretic efficacy should be on blocking reabsorption in the distal tubules.

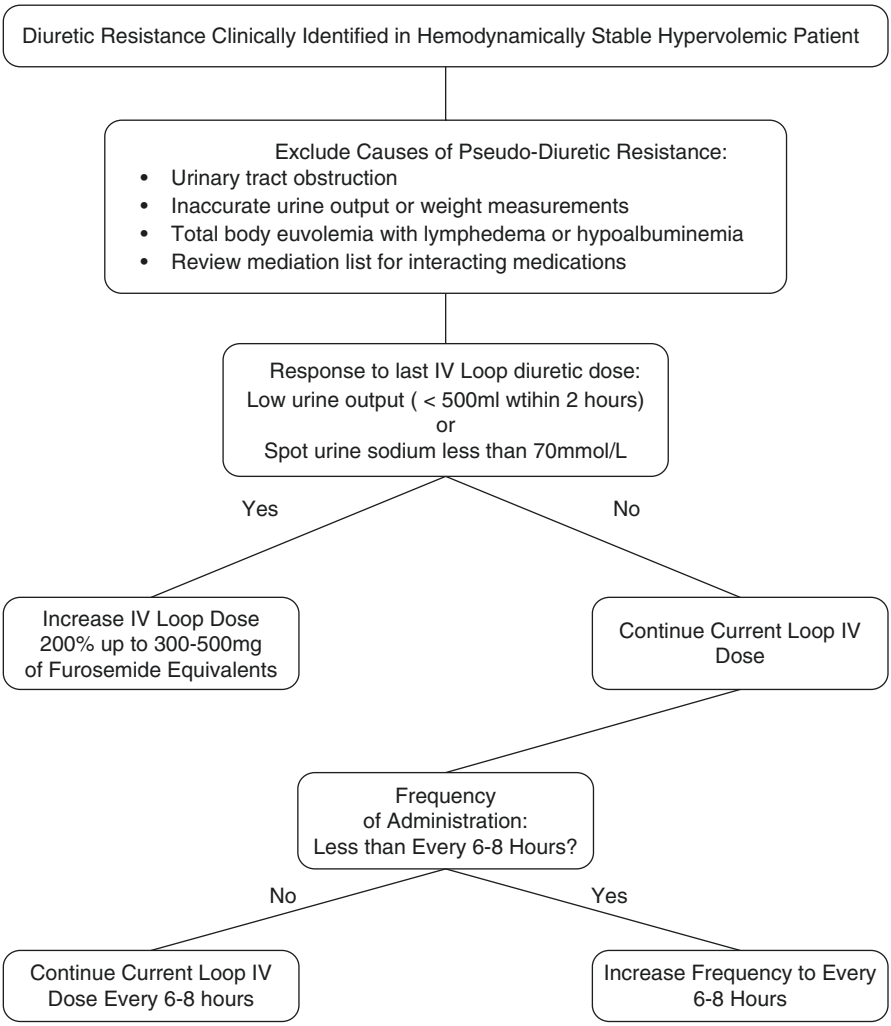

Fig. 11.3 Clinical decision process for addressing loop diuretic resistance

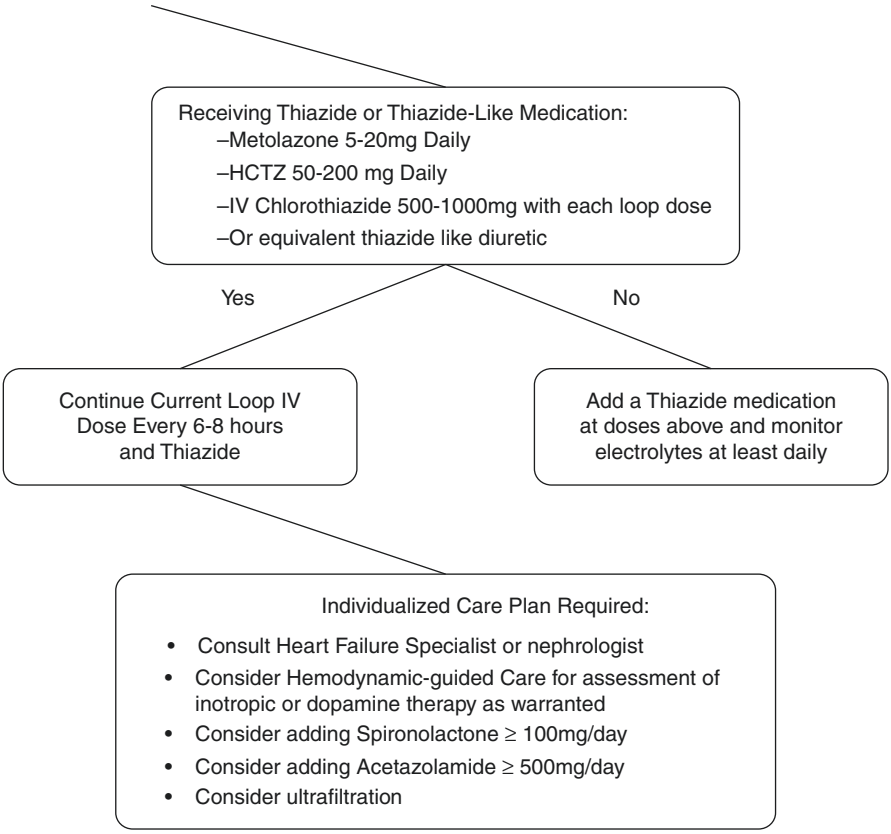

Fig. 11.3 (continued)

Combination Blockage of the Nephron in Diuretic Resistance

When approaching diuretic resistance, clinicians should first ensure an adequate loop diuretic dose and frequency are prescribed before considering therapeutic strategies targeting post-loop of Henle diuretic resistance (Fig. 11.3). Combination nephron blockade with metolazone has been associated with increased risk of electrolyte abnormalities, worsening renal function, and mortality compared to high-dose loop diuretics, indicating loop diuretics should be maximized as an initial strategy [87].

Thiazide(-like) Diuretics

Thiazide (and thiazide-like) medications are the most commonly utilized medications to overcome loop diuretic resistance [88–90]. Thiazides should be the first

option to add to loop diuretics, as they inhibit sodium reabsorption in the distal convoluted tubules where the majority of remaining sodium reabsorption occurs after the loop of Henle. Despite experience spanning 50 years, common misconceptions regarding combining thiazides and loop diuretics persist [89]. Metolazone is often referred to as superior to other thiazide agents, but no solid evidence supports the use of metolazone over other thiazides, even in patients with low eGFR [89, 91–93]. Administration of thiazides 30 min prior to loop diuretics is not evidence-based, as most studies administered both simultaneously [89]. Furthermore, the erratic and delayed absorption profile of metolazone makes this practice irrelevant clinically and unnecessarily increases complexity [94, 95]. IV chlorothiazide has only been compared to oral thiazides in small retrospective studies limiting definitive conclusions on efficacy differences [96]. Any thiazide at equipotent dose [97] in daily or divided doses is appropriate to add to loop diuretic therapy. Careful monitoring for hyponatremia, hypokalemia, and volume status is warranted with combination diuretic therapy to avoid adverse events [89].

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists at diuretic doses are employed with loop diuretics in cirrhotic ascites as the primary combination nephron blockade strategy [98, 99]. In AHF, non-diuretic doses (<50 mg/day) of mineralocorticoid receptor antagonists reduce morbidity and mortality [100], but investigations into larger, diuretic doses have been limited until the Aldosterone Targeted Neurohormonal Combined With Natriuresis Therapy—Heart Failure (ATHENA-HF) trial [101, 102]. The ATHENA-HF trial compared spironolactone 100 mg/day to placebo or continued non-diuretic dose spironolactone in patients with hypervolemic AHF treated with IV loop diuretics [103]. No difference in the primary endpoint of natriuretic peptide change or secondary outcomes such as net urine output, weight change, or titration of IV loop diuretic doses were found [103]. However, ATHENA-HF did not study a population with diuretic resistance and may have utilized insufficient spironolactone doses to achieve therapeutic concentrations of canrenone (active metabolite). Serum potassium levels were no different between spironolactone and placebo, supporting this possibility. Until future studies of diuretic doses of mineralocorticoid receptor antagonists in patients with diuretic resistance are conducted, this class should not be employed over thiazides in combination nephron blockade. Similarly, amiloride cannot be recommended over thiazides in combination nephron blockage because of the reduced capacity for sodium reabsorption in the collecting ducts relative to the distal convoluted tubules.

Vasopressin Antagonists

Vasopressin-2 receptor antagonists have been extensively investigated in AHF, with recent investigations focusing on the diuretic prowess [104]. Three trials comparing

tolvaptan to placebo in patients with hypervolemic AHF without diuretic resistance treated with only modest IV loop diuretics found increases in weight loss and urine output [105–107]. However, clinical endpoints such as improvement in dyspnea were not improved, possibly because sodium-free water excretion will have less impact on filling pressures than sodium-rich fluid excretion. Tolvaptan, which acts in the collecting duct, cannot be recommended over thiazides in combination nephron blockage at this time given the limited study in loop diuretic resistance.

Diuretics in the Proximal Tubules of the Nephron

Medications acting in the proximal convoluted tubules such as acetazolamide have shown promise in preliminary investigation of combination nephron blockade and are undergoing further investigation in the Acetazolamide in Decompensated heart failure with Volume Overload (ADVOR) trial [108, 109]. Acetazolamide may be a promising diuretic to add when diuretic resistance persists despite combination nephron blockade with loop diuretics and thiazides but there is no conclusive evidence up to date.

In conclusion, diuretic resistance is problematic to universally define but prevalent in AHF. The mechanisms driving diuretic resistance are diverse and the subsequent strategies should be specific to the mechanism. Optimization of loop diuretic regimens should be the primary strategy followed by combination nephron blockage with thiazides. Several additional strategies are promising but require further investigation before they can be recommended.

Treatment Pearls for the Case Vignette

In the case vignette, a first step would be to increase the IV furosemide dose to 200–240 mg IV bolus to overcome potential loop of Henle diuretic resistance given the low urinary output of the patient with 120 mg. In addition, it is reasonable to increase frequency of furosemide bolus dosing up to every 6 or 8 h in an attempt to overcome post-diuretic sodium retention.

Combination nephron blockage should be considered if the diuretic response is not restored on furosemide 240 mg IV every 6 to 8 h. Medical options then include thiazide diuretics, which block sodium reabsorption in the distal convoluted tubules and have the most empirical evidence in support. Alternatives such as mineralocorticoid receptor antagonists, epithelial sodium channel antagonists such as amiloride, vasopressin antagonists and proximal-working diuretics might be employed in individual cases.

References

1. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006;27:2725–36.
2. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol. 2014;63:1123–33.
3. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2007;153:1021–8.
4. Chakko S, Woska D, Martinez H, et al. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. Am J Med. 1991;90:353–9.
5. Elder A, Japp A, Verghese A. How valuable is physical examination of the cardiovascular system? BMJ. 2016;354:i3309.
6. Drazner MH, Hellkamp AS, Leier CV, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail. 2008;1:170–7.
7. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA. 1989;261:884–8.
8. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J. 2015;36:1437–44.
9. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail. 2011;4:685–91.
10. Michel A, Martin-Perez M, Ruigomez A, Garcia Rodriguez LA. Incidence and risk factors for severe renal impairment after first diagnosis of heart failure: a cohort and nested case-control study in UK general practice. Int J Cardiol. 2016;207:252–7.
11. Cooper LB, Mentz RJ, Gallup D, et al. Serum bicarbonate in acute heart failure: relationship to treatment strategies and clinical outcomes. J Card Fail. 2016;22:738–42.
12. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52:1527–39.
13. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions: insights from the ESCAPE trial. J Am Coll Cardiol. 2008;51:1268–74.
14. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53:589–96.
15. Lala A, McNulty SE, Mentz RJ, et al. Relief and recurrence of congestion during and after hospitalization for acute heart failure: insights from diuretic optimization strategy evaluation in acute decompensated heart failure (DOSE-AHF) and cardiorenal rescue study in acute decompensated heart failure (CARESS-HF). Circ Heart Fail. 2015;8:741–8.
16. Kociol RD, McNulty SE, Hernandez AF, et al. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. Circ Heart Fail. 2013;6:240–5.
17. Neuberg GW, Miller AB, O'Connor CM, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J. 2002;144:31–8.
18. Testani JM, Cappola TP, Brensinger CM, Shannon RP, Kimmel SE. Interaction between loop diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. J Am Coll Cardiol. 2011;58:375–82.
19. Yilmaz MB, Gayat E, Salem R, et al. Impact of diuretic dosing on mortality in acute heart failure using a propensity-matched analysis. Eur J Heart Fail. 2011;13:1244–52.

20. Testani JM, Brisco MA, Turner JM, et al. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail. 2014;7:261–70.
21. Ambrosy AP, Cerbin LP, Armstrong PW, et al. Body weight change during and after hospitalization for acute heart failure: patient characteristics, markers of congestion, and outcomes: findings from the ASCEND-HF trial. JACC Heart Fail. 2017;5:1–13.
22. Testani JM, Brisco MA, Kociol RD, et al. Substantial discrepancy between fluid and weight loss during acute decompensated heart failure treatment. Am J Med. 2015;128:776–83 e4.
23. Zile MR, Bennett TD, St John Sutton M, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation. 2008;118:1433–41.
24. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation. 2007;116:1549–54.
25. Verbrugge FH, Nijst P, Dupont M, Penders J, Tang WH, Mullens W. Urinary composition during decongestive treatment in heart failure with reduced ejection fraction. Circ Heart Fail. 2014;7:766–72.
26. Testani JM, Hanberg JS, Cheng S, et al. Rapid and highly accurate prediction of poor loop diuretic natriuretic response in patients with heart failure. Circ Heart Fail. 2016;9:e002370.
27. John KA, Cogswell ME, Campbell NR, et al. Accuracy and usefulness of select methods for assessing complete collection of 24-hour urine: a systematic review. J Clin Hypertens (Greenwich). 2016;18:456–67.
28. Nabavizadeh P, Ghadermarzi S, Fakhri M. A new method to make 24-hour urine collection more convenient: a validity study. Int J Nephrol. 2014;2014:718147.
29. Brinkley DM Jr, Burpee LJ, Chaudhry SP, et al. Spot urine sodium as triage for effective diuretic infusion in an ambulatory heart failure unit. J Card Fail. 2018;24:349–54.
30. Singh D, Shrestha K, Testani JM, et al. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. J Card Fail. 2014;20:392–9.
31. Patarroyo M, Wehbe E, Hanna M, et al. Cardiorenal outcomes after slow continuous ultrafiltration therapy in refractory patients with advanced decompensated heart failure. J Am Coll Cardiol. 2012;60:1906–12.
32. Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. J Am Coll Cardiol. 2012;59:2145–53.
33. Mentz RJ, Stevens SR, DeVore AD, et al. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. JACC Heart Fail. 2015;3:97–107.
34. Hasselblad V, Gattis Stough W, Shah MR, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail. 2007;9:1064–9.
35. Hanberg JS, Tang WHW, Wilson FP, et al. An exploratory analysis of the competing effects of aggressive decongestion and high-dose loop diuretic therapy in the DOSE trial. Int J Cardiol. 2017;241:277–82.
36. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805.
37. Ellison DH, Felker GM. Diuretic treatment in heart failure. N Engl J Med. 2017;377:1964–75.
38. Brater DC. Diuretic therapy. N Engl J Med. 1998;339:387–95.
39. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. J Am Soc Nephrol. 2002;13:798–805.
40. Beermann B, Midskov C. Reduced bioavailability and effect of furosemide given with food. Eur J Clin Pharmacol. 1986;29:725–7.
41. Phakdeekitcharoen B, Boonyawat K. The added-up albumin enhances the diuretic effect of furosemide in patients with hypoalbuminemic chronic kidney disease: a randomized controlled study. BMC Nephrol. 2012;13:92.
42. Loon NR, Wilcox CS, Unwin RJ. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. Kidney Int. 1989;36:682–9.

43. McCrindle JL, Li Kam Wa TC, Barron W, Prescott LF. Effect of food on the absorption of frusemide and bumetanide in man. Br J Clin Pharmacol. 1996;42:743–6.
44. Nakahama H, Orita Y, Yamazaki M, et al. Pharmacokinetic and pharmacodynamic interactions between furosemide and hydrochlorothiazide in nephrotic patients. Nephron. 1988;49:223–7.
45. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. Circulation. 2010;121:2592–600.
46. Gottlieb SS, Stebbins A, Voors AA, et al. Effects of nesiritide and predictors of urine output in acute decompensated heart failure: results from ASCEND-HF. J Am Coll Cardiol. 2013;62:1177–83.
47. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002;287:1541–7.
48. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013;310:2533–43.
49. Packer M, O'Connor C, McMurray JJV, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med. 2017;376:1956–64.
50. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013;381:29–39.
51. Chen HH, Redfield MM, Nordstrom LJ, Cataliotti A, Burnett JC Jr. Angiotensin II AT1 receptor antagonism prevents detrimental renal actions of acute diuretic therapy in human heart failure. Am J Physiol Renal Physiol. 2003;284:F1115–9.
52. Kula AJ, Hanberg JS, Wilson FP, et al. Influence of titration of neurohormonal antagonists and blood pressure reduction on renal function and decongestion in decompensated heart failure. Circ Heart Fail. 2016;9:e002333.
53. Guazzi MD, Agostoni P, Perego B, et al. Apparent paradox of neurohumoral axis inhibition after body fluid volume depletion in patients with chronic congestive heart failure and water retention. Br Heart J. 1994;72:534–9.
54. Torsemide [package insert]. Roche pharmaceuticals IN, NJ.; April 2003.
55. Furosemide [package insert]. Sanofi-aventis L, Bridgewater, NJ; November 2012.
56. Bumetanide [package insert]. Bedford Pharmaceuticals I, Bedford, OH.; February 2010.
57. Arques S, Ambrosi P. Human serum albumin in the clinical syndrome of heart failure. J Card Fail. 2011;17:451–8.
58. Chalasani N, Gorski JC, Horlander JC Sr, et al. Effects of albumin/furosemide mixtures on responses to furosemide in hypoalbuminemic patients. J Am Soc Nephrol. 2001;12:1010–6.
59. Elwell RJ, Spencer AP, Eisele G. Combined furosemide and human albumin treatment for diuretic-resistant edema. Ann Pharmacother. 2003;37:695–700.
60. Bleske BE, Clarke MM, Wu A, Dorsch MP. The effect of continuous infusion loop diuretics in patients with acute decompensated heart failure with hypoalbuminemia. J Cardiovasc Pharmacol Ther. 2013;18:334–7.
61. Grodin JL, Lala A, Stevens SR, et al. Clinical implications of serum albumin levels in acute heart failure: insights from DOSE-AHF and ROSE-AHF. J Card Fail. 2016;22:884–90.
62. Nijst P, Verbrugge FH, Grieten L, et al. The pathophysiological role of interstitial sodium in heart failure. J Am Coll Cardiol. 2015;65:378–88.
63. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology. 2001;96:132–43.
64. Gupta D, Georgiopoulou VV, Kalogeropoulos AP, et al. Dietary sodium intake in heart failure. Circulation. 2012;126:479–85.
65. Paterna S, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. Eur J Heart Fail. 2000;2:305–13.
66. Paterna S, Di Pasquale P, Parrinello G, et al. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hyper-

tonic saline solution versus high-dose furosemide alone in refractory congestive heart failure: a double-blind study. J Am Coll Cardiol. 2005;45:1997–2003.
67. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. Am Heart J. 2003;145:459–66.
68. Gandhi S, Mosleh W, Myers RB. Hypertonic saline with furosemide for the treatment of acute congestive heart failure: a systematic review and meta-analysis. Int J Cardiol. 2014;173:139–45.
69. Wilson DR, Honrath U, Sonnenberg H. Furosemide action on collecting ducts: effect of prostaglandin synthesis inhibition. Am J Phys. 1983;244:F666–73.
70. Nies AS, Gal J, Fadul S, Gerber JG. Indomethacin-furosemide interaction: the importance of renal blood flow. J Pharmacol Exp Ther. 1983;226:27–32.
71. Shem S. The house of god. London: Bodley Head; 1979.
72. Sabatine MS, Massachusetts General Hospital. Pocket medicine. Sixth edition. ed. Philadelphia, PA: Wolters Kluwer; 2017
73. Ter Maaten JM, Rao VS, Hanberg JS, et al. Renal tubular resistance is the primary driver for loop diuretic resistance in acute heart failure. Eur J Heart Fail. 2017;19:1014–22.
74. Kirchner KA, Voelker JR, Brater DC. Intratubular albumin blunts the response to furosemide-A mechanism for diuretic resistance in the nephrotic syndrome. J Pharmacol Exp Ther. 1990;252:1097–101.
75. Kirchner KA, Voelker JR, Brater DC. Binding inhibitors restore furosemide potency in tubule fluid containing albumin. Kidney Int. 1991;40:418–24.
76. Green TP, Mirkin BL. Resistance of proteinuric rats to furosemide: urinary drug protein binding as a determinant of drug effect. Life Sci. 1980;26:623–30.
77. Charokopos A, Hanberg JS, Rao V, et al. Urine and serum albumin are not major determinants of diuretic resistance in heart failure. J Card Fail. 2016;22:S17.
78. Agarwal R, Gorski JC, Sundblad K, Brater DC. Urinary protein binding does not affect response to furosemide in patients with nephrotic syndrome. J Am Soc Nephrol. 2000;11:1100–5.
79. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol. 1996;28:376–82.
80. Gallagher KL, Jones JK. Furosemide-induced ototoxicity. Ann Intern Med. 1979;91:744–5.
81. Cox ZL, Lenihan DJ. Loop diuretic resistance in heart failure: resistance etiology-based strategies to restoring diuretic efficacy. J Card Fail. 2014;20:611–22.
82. Felker GM, O'Connor CM, Braunwald E. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? Circ Heart Fail. 2009;2:56–62.
83. Rao VS, Planavsky N, Hanberg JS, et al. Compensatory distal reabsorption drives diuretic resistance in human heart failure. J Am Soc Nephrol. 2017;28:3414–24.
84. Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med. 1991;114:886–94.
85. Stanton BA, Kaissling B. Adaptation of distal tubule and collecting duct to increased Na delivery. II. Na+ and K+ transport. Am J Phys. 1988;255:F1269–75.
86. Stanton BA, Kaissling B. Regulation of renal ion transport and cell growth by sodium. Am J Phys. 1989;257:F1–10.
87. Brisco-Bacik MA, Ter Maaten JM, Houser SR, et al. Outcomes associated with a strategy of adjuvant metolazone or high-dose loop diuretics in acute decompensated heart failure: a propensity analysis. J Am Heart Assoc. 2018;7(18):e009149.
88. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367:2296–304.
89. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56:1527–34.
90. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):e240–e327.

91. Channer KS, McLean KA, Lawson-Matthew P, Richardson M. Combination diuretic treatment in severe heart failure: a randomised controlled trial. Br Heart J. 1994;71:146–50.
92. Knauf H, Mutschler E. Diuretic effectiveness of hydrochlorothiazide and furosemide alone and in combination in chronic renal failure. J Cardiovasc Pharmacol. 1995;26:394–400.
93. Fliser D, Schroter M, Neubeck M, Ritz E. Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. Kidney Int. 1994;46:482–8.
94. Sica DA. Metolazone and its role in edema management. Congest Heart Fail. 2003;9:100–5.
95. Metolazone [package insert]; Mylan Pharmaceuticals Inc; Morgantown W. October 2004.
96. Kissling KT, Pickworth KK. Comparison of the effects of combination diuretic therapy with oral hydrochlorothiazide or intravenous chlorothiazide in patients receiving intravenous furosemide therapy for the treatment of heart failure. Pharmacotherapy. 2014;34:882–7.
97. Goodman LS, Brunton LL, Chabner B, Knollmann BC. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill; 2011.
98. Gines P, Cardenas A, Arroyo V, Rodes J. Management of cirrhosis and ascites. N Engl J Med. 2004;350:1646–54.
99. European Association for the Study of the L. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53:397–417.
100. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341:709–17.
101. Bansal S, Lindenfeld J, Schrier RW. Sodium retention in heart failure and cirrhosis: potential role of natriuretic doses of mineralocorticoid antagonist? Circ Heart Fail. 2009;2:370–6.
102. Butler J, Hernandez AF, Anstrom KJ, et al. Rationale and design of the ATHENA-HF Trial: aldosterone targeted neurohormonal combined with natriuresis therapy in heart failure. JACC Heart Fail. 2016;4:726–35.
103. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. JAMA Cardiol. 2017;2:950–8.
104. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007;297:1319–31.
105. Matsue Y, Suzuki M, Torii S, et al. Clinical effectiveness of tolvaptan in patients with acute heart failure and renal dysfunction. J Card Fail. 2016;22:423–32.
106. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. J Am Coll Cardiol. 2017;69:1399–406.
107. Konstam MA, Kiernan M, Chandler A, et al. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. J Am Coll Cardiol. 2017;69:1409–19.
108. Verbrugge FH, Dupont M, Bertrand PB, et al. Determinants and impact of the natriuretic response to diuretic therapy in heart failure with reduced ejection fraction and volume overload. Acta Cardiol. 2015;70:265–73.
109. Acetazolamide in Decompensated Heart Failure With Volume OveRload (ADVOR). 2018. Accessed June 2018, at https://clinicaltrials.gov/ct2/show/NCT03505788?term=mullens+acetazolamide&cond=heart+failure&rank=1.

Diuretic Therapy Complicated by Hyponatremia

12

Frederik H. Verbrugge

Case Vignette

Mr. Y is a 62 year-old white man who presents at the emergency department with shortness of breath and swollen legs. His past medical history is notable for hypertension, diabetes and an ischemic cardiomyopathy for which he received coronary artery bypass grafting 8 years ago. His left ventricular ejection fraction measured on transthoracic echocardiography 6 months before the current presentation was 43%. Maintenance therapy includes aspirin, atorvastatin, bisoprolol 5 mg daily, lisinopril 10 mg daily and furosemide 40 mg daily. Laboratory results at presentation show a serum creatinine level of 1.52 mg/dL. Mr. Y is admitted to the hospital with a tentative diagnosis of acute heart failure and treated with an intravenous bolus of furosemide 80 mg on 2 consecutive days. On the morning of the second day, net fluid loss is 792 mL. Mr. Y indicates that he is feeling better, but on clinical examination bilateral pitting edema and orthopnea are still present. The serum creatinine has risen to 1.93 mg/dL, serum sodium is 132 mmol/L, serum potassium 3.1 mmol/L, and serum chloride is 94 mmol/L.

Chapter Key Points

- Incidence and risk factors for worsening renal function and electrolyte disturbances in acute heart failure
- Prognostic impact of worsening renal function in acute heart failure, and relationship between worsening renal function and volume overload
- Treatment strategies when a rise in serum creatinine is observed during decongestive treatment in acute heart failure with a focus on renal preservation

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Brief Discussion of the Case

The case vignette describes a typical male patient with diabetes and hypertension who has developed an ischemic cardiomyopathy, presumably due to multi-vessel coronary artery disease given his remote history of coronary artery bypass grafting. His most recent left ventricular ejection fraction (LVEF) is just above 40%, the threshold below which he would meet the definition of heart failure with reduced ejection fraction (HFrEF) and qualify for most evidence-based treatments according to current guidelines [1, 2]. The European Society of Cardiology guidelines have now defined heart failure with mid-range ejection fraction (LVEF 40–49%) to stimulate more research in such patients [2]. Some data suggest that pharmacological HFrEF treatments are beneficial in mid-range ejection fraction patients as well [3, 4]. Moreover, the patient from this case vignette might have HFrEF with (partly) recovered LVEF, strengthening the rationale for classic pharmacological HFrEF therapies.

Overall, this patient seems well treated with aspirin and a statin for established coronary artery disease, as well as an angiotensin-converting enzyme inhibitor (ACE-I) and beta blocker for heart failure. The need for maintenance therapy with furosemide indicates that he should have been considered symptomatic, even before the current presentation with acute heart failure (AHF). One could therefore argue whether a mineralocorticoid receptor agonist (MRA) is indicated. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial has demonstrated that eplerenone reduces mortality as well as heart failure hospitalizations in mildly symptomatic HFrEF patients with LVEF <35% [5]. Although the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial with spironolactone was negative for the same end-point in patients with LVEF >45%, patients towards the lower end of the LVEF spectrum tended to have better outcomes with spironolactone and the trial was positive in patients with elevated natriuretic peptide levels [3, 6]. In the absence of significant hyp0erkalemia (>5 mmol/L), I would recommend introduction of an MRA at low dose with close follow-up of serum potassium levels. Yet, the current setting of AHF with worsening renal function (WRF) is a reason to delay that decision.

Further, both ACE-I and beta blocker therapy in the case vignette are approximately 50% below target doses indicated by the guidelines [1, 2]. Up-titration of neurohumoral blocker therapy to target dose in HFrEF is associated with better prognosis and should be pursued in the absence of contraindications [7]. Currently, there is insufficient evidence to recommend switching from an ACE-I to the angiotensin receptor neprilysin inhibitor sacubitril/valsartan in patients with mid-range LVEF, as only HFrEF patients with LVEF <40% were included in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (*PARADIGM-HF*) trial [8]. Nonetheless, it should be noted that high serum creatinine levels and hyp0erkalemia occurred less frequent in the sacubitril/valsartan group, making it an important consideration in HFrEF patients with borderline renal function. The Prospective Comparison of ARNI with

ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) trial will provide more insight whether this also apply in patients with preserved LVEF [9].

The patient in this case vignette now comes in with a typical presentation of AHF and clear signs of volume overload, the most frequent reason for hospital admission in heart failure [10]. A thorough history-taking to identify reasons for worsening heart failure should be the first priority. Compliance with sodium restriction, unexpected fluid/electrolyte loss (i.e., diarrhoea, vomiting, or excessive perspiration) and introduction or dose increases of nephrotoxic medications are also important to assess, especially in patients with WRF and electrolyte disorders like the one described in the case vignette. Intravenous loop diuretics for are considered standard of care to treat volume overload in AHF. In the Acute Decompensated Heart Failure Registry (ADHERE), 88% of patients received them for a mean duration of 3 days, in 63% as the sole therapy administered [11]. As loop diuretic use in AHF is largely based on empirical evidence, the optimal agent, dose, administration schedule and route remains unclear. Doubling the patients' oral maintenance dose resembles the approach evaluated in the Diuretic Optimization Strategies Evaluation (DOSE) trial, with no meaningful differences observed between continuous versus intermittent bolus administration [12]. Importantly, as the threshold for loop diuretic efficacy increases at low glomerular filtration rate (GFR), it is important to increase the dose in patients with chronic kidney disease [13]. When calculating the estimated GFR of the patient in this case vignette at baseline (48 mL/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration formula), 80 mg of furosemide seems a reasonable dose to start.

Despite subjective improvement in the condition of the patient, persistent congestion is observed, together with a rise in serum creatinine >0.3 mg/dL, often labelled as WRF in cardio-renal literature. This constellation puts the patient at high risk for both subsequent mortality and (early) readmissions [14]. Accumulating evidence suggests that response to loop diuretic therapy itself is an independent predictor of outcome in AHF [15, 16]. In this case vignette, a cumulative furosemide dose of 160 mg is administered over a 48 h interval, yielding a net negative fluid balance of 792 mL, corresponding to 198 mL per 40 mg furosemide, which indicates substantial diuretic resistance. Finally, low serum levels of sodium, chloride, and potassium have all been associated with worse outcomes in AHF, indicating that the patient from the case vignette is at very high risk for adverse outcomes [17–19]. In this chapter, the epidemiology and pathophysiology of WRF and electrolyte disturbances in AHF are discussed and a management approach is suggested.

Worsening Renal Function

Incidence

An increase in serum creatinine is frequently observed during decongestive treatment with intravenous diuretics in AHF. Depending on the exact cut-off chosen, its

incidence is 15–60% [20]. In a study of 1002 patients presenting with AHF treated with intravenous loop diuretics, it was found that a >0.3 mg/dL increase in serum creatinine yields the best trade-off between sensitivity and specificity to predict in-hospital mortality and prolonged hospital stay >10 days [20]. Based on these findings, WRF defined as a >0.3 mg/dL rise in serum creatinine has often been used as an outcome parameter in cardiorenal literature. Its incidence is approximately 30–35% [20, 21].

Prognostic Importance

On a population level, WRF in AHF is associated with a 75% increased relative risk for all-cause mortality [22]. However, this is partly due to WRF being reflective of underlying chronic kidney disease. Indeed, WRF occurs more frequently in patients with a lower underlying GFR [21]. Furthermore, baseline and persistent renal impairment are much stronger predictors of adverse outcome in AHF than incident WRF itself [22, 23]. Moreover, a decreasing versus stable serum creatinine during decongestion in AHF is also associated with worse prognosis [24]. This indicates that the acute change in serum creatinine is probably not causally related to mortality, but rather a marker of risk. Further supporting this observation is that in specific situations such as after starting an ACE-I, WRF is not associated with worse outcome [25].

Worsening Renal Function and Decongestion Success

It has been demonstrated clearly that if WRF occurs in the setting of diuretic resistance and persistent congestion, prognosis is exceedingly poor [14]. In contrast, when accompanied by hemoconcentration as a marker of successful decongestion, it might even be associated with better outcome [26]. Therefore, WRF on its own should not be a reason to withdraw decongestive therapies when volume overload is still present. Instead, focusing on diuretic response and how to improve it in case of diuretic resistance should be the main focus to guide treatment [16].

Avoiding Harmful Worsening Renal Function

As explained above, WRF in the context of successful decongestion and hemoconcentration is actually a good prognostic sign that should not be avoided at all cost. Yet, structural nephron damage with loss of glomeruli leading to persistent renal impairment must be prevented [23]. It is reassuring that markers of tubular injury increase only modestly during decongestive treatment in AHF and in general are poor predictors of persistent renal impairment [27, 28]. This reflects that most cases are probably caused by transient hemodynamic changes. Indeed, arterial hypotension is a major contributor to WRF in AHF [29, 30]. Arterial blood pressure is a

direct determinant of the glomerular capillary hydrostatic pressure that drives glomerular filtration [31]. Although the nephron has intrinsic autoregulation systems to stabilize renal blood flow and GFR in the face of an ever changing arterial blood pressure, these mechanisms are exhausted when mean arterial pressure falls below ~60 mmHg [32]. Therefore, it seems prudent to avoid hypotensive episodes, especially when prolonged, during decongestive treatment in AHF. Alternatively, abdominal congestion with increased intra-abdominal pressure is another potentially reversible cause of WRF [33, 34]. A higher intra-abdominal pressure translates into higher renal interstitial pressure that directly opposes GFR [35]. When meaningful ascites is present, lowering the intra-abdominal pressure by paracentesis might be considered to improve the GFR [34].

Common Electrolyte Disturbances During Decongestive Treatment

Hyponatremia and Hypochloremia

Epidemiology

Hyponatremia frequently poses a therapeutic challenge in AHF. In a sub-analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, including 47,647 patients with AHF, hyponatremia was present in approximately 20% upon admission [17]. In addition, the incidence of hospital-acquired hyponatremia during decongestive treatment for AHF is 15–25% [36, 37]. The pathophysiology of hyponatremia is complex and treating physicians should differentiate between depletion versus dilution hyponatremia [38]. The former is caused by ubiquitous use of powerful sodium-wasting diuretics, often with concomitant potassium and magnesium losses, and simply treated by repletion with saline. However, administration of isotonic saline in dilution hyponatremia may further depress serum sodium concentration, as the problem is impaired water excretion rather than sodium deficiency.

Prognostic Impact

Hyponatremia is an established risk marker in AHF [39–41]. However, studies examining specifically the prognostic impact of hyponatremia correction have yielded conflicting results [42, 43]. Recent evidence suggests that hypochloremia may be an even stronger predictor of adverse outcomes in AHF [18]. Interestingly, after correction for serum chloride levels, the presence of hyponatremia seems no longer predictive of worse prognosis. The exact reasons for this observation remain unclear, but it has been found that hypochloremia is an important factor in loop diuretic resistance [44].

General Approach

When encountering a patient with AHF and hyponatremia (or hypochloremia), it is important to identify its cause and provide specific treatment (Fig. 12.1) [38]. First,

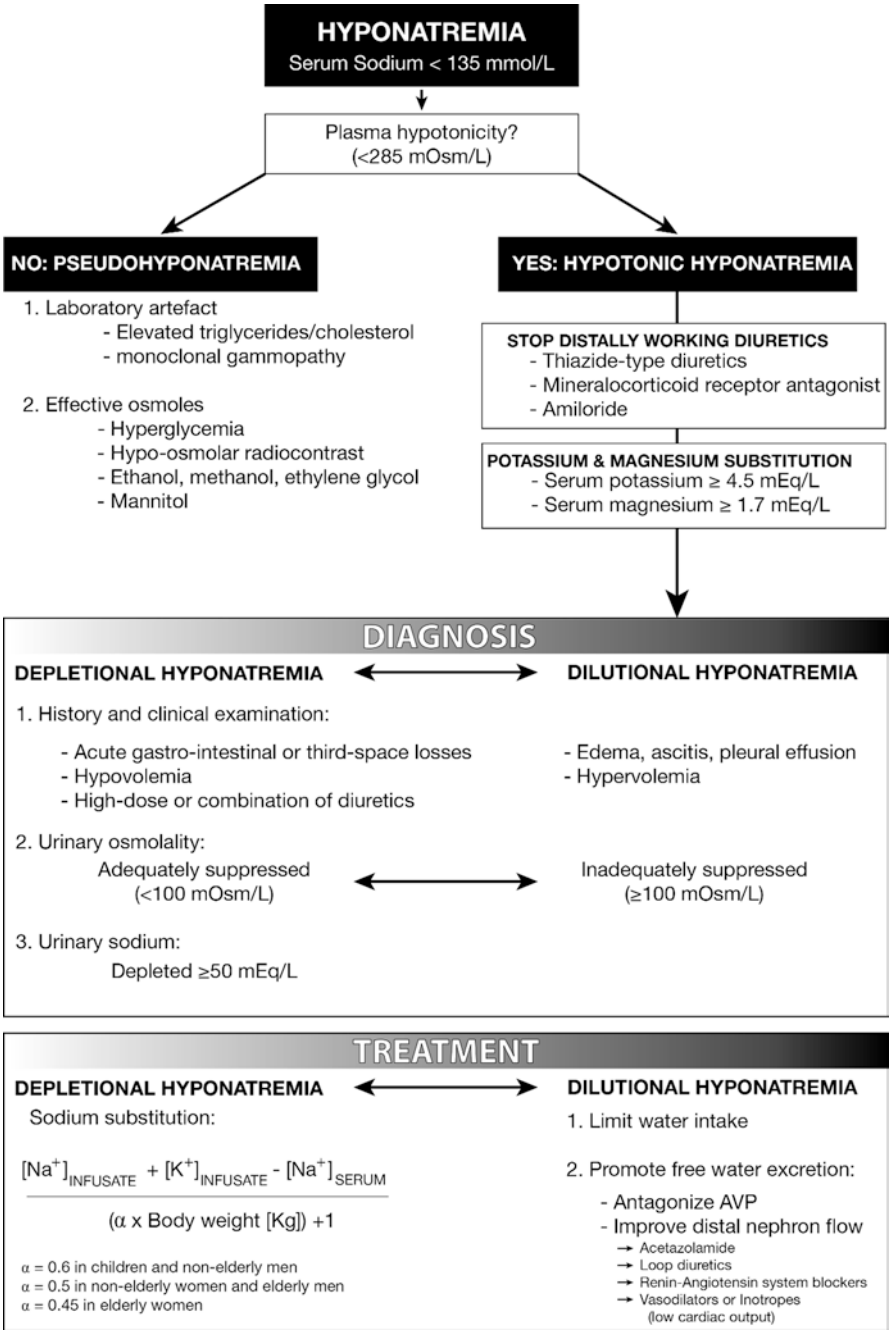

Fig. 12.1 Approach to hyponatremia in heart failure

the possibility of pseudohyponatremia or the presence of normal serum osmolality should be considered. Pseudohyponatremia may be due to hyperglycemia or the administration of contrast agents and is associated with favorable outcome irrespective of its treatment. Next, diuretic agents that impair free water excretion such as thiazide-type diuretics, amiloride and MRA are a frequent cause of hyponatremia and withholding them until correction of hyponatremia should be considered. As low potassium and magnesium levels lead to sodium shifting from the extracellular towards the intracellular compartment, aiming for high to normal serum levels may help to prevent/ameliorate hyponatremia. If hyponatremia is still present despite these general precautions, plasma dilution should be differentiated from sodium depletion.

Sodium Depletion Versus Plasma Dilution

The presence of clinical signs reflecting hypovolemia and/or intensive diuretic regiments may suggest sodium depletion. If in doubt, one might consider a fluid challenge with 1 L of isotonic saline over 24 h, measuring the effect on serum sodium levels. However, this should be avoided in case of clear fluid overload and/or severe hyponatremia (serum sodium <125 mmol/L). Indeed, signs of volume overload indicate a component of dilutional hyponatremia, in which case an improvement is unlikely and the risk of further deteriorating congestion substantial. Alternatively, one could measure urine osmolality, which should be adequately suppressed (<100 mOsm/L) in patients with sodium depletion, but not in patients with dilution hyponatremia. If urine osmolality is >150 mOsm/L, isotonic solutions should certainly be avoided as administration would result in further worsening of hyponatremia. Finally, very low urinary sodium and/or chloride concentrations (≤50 mmol/L) are a relatively strong argument for electrolyte depletion in AHF [45].

Treatment of Dilution Hyponatremia

Loop diuretics Loop diuretics facilitate water excretion by impairing the urinary concentration capacity of the kidneys [38]. Therefore, they lead to the production of hypotonic urine and, in the absence of diuretic resistance, are unfrequently associated with hyponatremia. As loop diuretics are cheap and readily available, they remain the first-line therapy to treat volume overload in AHF with dilution hyponatremia.

Acetazolamide Acetazolamide is an old and largely forgotten diuretic targeting the proximal tubules in the nephron. It exerts its diuretic effect through inhibition of carbonic anhydrase, resulting in urinary sodium bicarbonate wasting [32]. By inhibiting sodium reabsorption proximal in the tubular system, it leads to a higher flux of tubular fluid throughout more distal parts of the nephron. As the dilution capacity of the kidneys directly depends on this flux through the distal nephron, acetazolamide improves free water excretion, making it a particularly attractive diuretic to use in combination with loop diuretics in case of dilution hyponatremia [38].

Hypertonic saline The addition of hypertonic saline to improve loop diuretic efficacy in AHF is a controversial issue. Although counterintuitive from a pathophysiological point of view, some small studies have suggested more efficient decongestion and better renal preservation when loop diuretics are combined with hypertonic saline (Table 12.1) [46–51]. Importantly, decreases in plasma renin activity, inflammatory markers and even natriuretic peptide levels have been demonstrated with hypertonic saline administration in AHF patients who receive loop diuretics [52, 53]. Still, it remains difficult to draw any firm conclusions as these improvements with sodium loading might be confounded by the use of high doses of loop diuretics that might have induced these alterations. Patients with hyponatremia might benefit more from the addition of hypertonic saline to loop diuretics, as serum sodium levels are more easily corrected.

Table 12.1 Studies on hypertonic saline in patients with acute decompensated heart failure

Author (Journal, Year)	Number of patients	Treatment	Outcome
Paterna et al. (*Eur J Heart Fail*, 2000) [46]	60	IV furosemide 500–1000 mg with versus without 150 mL 1.4–4.6% hypertonic saline BID	Increase in diuresis, natriuresis and serum sodium levels; decrease in serum creatinine; and shorter hospitalization time with hypertonic saline
Licata et al. (*Am Heart J*, 2003) [47]	107	IV furosemide 500–1000 mg with versus without 150 mL 1.4–4.6% hypertonic saline BID	Increase in diuresis, natriuresis and serum sodium levels; decrease in serum creatinine; and improved survival with hypertonic saline
Paterna et al. (*J Am Coll Cardiol*, 2005) [52]	94	IV furosemide 500–1000 mg with versus without 150 mL 1.4–4.6% hypertonic saline BID	Increase in diuresis and natriuresis; decrease in BNP levels; shorter hospitalization time; and lower 30-day readmission rate with hypertonic saline
Parrinello et al. (*J Card Fail*, 2011) [48]	133	IV furosemide 250 mg plus 150 mL 3% hypertonic saline BID versus IV furosemide 250 mg BID plus low sodium diet (<80 mmol)	Increase in diuresis, natriuresis and serum sodium levels; improved renal function; and faster reduction of echo-PCWP with hypertonic saline
Paterna et al. (*Am J Med Sci*, 2011) [49]	1771	IV furosemide 250 mg plus 150 mL 3% hypertonic saline BID versus IV furosemide 250 mg BID plus low sodium diet (<80 mmol)	Increase in diuresis, natriuresis and serum sodium levels; decrease in serum creatinine; shorter hospitalization time; lower readmission rate; and improved survival with hypertonic saline
Issa et al. (*Int J Cardiol*, 2013) [50]	34	100 mL 7.5% hypertonic saline BID versus placebo during 3 days	Improved in glomerular and tubular biomarkers with hypertonic saline
Okuhara et al. (*J Card Fail*, 2014) [51]	44	500 mL 1.7% hypertonic saline versus glucose 5% with 40 mg furosemide	Improved GFR and better diuresis with hypertonic saline

Table 12.2 Studies on AVP antagonists in patients with acute decompensated heart failure and hyponatremia

Author (Journal, Year)	Number of patients	Treatment	Outcome
Gheorghiade et al. (*Circulation*, 2003) [58]	71/254 (subgroup analysis)	Tolvaptan 30 mg, 45 mg or 60 mg versus placebo	Normalization of serum sodium after 24 h, greater decrease in body weight and edema, increased urine output with tolvaptan
Gheorghiade et al. (*JAMA*, 2004) [59]	51/319 (subgroup analysis)	Tolvaptan 30 mg, 60 mg or 90 mg versus placebo	Normalization of serum sodium with tolvaptan
Ghali et al. (*J Clin Endocrinol Metab*, 2006) [60]	19/74 (subgroup analysis)	Conivaptan 40 mg or 80 mg versus placebo	Normalization of serum sodium with conivaptan
Zeltser et al. (*Am J Nephrol*, 2007) [61]	28/84 (subgroup analysis)	Conivaptan 40 mg or 80 mg versus placebo	Increase in serum sodium concentration with conivaptan
Konstam et al. (*JAMA*, 2007) [62]	1157/4133 (subgroup analysis)	Tolvaptan 30 mg versus placebo	No effect on mortality or rehospitalisation, significant increase in serum sodium with tolvaptan
Aronson et al. (*Eur J Heart Fail*, 2011) [56]	90/118 (subgroup analysis)	Satavaptan 25 mg or 50 mg versus placebo	Increase in serum sodium concentration with satavaptan

Arginine-vasopressin antagonists Arginine-vasopressin antagonists are the only medication class that directly promotes free water excretion by its mechanism of action, which is prevention of aquaporin-2 channel availability in the collecting ducts of the nephron that is needed for water reabsorption [54, 55]. Three oral V2-receptor antagonists (tolvaptan, satavaptan and lixivaptan) have been tested in AHF and are efficacious in reversing hyponatremia in this context [56–59]. Similar data are available for conivaptan, an intravenous agent which antagonizes both the V2- and V1a-receptor [55, 60, 61]. In Table 12.2, a summary is presented of currently available evidence on arginine-vasopressin antagonists in patients with AHF and hyponatremia. Importantly the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), including 4133 patients with AHF but without hyponatremia as an inclusion criterion, compared tolvaptan with placebo and was powered for clinical end-point analysis [62]. The overall trial did not show a significant reduction in all-cause mortality or readmission rates, but interestingly a sub-analysis in patients presenting with pronounced hyponatremia (<130 mmol/L) did suggest improved survival free from cardiovascular death or readmission [57, 62]. Yet, this promising finding warrants further study in an adequately powered randomized clinical trial.

Hypernatremia

Hypernatremia is rather infrequent during decongestive treatment in AHF. Its incidence has been less systematically studied when compared to hyponatremia, but is

probably <5% [63]. Similar to hyponatremia, hypernatremia in AHF is associated with higher in-hospital mortality, prolonged hospitalization and increased healthcare costs [63, 64]. Its most common cause is likely over-diuresis with excessive free water loss in patients unable to drink because of illness or frailty. Such cases are easily managed by decreasing the dose of diuretics and offering more free water, either through oral or intravenous administration. It is important to acknowledge that loop diuretics induce the production of hypotonic urine [65]. Therefore, they generally remove more water that sodium. Frequent use of these agents in combination with iso- or hypertonic fluids (most often in mechanically ventilated patients in the intensive care unit) might occasionally cause the situation of hypervolemic hypernatremia. In HFrEF patients, aldosterone breakthrough further exacerbates this problem [66, 67]. Thiazide-type diuretics, MRA and amiloride, used alone or in combination, are the preferred agents to add in such cases because they increase the urinary sodium concentration directly, thereby limiting free water excretion [38].

Potassium Derangements

Hypokalemia and hyperkalemia are common electrolyte abnormalities in chronic heart failure, both associated with worse survival [68]. Due to the ubiquitous use of potassium-losing loop and thiazide-type diuretics, potassium losses are exacerbated during decongestive treatment for AHF, often necessitating the need for oral and/or intravenous repletion therapy. It is important to acknowledge that concomitant magnesium losses may cause refractory hypokalemia and predispose to cardiac arrhythmias, so clinicians should have a low threshold to provide magnesium supplements in AHF patients who develop hypokalaemia [69]. Moreover, both hypokalemia and hypomagnesemia may contribute to hyponatremia by shifting sodium into the intracellular compartment [38]. In contrast, hyperkalemia in AHF occurs almost exclusively in patients with advanced chronic kidney disease and low GFR. The treatment of hyperkalemia is similar, irrespectively the presence of AHF. However, its most important implication is a contraindication for the use of MRA and/or (uptitration of) renin-angiotensin system inhibitors. Whether this is an absolute or relative contraindication depends on the severity of hyp0erkalemia and the reversibility of kidney dysfunction. Interestingly, new agents like zirconium cyclosilicate and patiromer that impair potassium absorption in the gut offer the prospect of preventing the problem of hyp0erkalemia and still allow these important evidence-based treatments in heart failure [70, 71].

Treatment Pearls for the Case Vignette

The patient from the case vignette demonstrates clear signs of persistent volume overload (i.e., the combination of edema and orthopnea) despite adequately dosed bolus therapy with loop diuretics. Notwithstanding the presence of WRF, this should

be a strong incentive to pursue further decongestion with diuretic therapy as outcomes are abysmal when volume overload persists. Reasons for the poor loop diuretic response should be considered. Hypotension is a major contributor to WRF as well as diuretic resistance and should be avoided. If necessary, neurohumoral blocker therapy with lisinopril and/or bisoprolol could temporarily be decreased or even withheld. If renal perfusion is severely compromised due to low cardiac output, this should be addressed with sodium nitroprusside, inotropes, or even mechanical assist devices, depending on the arterial blood pressure and severity of cardiogenic shock. I would have a low threshold for paracentesis when meaningful ascites is present in a patient like the one described by the case vignette, as elevated intra-abdominal pressure is another potentially reversible cause of WRF.

With the estimated GFR down to 36 mL/min/1.73 m^2, my recommendation would be to increase the dose of subsequent furosemide bolus therapy to 120 mg. In addition, more frequent administrations at 6 h intervals are indicated to avoid post-diuretic sodium retention. Alternatively, loop diuretic therapy could be administered through continuous infusion, but this strategy is associated with more pronounced neurohumoral activation that could potentially aggravate hyponatremia [72]. Besides, I would consider compression stockings to recruit peripheral oedema more easily and albumin administration if serum levels are below 3.0 g/dL, which may impair furosemide delivery at its site of action in the nepron [13].

My final recommendation would be to add an intravenous bolus of acetazolamide 500 mg OD to the current diuretic regimen. Sequential nephron blockade with thiazide-type diuretics or high-dose MRA would be an alternative to break diuretic resistance, yet expected to exacerbate hyponatremia as free water excretion by the kidneys is impaired with these agents [38]. In contrast, acetazolamide increases free water excretion, making it an attractive agent when dilution hyponatremia is present in AHF. As urinary potassium and magnesium losses are exacerbated by combination diuretic therapy and may contribute to hyponatremia by shifting sodium to the intracellular compartment, I would provide intravenous and/or oral repletion therapy. If worsening hyponatremia would occur despite this treatment approach, administration of hypertonic saline or vasopressin antagonists would be among my considerations. Importantly, after successful decongestion, optimizing therapies for chronic heart failure as described above is important to prevent recurrence or worsening of hyponatremia.

References

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):e240–327.
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18:891–975.

3. Solomon SD, Claggett B, Lewis EF, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J. 2016;37:455–62.
4. Lund LH, Claggett B, Liu J, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 2018;20:1230–9.
5. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364:11–21.
6. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383–92.
7. Verbrugge FH, Duchenne J, Bertrand PB, Dupont M, Tang WH, Mullens W. Uptitration of renin-angiotensin system blocker and beta-blocker therapy in patients hospitalized for heart failure with reduced versus preserved left ventricular ejection fractions. Am J Cardiol. 2013;112:1913–20.
8. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.
9. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: Rationale and Design of the PARAGON-HF Trial. JACC Heart Fail. 2017;5:471–82.
10. Adams KF Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149:209–16.
11. Fonarow GC, Corday E. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. Heart Fail Rev. 2004;9:179–85.
12. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805.
13. Ellison DH, Felker GM. Diuretic treatment in heart failure. N Engl J Med. 2017;377:1964–75.
14. Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail. 2012;5:54–62.
15. Testani JM, Brisco MA, Turner JM, et al. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail. 2014;7:261–70.
16. Verbrugge FH, Mullens W, Tang WH. Management of cardio-renal syndrome and diuretic resistance. Curr Treat Options Cardiovasc Med. 2016;18:11.
17. Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J. 2007;28:980–8.
18. Grodin JL, Simon J, Hachamovitch R, et al. Prognostic role of serum chloride levels in acute decompensated heart failure. J Am Coll Cardiol. 2015;66:659–66.
19. Salah K, Pinto YM, Eurlings LW, et al. Serum potassium decline during hospitalization for acute decompensated heart failure is a predictor of 6-month mortality, independent of N-terminal pro-B-type natriuretic peptide levels: an individual patient data analysis. Am Heart J. 2015;170:531–42.e1.
20. Gottlieb SS, Abraham W, Butler J, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail. 2002;8:136–41.
21. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004;43:61–7.
22. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35:455–69.

23. Krishnamoorthy A, Greiner MA, Sharma PP, et al. Transient and persistent worsening renal function during hospitalization for acute heart failure. Am Heart J. 2014;168:891–900.
24. Testani JM, McCauley BD, Chen J, Coca SG, Cappola TP, Kimmel SE. Clinical characteristics and outcomes of patients with improvement in renal function during the treatment of decompensated heart failure. J Card Fail. 2011;17:993–1000.
25. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail. 2011;4:685–91.
26. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122:265–72.
27. Dupont M, Shrestha K, Singh D, et al. Lack of significant renal tubular injury despite acute kidney injury in acute decompensated heart failure. Eur J Heart Fail. 2012;14:597–604.
28. Verbrugge FH, Dupont M, Shao Z, et al. Novel urinary biomarkers in detecting acute kidney injury, persistent renal impairment, and all-cause mortality following decongestive therapy in acute decompensated heart failure. J Card Fail. 2013;19:621–8.
29. Testani JM, Coca SG, McCauley BD, Shannon RP, Kimmel SE. Impact of changes in blood pressure during the treatment of acute decompensated heart failure on renal and clinical outcomes. Eur J Heart Fail. 2011;13:877–84.
30. Dupont M, Mullens W, Finucan M, Taylor DO, Starling RC, Tang WH. Determinants of dynamic changes in serum creatinine in acute decompensated heart failure: the importance of blood pressure reduction during treatment. Eur J Heart Fail. 2013;15:433–40.
31. Verbrugge FH, Grieten L, Mullens W. Management of the cardiorenal syndrome in decompensated heart failure. Cardiorenal Med. 2014;4:176–88.
32. Verbrugge FH, Dupont M, Steels P, et al. The kidney in congestive heart failure: 'are natriuresis, sodium, and diuretics really the good, the bad and the ugly?'. Eur J Heart Fail. 2014;16:133–42.
33. Mullens W, Abrahams Z, Skouri HN, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol. 2008;51:300–6.
34. Mullens W, Abrahams Z, Francis GS, Taylor DO, Starling RC, Tang WH. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. J Card Fail. 2008;14:508–14.
35. Verbrugge FH, Dupont M, Steels P, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol. 2013;62:485–95.
36. Konishi M, Haraguchi G, Ohigashi H, et al. Progression of hyponatremia is associated with increased cardiac mortality in patients hospitalized for acute decompensated heart failure. J Card Fail. 2012;18:620–5.
37. Shchekochikhin DY, Schrier RW, Lindenfeld J, Price LL, Jaber BL, Madias NE. Outcome differences in community- versus hospital-acquired hyponatremia in patients with a diagnosis of heart failure. Circ Heart Fail. 2013;6:379–86.
38. Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH, Mullens W. Hyponatremia in acute decompensated heart failure: depletion versus dilution. J Am Coll Cardiol. 2015;65:480–92.
39. Gheorghiade M, Rossi JS, Cotts W, et al. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. Arch Intern Med. 2007;167:1998–2005.
40. Sato N, Gheorghiade M, Kajimoto K, et al. Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND registry). Am J Cardiol. 2013;111:1019–25.
41. Verbrugge FH, Grodin JL, Mullens W, Taylor DO, Starling RC, Tang WH. Transient hyponatremia during hospitalization for acute heart failure. Am J Med. 2016;129:620–7.
42. Madan VD, Novak E, Rich MW. Impact of change in serum sodium concentration on mortality in patients hospitalized with heart failure and hyponatremia. Circ Heart Fail. 2011;4:637–43.
43. Lee SE, Choi DJ, Yoon CH, et al. Improvement of hyponatraemia during hospitalisation for acute heart failure is not associated with improvement of prognosis: an analysis from the Korean Heart Failure (KorHF) registry. Heart. 2012;98:1798–804.

44. Hanberg JS, Rao V, Ter Maaten JM, et al. Hypochloremia and diuretic resistance in heart failure: mechanistic insights. Circ Heart Fail. 2016;9. pii: e003180.
45. Verbrugge FH, Nijst P, Dupont M, Penders J, Tang WH, Mullens W. Urinary composition during decongestive treatment in heart failure with reduced ejection fraction. Circ Heart Fail. 2014;7:766–72.
46. Paterna S, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. Eur J Heart Fail. 2000;2:305–13.
47. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. Am Heart J. 2003;145:459–66.
48. Parrinello G, Paterna S, Di Pasquale P, et al. Changes in estimating echocardiography pulmonary capillary wedge pressure after hypersaline plus furosemide versus furosemide alone in decompensated heart failure. J Card Fail. 2011;17:331–9.
49. Paterna S, Fasullo S, Parrinello G, et al. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York Heart Association class III (Class C) (SMAC-HF Study). Am J Med Sci. 2011;342:27–37.
50. Issa VS, Andrade L, Ayub-Ferreira SM, et al. Hypertonic saline solution for prevention of renal dysfunction in patients with decompensated heart failure. Int J Cardiol. 2013;167:34–40.
51. Okuhara Y, Hirotani S, Naito Y, et al. Intravenous salt supplementation with low-dose furosemide for treatment of acute decompensated heart failure. J Card Fail. 2014;20:295–301.
52. Paterna S, Di Pasquale P, Parrinello G, et al. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hypertonic saline solution versus high-dose furosemide alone in refractory congestive heart failure: a double-blind study. J Am Coll Cardiol. 2005;45:1997–2003.
53. Tuttolomondo A, Pinto A, Di Raimondo D, et al. Changes in natriuretic peptide and cytokine plasma levels in patients with heart failure, after treatment with high dose of furosemide plus hypertonic saline solution (HSS) and after a saline loading. Nutr Metab Cardiovasc Dis. 2011;21:372–9.
54. JJt F, Konstam MA, Udelson JE. Arginine vasopressin antagonists for the treatment of heart failure and hyponatremia. Circulation. 2008;118:410–21.
55. Chen SY, Abrahams Z, Sokos GG, et al. Conivaptan: potential therapeutic implications in heart failure. Recent Pat Cardiovasc Drug Discov. 2008;3:137–40.
56. Aronson D, Verbalis JG, Mueller M, Krum H. Short- and long-term treatment of dilutional hyponatraemia with satavaptan, a selective arginine vasopressin V2-receptor antagonist: the DILIPO study. Eur J Heart Fail. 2011;13:327–36.
57. Hauptman PJ, Burnett J, Gheorghiade M, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. J Card Fail. 2013;19:390–7.
58. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation. 2003;107:2690–6.
59. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA. 2004;291:1963–71.
60. Ghali JK, Koren MJ, Taylor JR, et al. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. J Clin Endocrinol Metab. 2006;91:2145–52.
61. Zeltser D, Rosansky S, van Rensburg H, Verbalis JG, Smith N. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. Am J Nephrol. 2007;27:447–57.
62. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007;297:1319–31.

63. Shorr AF, Tabak YP, Johannes RS, Gupta V, Saltzberg MT, Costanzo MR. Burden of sodium abnormalities in patients hospitalized for heart failure. Congest Heart Fail. 2011;17:1–7.
64. Deubner N, Berliner D, Frey A, et al. Dysnatraemia in heart failure. Eur J Heart Fail. 2012;14:1147–54.
65. Ali SS, Olinger CC, Sobotka PA, et al. Loop diuretics can cause clinical natriuretic failure: a prescription for volume expansion. Congest Heart Fail. 2009;15:1–4.
66. Hensen J, Abraham WT, Durr JA, Schrier RW. Aldosterone in congestive heart failure: analysis of determinants and role in sodium retention. Am J Nephrol. 1991;11:441–6.
67. Schrier RW. Aldosterone 'escape' vs 'breakthrough'. Nat Rev Nephrol. 2010;6:61.
68. Hoss S, Elizur Y, Luria D, Keren A, Lotan C, Gotsman I. Serum potassium levels and outcome in patients with chronic heart failure. Am J Cardiol. 2016;118:1868–74.
69. Leier CV, Dei Cas L, Metra M. Clinical relevance and management of the major electrolyte abnormalities in congestive heart failure: hyponatremia, hypokalemia, and hypomagnesemia. Am Heart J. 1994;128:564–74.
70. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med. 2015;372:222–31.
71. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372:211–21.
72. Mentz RJ, Stevens SR, DeVore AD, et al. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. JACC Heart Fail. 2015;3:97–107.

A Patient with Abdominal Congestion

13

Pieter Martens and Wilfried Mullens

Abbreviations

AHF	acute heart failure
CHF	Chronic Heart Failure
NP	natriuretic peptides
WRF	worsening of renal function

Case Vignette

Mrs. X is a 82 y/o woman with an idiopathic dilated cardiomyopathy, as well as moderately severe mitral and tricuspid valve regurgitation, who has been admitted for decompensated heart failure three times during the previous year despite adherence to low salt intake, a multi-disciplinary HF care program. Upon a scheduled outpatient evaluation 2 weeks after her latest admission, she complains from general malaise, a loss of appetite and exercise intolerance. Despite poor food intake, she has gained 5 kg of body weight since discharge. Current medications, which could not be further optimized due to symptomatic hypotension, include Ramipril 5 mg daily, carvedilol 3.125 TID, spironolactone 50 mg daily, and bumetanide 1 mg daily. Blood pressure is 86/54 mmHg in the upright position. Serum albumin is 2.6 g/dL and the serum creatinine has risen from 1.56 mg/dL at hospital discharge to 1.98 mg/dL now. Abdominal ultrasound confirms the clinical suspicion of ascites.

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Chapter Key Points

- Abdominal congestion with elevated IAP is present in up to 60% of patients with ADHF
- Both right sided abdominal congestion (elevated CVP) and an elevated IAP are strongly associated with WRF
- Decongestive therapy can reduce venous congestion and can reduce IAP
- If IAP remains high, despite decongestive therapy, ascites paracentesis or ultrafiltration can be employed to reduced IAP, which is associated with an improvement in renal function

Brief Discussion of the Case

Mrs. X has had several ADHF hospitalizations in the previous year, putting her at great risk for a recurrent episode. Her underlying cardiac substrate (heart failure with also tricuspid valve regurgitation) makes her vulnerable to abdominal congestion, as in these cases a high right atrial pressure is often present. The presenting symptoms are indicative of abdominal congestion (loss of appetite). Given the increase in body weight despite poor oral intake, the presence of volume excess (volume overload) can be assumed. It is clear that the maintenance regimen of oral loop diuretics are insufficient to maintain a decongested state. At presentation her MAP is borderline low (65 mmHg) and laboratory values indicate WRF. In this case, we would proceed with administering loop diuretics intravenously, as oral uptake is expected to be diminished. An intravenous dose of 2.5 mg bumetanide IV (2.5 times the ambulatory dose) seems appropriate. The dose can be divided in to two separate dosages (e.g. 8 AM and 12 AM) in order to avoid post-dosing kidney sodium avidity. In the absence of hyperkalemia and frank hypotension (MAP < 65 mmHg), we would consider continuing the ACE-inhibitor or beta-blocker. Given the borderline low MAP, additional therapy with vasodilators to enhance abdominal venous capacitance is not possible. However, this might be useful in the patient with a higher blood pressure (especially if SVR is high). Given the older age of the patient, a Foley-catheter would probably be necessary in order to correctly measure output and natriuretic response to the diuretic regimen. The placement of a Foley-catheter allows to measure IAP. If IAP would be elevated, we would consider performing a paracentesis of the ascites fluid, with appropriate laboratory evaluation of the aspiration fluid. The ultimate goal of therapy will be to completely decongest the patient before discharge. Depending on the physical evaluation (presence of persisting congestion?) and natriuretic response to the diuretic regimen, higher doses of loop diuretics or a combinational diuretic regimen might be necessary. If despite these therapies congestion and volume overloads persists, bail-out with ultrafiltration might be necessary. Ultrafiltration has also been shown to reduce IAP in patients with an elevated IAP. Before discharge efforts should be made to optimize maintenance therapy with neurohormonal blockers.

Introduction

Despite growing knowledge on acute heart failure, congestion remains a frequent and primary reason for patients presenting with acute decompensated heart failure (ADHF) [1]. Congestion is defined as signs and symptoms of extravascular fluid accumulation, instigated by increased cardiac filling pressures. This extravascular fluid accumulation can manifest in distinct anatomic locations, including the pleural space, alveolar space, interstitium of the skin or bowel wall and the abdominal cavity. The abdominal cavity consist of walls with both an inflexible character (e.g. bones) and with a flexible character (abdominal wall or diaphragm). At accumulations of low intra-abdominal volumes, the abdominal wall exhibits a high compliance, allowing some distention of the abdominal wall without a simultaneous increase in intra-abdominal pressure (IAP) [2]. However, once a critical volume has accumulated in the abdominal cavity, the abdominal wall compliance drops, resulting in a progressive increase of IAP. This chapter focusses on the importance of intra-abdominal congestion in worsening of renal function (WRF).

Incidence and Prognosis of Elevated Intra-abdominal Pressure in Acute Heart Failure

An increase in IAP has extensively been studied in critically ill patients and has been associated with organ dysfunction potentially leading to intra-abdominal catastrophes. Definitions on the normal and abnormal range of IAP have been defined during the World Congress on Abdominal Compartment Syndrome, by a group of experts in the field of critical care medicine [3]. The normal range of IAP has been defined as a pressure equal to atmospheric pressure. An elevated IAP is defined as ≥8 mmHg, with a pressure ≥12 mmHg being defined as intra-abdominal hypertension (IAH). The presence of an elevated IAP or IAH is an independent predictor of adverse outcome, even after correcting for important critical care medicine covariates inclusive of pH, lactate levels, base deficit and hourly urine output [4]. Furthermore, the term abdominal compartment syndrome is reserved for a high risk patient group with an IAP above 20 mmHg, which simultaneously results in new-onset organ dysfunction. The prevalence of IAH (IAP ≥ 12 mmHg) has been determined by several prospective observational studies on both medical and surgical intensive care units, which has been found to range between 32% and 54% [5]. Limited data is available on the prevalence of elevated IAP in patients with ADHF. One prospective single-center evaluation in patients with heart failure with reduced ejection fraction hospitalized for ADHF at a specialized heart failure intensive care unit documented (N = 40) that 60% of patients had an elevated IAP (≥8 mmHg) [6]. In that cohort the mean IAP was 8 ± 4 mmHg, and most patients did not have significant ascites. Also IAP dropped in most patients after decongestive therapy. All patients had a severely decreased left ventricular ejection fraction (19 ± 9%) and exhibited severe functional limitation (New York Heart

Association-class ≥III). Surprisingly little data is available on the prevalence of ascites in patients with ADHF. Indeed, most ADHF-trials published the last decade, do not report on the prevalence of ascites in the enrolled patients. The recent SECRET of CHF trial assessing the role of tolvaptan in patients with ADHF, reported that 16% of enrolled patients (N = 41/250) had ascites at the time of enrolment [7]. However, no data is available on the correlation between the presence of ascites and IAP in ADHF [3]. Importantly, ADHF also presents with increased venous congestion further promoting intra-abdominal organ congestion and dysfunction [1]. In a sealed compartment such as the abdominal cavity, a rise in pressure (ΔP) equals a rise in volume (ΔV) multiplied by the compliance (C); thus $\Delta P = C \times \Delta V$. Nevertheless, the swiftness in which intra-abdominal fluid builds-up also determines the compliance. For instance, chronic changes in intra-abdominal volume, as occur during pregnancy, are often not associated with significant pressure rises as compliance of the abdominal wall gradually increases.

In ADHF the presence of an elevated IAP is associated with a higher serum creatinine [6]. Furthermore, a reduction of IAP is strongly associated with improvement of renal function [8]. On the other hand, patients manifest with WRF during AHDF often manifest with a progressive increase in IAP.

Assessment of Abdominal Congestion in Heart Failure

The sensitivity of physical examination in detecting an elevated IAP is very low (40–60%) and is insufficient for clinical practice [9]. Several techniques have been developed the last decades to directly (needle puncture of the abdomen) or indirectly measure the abdominal pressure (via a pressure transducing system being placed in the bladder, uterine, stomach or colon). However, the bladder technique forms the most validated and widely adopted technique, due to its reproducibility, low-cost and low technical requirements [2, 3]. During the bladder technique (also called the transvesical method), a standard Foley Catheter is used which is connected with a pressure transducer placed in-line with the iliac crest at the mid-axillary line (see Fig. 13.1). The Foley catheter is flushed with a maximal volume of 50-mL of sterile saline via the aspiration port of the Foley catheter, with the drainage tube clammed to allow a fluid-filled column to develop into the bladder catheter. A pressure transducer is then inserted in the aspiration port and the pressure is subsequently measured. Several important principles should be applied to allow for standardized measurement of IAP using the bladder technique: First, IAP is measured at end-expiration (when the diaphragm is relaxed). Secondly, the patient should relax the abdominal wall. Third, the flushing volume should never exceed 50 mL, as higher values could lead to bladder distention generating false values of IAP and could lead to discomfort. Fourth, IAP should always be measured in a supine position. Fifth, a preference should be given to electronic pressure transducers as they convey the pressures in units of mmHg, allowing for convenient interpretation of the IAP. However, if electronic pressure transducers are not readily available a water filled column can be used with recalibration of the value measured in cm H_2O to mmHg (1 mmHg = 1.36 cm H_2O). Taking such precautions into account, one can

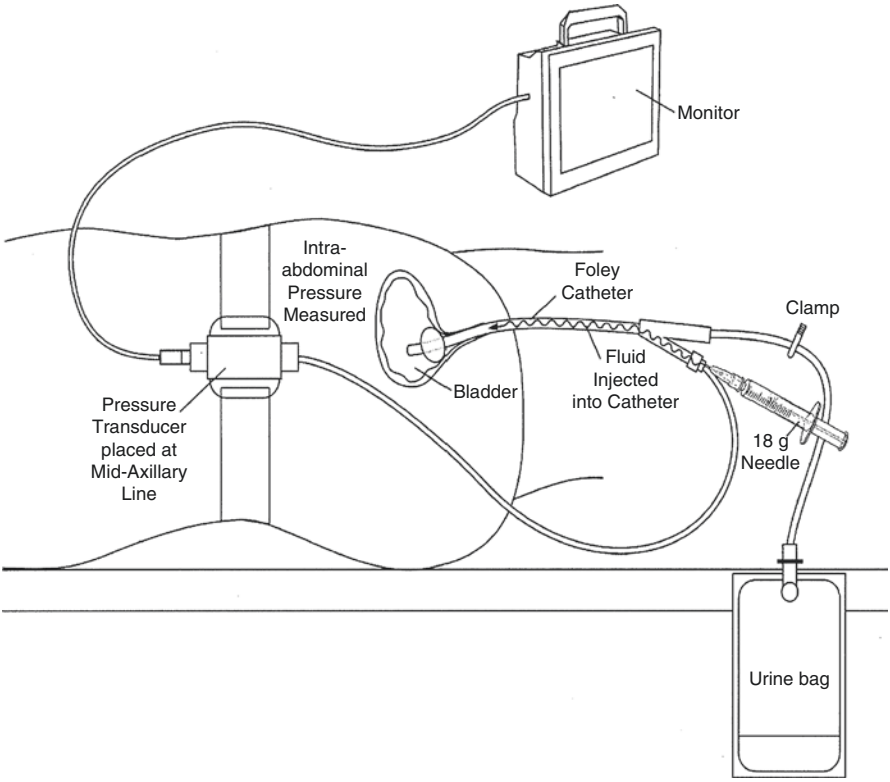

Fig. 13.1 Transvesical method for measuring intra-abdominal pressure. (Adapted from Mullens with permission)

excellently reproduce IAP-measurements. Indeed, in patients with ADHF, the inter- and intra-observer variability of IAP measurements were found to be 5% respectively 4% [6]. During the work-up of the etiology of ascites in ADHF, ascites fluid should be sampled. It should exhibit a high Serum-Ascites Albumin Gradient (SAAG >1.1 g/dL) with a high ascites albumin content (>2.5 g/dL) in ADHF. Elevated natriuretic peptide and the clinical picture of heart failure allows for further differentiation with other pre-hepatic etiologies of high SAAG-ascites (e.g. Budd-Chiari) [10].

Pathophysiology of Abdominal Congestion Leading to Kidney Dysfunction

Abdominal Venous Congestion

WRF often complicates the trajectory of ADHF within the first couple of days of hospitalization and is a strong predictor of adverse outcome [11]. Historically, a poor forward flow (low cardiac output) has been considered as the main hemodynamic infliction in heart failure resulting in a progressive decline of kidney function.

However, growing evidence supports the role of systemic congestion (backward failure) in the development of WRF in patients admitted with ADHF. In a prospective series of 145 heart failure patients with a reduced ejection fraction (left ventricular ejection fraction = 20 ± 8%) central venous pressure was the cardiac hemodynamic variable with the strongest association with WRF during the treatment of ADHF (see Fig. 13.2), hereby outperforming cardiac index [12].

In patients with increased right sided filling pressure, abdominal venous congestion will be universally present. This as the venous compartment ensures venous return. Therefore, venous pressures in the abdominal compartment should be higher than in the right atrium [13]. The abdominal venous compartment consists of both the splanchnic veins draining in the portal vein and passing through the liver eventually draining via

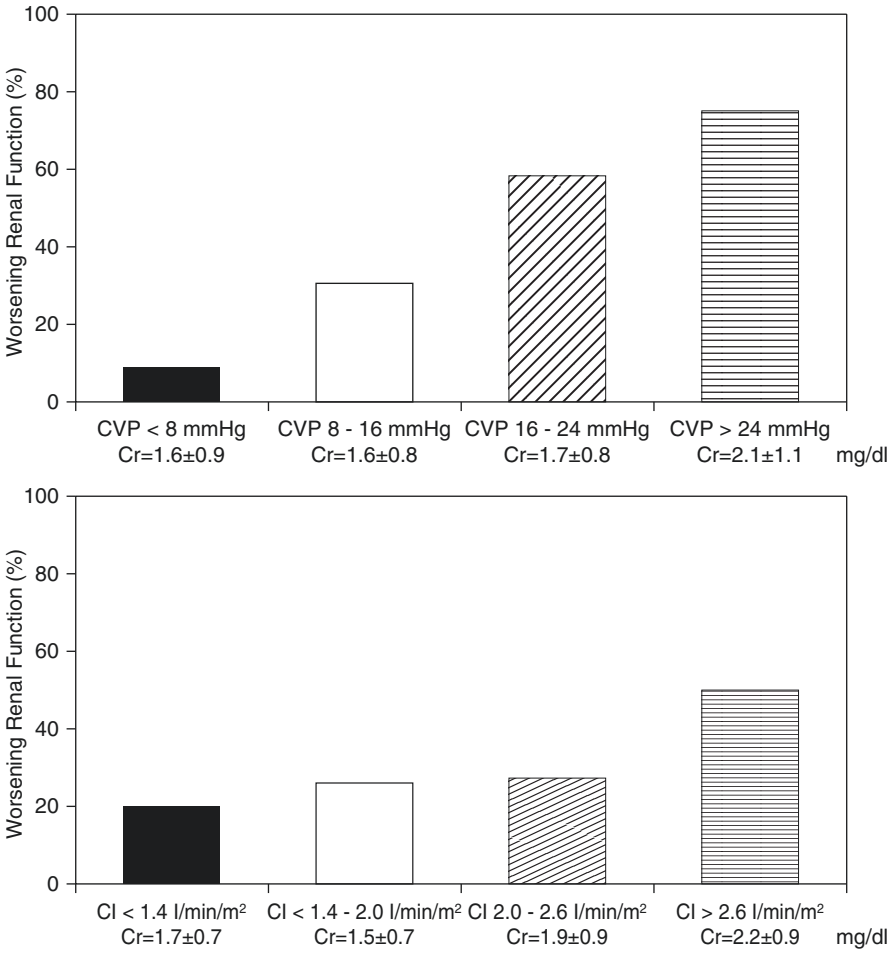

Fig. 13.2 Prevalence of WRF according to categories of admission CVP, CI, SBP and PCWP. CVP denotes central venous pressure, CI denotes cardiac index, SBP denotes systolic blood pressure, and PCWP denotes pulmonary wedge pressure. (Adapted from Mullens with permission)

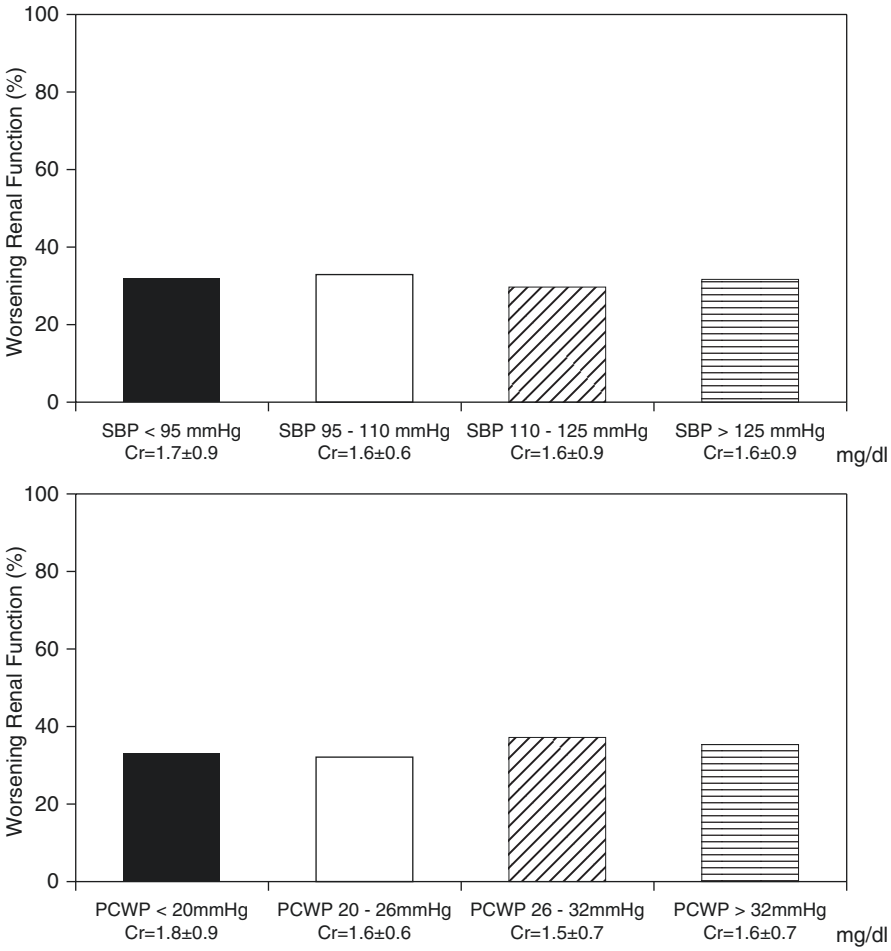

Fig. 13.2 (continued)

the hepatic veins in the inferior vena cava. Additionally, the retroperitoneal inferior vena cava directly drains venous blood originating from the kidneys. In normal physiologic circumstances the splanchnic venous system serves as a vehicle for returning venous blood to the heart, but also guards the heart against under-filling by maintaining a reservoir function [14, 15]. Indeed, some of the volume in the splanchnic veins does not contribute to central venous pressure (unstressed volume). However, it can be recruited, such as in situations of bleeding, by α-adrenergic mediated venoconstriction. In heart failure, several alterations occur at this level, and chronic neurohormonal activation can result in chronic sodium and water retention, hereby expanding the splanchnic venous reservoir [1]. However, overzealous plasma volume expansion (which is mainly buffered in the splanchnic venous system) can result in a lower compliance of the splanchnic veins resulting in abdominal venous congestion. Furthermore chronic adrenergic

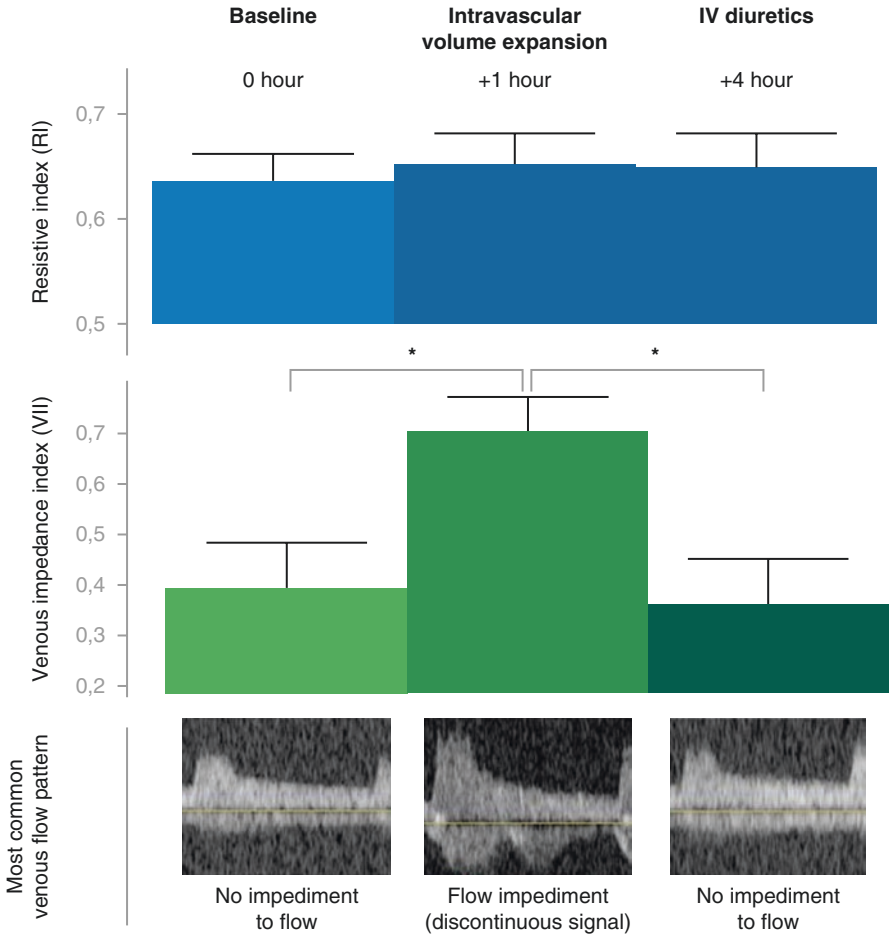

Fig. 13.3 Venous flow patterns in heart failure patients in baseline compensated status, during volume expansion and during therapy with IV diuretics. (Adapted from Nijst with permission)

activation might also directly result in venoconstriction as the splanchnic veins are highly innervated with α-adrenergic receptors [16]. Therefore, even without an increase in plasma volume, abdominal congestion can occur due to splanchnic venoconstriction. In the setting of ADHF, a high adrenergic tonus will often lead to vasoconstriction of the arterioles of the splanchnic system (often measured as a high systemic vascular resistance [SVR]), which results in a passive recoil force in the splanchnic venous, further enhancing abdominal venous congestion in addition to direct venoconstriction [16]. Interestingly, abdominal venous congestion might be earlier detectable than a rise in cardiac filling pressures in the patient on the verge of decompensation [17]. More recently, progressive (abdominal) venous congestion has been shown to impede renal venous outflow (Fig. 13.3), which is associated with a reduced natriuretic renal response in patients with heart failure. Renal venous outflow abnormalities can manifest, even before a rise in cardiac filling pressures are noted [17].

Extrinsic Kidney and Kidney Outflow Compression

In addition to a poor trans-renal pressure gradient mediated by backward failure (high venous outflow pressures) and forward cardiac failure (low kidney perfusion pressure), extrinsic kidney compression can result in further WRF in heart failure patients [6]. Importantly, the kidney is an encapsulated organ so intra-renal interstitial fluid built-up will further increase the parenchymateous pressures. Indeed, as earlier alluded to, an increased IAP is strongly associated with WRF, and reductions in IAP are associated with improvement in renal function (measured as a decline in plasma creatinine). A high IAP can mechanically obstruct the glomerular filtration force [2, 3]. The perfusion pressure of the abdomen is an important determinant of the perfusion of the visceral organs. Abdominal perfusion pressure (APP) is calculated as mean arterial pressure (MAP) minus the obstruction to venous outflow by the IAP. Elevated IAP induced kidney function is proposedly mediate by a low renal perfusion pressure and low renal filtration gradient (FG). The filtration gradient is the mechanical force across the glomerulus and equals the difference between the glomerular filtration pressure (GFP) and the proximal tubular pressure (PTP) [2, 3]. In the presence of an elevated IAP, PTP may be assumed to be equal to IAP and GFP is equated as MAP minus IAP. Therefore, the FG = GFP-PTP or FG = MAP – 2x IAP. During decongestive therapy in patients with ADHF, both a reduction in IAP and an increase in FG results in an improvement of serum creatinine [8].

Bowel Wall Congestion – Altered Pharmacology and Inflammation

During ADHF increased hydrostatic venous pressures in the abdomen result in net more filtration at the level of the microcirculation [1]. This can result in the formation of bowel wall edema, if lymphatic reabsorption forces are overwhelmed. Several observational studies in heart failure patients with reduced ejection fraction have shown that patients with high right atrial pressure often manifest with increased bowel wall thickness on abdominal ultrasound. It is well recognized that such formation of abdominal congestion is associated with a reduced appetite and a sensation of abdominal satiety [18, 19]. Furthermore, it is well documented that in the presence of abdominal edema the uptake of oral loop diuretics become less predictable. This results in a reduced bio-availability of loop diuretics in the circulation and potentially leading to incessant congestion. Furthermore, the villi in the bowel wall are very sensitive to changes in blood flow due to the countercurrent system in their arteriovenous supply. Therefore, a state of low cardiac output and venous congestion often results in villi tip ischemia, which is associated with increased bowel wall permeability. This lead to translocation of gram-negative bacteria that normally only reside in the bowel lumen. These gram negative bacteria carry lipopolysaccharides (LPS) on their cell walls, which activate the immune system [18, 19]. Hereby contributing to the overall state of inflammation often seen in heart failure. Interestingly, in patients with cirrhosis, the LPS-induced endotoxicity is strongly associated with the development of hepatorenal syndrome [20].

Treatment Strategies for Abdominal Congestion in Acute Heart Failure

Relieving Congestion During ADHF

As increased filling pressures (congestion) drive the progression of the disease in ADHF and strongly determine symptoms, the goal of therapy should be to completely relief congestion [21]. Lingering congestion following discharge is one of the strongest predictors of adverse outcome following a heart failure hospitalization. Furthermore, hemoconcentration (a marker of relieving excessive plasma volume) is associated with improved outcome in ADHF [22]. As earlier alluded to, increased venous filling pressures can occur both if the increased plasma volume overshoots the splanchnic venous buffering capacity or due to a reduced compliance of the splanchnic venous system. With the former mechanism often being labeled volume overload and the latter mechanism being labeled volume misdistribution. Clearly in clinical practice both these mechanisms (plasma volume expansion and reduced venous capacitance) overlap and contribute to the presence of congestion. If the ADHF-patient clearly manifest with signs of volume overload (e.g. weight gain, pleural effusion, peripheral edema, ascites, ..), than the goal of therapy should be to completely get rid of excessive volume. Loop diuretics remain the cornerstone of diuretic therapy in AHF, with almost 90% of patients receiving intravenous loop diuretics in the ADHERE database [23]. Furthermore, in 63% of patients, loop diuretics are the sole drug therapy being used to combat AHF [23]. In the DOSE trial, no difference was seen between continuous versus bolus infusion. However, patients receiving a high dose of furosemide (median dose of 773 mg vs 358 mg over 72 hours), demonstrated a trend towards faster dyspnea relief and a significantly higher net fluid and weight loss [24]. Adjusting the employed dose of loop diuretics is often necessary when a low glomerular filtration rate is present, with higher doses needed in this setting. Furthermore, recently it has been illustrated that early initiation of loop diuretics might be associated with better outcome [25]. In the case of severe abdominal congestion loop diuretics should be administered intravenous as bowel congestions make oral absorption of loop diuretics less predictable. However, a fair proportion of patients do not attain decongestion despite therapy with a loop diuretic. In these patients it is less clear if further loop diuretic dose uptitration or combinational diuretic therapy should be employed. Several additional agents with a diuretic property such as thiazides, high dose mineralocorticoid receptor antagonists, acetazolamide or sodium glucose linked transporters can be used. A detailed description of their use spans beyond the scope of this chapter.

When volume redistribution is driving congestion, the goal of therapy should be to enhance venous capacitance function and lower cardiac filling pressures [26]. To achieve this goal a combination of vasodilators and lower doses of intravenous diuretics are often employed. Again a detailed discussion spans beyond the scope of the chapter but have been published previously.

Reducing IAP Specifically

In case of the presence of ascites with an elevated IAP, paracentesis has been shown to effectively reduce the volume overload in third space while at the same time resulting an improvement in renal function. One small hypothesis generating study documented that reduction of ascites true either paracentesis of ultrafiltration resulted in a reduction in IAP which was associated with an improvement in renal function [8]. These strategies might be important in patients who exhibit a progressive increase in IAP during the ADHF hospitalization, as these patients are extremely vulnerable to WRF. A therapeutic flowchart to the approach of elevated IAP in ADHF is reflected in Fig. 13.4.

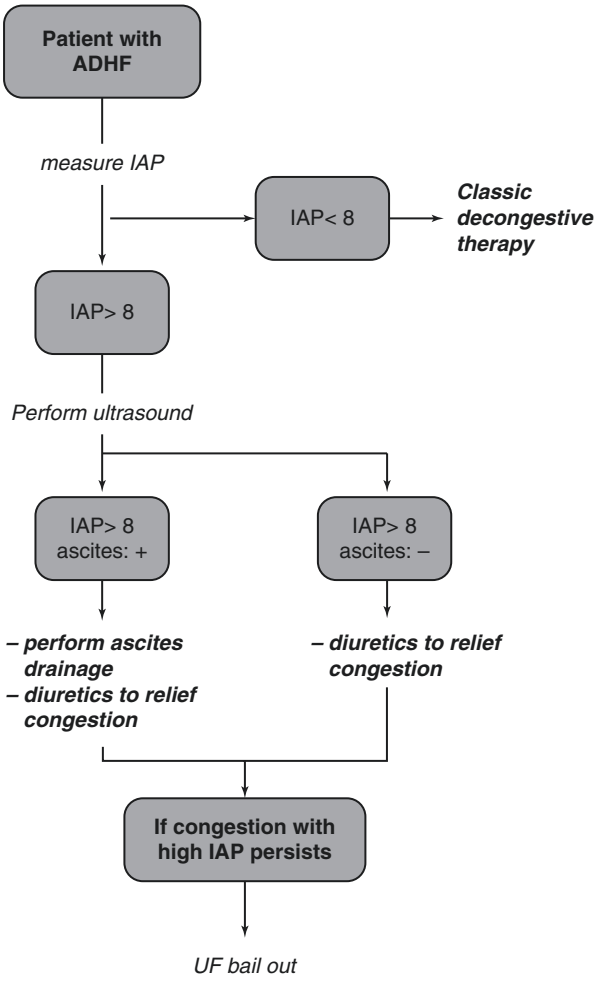

Fig. 13.4 Therapeutic flowchart to elevated IAP in ADHF

Optimal Guideline Recommended Therapies and Sodium Restriction

In addition to achieving decongestion, perhaps one of the most effective interventions is the optimization of a comprehensive discharge policy. Titration of neurohormonal blockers including beta-blockers, ACE-inhibitors, Angiotensin receptor blockers, angiotensin receptor/neprilysin inhibitors and mineralocorticoid receptor antagonists are essential. Furthermore, initiation of ambulatory rehabilitation, instituting a low salt diet with fluid restriction, formulating a stable dose of oral diuretics and close discharge follow-up, are also the backbones of this optimal discharge policy [27]. In OPTIMIZE-HF presence of beta-blockers and ACE-inhibitors were strongly associated with better post-discharge outcome [28]. Importantly, a recent analysis indicates that achieving decongestion and up-titrating ACE-inhibition is not mutually exclusive but synergistic [29]. Indicating that optimization of medical therapy should already be tried during decongestion.

References

1. Verbrugge FH, Dupont M, Steels P, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol. 2013;62:485–95.
2. Cheatham ML, Malbrain ML, Kirkpatrick A, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. II. Recommendations. Intensive Care Med. 2007;33:951–62.
3. Malbrain ML, Cheatham ML, Kirkpatrick A, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. Intensive Care Med. 2006;32:1722–32.
4. Cheatham ML, White MW, Sagraves SG, Johnson JL, Block EF. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. J Trauma. 2000;49:621–6.
5. Malbrain ML, Chiumello D, Pelosi P, et al. Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study. Intensive Care Med. 2004;30:822–9.
6. Mullens W, Abrahams Z, Skouri HN, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol. 2008;51:300–6.
7. Konstam MA, Kiernan M, Chandler A, et al. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. J Am Coll Cardiol. 2017;69:1409–19.
8. Mullens W, Abrahams Z, Francis GS, Taylor DO, Starling RC, Tang WH. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. J Card Fail. 2008;14:508–14.
9. Kirkpatrick AW, Brenneman FD, McLean RF, Rapanos T, Boulanger BR. Is clinical examination an accurate indicator of raised intra-abdominal pressure in critically injured patients? Can J Surg. 2000;43:207–11.
10. Martens P, Nevens F. Budd-Chiari syndrome. United European Gastroenterol J. 2015;3:489–500.
11. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000;102:203–10.
12. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53:589–96.
13. Guyton AC. Physiology of heart failure. Trans Am Coll Cardiol. 1957;7:214–24.

14. Gelman S. Venous function and central venous pressure: a physiologic story. Anesthesiology. 2008;108:735–48.
15. Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. Am J Physiol. 1957;189:609–15.
16. Guyton AC. The systemic venous system in cardiac failure. J Chronic Dis. 1959;9:465–75.
17. Nijst P, Martens P, Dupont M, Tang WHW, Mullens W. Intrarenal flow alterations during transition from euvolemia to intravascular volume expansion in heart failure patients. JACC Heart Fail. 2017;5:672–81.
18. Sandek A, Bauditz J, Swidsinski A, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol. 2007;50:1561–9.
19. Sandek A, Swidsinski A, Schroedl W, et al. Intestinal blood flow in patients with chronic heart failure: a link with bacterial growth, gastrointestinal symptoms, and cachexia. J Am Coll Cardiol. 2014;64:1092–102.
20. Gines P, Schrier RW. Renal failure in cirrhosis. N Engl J Med. 2009;361:1279–90.
21. Martens P, Nijst P, Mullens W. Current approach to decongestive therapy in acute heart failure. Curr Heart Fail Rep. 2015;12:367–78.
22. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122:265–72.
23. Fonarow GC, Corday E. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. Heart Fail Rev. 2004;9:179–85.
24. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805.
25. Matsue Y, Damman K, Voors AA, et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. J Am Coll Cardiol. 2017;69:3042–51.
26. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Kardiol Pol. 2016;74:1037–147.
27. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. J Am Coll Cardiol. 2013;61:391–403.
28. Fonarow GC, Abraham WT, Albert NM, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. JAMA. 2007;297:61–70.
29. Kula AJ, Hanberg JS, Wilson FP, et al. Influence of titration of neurohormonal antagonists and blood pressure reduction on renal function and decongestion in decompensated heart failure. Circ Heart Fail. 2016;9:e002333.

Hepato-renal Dysfunction in a Patient with Advanced Heart Failure

14

Bryan T. Lawlor and Justin L. Grodin

Case Vignette

Mr. Y is a 42 year-old male with a history of tricuspid valve endocarditis diagnosed 7 years ago as a consequence of intravenous drug abuse. At that time, he was treated conservatively with antibiotics. Afterwards, he successfully attended a rehabilitation program and was followed in the outpatient cardiology clinic for moderate tricuspid valve regurgitation for 4 years before being lost to follow-up. Today, Mr. Y presents to the emergency department with progressive exercise intolerance and anasarca. He stopped taking his medications as they made him feel unwell. On physical examination, Mr. Y has abdominal distention with shifting dullness to percussion. Echocardiography demonstrates severe tricuspid valve regurgitation and a severely dilated right ventricle with TAPSE 12 mm. The total bilirubin is 3.4 mg/dL and the serum sodium is 130 mEq/L. The INR is 1.8 and serum albumin level is 28 g/dL. The serum creatinine, which was normal 3 years ago, is now 3.07 mg/dL corresponding to an eGFR of 28 mL/min/1.73 m^2.

Chapter Key Points

- Incidence and diagnosis of hepatic dysfunction in heart failure
- How to evaluate liver disease in heart failure
- Hepatorenal interactions in heart failure

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Brief Discussion of the Case

The patient presents with right heart failure related to severe tricuspid regurgitation. He has evidence of significant hepatic and renal dysfunction. The patient's presenting MELD score is 31, estimating at 52.6% 3-month mortality. The patient should be further evaluated with an abdominal ultrasound and echo-Doppler study of the portal venous system. Additional contributing or reversible causes of cirrhosis, particularly viral hepatitis in the setting of his prior intravenous drug abuse, should be investigated and treated if diagnosed. Paracentesis may be considered in the presence of ascites to assist in the diagnosis of the underlying etiology, rule out spontaneous bacterial peritonitis, and alleviate intraabdominal pressure. In this case of significant liver disease, and particularly if there are supporting findings of cirrhosis, liver biopsy should be discussed in consultation with a hepatology specialist. Nephrology consultation is advised to assist in assessing for additional contributing etiologies for the patient's renal dysfunction in addition to the expected cardio-renal and hepato-renal mechanisms; HRS is a diagnosis of exclusion.

Overview of Cardiac, Hepatic, and Renal Interactions

The interactions between the heart and the liver, both directly and indirectly, by way of common interactions with the kidneys, are complex and numerous. Patients with heart failure, particularly right-sided heart failure, are at risk for developing congestive hepatopathy and cardiac cirrhosis [1–3]. Further, in patients with severely low cardiac output, as in cardiogenic shock, poor perfusion can result in ischemic hepatitis and necrosis [1, 4, 5]. Conversely, patients with cirrhosis may develop secondary cardiac manifestations, encompassed in an entity known as cirrhotic cardiomyopathy [1, 6, 7]. The pathogenesis of cardiac cirrhosis and cirrhotic cardiomyopathy are discussed in detail as the mechanisms of these disease entities provide valuable insight into the vast pathological interactions between these two organs. That is, cardiac dysfunction may worsen hepatic function, and hepatic dysfunction may worsen cardiac function. The progressive failure of both the heart and the liver ultimately results in decreased renal perfusion and consequent renal failure through both hepato-renal and cardio-renal mechanisms.

Liver Dysfunction in Heart Failure

Primary cardiac dysfunction resulting in decreased cardiac output and congestion may both contribute to hepatic dysfunction. This hepatic dysfunction occurs commonly, though the prevalence in patients with chronic advanced heart failure is not well-known [8]. In a cohort of patients with acute decompensated heart failure requiring inotropes, it was reported that approximately half had evidence of

cardio-hepatic dysfunction [9]. Typically, acute decreases in cardiac output as with cardiogenic shock result in acute liver injury, while chronic congestion may result in cirrhosis [1, 10].

Low Cardiac Output and Ischemic Hepatitis

The liver is a highly vascular and metabolic organ that may receive up to 25% of the cardiac output [1]. Therefore, a decrease in cardiac output resulting in hypoperfusion can cause significant injury and dysfunction. Severe acute heart failure with cardiogenic shock will typically result in more dramatic cases of ischemic hepatitis [1, 10]. The pattern of injury is typically hepatocellular rather than cholestatic with peak elevations in serum transaminase levels occurring 1–3 days after the onset of the insult. If perfusion is improved, levels may normalize in 5–10 days from the onset of the insult [11, 12]. Acute kidney injury from hypoperfusion is commonly present and can progress to acute tubular necrosis [12].

A variant of ischemic hepatitis, termed "cardiogenic hepatic injury and renal impairment" has been described and highlights important hepato-renal interactions in heart failure [13, 14]. In this syndrome, patients with advanced heart failure developed acute severe hepatic injury and renal insufficiency predominantly following acute heart failure in the absence of overt hypotension. While the proposed pathogenesis was speculative, several interesting observations were made. Notably, the syndrome occurred almost exclusively in patients with chronic heart failure. Excess renin-angiotensin-aldosterone system (RAAS) and sympathetic activation, hypoxia, cytokine release, and free radical injury were proposed to contribute to the pathogenesis.

Congestive Hepatopathy and Cardiac Cirrhosis

Congestion resulting from heart failure can result in significant liver injury as well. The hepatic veins do not have valves and are unable to compartmentalize and modulate an increase in central venous pressure [1, 15]. Hepatic blood flow is impaired and this insult causes centrilobular necrosis and subsequent connective tissue formation, which is the primary mechanism of cardiac cirrhosis [10, 15]. The caudal vector of venous pressure elevation from the heart results in proportional systemic venous hypertension along with hepatic vein hypertension, creating a unique phenotype of cirrhosis in which portal hypertension and esophageal varices are uncommon [16, 17]. Patients often present with jaundice, ascites, and edema [1, 17].

Clinically, this damage is often associated with right-sided heart failure and results in a predominantly cholestatic pattern of liver injury, with the degree of injury correlating with the severity of heart failure, elevation in central venous pressure, and degree of tricuspid regurgitation [16–19]. Conversely, transaminase levels may be normal to only modestly elevated. Albumin levels are often decreased due to the impairment in hepatic synthetic function [1, 8].

Tricuspid Regurgitation and Liver Dysfunction

The presence of tricuspid regurgitation has been associated with liver function abnormalities and in particular, congestive hepatopathy [20, 21]. This is likely related to similar mechanisms that give rise to congestive hepatopathy, but with additional consequence from the pulsatile pattern of injury due to the regurgitant jet [18]. The presence of moderate to severe TR significantly correlates with the degree of hepatic fibrosis seen on liver biopsy, and is also associated with a higher incidence of renal dysfunction [22].

Cirrhotic Cardiomyopathy

The term cirrhotic cardiomyopathy has become recognized as a clinical syndrome involving systolic and diastolic dysfunction, as well as electrophysiological disturbances attributed to primary liver cirrhosis [1, 7, 23–26]. The pathogenesis and hemodynamic consequences of cirrhotic cardiomyopathy provide insight into how the consequence of liver dysfunction in cardiac cirrhosis may feedback and contribute to worsening heart failure and renal function in a bidirectional manner.

Systolic Dysfunction in Cirrhosis

Systolic dysfunction and impaired contractility in cirrhotic cardiomyopathy have been attributed to several pathologic molecular mechanisms identified in experimental models. Dysfunction in cardiac beta-adrenergic receptors, disruption in plasma membrane fluidity, altered flux through membrane calcium channels, and increased pathological effects of signaling factors including nitric oxide and cytokines have been implicated [1, 23]. While there is marked splanchnic arterial vasodilation and decreased systemic vascular resistance in patients with cirrhosis that may augment cardiac output, the underlying systolic dysfunction combined with this vasodilation yields a net effect of decreased systemic pressure [1, 2, 27–29]. Vasoconstrictor agents that increase systemic vascular resistance may unmask and exacerbate this systolic dysfunction, while vasodilators, such as angiotensin-converting enzyme inhibitors (ACE-Is) used to manage heart failure, may further decrease systemic perfusion due to more profound vasodilation [1, 23, 30, 31]. In cases of increased metabolic stress such as exercise and infection, systolic dysfunction may similarly become unmasked [32–34]. Ultimately, decreased perfusion of the kidneys through these pathways results in renal injury, as well as further salt and water retention giving rise to decompensation with worsened ascites and congestion [1, 30, 35–37]. A further increase in ascites may result in increased abdominal pressure and may contribute to renal failure by impairing renal blood flow [38].

Diastolic Dysfunction in Cirrhosis

Diastolic dysfunction is very common in cirrhotic patients with a prevalence of at least 50% [39]. Myocardial fibrosis, subendothelial edema, and in particularly, left ventricular hypertrophy, have been identified as mechanisms contributing to restrictive diastolic filling [36, 40, 41]. The presence of diastolic dysfunction correlates with more severe decompensation and particularly with the presence of ascites. It is hypothesized that the increased central venous pressure from impaired diastolic filling may directly contribute to the development of ascites [39]. While the pathogenesis of diastolic dysfunction is not well-detailed, it may relate to altered function and ratios of collagen and titins in the myocardium [1, 35]. The presence of diastolic dysfunction is predictive of a worsened prognosis in cirrhotic patients. In particular, cirrhotic patients with diastolic dysfunction who undergo transjugular intrahepatic portosystemic shunt insertion are more likely to experience decreased effectiveness and greater complications and mortality, perhaps related to the inability to tolerate increased preload [39, 42].

Electrophysiological Abnormalities in Cirrhosis

Chronotropic incompetence, electromechanical dyssynchrony, and QT interval prolongation are the primary electrophysiological disturbances found in patients with cirrhotic cardiomyopathy [1, 11, 43, 44]. Similar to the pathogenesis of systolic dysfunction in cirrhotic cardiomyopathy, desensitization and downregulation of beta-adrenergic receptors likely has an important role in the development of chronotropic incompetence [1, 43]. While patients are not usually bradycardic, they exhibit an inability to augment cardiac output through heart rate and are likely to also require increased beta-agonist doses when inotropic support is needed [45, 46]. As a result, beta-blocker administration used to manage patients with heart failure may further exacerbate this. The clinical relevance of electromechanical uncoupling and QT interval prolongation is not well-understood, but perhaps related to myocardial receptor dysfunction and impaired filtering of cardiotoxins, respectively [43, 44].

Hepato-renal Disease and Heart Failure

Hepato-renal syndrome (HRS) is serious complication resulting in severe renal failure in patients with advanced chronic liver disease. Type 1 HRS is characterized by the rapid development of renal failure and is defined as a two-fold increase in serum creatinine to a level greater than 2.5 mg/dL within 2 weeks [47]. Type II HRS involves a slower course and the gradual loss of renal function with characteristic ascites refractory to diuretic therapy [47, 48]. Several mechanisms have been described involving pathological splanchnic vasodilation and RAAS activation, but alterations in hemodynamics and cardiac dysfunction have emerged as contributing factors as well [49, 50]. These pathways provide insight into additional mechanisms that potentiate hepato-renal disease in heart failure.

Pathogenesis of Hepato-renal Syndrome

The development of HRS is primarily due to decreased renal perfusion through several mechanisms. A hepato-renal reflex triggered by an increase in hepatic sinusoidal pressure or decrease in portal flow results in decreased renal blood flow, possibly through increased intrahepatic adenosine accumulation, and contributes to fluid retention [51, 52]. Secondly, excess splanchnic vasodilation, related to increased effects of nitric oxide and prostaglandins, causes a redistribution of blood volume and a decrease in effective circulating volume. This leads to activation of the RAAS, which pathologically increases systemic vasoconstriction, including to the kidneys. This promotes further fluid retention resulting in congestion and ascites [1, 53]. As with cardiac cirrhosis and cirrhotic cardiomyopathy, the development of tense ascites increases intraabdominal pressure and consequently impairs renal blood flow.

Altered Hemodynamics and Cardiac Dysfunction in Hepato-renal Syndrome

The systemic hemodynamics of patients with HRS have been investigated more recently after it was reported that these patients had a significantly lower cardiac output and index even prior to developing HRS. These patients had a lower renal blood flow, but interestingly were not found to have an elevated pulmonary capillary wedge pressure (PCWP) [50, 54]. In a small cohort, following the development of HRS, cardiac output and mean arterial pressure declined further with PCWP remaining relatively unchanged while systemic vascular resistance did not decrease. Stroke volume was also decreased in these patients, likely related to a persistent low effective circulating volume [50]. Vasoconstrictor activity was noted to be elevated, which may have impaired systolic function due to increased afterload. Excess neurohumoral activity may also contribute to myocardial hypertrophy and fibrosis resulting in diastolic dysfunction as well [55, 56].

With increased recognition of and insights into the pathogenesis of cirrhotic cardiomyopathy, similar mechanisms have been proposed to be important contributors to the development of these altered hemodynamics. Of particular importance seems to be the unmasking of systolic dysfunction and a reduction in cardiac output under physiologic stress, resulting in decreased renal blood flow and consequent renal failure [32]. Patients with advanced cirrhosis are known to have chronic elevations in proinflammatory cytokines and vasoactive hormones that may contribute to myocardial systolic and diastolic dysfunction at baseline, in line with the pathogenesis of cirrhotic cardiomyopathy [57, 58]. Under stress, these substances are activated further and without appropriate cardiac reserve, exacerbation of the pathological vasodilation ensues [57–59]. Myocardial dysfunction may worsen as well, further decreasing renal blood flow and causing renal failure [57].

Hepato-renal Interactions in Heart Failure

In summary, the pathological interactions between the heart and the liver that occur in heart failure are complex and bidirectional. Liver dysfunction resulting from heart failure in the form of congestive hepatopathy, cardiac cirrhosis, or ischemic hepatitis may in turn worsen cardiac function and contribute to renal insufficiency. The pathogenesis of the clinical entities of cirrhotic cardiomyopathy and HRS provide insight into these mechanisms. Specifically, hepatic dysfunction may result in worsened systolic, diastolic, and chronotropic function, thereby reducing forward flow and contributing to further liver congestion, ascites, and renal hypoperfusion. Additionally, this hepatic dysfunction may produce pathological elevation of cytokines and other vasoactive substances that cause pathological RAAS activation and renal vasoconstriction. The renal failure that ensues is therefore the consequence of both hepato-renal and cardio-renal pathological mechanisms.

Management of Hepato-renal Disease in Advanced Heart Failure

Therapy for hepato-renal disease largely follows therapy for advanced heart failure with the goals of alleviating congestion and promoting systemic flow. However, additional caution with titration of conventional therapies is required in cases of severe liver dysfunction due to altered pharmacokinetics and potential exacerbation of hepato-renal interactions.

Guideline-Directed Medical Therapy

Titration of medical therapy including beta-blockers and ACE-Is and angiotensin receptor blockers (ARBs) to optimal doses can be limited by competing detrimental effects including systolic depression, chronotropic blunting, and excessive vasodilation resulting in decreased end-organ perfusion. However, due to the mortality benefit and potential to improve cardiac dysfunction and hemodynamics in chronic disease—and consequently hepato-renal dysfunction—these therapies should be initiated in stable patients.

ACE-Is and ARBs may augment cardiac output and promote cardiac reverse remodeling. Therapy should be initiated at low doses and titrated slowly due to variable prodrug activation, bioavailability, and exacerbation of pathological vasodilation [60–64]. ACE-Is including enalapril, ramipril, fosinopril, trandolapril, quinapril, benazepril, and moexipril all require transformation by the liver into active metabolites and higher doses may be needed [60]. Dose adjustments with valsartan and irbesartan are not required, but lower doses of losartan are needed due to increased bioavailability [61–64]. A low dose aldosterone antagonist is also recommended for mortality benefit and may be particularly helpful in patients with ascites [11, 26].

Beta-blockers may decrease cardiac work, optimize filling and contractility, and promote reverse remodeling in heart failure. Except with propranolol, while dose adjustments are not typically needed in patients with liver dysfunction, titration should be performed slowly as well, monitoring for worsened systolic dysfunction and chronotropic incompetence [65–69]. In cirrhotic patients with refractory ascites, beta-blockers have been shown to be associated with poor survival, possibly related to renal insufficiency due to exacerbation or unmasking of similar systolic dysfunction found in cirrhotic patients with overt HRS [57, 70, 71]. In patients presenting with HRS, beta-blockade discontinuation is recommended [72].

Diuretic Therapy

Loop diuretics are a mainstay of therapy for volume and symptom management in patients with chronic heart failure and liver disease. Absorption may be limited due to edema in heart failure and cirrhosis [68]. Patients with liver dysfunction have also been observed to have a reduced natriuretic response to loop diuretics independent of renal function [73, 74]. In renal insufficiency, higher doses may be needed to achieve the same diuretic effect [75]. In cases of HRS, while diuretics may be needed after stabilization to relieve congestion, they may contribute to a decrease in the effective circulating volume and renal hypoperfusion. In these cases, discontinuation of diuretic therapy and administration of albumin is recommended [76]. This may increase cardiac output in cirrhotic patients with mild cardiac dysfunction, but should be used judiciously under close hemodynamic monitoring or avoided in patients with advanced heart failure.

Inotropes and Vasopressors

Several vasoactive agents have been investigated in the treatment of HRS. Terlipressin, a vasopressin analogue, has historically been acknowledged as effective and favored as the treatment of choice in many countries [77, 78]. However, likely due to increased afterload, terlipressin reduces cardiac output in patients with cirrhosis [11, 79]. Dopamine has been considered and used with some studies reporting a possible benefit [13] but disputed in others [80]. Generally, monotherapy with dobutamine and dopamine for HRS is no longer recommended. However, dopamine in combination with furosemide and albumin have shown some promise in the treatment of HRS [81]. Dopamine has been shown to cause splanchnic vasoconstriction, thereby opposing the pathological vasodilation, in addition to acting as a positive inotrope to improve cardiac contractility [82–84].

Clinical improvement of HRS complicating cirrhotic cardiomyopathy with dobutamine administration was recently described in a case report [48]. This patient was treated with norepinephrine prior to the dobutamine infusion, but objective benefit in systolic function was documented on dobutamine alone with strain echocardiography with ejection fraction of 62.3% and global longitudinal

strain of 29%. When the dobutamine infusion was discontinued, repeat imaging documented an ejection fraction of 51.8% and global longitudinal strain of 18%. Norepinephrine is also commonly used in cases of shock and where terlipressin is not readily available including the United States. The positive inotropic effects of norepinephrine may also be important in augmenting cardiac output to promote renal perfusion [76]. For patients with hepato-renal disease complicating heart failure without overt HRS, inotropic and vasopressor therapy may considered for Profile C heart failure and cardiogenic shock as per the current standard of care.

Advanced Therapies

Advanced therapies including left ventricular assist device (LVAD) implantation and orthotopic heart transplantation (OHT) have shown promise in improving hepato-renal dysfunction in patients with advanced heart failure. In patients with mild hepatic dysfunction, LVAD therapy often improves liver function tests post-implantation [1, 85, 86]. Conversely, the presence of severe liver dysfunction, represented through the model for end-stage liver disease (MELD), both prior to and post-LVAD implantation is predictive of higher morbidity and mortality [87–90]. The improvement in hepato-renal function after LVAD implantation is attributed to the improvement in systemic hemodynamics and blood flow. However, liver dysfunction may also occur after LVAD implantation. This may be due to several perioperative factors, but more prominently related to worsening right heart failure, in which decompensation occurs due to the increased preload received by the right ventricle after improved left-sided flow [87].

Similarly, liver dysfunction, reflected in MELD scores, is predictive of poor clinical outcomes and mortality after OHT [91, 92]. However, hepato-renal function can also significantly improve after OHT due to improvement in biventricular systolic function and systemic blood flow. Cholestatic parameters were the first to improve, followed by transaminase measurements over a longer period of time up to 12 months [92, 93]. While patients with severe liver disease and cirrhosis were not included, and irreversible hepatic cirrhosis is generally considered a contraindication to single-organ OHT due to high postoperative morbidity and mortality, select patients with cardiac cirrhosis may be considered [94].

The complete regression of cardiac cirrhosis in a patient 10 years following OHT has been reported [91]. Conversely, in cases of cirrhotic cardiomyopathy, liver transplantation may lead to improvement and reversal of the cardiomyopathy [11, 95, 96]. Combined heart and liver transplantation may be considered for patients with advanced heart failure and irreversible cirrhosis [97]. The reported rate of progressive renal failure requiring renal replacement therapy after liver transplant in patients with HRS has been reported at 7% [98, 99], though it is not clear what the impact of combined heart and liver transplantation would have in ameliorating this in cases of HRS complicating advanced heart failure. Lastly, while combined heart-liver-kidney transplantation has been rarely performed for other clinical scenarios, the option may be entertained at large experienced transplant centers [97, 100].

Future Directions

The presence of myocardial dysfunction in patients with cirrhosis as well as HRS has offered insight into the pathogenesis of hepato-renal dysfunction in patients with heart failure. These complex interactions must be explored further to improve management in this sick population. In particular, the hemodynamic and neurohormonal changes involving the liver and kidneys that occur as heart failure progresses to the advanced stages must be clarified further with the goal of mitigating clinical hepato-renal dysfunction. Agents that improve cardiac function, promote reverse remodeling, decrease renal vasoconstriction to promote blood flow, and inhibit pathological splanchnic vasodilation are potential goals of therapy. As with all patients with advanced heart failure, reconciling this hepato-renal dysfunction with proper selection and timing of initiating advanced therapies requires further study as well.

Treatment Pearls for the Case Vignette

Treatment should be directed towards optimizing right ventricular function and forward flow to improve systemic perfusion and relieve congestion. Aggressive diuretic therapy should be initiated, but will likely need to be combined with strategies to optimize cardiac output and end-organ perfusion. When stabilized, surgical or percutaneous tricuspid valve repair may be considered and discussed with interventional cardiology and cardiac surgery. However, given the degree of severe dilation and depression of the right ventricle, advanced therapies, namely transplant, may be the only durable option and his candidacy should be evaluated in consultation with a multidisciplinary team.

References

1. Møller S, Bernardi M. Interactions of the heart and the liver. Eur Heart J. 2013;34(36):2804–11.
2. Dunn GD, Hayes P, Breen KJ, Schenker S. The liver in congestive heart failure: a review. Am J Med Sci. 1973;265(3):174–89.
3. Kubo SH, Walter BA, John DH, Clark M, Cody RJ. Liver function abnormalities in chronic heart failure. Influence of systemic hemodynamics. Arch Intern Med. 1987;147(7):1227–30.
4. Seeto RK, Fenn B, Rockey DC. Ischemic hepatitis: clinical presentation and pathogenesis. Am J Med. 2000;109(2):109–13.
5. Henrion J, Schapira M, Luwaert R, Colin L, Delannoy A, Heller FR. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. Medicine (Baltimore). 2003;82(6):392–406.
6. Mohamed R, Forsey PR, Davies MK, Neuberger JM. Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease. Hepatology. 1996;23(5):1128–34.
7. Cazzaniga M, Salerno F, Pagnozzi G, Dionigi E, Visentin S, Cirello I, et al. Diastolic dysfunction is associated with poor survival in patients with cirrhosis with transjugular intrahepatic portosystemic shunt. Gut. 2007;56(6):869–75.
8. Ambrosy AP, Vaduganathan M, Huffman MD, Khan S, Kwasny MJ, Fought AJ, et al. Clinical course and predictive value of liver function tests in patients hospitalized for worsening heart failure with reduced ejection fraction: an analysis of the EVEREST trial. Eur J Heart Fail. 2012;14(3):302–11.

9. Nikolaou M, Parissis J, Yilmaz MB, Seronde MF, Kivikko M, Laribi S, et al. Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure. Eur Heart J. 2013;34(10):742–9.
10. Birrer R, Takuda Y, Takara T. Hypoxic hepatopathy: pathophysiology and prognosis. Intern Med. 2007;46(14):1063–70.
11. Fouad YM, Yehia R. Hepato-cardiac disorders. World J Hepatol. 2014;6(1):41–54.
12. Alvarez AM, Mukherjee D. Liver abnormalities in cardiac diseases and heart failure. Int J Angiol. 2011;20(3):135–42.
13. Naschitz JE, Yeshurun D, Shahar J. Cardiogenic hepatorenal syndrome. Angiology. 1990;41(11):893–900.
14. Naschitz J, Abinader E, Elias N, Sabo E, Yeshurun D, Zuckerman E. Cardiogenic hepatic injury-renal impairment. J Clin Basic Cardiol. 2000;3(1):35–8.
15. Sherlock S. The liver in heart failure; relation of anatomical, functional, and circulatory changes. Br Heart J. 1951;13(3):273–93.
16. Myers RP, Cerini R, Sayegh R, Moreau R, Degott C, Lebrec D, et al. Cardiac hepatopathy: clinical, hemodynamic, and histologic characteristics and correlations. Hepatology. 2003;37(2):393–400.
17. Kavoliuniene A, Vaitiekiene A, Cesnaite G. Congestive hepatopathy and hypoxic hepatitis in heart failure: a cardiologist's point of view. Int J Cardiol. 2013;166(3):554–8.
18. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. Am J Cardiol. 2002;90(12):1405–9.
19. Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. Eur J Clin Invest. 2012;42(2):153–63.
20. Jiménez-Romo F. Tricuspid liver. Arch Inst Cardiol Mex. 1972;42(2):243–6.
21. Mikami T, Kudo T, Sakurai N, Kanamori K, Sakamoto S, Tanabe Y, et al. Grading of tricuspid regurgitation by pulsed Doppler echocardiography and liver function tests. J Cardiogr. 1984;14(2):353–8.
22. Maleki M, Vakilian F, Amin A. Liver diseases in heart failure. Heart Asia. 2011;3(1):143–9.
23. Krag A, Bendtsen F, Mortensen C, Henriksen JH, Møller S. Effects of a single terlipressin administration on cardiac function and perfusion in cirrhosis. Eur J Gastroenterol Hepatol. 2010;22(9):1085–92.
24. Glenn TK, Honar H, Liu H, ter Keurs HE, Lee SS. Role of cardiac myofilament proteins titin and collagen in the pathogenesis of diastolic dysfunction in cirrhotic rats. J Hepatol. 2011;55(6):1249–55.
25. Bernardi M, Maggioli C, Dibra V, Zaccherini G. QT interval prolongation in liver cirrhosis: innocent bystander or serious threat? Expert Rev Gastroenterol Hepatol. 2012;6(1):57–66.
26. Pudil R, Pelouch R, Praus R, Vasatova M, Hulek P. Heart failure in patients with liver cirrhosis. Cor et Vasa. 2013;55(4):e391–6.
27. Schrier RW. Decreased effective blood volume in edematous disorders: what does this mean? J Am Soc Nephrol. 2007;18(7):2028–31.
28. Henriksen JH, Fuglsang S, Bendtsen F, Christensen E, Møller S. Arterial compliance in patients with cirrhosis: stroke volume-pulse pressure ratio as simplified index. Am J Physiol Gastrointest Liver Physiol. 2001;280(4):G584–94.
29. Timoh T, Protano MA, Wagman G, Bloom M, Vittorio TJ. A perspective on cirrhotic cardiomyopathy. Transplant Proc. 2011;43(5):1649–53.
30. Møller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut. 2008;57(2):268–78.
31. Fouad TR, Abdel-Razek WM, Burak KW, Bain VG, Lee SS. Prediction of cardiac complications after liver transplantation. Transplantation. 2009;87(5):763–70.
32. Ruiz-del-Arbol L, Urman J, Fernández J, González M, Navasa M, Monescillo A, et al. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. Hepatology. 2003;38(5):1210–8.
33. Mocarzel LOC, Rossi MM, Miliosse BM, Lanzieri PG, Gismondi RA. Cirrhotic cardiomyopathy: a new clinical phenotype. Arq Bras Cardiol. 2017;108(6):564–8.

34. Wiese S, Hove JD, Bendtsen F, Møller S. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. Nat Rev Gastroenterol Hepatol. 2014;11(3):177–86.
35. Wong F. Cirrhotic cardiomyopathy. Hepatol Int. 2009;3(1):294–304.
36. Gaskari SA, Honar H, Lee SS. Therapy insight: cirrhotic cardiomyopathy. Nat Clin Pract Gastroenterol Hepatol. 2006;3(6):329–37.
37. Solà E, Ginès P. Renal and circulatory dysfunction in cirrhosis: current management and future perspectives. J Hepatol. 2010;53(6):1135–45.
38. Umgelter A, Reindl W, Franzen M, Lenhardt C, Huber W, Schmid RM. Renal resistive index and renal function before and after paracentesis in patients with hepatorenal syndrome and tense ascites. Intensive Care Med. 2009;35(1):152–6.
39. Wong F, Villamil A, Merli M, Romero G, Angeli P, Caraceni P, et al. Prevalence of diastolic dysfunction in cirrhosis and its clinical significance. Hepatology. 2011;54(Suppl 1):A475–576.
40. Saner FH, Neumann T, Canbay A, Treckmann JW, Hartmann M, Goerlinger K, et al. High brain-natriuretic peptide level predicts cirrhotic cardiomyopathy in liver transplant patients. Transpl Int. 2011;24(5):425–32.
41. Heuer A, Gehl A, Puschel K, Sydow K, Lohse A, Luth S. High rate of cardiac abnormalities in a post-mortem analysis of patients suffering from liver cirrhosis. J Hepatol. 2011;54(Suppl 1):S69.
42. Rabie RN, Cazzaniga M, Salerno F, Wong F. The use of E/A ratio as a predictor of outcome in cirrhotic patients treated with transjugular intrahepatic portosystemic shunt. Am J Gastroenterol. 2009;104(10):2458–66.
43. Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. J Hepatol. 2006;44(5):994–1002.
44. Bernardi M, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. Hepatology. 1998;27(1):28–34.
45. Ramond MJ, Comoy E, Lebrec D. Alterations in isoprenaline sensitivity in patients with cirrhosis: evidence of abnormality of the sympathetic nervous activity. Br J Clin Pharmacol. 1986;21(2):191–6.
46. Ruiz-del-Arbol L, Monescillo A, Jimenéz W, Garcia-Plaza A, Arroyo V, Rodés J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology. 1997;113(2):579–86.
47. Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology. 1996;23(1):164–76.
48. Mocarzel L, Lanzieri P, Nascimento J, Peixoto C, Ribeiro M, Mesquita E. Hepatorenal syndrome with cirrhotic cardiomyopathy: case report and literature review. Case Reports Hepatol. 2015;2015:573513.
49. Lenz K. Hepatorenal syndrome--is it central hypovolemia, a cardiac disease, or part of gradually developing multiorgan dysfunction? Hepatology. 2005;42(2):263–5.
50. Ruiz-del-Arbol L, Monescillo A, Arocena C, Valer P, Ginès P, Moreira V, et al. Circulatory function and hepatorenal syndrome in cirrhosis. Hepatology. 2005;42(2):439–47.
51. Lang F, Tschernko E, Schulze E, Ottl I, Ritter M, Völkl H, et al. Hepatorenal reflex regulating kidney function. Hepatology. 1991;14(4 Pt 1):590–4.
52. Ming Z, Smyth DD, Lautt WW. Decreases in portal flow trigger a hepatorenal reflex to inhibit renal sodium and water excretion in rats: role of adenosine. Hepatology. 2002;35(1):167–75.
53. Arroyo V, Guevara M, Ginès P. Hepatorenal syndrome in cirrhosis: pathogenesis and treatment. Gastroenterology. 2002;122(6):1658–76.
54. Krag A, Bendtsen F, Henriksen JH, Møller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. Gut. 2010;59(1):105–10.
55. Pozzi M, Carugo S, Boari G, Pecci V, de Ceglia S, Maggiolini S, et al. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. Hepatology. 1997;26(5):1131–7.
56. Torregrosa M, Aguadé S, Dos L, Segura R, Gónzalez A, Evangelista A, et al. Cardiac alterations in cirrhosis: reversibility after liver transplantation. J Hepatol. 2005;42(1):68–74.

57. Krag A, Bendtsen F, Burroughs AK, Møller S. The cardiorenal link in advanced cirrhosis. Med Hypotheses. 2012;79(1):53–5.
58. Albillos A, de la Hera A, González M, Moya JL, Calleja JL, Monserrat J, et al. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. Hepatology. 2003;37(1):208–17.
59. Stahl W, Bracht H, Radermacher P, Thomas J. Year in review 2009: critical care – shock. Crit Care. 2010;14(6):239.
60. Daskalopoulos G, Pinzani M, Murray N, Hirschberg R, Zipser RD. Effects of captopril on renal function in patients with cirrhosis and ascites. J Hepatol. 1987;4(3):330–6.
61. Brookman LJ, Rolan PE, Benjamin IS, Palmer KR, Wyld PJ, Lloyd P, et al. Pharmacokinetics of valsartan in patients with liver disease. Clin Pharmacol Ther. 1997;62(3):272–8.
62. Gillis JC, Markham A. Irbesartan. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in the management of hypertension. Drugs. 1997;54(6):885–902.
63. Markham A, Goa KL. Valsartan. A review of its pharmacology and therapeutic use in essential hypertension. Drugs. 1997;54(2):299–311.
64. Marino MR, Langenbacher KM, Raymond RH, Ford NF, Lasseter KC. Pharmacokinetics and pharmacodynamics of irbesartan in patients with hepatic cirrhosis. J Clin Pharmacol. 1998;38(4):347–56.
65. Kirch W, Schäfer-Korting M, Mutschler E, Ohnhaus EE, Braun W. Clinical experience with atenolol in patients with chronic liver disease. J Clin Pharmacol. 1983;23(4):171–7.
66. Buchi KN, Rollins DE, Tolman KG, Achari R, Drissel D, Hulse JD. Pharmacokinetics of esmolol in hepatic disease. J Clin Pharmacol. 1987;27(11):880–4.
67. Zaman R, Jack DB, Wilkins MR, Kendall MJ. Lack of effect of liver disease on the pharmacokinetics of acebutolol and diacetolol: a single dose study. Biopharm Drug Dispos. 1985;6(2):131–7.
68. Fredrick MJ, Pound DC, Hall SD, Brater DC. Furosemide absorption in patients with cirrhosis. Clin Pharmacol Ther. 1991;49(3):241–7.
69. Garguichevich JJ, Ramos JL, Gambarte A, Gentile A, Hauad S, Scapin O, et al. Effect of amiodarone therapy on mortality in patients with left ventricular dysfunction and asymptomatic complex ventricular arrhythmias: Argentine Pilot Study of Sudden Death and Amiodarone (EPAMSA). Am Heart J. 1995;130(3 Pt 1):494–500.
70. Krag A, Bendtsen F, Møller S. Does cardiac dysfunction explain deleterious effects of beta-blockers in cirrhosis and refractory ascites? Hepatology. 2011;53(1):370–1.
71. Sersté T, Melot C, Francoz C, Durand F, Rautou PE, Valla D, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology. 2010;52(3):1017–22.
72. Krag A, Wiest R, Albillos A, Gluud LL. The window hypothesis: haemodynamic and non-haemodynamic effects of β-blockers improve survival of patients with cirrhosis during a window in the disease. Gut. 2012;61(7):967–9.
73. Grodin JL, Gallup D, Anstrom KJ, Felker GM, Chen HH, Tang WHW. Implications of Alternative Hepatorenal Prognostic Scoring Systems in Acute Heart Failure (from DOSE-AHF and ROSE-AHF). Am J Cardiol. 2017;119(12):2003–9.
74. Brater DC. Diuretic therapy. N Engl J Med. 1998;339(6):387–95.
75. Oh SW, Han SY. Loop diuretics in clinical practice. Electrolyte Blood Press. 2015;13(1):17–21.
76. Lenz K, Buder R, Kapun L, Voglmayr M. Treatment and management of ascites and hepatorenal syndrome: an update. Therap Adv Gastroenterol. 2015;8(2):83–100.
77. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397–417.
78. Cavallin M, Kamath PS, Merli M, Fasolato S, Toniutto P, Salerno F, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. Hepatology. 2015;62(2):567–74.
79. Narahara Y, Kanazawa H, Taki Y, Kimura Y, Atsukawa M, Katakura T, et al. Effects of terlipressin on systemic, hepatic and renal hemodynamics in patients with cirrhosis. J Gastroenterol Hepatol. 2009;24(11):1791–7.
80. Angeli P, Volpin R, Gerunda G, Craighero R, Roner P, Merenda R, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology. 1999;29(6):1690–7.

81. Srivastava S, Shalimar, Vishnubhatla S, Prakash S, Sharma H, Thakur B, et al. Randomized controlled trial comparing the efficacy of terlipressin and albumin with a combination of concurrent dopamine, furosemide, and albumin in hepatorenal syndrome. J Clin Exp Hepatol. 2015;5(4):276–85.
82. Richardson PD, Withrington PG. Responses of the canine hepatic arterial and portal venous vascular beds to dopamine. Eur J Pharmacol. 1978;48(4):337–49.
83. Hirsch LJ, Ayabe T, Glick G. Direct effects of various catecholamines on liver circulation in dogs. Am J Physiol. 1976;230(5):1394–9.
84. Loeb HS, Bredakis J, Gunner RM. Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. Circulation. 1977;55(2):375–8.
85. Rose EA, Moskowitz AJ, Packer M, Sollano JA, Williams DL, Tierney AR, et al. The REMATCH trial: rationale, design, and end points. Randomized evaluation of mechanical assistance for the treatment of congestive heart failure. Ann Thorac Surg. 1999;67(3):723–30.
86. Russell SD, Rogers JG, Milano CA, Dyke DB, Pagani FD, Aranda JM, et al. Renal and hepatic function improve in advanced heart failure patients during continuous-flow support with the HeartMate II left ventricular assist device. Circulation. 2009;120(23):2352–7.
87. Wadia Y, Etheridge W, Smart F, Wood RP, Frazier OH. Pathophysiology of hepatic dysfunction and intrahepatic cholestasis in heart failure and after left ventricular assist device support. J Heart Lung Transplant. 2005;24(4):361–70.
88. Matthews JC, Pagani FD, Haft JW, Koelling TM, Naftel DC, Aaronson KD. Model for end-stage liver disease score predicts left ventricular assist device operative transfusion requirements, morbidity, and mortality. Circulation. 2010;121(2):214–20.
89. Bonde P, Ku NC, Genovese EA, Bermudez CA, Bhama JK, Ciarleglio MM, et al. Model for end-stage liver disease score predicts adverse events related to ventricular assist device therapy. Ann Thorac Surg. 2012;93(5):1541–7; discussion 7–8.
90. Yang JA, Kato TS, Shulman BP, Takayama H, Farr M, Jorde UP, et al. Liver dysfunction as a predictor of outcomes in patients with advanced heart failure requiring ventricular assist device support: Use of the Model of End-stage Liver Disease (MELD) and MELD eXcluding INR (MELD-XI) scoring system. J Heart Lung Transplant. 2012;31(6):601–10.
91. Crespo-Leiro MG, Robles O, Paniagua MJ, Marzoa R, Naya C, Flores X, et al. Reversal of cardiac cirrhosis following orthotopic heart transplantation. Am J Transplant. 2008;8(6):1336–9.
92. Chokshi A, Cheema FH, Schaefle KJ, Jiang J, Collado E, Shahzad K, et al. Hepatic dysfunction and survival after orthotopic heart transplantation: application of the MELD scoring system for outcome prediction. J Heart Lung Transplant. 2012;31(6):591–600.
93. Dichtl W, Vogel W, Dunst KM, Grander W, Alber HF, Frick M, et al. Cardiac hepatopathy before and after heart transplantation. Transpl Int. 2005;18(6):697–702.
94. Hsu RB, Chang CI, Lin FY, Chou NK, Chi NH, Wang SS, et al. Heart transplantation in patients with liver cirrhosis. Eur J Cardiothorac Surg. 2008;34(2):307–12.
95. Chayanupatkul M, Liangpunsakul S. Cirrhotic cardiomyopathy: review of pathophysiology and treatment. Hepatol Int. 2014;8(3):308–15.
96. Sampathkumar P, Lerman A, Kim BY, Narr BJ, Poterucha JJ, Torsher LC, et al. Post-liver transplantation myocardial dysfunction. Liver Transpl Surg. 1998;4(5):399–403.
97. Te HS, Anderson AS, Millis JM, Jeevanandam V, Jensen DM. Current state of combined heart-liver transplantation in the United States. J Heart Lung Transplant. 2008;27(7):753–9.
98. Wadei HM, Mai ML, Ahsan N, Gonwa TA. Hepatorenal syndrome: pathophysiology and management. Clin J Am Soc Nephrol. 2006;1(5):1066–79.
99. Gonwa TA, Klintmalm GB, Levy M, Jennings LS, Goldstein RM, Husberg BS. Impact of pretransplant renal function on survival after liver transplantation. Transplantation. 1995;59(3):361–5.
100. Nelson LM, Penninga L, Sander K, Hansen PB, Villadsen GE, Rasmussen A, et al. Long-term outcome in patients treated with combined heart and liver transplantation for familial amyloidotic cardiomyopathy. Clin Transpl. 2013;27(2):203–9.

Low Output Heart Failure: The Cold and Wet Patient

15

Antonio Christophy and J. Thomas Heywood

Case Vignette

A 57 year old African American gentleman is admitted with increasing dyspnea and confusion. He is known with a history of non-ischemic cardiomyopathy for 5 years. His most recent ejection fraction is 20%. Past medical history is significant for type 2 diabetes and stage III chronic kidney disease. One month previously he was admitted for non-focal neurological symptoms. Acute stroke was ruled out, but no clear diagnosis was made and the possibility of dementia was mentioned. On physical examination his blood pressure is 100/80 mmHg with a heart rate of 91 bpm. Jugular venous pressure is 9 cmH_2O with a positive abdominojugular reflux. Lungs are clear, there is a 1+ parasternal lift and a 2/6 holosystolic murmur at the apex. The patient's extremities reveal edema in both the ankles with coolness from the mid-leg to the feet. The neurological exam is again non-focal, with a somnolent and disoriented patient. Pertinent laboratory results are a creatinine of 3.5 mg/dL (previously 1.8 mg/dL) and blood urea nitrogen of 43 mg/dL. Lactate is mildly elevated at 1.1 mmol/L with normal pH. Liver function tests are also abnormal with a total bilirubin of 2.2 mg/dL and aspartate transaminase of 62 U/L. A pulmonary artery catheter is placed with the

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following findings: right atrial pressure 7 mmHg, pulmonary artery pressure 42/28 mmHg with a pulmonary arterial wedge pressure of 24 mmHg. The thermodilution cardiac output is 2.4 L/min with a cardiac index of 1.1 L/min/m^2. His systemic vascular resistance is calculated at 2600 dynes/s/cm^{-5}. The patient is placed on dobutamine 3 μg/kg/min, oral hydralazine and oral nitrates. Over the next week, his creatinine falls to 2.3 mg/dL and his mental status clears completely. Inotrope weaning is attempted but not successful due to worsening urine output and reduced blood pressure. Work-up is begun for advanced therapies including left ventricular assist device and/or cardiac transplantation. He is discharged on intravenous continuous dobutamine. One week after discharge, his serum creatinine is 1.5 mg/dL.

Chapter Key Points

- Relationship between cardiac output and renal function
- How to optimize cardiac output in cardiorenal syndrome
- Use of vasodilators versus inotropes in cardiorenal syndrome

Brief Discussion of the Case

Clinical evaluation of a patient, although imperfect and often haphazardly performed in the modern era, should be a cornerstone of heart failure management [1]. Nohria and Stevenson have demonstrated that hemodynamic profiling via physical examination was able to predict survival in patients with advanced heart failure [2]. The four hemodynamic profiles have continued to be used in clinical practice (Fig. 15.1). In this hemodynamic profile, congestion is defined as a recent history of orthopnea and/or evidence of jugular venous distention, rales, hepatojugular reflux, ascites, peripheral edema, leftward radiation of the pulmonic heart sounds, or a square wave blood pressure response to Valsalva maneuver. Conversely, hypoperfusion is suggested by a narrow proportional pulse pressure [(systolic – diastolic blood pressure)/systolic blood pressure < 25%], pulsus alternans, symptomatic hypotension (without orthostasis), cool extremities, and/or impaired mentation. The patient described above fits the profile of the *cold & wet* patient. This profile is prognostically dire with a harms ratio of death or urgent transplant of 2.48, even when corrected by multivariate analysis [2]. Moreover the presence of cardiorenal syndrome suggests a high inpatient mortality of 20% [3].

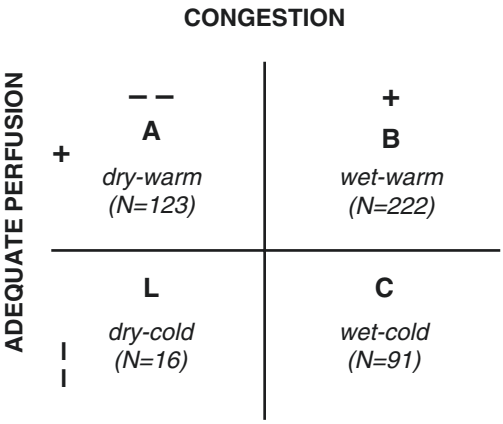

Fig. 15.1 Schematic for assessment of clinical profiles. Congestion was assessed by the presence of orthopnea, jugular venous distention, rales, hepatojugular reflux, ascites, peripheral edema, leftward radiation of the pulmonic heart sound, or a square-wave blood pressure response to the Valsalva maneuver. Compromised perfusion was assessed by the presence of a narrow proportional pulse pressure, pulsus alternans, symptomatic hypotension (without orthostasis), cool extremities, and/or impaired mentation

The Hemodynamic Model for Heart Failure

Until the advent of the neurohumoral hypothesis, heart failure was seen as a hemodynamic disorder that should be corrected by the use of inotropes and diuretics [4]. Perhaps as a holdover from this hemodynamic paradigm, the etiology for worsening renal function in patients with heart failure has generally been assumed to be the result of low cardiac output. There are some data to support this view. Physiologic studies in patients with advanced heart failure have provided evidence that cardiac output could be improved by adding positive inotropic agents or reducing afterload [1, 5, 6]. Patients often improve when inotropes are added with improvements of serum creatinine observed at the same time. Data exist that with very low cardiac index <1.5 L/min/m^2, renal blood flow is reduced with a consequent worsening of renal function [7]. Prolonged hypotension, often associated with reduced cardiac output, has long been shown to cause worsening renal function and even acute tubular necrosis [8].

Blood Pressure or Cardiac Output?

As the evidence for the survival benefits of neurohumoral modulators increased, the role of positive inotropic agents have been questioned on several fronts. Use of inotropes, whether used intravenously or oral, is associated with increased mortality [9, 10].

On the other hand, drugs which decrease contractility (e.g. beta blockers) improve survival and ventricular function over the long-term [11–13]. Casting more doubt on the role of low cardiac output as the cause of cardiorenal syndrome, a pivotal study by Mullens et al. in patients with hemodynamic monitoring for advanced heart failure has demonstrated that high central venous pressure rather than low cardiac output is more frequently associated with worsening renal function [14]. This confirms animal data about the detrimental effect of high central venous pressure on renal function [15, 16]. Finally, the beneficial effect of inotropes may be related more to their improvement in blood pressure rather than a rise in cardiac output [9].

Treatment Pearls for the Case Vignette

So how should we evaluate the patient from the case vignette in the light of these data? Clearly the patient displays an advanced stage of heart failure complicated by cardiorenal syndrome. The creatinine has more than doubled and there is even mental impairment suggesting low cerebral perfusion. Mental alteration is common in shock and pre-shock states and patients undergoing cardiac transplantation have reduced cerebral blood flow [17, 18]. Cold extremities are also associated with shock and thought to be due to low cardiac output or reduced blood pressure. Indeed, cardiac index is severely reduced at nearly 1 L/min/m^2. Blood pressure, although reduced, is not at a level that is commonly thought of as shock (mean arterial pressure <60 mmHg). Hence systemic vascular resistance is very high, masking severely depressed cardiac function. The latter is amenable to pharmacological treatment (e.g. hydralazine). Filling pressures are elevated, but not to the extent to invoke renal congestion as a cause of cardiorenal syndrome. In this case, the presentation of the patient with kidney dysfunction seems predominantly related to low cardiac output, which was relieved by a combination of drugs to improve contractility and reduce afterload.

In this case, invasive hemodynamics are obtained on admission, which plays a key role in identifying the patient's severe reduction in cardiac index and markedly elevated systemic vascular resistance. This information leads to the initiation of an inotrope and oral vasodilators. Later, efforts to wean the inotrope were unsuccessful because of a reduction in urine output. The patient is fortunate that renal dysfunction is reversible, but it is imperative in these situations to realize that this is now advanced stage D heart failure and the clinical improvement is temporary [9, 19]. Inotropic therapy has shown to improve cardiac output/index, improve peripheral blood flow, renal function, vasodilate and with dopamine at higher doses improves blood pressure [6, 19–21]. Although, inotropic agents have never been shown to improve mortality, they have had a significant impact on quality of life and reduction in hospitalizations for advanced heart failure patients. These findings have also shown cost reduction when factoring in readmission costs [21]. Unfortunately, yearly mortality approaches 50%, even when inotropes are continued. Left ventricular assist devices or cardiac transplantation offers a much better prognosis in appropriately selected patients [1, 20, 21]. In many cases palliative care may be considered early on.

Treatment Pearls from the Case Vignette

This case underscores the need to individualize therapy for the cardiorenal syndrome in advanced congestive heart failure. There has been a paradigm shift in our conceptualization of worsening renal function away from an absolute need to increase cardiac output to a focus on relieving venous congestion. However, whereas venous congestion is often the cause of worsening renal function it is clearly not *always* the cause. A simple thought experiment in which the cardiac index is reduced from 2 L/min/m^2 to 1.5 L/min/m^2, 1.0 L/min/m^2, and finally 0.5 L/min/m^2 convinces one that there is some very low index above zero where renal function would be impaired even if blood pressure could be maintained. Data exist that with a cardiac index <1.5 L/min/m^2, renal blood flow is significantly impaired [7]. Fundamentally when approaching a patient with developing cardiorenal syndrome, clinicians must ask themselves: "Why does this patient has renal impairment?" The potential answers are venous congestion, low perfusion pressure, severely reduced cardiac index, intrinsic renal disease, or obstruction. Of course, the situation may arise where multiple elements may play a role. Simple bedside evaluation including volume assessment (neck veins, hand-held ultrasound, etc.), blood pressure determination, and examination of the extremities for adequacy of perfusion as a surrogate for cardiac index and/or increased systemic vascular resistance can provide clues to the astute clinician where the hemodynamic derangement lies and how it may be reversed [2, 22–24]. In critical situations when shock is present, there may be no substitute for invasively obtained hemodynamics (Table 15.1) [1, 25]. The clinician's role is to identify these abnormalities and to address each derangement. This may be as simple as adjusting a diuretic or as complex as emergency mechanical circulatory support. Understanding the pathophysiology of the cardiorenal syndrome is key and time is of the essence.

Table 15.1 Management of the cold & wet patient

1.	**Recognition –** *Recognition of the volume overloaded, hypo-perfused patient is key because of increased mortality associated with the syndrome. In some patients the syndrome can develop over months and, if not recognized, can become severe and untreatable very quickly*
(a)	Volume overload, e.g. elevated neck veins, peripheral edema, pleural effusions
(b)	Reduced perfusion e.g. reduced blood pressure, reduced pulse pressure, mental confusion, cool extremities
2.	**Risk Stratification –** *The cold wet patient exists as a continuum from mild volume overload/hypoperfusion to frank shock with critical end organ injury. Risk stratification is key to determining the severity of the insult and to begin to formulate a plan for dealing with the patient at hand. Each patient presentation is unique and must be assessed in terms of their physiology but also their goals for care*
(a)	End organ hypoperfusion
(i)	Degree of renal dysfunction, acute vs chronic
(ii)	Presence and degree of elevated liver enzymes
(iii)	Presence and degree of mental confusion

(continued)

Table 15.1 (continued)

(b) Invasive hemodynamics
(i) Quantify degree of hemodynamic abnormalities and avenues of improvement
(c) Degree of volume overload versus severity of hypoperfusion
(i) Integrating physical exam, echocardiography and invasive hemodynamics as necessary
3. Management – *Treatment of the cold wet patient depends on recognition, risk assessment and presentation. Aggressive and rapid management can be lifesaving but is not appropriate for all individuals*
(a) Mild (normotensive, volume overload, mild end organ dysfunction)
(i) Diuretics as needed
(ii) Inotropes in selected cases
(b) Moderate (hypotensive, moderate end organ dysfunction)
(i) Invasive hemodynamics usually helpful
(ii) Short term inotropes without hemodynamics in selected individuals (palliative approach)
(iii) Inotropes/afterload reduction based on hemodynamic assessment
(iv) Balloon pump, catheter based mechanical support for more severe reduction of perfusion
(v) Pressor support for hypotension
(vi) Diuretics once blood pressure and perfusion improved
(vii) Evaluate for advanced therapies
(c) Severe (frank shock, acidosis, significant end organ dysfunction)
(i) Rapid assessment of patient goals/candidacy for advanced therapies
(ii) Emergent pressors/inotropes
(iii) Rapid use of high flow catheter support
(iv) Urgent ECMO support may be first therapy in extremely critical situation
(v) Evaluate for advanced therapies if stabilization occurs, i.e. LVAD and cardiac transplant
(vi) Palliative care either initially or if resuscitation fails

References

1. H. F. S. of America. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16(6):e1–2.
2. Nohria A, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 2003;41(10):1797–804.
3. Fonarow GC, Adams KF, Abraham WT, Yancy CW, Boscardin WJ, S. G. for the ADHERE Scientific Advisory Committee. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA. 2005;293(5):572–80.
4. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol. 1992;20(1):248–54.
5. Ungar A, et al. Renal, but not systemic, hemodynamic effects of dopamine are influenced by the severity of congestive heart failure. Crit Care Med. 2004;32(5):1125–9.
6. Westman L, Järnberg P-O. Effects of dobutamine on haemodynamics and renal function in patients after major vascular surgery. Acta Anaesthesiol Scand. 1987;31(3):253–7.
7. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Drugs. 1990;39(4):10–21.

8. Dupont M, Mullens W, Finucan M, Taylor DO, Starling RC, Tang WHW. Determinants of dynamic changes in serum creatinine in acute decompensated heart failure: the importance of blood pressure reduction during treatment. Eur J Heart Fail. 2013;15(4):433–40.
9. Toma M, Starling RC. Inotropic therapy for end-stage heart failure patients. Curr Treat Options Cardiovasc Med. 2010;12(5):409–19.
10. Gorodeski EZ, Chu EC, Reese JR, Shishehbor MH, Hsich E, Starling RC. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. Circ Heart Fail. 2009;2(4):320–4.
11. Packer M, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002;106(17):2194–9.
12. Hjalmarson Å, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). JAMA. 2000;283(10):1295–302.
13. Beta-Blocker Evaluation of Survival Trial Investigators, Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, Bristow MR, Lavori PW. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344(22):1659–67.
14. Mullens W, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(7):589–96.
15. Firth JD, Raine AEG, Ledingham JGG. Raised venous pressure: a direct cause of renal sodium retention in oedema? Lancet. 1988;331(8593):1033–6.
16. Winton FR. The influence of venous pressure on the isolated mammalian kidney. J Physiol. 1931;72(1):49–61.
17. Califf RM, Bengtson JR. Cardiogenic shock. N Engl J Med. 1994;330(24):1724–30.
18. Gruhn N, et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. Stroke. 2001;32(11):2530–3.
19. Leier CV, Binkley PE. Parenteral inotropic support for advanced congestive heart failure. Prog Cardiovasc Dis. 1998;41(3):207–24.
20. Leier CVMD, Heban PTMD, Huss PRN, Bush CAMD, Lewis RPMD. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. Circulation. 1978;58(3):466–75.
21. Upadya S, et al. Home continuous positive inotropic infusion as a bridge to cardiac transplantation in patients with end-stage heart failure. J Heart Lung Transplant. 2004;23(4):466–72.
22. Kimura BJ. Point-of-care cardiac ultrasound techniques in the physical examination: better at the bedside. Heart. 2017;103(13):987–94.
23. Simon MA, Schnatz RG, Romeo JD, Pacella JJ. Bedside ultrasound assessment of jugular venous compliance as a potential point-of-care method to predict acute decompensated heart failure 30-day readmission. J Am Heart Assoc Cardiovasc Cerebrovasc Dis. 2018;7(15):e008184.
24. Garibyan VN, Amundson SA, Shaw DJ, Phan JN, Showalter BK, Kimura BJ. Lung ultrasound findings detected during inpatient echocardiography are common and associated with short- and long-term mortality. J Ultrasound Med. 2018;37(7):1641–8.
25. Meersch M, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med. 2017;43(11):1551–61.

Cardiorenal Syndrome in a Patient with Mechanical Circulatory Support

16

Andrew Xanthopoulos, Filippos Triposkiadis, and Randall C. Starling

Case Vignette

Mr. Y is a 62 y/o man with an ischaemic cardiomyopathy, who is admitted at the intensive care unit with cardiogenic shock. Four months ago, he suffered an anterior myocardial infarction while being at work at his office. An urgent primary percutaneous coronary intervention with placement of a drug-eluting stent was performed for a proximal left anterior descendens occlusion, but only TIMI 1 flow was obtained. After a prolonged hospitalization of 52 days, Mr. Y was able to leave the hospital. His medications included aspirin, ticagrelor 90 mg twice daily, pantoprazole, atorvastatin, lisinopril 5 mg daily, carvedilol 3.125 mg twice daily and furosemide 80 mg twice daily. On admission, blood pressure is 85/46 mmHg. Right heart catheterization demonstrates a central venous pressure of 15 mmHg and a pulmonary capillary wedge pressure of 34 mmHg. The cardiac index is 1.4 L/min/m^2. The serum creatinine is 2.63 mg/dL. Right ventricular function is normal on echocardiography. A decision is made to implant a left ventricular assist device (HeartMate III). The implantation is uneventful. After 6 days the serum creatinine has dropped to 1.43 mg/dL.

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Chapter Key Points

- Importance of renal function in the decision-making about mechanical circulatory support
- Improvement of renal function under mechanical circulatory support

Brief Discussion of the Case

The patient in the case vignette presents with cardiogenic shock: low blood pressure, low cardiac index, high central venous pressure (CVP) and high pulmonary arterial wedge pressure (PAWP). As a consequence he demonstrates renal failure (serum creatinine 2.63 mg/dL). Cardiovascular disorders and diseases are often associated with kidney disease and vice versa. The underlying mechanisms are complex and most likely multifactorial. In this regard, renal dysfunction is common in patients with heart failure, especially in those in the advanced stages of the disease. Among mechanical circulatory support (MCS) devices employed in this setting, left ventricular assist devices (LVADs), used either as a bridge to transplantation (BTT) or as destination therapy (DT) reduce morbidity and mortality, as well as improve functional state in advanced heart failure. The implantation of LVADs is accompanied by short-term improvements in renal function, whereas data on long-term outcomes is inconclusive. Indeed, patients with baseline severe renal dysfunction should not be excluded from LVAD implantation, as this functional impairment may be reversible. Conversely, acute kidney injury (AKI) is not uncommon after LVAD implantation and it is followed by high mortality rates. The etiology for the development of AKI in LVAD patients is multifactorial and includes pre-renal, intrarenal, and post-renal mechanisms. Whether the different types of MCS devices (pulsatile vs non-pulsatile) have a clinically significant different pathophysiologic effect on renal function has not yet been delineated. The emerging role of percutaneous MCS devices (intra-aortic balloon pump, TandemHeart system, Cardiobridge support device, and Impella) on the preservation or restauration of renal function deserves further investigation.

Introduction

Heart failure is a clinical syndrome associated with several comorbidities such as anemia, sleep apnea, chronic obstructive pulmonary disease, liver and renal dysfunction. Conversely, each of the above-mentioned comorbidities is associated with higher incidence of heart failure. This bidirectional association is complex, as it is affected by several confounding factors such as age, hypertension, atherosclerosis, and diabetes. Inflammation links heart failure with comorbidities and the comorbidities themselves make this interplay even more diverse [1]. The heart and the kidneys are two organs with significant contribution to cardiovascular homeostasis

[2]. Although under normal conditions each change (increase or decrease) of atrial pressure or decrease of renal perfusion triggers essential homeostatic mechanisms, in situations where cardiac or renal disease exist, homeostatic mechanisms are malfunctioning [2]. Interestingly, chronic kidney disease (CKD), similar to heart failure, is characterized by several coexistent morbidities such as cardiovascular, hematologic, musculoskeletal, and neurologic disorders [2].

The increasing number of advanced heart failure patients not responding to conventional pharmacological and device therapies necessitates the use of specific, advanced heart failure therapies. Those include the mechanical circulatory support (MCS) devices and heart transplantation [3]. Among MCS devices, left ventricular assist devices (LVADs), used either as BTT or DT exhibit favorable results regarding patients' morbidity, mortality, functional state, and quality of life [4–7]. The efficacy of the continuous flow axial HeartMate II as a BTT or DT [8, 9] is well established with the major limitation being an increased incidence of thrombosis events (device thrombosis and stroke) [10]. The risk of these complications is reduced with the introduction of the fully magnetically levitated circulatory pump (HeartMate III) [11, 12]. Meanwhile, the expansion of MCS devices' use in the advanced heart failure population opens new areas of research such as the effects of MCS on renal function, the importance of renal function in the decision-making about MCS and the impact of renal function with different types of MCS. Those topics are discussed in this chapter. Indeed, renal dysfunction is a known risk factor that must be carefully evaluated before MCS.

Renal Function Pre-implantation of a Left Ventricular Assist Device

Pathophysiology or Renal Function in Advanced Heart Failure

The heart and kidneys closely interact. Under normal conditions, the renal blood flow corresponds to 20% of the cardiac output and it is regulated by intra-abdominal pressure, renal vascular resistance and the difference between renal arterial and venous pressure [13]. An important homeostatic mechanism of the kidney is called *autoregulation*. The goal of this mechanism is to keep the glomerular filtration rate (GFR) inside a narrow range by adjusting the resistance of the afferent arterioles in response to renal arterial pressure and flow fluctuations through the nephron [13]. In situations where the renal blood flow drops, a number of protective mechanisms are triggered such as redistribution of blood flow for the preservation of renal perfusion and glomerulotubular feedback [13].

Renal impairment is a common finding in heart failure patients and is associated with worse prognosis [14–16]. The pathophysiological mechanisms include advanced age, hypertension, diabetes, and eventually atherosclerosis, which may affect both the heart and kidneys. Abnormal hemodynamic parameters such as reduced cardiac output and specifically increased CVP have also been implicated in the pathogenesis of renal dysfunction in heart failure [17–19]. Intrinsic renal disease

and inflammation may reduce the ability of the kidneys to respond to heart failure-induced hemodynamic alterations leading to renal failure [16]. The use of high doses of diuretics, commonly employed in advanced heart failure patients, is associated with impaired glomerular filling, decreased drug filtration and delivery into the intra-tubular filtrate and finally acute renal dysfunction with diuretic resistance [16, 20–24]. Finally, factors such as the activated renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), release of adenosine and arginine-vasopressin, endothelial dysfunction, and anaemia contribute to the development of CKD in heart failure patients [19, 25].

The Role of Renal Function in the Decision-Making About Left Ventricular Assist Device Implantation

In-hospital worsening renal function (WRF) often occurs in acute heart failure and has been considered a predictor of adverse outcomes [25–28]. However, there is increasing evidence that transient WRF, especially when it is combined with effective decongestion with diuretics, is not necessarily accompanied by adverse outcomes [29, 30]. The results, however, regarding the response of renal dysfunction to MCS are conflicting. Khot et al., found that the use of pulsatile flow LVADs (Thoratec HeartMate or Novacor left ventricular assist system) may significantly improve renal function in cardiogenic shock and severe renal failure (defined as creatinine values ≥3 mg/dL) and that survival following MCS in cardiogenic shock is not affected by the presence or absence of CKD [31]. These findings led the investigators to the conclusion that the presence of severe renal dysfunction in cardiogenic shock is not a contraindication for the use of MCS as a BTT. On the contrary, another study has highlighted the importance of early LVAD implantation in patients presenting with cardiogenic shock, before significant renal functional deterioration occurs [32].The researchers examined 82 patients who underwent LVAD implantation (Nipro, Jarvik2000, HeartMate II, EvaHeart, DuraHeart and HeartWare) and categorized them based on their INTERMACS levels into two groups (group 1: INTERMACS level 1 vs. group 2: INTERMACS levels 2, 3). The most common cause of early mortality was pre-operative multi-organ failure and pre-operative renal dysfunction (creatinine cut-off ≥1.96 mg/dL) was found to be an independent predictor of early (perioperative) mortality.

Sandner et al. investigated in a retrospective manner, 86 advanced heart failure patients who underwent continuous flow LVAD implantation and concluded that although LVAD use is associated with better survival, patients exhibiting a pre-implantation GFR <60 mL/min/1.73 m^2 manifested significantly higher mortality rates [33]. Hence, the authors highlight the need for careful selection of LVAD candidates. Similarly, Butler et al. found that patients with pre-implantation severe kidney dysfunction (defined as creatinine clearance <47 mL/min) exhibited the worst outcomes after pulsatile flow LVAD implantation (Novacor LVADs) in comparison to patients with better renal function [34]. However, they highlighted the beneficial effects of LVAD use irrespective from patients' renal function on

outcomes, which were even observed in the group that showed a pre-implantation creatinine clearance ≤50 mL/min. The authors also claimed that even though severe CKD should be considered as a relative contraindication to LVAD implantation (due to subsequent high mortality rates), these patients should not be precluded from LVAD implantation and future research should identify the pre-operative risk factors that will determine whether patients will or will not benefit from MCS [34].

Kirklin et al. examined the effect of renal dysfunction in patients with coexisting heart failure and renal failure undergoing continuous flow LVAD implantation from the INTERMACS registry [35]. The investigators classified the patients in three groups, based on their pre-procedural renal function: (a) severe CKD (renal replacement therapy and/or an estimated GFR <30 mL/min/1.73 m^2); (b) moderate CKD (estimated eGFR 30–59 mL/min/1.73 m^2 or blood urea nitrogen >60 mg/dL); and c) mild or no renal dysfunction (estimated GFR ≥60 mL/min/1.73 m^2 and blood urea nitrogen <60 mg/dL). Patients with severe CKD exhibited the worst short-term survival after 3 months. The main causes of death included cardiac failure (31%), a central nervous system event (17%), multisystem organ failure (11%), and infection (11%). The investigators suggested that a careful selection of LVAD candidates should be implemented and proposed the use of temporary MCS devices in patients with severe renal failure, before implantation of an LVAD. Lastly, Singh et al. examined the effect of pre-MCS renal impairment on renal function outcomes after heart transplantation [36]. The researchers observed an improvement of renal function (i.e., creatinine clearance) after the implementation of MCS (biventricular assist devices and LVADs) and stated that renal outcomes after heart transplantation were probably associated mainly with the optimal GFR during MCS support. In general, although irreversible renal dysfunction and treatment with renal replacement therapy are considered an absolute contraindication to LVAD implantation as DT, advanced heart failure patients with recent-onset renal dysfunction should not be excluded from LVAD treatment when a nephrology consultant anticipates improvement post LVAD and acceptable residual renal reserve [6, 37].

Renal Function After Implantation of a Left Ventricular Assist Device

Short and Long-Term Outcomes

In most heart failure patients, there is a short-term improvement of renal function following LVAD implantation [38]. However, the evidence on long-term outcomes is inconclusive [37] (Table 16.1). The beneficial underlying pathophysiological mechanisms of LVAD use for patients' renal function include hemodynamic and non-hemodynamic parameters such as the augmentation of renal blood flow, decrease in RAAS and SNS activation, and finally the reduction of inactivation of nitric oxide (NO) [38, 39]. Predicting renal function changes after LVAD implantation may guide critical clinical decisions. For example, a patient with refractory renal failure after LVAD implantation as a BTT may be a candidate not only for

Table 16.1 Outcomes of renal function after left ventricular assist device (LVAD) implantation

Study	MCS type	N=	Pre-implantation renal function	Follow up	Post-implantation renal function	Conclusion
Sandner SE, et al. *Ann Thorac Surg*. 2009;87(4):1072–8.	CF	86	**Group with eGFR > 60 mL/min/1.73 m²** BUN: 21 ± 7 mg/dL Cr: 1.0 ± 0.1 mg/dL **Group with eGFR < 60 mL/min/1.73 m²** BUN: 44 ± 20 mg/dL Cr: 1.6 ± 0.4 mg/dL	1, 3 and 6 months	Patients with eGFR <60 mL/min/1.73 m² manifested an overall improvement of eGFR from implant to 1,3 and 6 months Patients with eGFR >60 mL/min/1.73 m² exhibited only an early improvement of eGFR from implant to month 1	Renal function improves after LVAD implantation
Russell SD, et al. *Circulation*. 2009;120(23):2352–7	CF	309	BUN: 29 ± 16 mg/dL Cr: 1.4 ± 0.5 mg/dL	1, 3, 5, 7, 11, 14, and 21 days 1 to 6 months	After a slight early increase in Cr, renal function improved in patients with kidney dysfunction, stabilizing by approximately 1–2 months of LVAD support. No significant changes in patients with normal kidney function	LVAD improves renal function in patients with baseline dysfunction and does not impair renal function in patients with normal renal function at baselines
Hasin T, et al. *J Am Coll Cardiol*. 2012;59(1):26–36	CF	83	eGFR: 53 ± 21 mL/min/1.73 m²	1, 3 and 6 months	eGFR increased significantly at 1 month and remained above pre-LVAD values at 3 and 6 months	Renal dysfunction is reversible and probably related to poor renal perfusion

Kirklin JK, et al. *J Heart Lung Transplant.* 2013;32(12):1205–13	CF	4917	Mild or no renal dysfunction (n = 3160) Moderate renal dysfunction (n = 1475) Severe renal dysfunction (n = 282)	1 week, 1, 3, 6, 12, 18, and 24 months	Surviving patients manifested significant improvements in renal function parameters within 1 month, which remained stable afterwards	Renal function improves early after LVAD implantation
Gupta S, et al. *Heart, Lung & Circulation.* 2014;23(10):963–9	CF	53	Cr: 109 ± 43 μmol/L	3 months	Cr decreased significantly	LVAD support improves renal function
Deo SV, et al. *Heart, Lung & Circulation.* 2014;23(3):229–33	CF	126	BUN: 27 [20–40] mg/dL Cr: 1.4 [1.2–1.9] mg/dL eGFR: 52 ± 20 mL/min/1.73 m^2	1, 6 and 12 months	After an initial reduction of Cr at 1 month, a gradual increase was noted over the study period	Renal function exhibits early improvement and then remains stable
Raichlin E, et al. *ASAIO Journal.* 2016;62(3):261–7	CF	165	BUN: 23 ± 10 mg/dL Cr: 1.3 ± 0.5 mg/dL eGFR: 64 ± 24 mL/min/1.73 m^2	1, 3, and 6 months 1 year	Patients with eGFR >40 mL/min/1.73 m^2 exhibited a significant early eGFR increase at 1 month and then a gradual decrease (1 year follow-up eGFR did not differ significantly from the pre-LVAD level). Patients with eGFR ≤40 mL/min/1.73 m^2 demonstrated significant early renal function improvement after 1 and 3 months, followed by stable eGFR values	Renal function in patients with eGFR ≤40 mL/min/1.73 m^2 benefit from LVAD support

(continued)

Table 16.1 (continued)

Study	MCS type	N=	Pre-implantation renal function	Follow up	Post-implantation renal function	Conclusion
Yoshioka D, et al. *Ann Thorac Surg.* 2017;103(3):717–24	CF	469	BUN: 37 ± 18 mg/dL Cr: 1.5 ± 0.6 mg/dL eGFR:58 ± 28 mL/min/1.73 m^2	1 and 6 months 1, 2 and 3 years	Renal function was significantly improved 1 month after LVAD implantation and gradually declined thereafter	LVAD improves renal function transiently with return to baseline after prolonged support
Brisco MA, et al. *Circ Heart Fail.* 2014;7(1):68–75	PF/CF	3363	Cr: 1.5 ± 0.8 mg/dL eGFR: 60 ± 35 mL/min/1.73 m^2	1 week 1, 3, and 6 months 1 year	eGFR improved transiently and by 1 year, it was only slightly above the pre-LVAD value	Early improvement in renal function after LVAD support is probably transient
Khot UN, et al. *J Am Coll Cardiol.* 2003;41(3):381–5	PF	18	Cr: 4.0 ± 0.7 mg/dL	VAD placement, transplantation, 1, 3, and 6 months post-transplantation	Renal function improvement	In severe renal insufficiency complicating cardiogenic shock, early mechanical support with VAD resulted in long-term recovery of renal function
Butler J, et al. *Ann Thorac Surg.* 2006;81(5):1745–51	PF	220	BUN: 35 ± 21 mg/dL Cr: 1.5 ± 0.8 mg/dL CrCl: 77 ± 46 mL/min	1–4 weeks	CrCl improvement	Renal function improves with LVAD use
Singh M, et al. *Ann Thorac Surg.* 2011;91(5):1348–54	PF/CF (BiVAD/LVAD)	116	CrCl: 58 mL/min pre-MCS CrCl: 70 mL/min pre-transplantation	2 weeks +1, 3, and 6 months post-MCS Pre-transplantation 2 weeks +1, 3, 6, and 12 months post-transplantation	Significant early improvement in CrCl, no further improvement beyond 1 month. After transplantation worsening renal function that was most pronounced after 2 weeks	MCS use leads to improvements in renal function

BiVADs biventricular ventricular assist device, *BUN* blood urea nitrogen, *CF* continuous flow, *Cr* creatinine, *CrCl* creatinine clearance, *eGFR* estimated glomerular filtration rate, *MCS* mechanical circulatory support, *PF* pulsatile flow, *VAD* ventricular assist device

heart, but also for renal transplantation [40]. Moreover, right ventricular failure is a common complication of LVAD implantation and severe right ventricular failure post-LVAD implantation is associated with peri-operative mortality, altered drug metabolism and diuretic resistance. Thus, several risk scores for the prediction of right ventricular failure after LVAD insertion have been developed [41].

Hasin et al., in a retrospective study of 83 consecutive patients who underwent continuous flow LVAD implantation, monitored the estimated GFR on admission and during follow-up (after 1, 3, and 6 months) and reported a significant improvement of renal function [40]. Furthermore, the authors reported that an increase in estimated GFR (from 40 ± 12 to 55 ± 18 mL/min/1.73 m^2) with optimal medical treatment before surgery was found to be a positive prognostic marker of improved renal function after LVAD implantation. Gupta et al. retrospectively reviewed 53 consecutive patients who received a HeartWare centrifugal continuous flow LVAD implantation [42]. They reported a significant decrease of creatinine values compared to baseline at 3 months post-implantation ($p < 0.001$).

Brisco et al. examined 3363 patients with MCS from the INTERMACS registry and reported a post-MCS early (during the first month) significant improvement of the estimated GFR (median improvement, 49%; $p < 0.001$) [43] compared to baseline values. However, this improvement after the first month, continued as a descending trajectory for up to 1 year of follow-up (median improvement, 7%; $p < 0.001$). Moreover, the investigators highlighted the adverse survival in patients who demonstrated substantial early or late changes in renal function (whether improvements or worsening). Russell et al. examined 309 advanced heart failure patients undergoing LVAD implantation as a BTT and analysed the effects of HeartMate II on renal and hepatic function [44]. The population enrolled in the study was divided into two groups based upon the pre-implantation renal (creatinine and blood urea nitrogen) and hepatic (aspartate transaminase, alanine transaminase, and total bilirubin) laboratory values. A significant improvement with time (up to 6 months) was observed in the group with abnormal values at baseline, whereas laboratory values remained unchanged in those with normal values at baseline. Another interesting study investigated the long-term effects of continuous flow LVAD devices on hepatic and renal function of advanced heart failure patients [45]. Regarding the entire cohort, the authors reported a significant decrease of serum creatinine at 1-month post-implantation ($p < 0.0001$) followed by a gradual increase over 1 year ($p = 0.0038$ from 1 to 6 months and $p = 0.05$ from 6 to 12 months). On the contrary, serum bilirubin demonstrated a descending trajectory throughout the study. Creatinine values at 1 year were significantly lower compared to the pre-procedure values ($p = 0.0003$). Regarding the high-risk cohort (defined as serum creatinine >1.9 mg/dL or serum bilirubin >1.5 mg/dL), the researchers observed a significant drop in creatinine at the end of 1-month follow-up ($p < 0.0005$) followed by a further decrease until 6 months ($p = 0.01$) and a stable course until the end of the study (1 year). Similarly to the entire cohort, the 1-year creatinine levels were significantly lower compared to the baseline values ($p = 0.0005$). The long-term effects of continuous flow LVADs on renal and hepatic function were also the scope of the study by Yoshioka et al. [46]. Regarding the subgroup of patients with pre-procedural estimated GFR

<60 mL/min/1.73 m^2, the initial estimated GFR increase 1-month post-implantation ($p < 0.05$ versus pre-operative values) was followed by a gradual estimated GFR decrease resulting in values comparable to baseline after 3 years. On the contrary, hepatic function (transaminases, bilirubin, MELD-IX score) remained normal in LVAD patients during the 3 years of follow-up. Raichlin et al., in a series of 165 consecutive heart failure patients who received HeartMate II LVADs, reported that patients with baseline estimated GFR >40 mL/min/1.73 m^2 (n = 135) exhibited a significant estimated GFR increase during the first month after implantation and subsequently a gradual decrease, resulting in 1-year follow-up values similar to those manifested before the operation, whereas patients with baseline estimated GFR ≤40 ml/min/1.73 m^2 (n = 30) demonstrated significant renal function improvement at 1 and 3 months, followed by stable estimated GFR values, albeit higher compared to the pre-procedural ones, until 1 year post-implantation [47]. Taken all together, although the use of LVADs is accompanied by favourable short-term improvements in renal function, there is uncertainty about the long-terms impact.

Acute Kidney Injury and Left Ventricular Assist Devices

A number of criteria have been proposed for the definition of acute kidney injury (AKI) [48]. According to the most recent Kidney Disease: Improving Global Outcomes (KDIGO) criteria, AKI is defined as any of the following: (a) Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 μmol/l) within 48 h; or (b) Increase in serum creatinine to ≥1.5 times its baseline, which is known or presumed to have occurred within the prior 7 days; or (c) Urine volume < 0.5 mL/kg/h for 6 h [49]. Interestingly, WRF is usually defined as a serum creatinine increase of ≥0.3 mg/dL compared to the admission value [30]. A recent study defined WRF as a change in serum creatinine ≥0.3 mg/dL during the first 5 days after admission [50].

Several pre-operative factors (serum creatinine >1.5 mg/dL, impaired right ventricular function, high CVP, older age, higher LVAD score, INTERMACS score 1 or 2, low albumin and total protein, low left ventricular end-diastolic diameters, kidney size <10 cm, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), intra-operative factors (longer cardiopulmonary bypass time, number of blood transfusions, bleeding >1 L), and post-operative factors (need for reoperation within 48 h, intra-aortic balloon pump, liver dysfunction, sepsis) have been associated with the development of AKI post-operatively [51, 52]. The aetiology for the development of AKI in LVAD patients is multifactorial and includes pre-renal (hypovolemia, heart failure exacerbation, cardiogenic shock, sepsis, renal arterial disease and drugs such as non-steroidal anti-inflammatory drugs or angiotensin-converting enzyme inhibitors), intrinsic renal (hemolysis, sepsis) and post-renal causes (tumors, stones, hematoma) [53]. However, a recent study has challenged the traditional perspective which perceives AKI in advanced heart failure patients as the result of reduced renal perfusion [54]. The authors examined 575 heart failure patients from the Evaluation Study of Congestive Heart Failure and

Pulmonary Artery Catheterization Effectiveness (ESCAPE) and investigated the association between their cardiac index and estimated GFR. They found an inverse correlation between the cardiac index and the estimated GFR ($r = -0.12$; $p = 0.02$) and no association between the cardiac index and the blood urea nitrogen or the blood urea nitrogen to creatinine ratio. Therefore, the authors concluded that impaired cardiac output is not the leading cause of renal dysfunction in patients with advanced heart failure.

Acute kidney injury is a frequent finding in advanced heart failure patients after LVAD implantation. The incidence of AKI post-LVAD implantation ranges from 7% to 56%, and it is accompanied by high short- and long-term mortality rates ranging from 57% to 93% [55]. The large variation in AKI incidence may be due to different definitions used for AKI, the baseline severity of heart failure (INTERMACS level), and the incidence and severity of pre-implantation CKD [50]. Alba et al. observed a significantly lower short-term survival rate at 15, 30, 90 and 130 days post-implantation ($p < 0.01$) in the group of patients who manifested AKI as defined by the RIFLE criteria [56] after LVAD implantation [57]. Another interesting study revealed the close inverse association between AKI (defined as renal failure requiring renal replacement therapy) and the 6-month survival for patients treated with an MCS as a BTT ($p < 0.01$) [58]. Regarding long-term outcomes, Topkara et al. followed retrospectively 201 patients who received LVADs, between 1996 and 2004, and reported that those who needed continuous veno-venous haemodialysis due to severe AKI manifested significantly worse survival rates at 1, 3, 5 and 7 years compared to those who did not ($p < 0.001$) [59]. Genovese et al. retrospectively analysed the early adverse outcomes and their association with 1-year mortality, in a series of 163 advanced heart failure patients who underwent MCS device implantation (LVADs or biventricular assist devices) between 1996 and 2008 and concluded that AKI (defined as abnormal kidney function requiring renal replacement therapy in patients who did not require this procedure before implant or a rise in serum creatinine >3 times normal baseline values or > 5 mg/dL) was the only significant and independent predictor of increased 1-year mortality. In particular, patients exhibiting AKI early after MCS device implantation manifested a three-fold increased risk of death during the first year after the procedure [60]. Similarly, Aik et al. examined the relationship between risk factors and adverse outcomes in 157 patients who received MCS. The investigators reported that AKI (defined as a $\geq 50\%$ increase in serum creatinine over the first 7 post-procedure days) was a significant predictor of 30-day and 365-day mortality. An interesting study examined the natural history of heart failure patients who developed severe renal failure after continuous flow LVAD implantation requiring renal replacement therapy either by continuous veno-venous hemofiltration dialysis (CVVHD) or hemodialysis, or both [61]. The investigators observed that patients who recovered from the operation and showed clinical improvement (New York Heart Association functional class I), managed to wean from the renal replacement therapy successfully. In conclusion, AKI not infrequently occurs after LVAD implantation and it is an independent risk factor of adverse short- and long-term prognosis.

Different Types of Mechanical Circulatory Support and Renal Function

The impact of different types of MCS devices on renal function is a conundrum (Table 16.2). For example, Welp et al. examined prospectively the impact of the LVAD type (pulsatile vs. non-pulsatile) on the plasma renin activity (PRA) and aldosterone levels in 20 advanced heart failure patients undergoing LVAD implantation [62]. The investigators found that the levels of PRA decreased to near normal values after 21 days of support both in pulsatile (EXCOR LVAD) and non-pulsatile (INCOR LVAD) devices. Interestingly, these levels remained stable until the end of the study (day 70). However, the group on pulsatile LVAD exhibited significantly lower PRA compared to the non-pulsatile group after 21 days of support, and this difference remained unchanged until the end of the study. Similar results were found concerning aldosterone levels. In particular, although aldosterone levels significantly dropped after the initial 3 weeks on both types of MCS and remained at near normal levels until day 70, the levels of aldosterone in the pulsatile group was significantly lower compared with the non-pulsatile group after 21 days of LVAD support and this difference didn't change until the end of the study. Apart from RAAS activation, several other pathophysiological mechanisms have been implicated in the development of renal impairment as the result of chronic non-pulsatile MCS exposure, including smooth muscle cell hypertrophy of renal cortex arteries and kidney peri-arteritis [43, 63, 64]. Nevertheless, it has been reported that even though the pulsatility is low in heart failure patients receiving continuous flow LVADs, the baroreflex sensitivity is preserved [65]. The study by Brisco et al. found no difference regarding the estimated GFR trajectory (significant early improvement followed by a late decline) post-implantation between continuous and pulsatile flow LVAD recipients [43]. Another study compared the renal outcomes of patients receiving continuous versus pulsatile flow LVADs as a BTT [66]. Both groups manifested a significant improvement of renal function (defined by estimated GFR) 1, 4, and 12 weeks post-LVAD implantation. Interestingly, no significant difference was observed as far as post-implantation renal function adverse outcomes between continuous and pulsatile LVADs. Yoshioka et al. showed that perioperative mortality in patients undergoing LVAD implantation depends more on the preoperative GFR than the type of LVAD device used (Nipro LVAD vs. other types of LVADs) [32]. Nadziakiewicz and colleagues compared the effects of continuous (HeartMate II or HeartWare) versus pulsatile (Polvad MEV) LVADs on renal function the first 30 days after implantation [67] and found no significant differences between the two groups [67]. A study examined retrospectively 58 advanced heart failure patients divided into three groups based on the LVAD type that they had received (centrifugal, axial, and pulsatile) [68]. The authors reported a significant improvement of renal function compared to baseline at month 1 and 3 after the LVAD implantation and concluded that centrifugal, axial and pulsatile LVADs provide adequate support on end-organ function in advanced heart failure patients. On the contrary, Slaughter et al. enrolled, in a randomized manner, 134 and 66 patients who underwent continuous and pulsatile flow LVADs implantation,

Table 16.2 Comparison of different types of mechanical circulatory support (MCS) and their impact on renal function

Study	MCS type	N=	Pre-implantation renal function	Follow-up	Post-implantation renal function	Conclusion
Sandner SE, et al. *J Heart Lung Transplant.* 2008;27(5):469–73	PF vs CF	92	**CF group** BUN: 34 ± 20 mg/dL Cr: 1.4 ± 0.6 mg/dL eGFR: 59 ± 22 mL/min/1.73 m^2 CrCl: 72 ± 27 mL/min **PF group** BUN: 39 ± 19 mg/dL Cr: 1.7 ± 0.6 mg/dL eGFR: 53 ± 21 mL/min/1.73 m^2 CrCl: 63 ± 30 mL/min	1, 2, 4, and 12 weeks Transplantation	CF group had renal function improvement from implantation up to week 12 (trend towards significance for overall improvement from implantation to transplantation) PF group had renal function improvement from implantation up to week 12	After LVAD implantation, renal function is comparable with CF vs PF devices
Kamdar F, et al. *J Heart Lung Transplant.* 2009;28(4):352–9	Centrifugal vs axial flow vs PF	58	**Centrifugal flow group** BUN: 24 ± 13 mg/dL Cr: 1.3 ± 0.5 mg/dL CrCl: 91 ± 43 mL/min **Axial flow group** BUN: 35 ± 19 mg/dL Cr: 2.3 ± 4.2 mg/dL CrCl: 87 ± 32 mL/min **PF group** BUN: 26 ± 12 mg/dL Cr: 1.2 ± 0.2 mg/dL CrCl: 91 ± 24 mL/min	1 and 3 months	Cr and BUN decreased significantly during study period for all 3 groups	Axial and centrifugal LVADs, compared with pulsatile LVADs, provide adequate circulatory support with similar renal benefits
Slaughter MS, et al. *N Engl J Med.* 2009;361(23):2241–51	PF vs CF	200	**CF group** Cr: 1.6 ± 0.6 mg/dL **PF group** Cr: 1.8 ± 0.7 mg/dL	Daily to weekly intervals and after hospital discharge monthly	Significantly lower rate of renal failure in CF versus PF LVADs	CF LVADs are accompanied by fewer adverse renal events compared to PF LVADs

(continued)

Table 16.2 (continued)

Study	MCS type	N=	Pre-implantation renal function	Follow-up	Post-implantation renal function	Conclusion
Welp H, et al. *Thorac Cardiovasc Surg*. 2010;58 Suppl 2:S185–8	PF vs non-PF	20	Plasma renin activity and aldosterone	Week 1–10	Plasma renin activity and aldosterone significantly decreased after 21 days in both PF and non-PF patients. After 3 weeks, plasma renin activity and aldosterone were significantly lower in PF vs non-PF patients.	PF devices are associated with a greater reduction in plasma renin activity and aldosterone
Jacobs S, et al. *Int J Artificial Organs*. 2014;37(5):364–70	Full (CF-LVAD) vs partial (synergy micropump)	61	**Full support group** BUN: 60 ± 23 mg/dL Cr: 1.3 ± 0.4 mg/dL eGFR: 68 ± 23 mL/min/1.73 m^2 **Partial support group** BUN: 85 ± 41 mg/dL Cr: 1.6 ± 0.6 mg/dL eGFR: 54 ± 26 mL/min/1.73 m^2	1, 3, 5, 10 and 14 days 1, 2, and 3 months	eGFR increased significantly in the first 2 weeks and remained significantly higher at 3 months	Significant improvement in renal function irrespective of the support type (full or partial), even if the preoperative renal function was severely impaired
Nadziakiewicz P, et al. *Transplant Proceed*. 2016;48(5):1775–80	PF vs CF	44	Cr similar at baseline in both groups (≈120 μmol/L)	0–10, 20, and 30 days	Slight early increase in Cr and then improvement. No significant differences between PF and CF	LVAD use improves renal function

CF, continuous flow, *Cr* creatinine, *LVAD* left ventricular assist device, *PF* pulsatile flow, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate

respectively [69] and reported a significantly lower rate of renal failure (defined as abnormal kidney function requiring renal replacement therapy in patients who did not require this procedure prior to implant) in advanced heart failure patients receiving continuous flow LVADs in comparison to those who had received pulsatile flow LVADs ($p < 0.001$). Notably, this study demonstrated no significant difference with respect to adverse hemorrhagic events (hemorrhagic stroke, bleeding requiring packed red blood cells, bleeding requiring surgery). Lastly, Jacobs et al. reported an improvement of renal function 3 months after full (continuous flow LVAD) or partial (Synergy micropump) mechanical support devices implantation [70]. A significant renal improvement was observed in the group of patients with pre-operative impaired renal function (defined as an estimated GFR <60 mL/min/1.73 m^2). This study underscores the beneficial effects of the Synergy micropump, a miniaturized LVAD used mostly as partial support in patients with renal dysfunction, 3 months after implantation. In conclusion the results of the above-mentioned studies are inconsistent. However, the evidence derived from the randomized HeartMate II versus HeartMate XVE trial indicates an advantage with continuous flow versus pulsatile flow LVADs with respect to adverse renal events.

Percutaneous Mechanical Circulatory Support and Renal Function

The emerging role of percutaneous MCS devices and their effects on renal function is also of great interest [71]. Among them, the most widely used are the intra-aortic balloon pump (IABP), TandemHeart system, Cardiobridge support device, extracorporeal membrane oxygenation (ECMO) and Impella [71]. The intra-aortic balloon pump is typically inserted through the femoral artery and is positioned in the descending aorta proximal to the renal arteries and distal to the left subclavian artery. By inflating at diastole and deflating before systole, the IABP increases cardiac output. Moreover, it increases renal blood flow as demonstrated by Doppler ultrasound tracings in high-risk patients with low left ventricular ejection fraction (<25%) [72]. Impella is a continuous-flow blood pump, positioned in the left ventricle across the aortic valve, which unloads the left ventricle by ejecting blood to the ascending aorta. Despite the theoretical advantages of Impella placement regarding cardiac output augmentation and renal perfusion increase, the effects of Impella use on renal function in relatively small case series are inconclusive [73, 74]. The TandemHeart system is a continuous flow extracorporeal system that produces a left atrial to femoral arterial bypass by circulating the oxygenated blood coming from the left atrium – via a transseptal cannula positioned in the femoral vein – to the femoral artery or abdominal aorta [71]. In this way, the system increases the cardiac index, blood pressure and urine output. Interestingly, small studies that examined the effects of the TandemHeart system as temporary circulatory support pump showed positive results on renal function [75] The system has been used in high-risk percutaneous coronary intervention patients, in patients with cardiogenic shock, and in those with severe heart failure due to myocarditis. It is contraindicated in

patients with advanced right ventricular failure, aortic insufficiency, ventricular septal defect, and peripheral vascular disease [76]. Lastly, the Cardiobridge support device is a continuous pump, percutaneously inserted in the descending aorta, which produces a pressure gradient, decreases afterload and therefore increases organ perfusion [71]. A study in small series of patients has demonstrated the beneficial effects on renal function (increased estimated GFR and decreased serum creatinine) of the Cardiobridge support device use in patients undergoing a high-risk percutaneous coronary intervention [77].

ECMO is a temporary percutaneous MCS system indicated for patients with cardiorespiratory failure. The outcomes with ECMO use seem to be favorable with respect to mortality, although definitive evidence is still lacking [78–81]. A number of pathophysiological mechanisms linking ECMO use and AKI have been proposed, including progression of pre-existing multisystemic disease, systemic inflammatory response, alterations in renal macro/microvasculature, nephrotoxic agents (i.e. antibiotics), hemolysis and oxidative stress, altered renal autoregulation and ischaemia-reperfusion injury [78, 82]. The role of percutaneous MCS on renal function is promising. However, additional randomized studies are needed.

Treatment Pearls for the Case Vignette

Based on the above-mentioned literature, the decision to implant an LVAD in a patient with cardiogenic shock and impaired renal function like in the case vignette, is reasonable [31]. In general, the short-term outcomes of LVAD implantation in advanced heart failure patients with renal dysfunction are beneficial [38]. Hence, not surprisingly the serum creatinine declined from 2.63 to 1.43 mg/dL, just 6 days after successful implantation of the LVAD. Furthermore, all current LVADs are continuous-flow devices, which in theory is important as the percentage of renal failure events has been demonstrated to be significantly lower in continuous versus pulsatile flow devices [69]. The implantation of the third-generation centrifugal continuous flow LVAD (HeartMate III), based on the Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3 (MOMENTUM 3) findings is associated with lower reoperation for pump malfunction, driven mainly by the lower rates of suspected or confirmed pump thrombosis, when compared to the axial continuous flow LVADs (HeartMate II) [11, 12]. Pump thrombosis is associated with haemolysis and haemoglobinuria is a potential nephrotoxin. Indeed, AKI is frequent in case of LVAD malfunction. Renal outcomes as reported with the HeartMate III appear comparable to the HeartMate II, but it should be noted that the inclusion and exclusion criteria based on renal function were stringent. Future avoidance of morbidity related to AKI and cardiorenal physiology will require solid evidence demonstrating the advantages of short-term percutaneous support devices that may optimize renal function prior to implantation of a durable LVAD, which requires cardiopulmonary bypass. The potential for resolution of right heart failure and normalization of the CVP after LVAD is another important factor to consider when determining the timing for LVAD surgery and the patient's risk.

References

1. Triposkiadis F, Starling RC, Boudoulas H, Giamouzis G, Butler J. The cardiorenal syndrome in heart failure: cardiac? Renal? Syndrome? Heart Fail Rev. 2012;17(3):355–66.
2. Boudoulas KD, Triposkiadis F, Parissis J, Butler J, Boudoulas H. The cardio-renal interrelationship. Prog Cardiovasc Dis. 2017;59(6):636–48.
3. Stewart GC, Givertz MM. Mechanical circulatory support for advanced heart failure: patients and technology in evolution. Circulation. 2012;125(10):1304–15.
4. Gustafsson F, Rogers JG. Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes. Eur J Heart Fail. 2017;19(5):595–602.
5. Pinney SP, Anyanwu AC, Lala A, Teuteberg JJ, Uriel N, Mehra MR. Left ventricular assist devices for lifelong support. J Am Coll Cardiol. 2017;69(23):2845–61.
6. Miller LW, Guglin M. Patient selection for ventricular assist devices: a moving target. J Am Coll Cardiol. 2013;61(12):1209–21.
7. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435–43.
8. Park SJ, Milano CA, Tatooles AJ, Rogers JG, Adamson RM, Steidley DE, et al. Outcomes in advanced heart failure patients with left ventricular assist devices for destination therapy. Circ Heart Fail. 2012;5(2):241–8.
9. Starling RC, Naka Y, Boyle AJ, Gonzalez-Stawinski G, John R, Jorde U, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol. 2011;57(19):1890–8.
10. Starling RC, Moazami N, Silvestry SC, Ewald G, Rogers JG, Milano CA, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. N Engl J Med. 2014;370(1):33–40.
11. Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC Jr, Colombo PC, et al. A fully magnetically levitated circulatory pump for advanced heart failure. N Engl J Med. 2017;376(5):440–50.
12. Mehra MR, Goldstein DJ, Uriel N, Cleveland JC Jr, Yuzefpolskaya M, Salerno C, et al. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. New Eng J Med. 2018;379:896–7.
13. Mullens W, Verbrugge FH, Nijst P, Tang WHW. Renal sodium avidity in heart failure: from pathophysiology to treatment strategies. Eur Heart J. 2017;38(24):1872–82.
14. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation. 2004;109(8):1004–9.
15. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35(7):455–69.
16. Giamouzis G, Butler J, Triposkiadis F. Renal function in advanced heart failure. Congest Heart Fail. 2011;17(4):180–8.
17. Damman K, Navis G, Smilde TD, Voors AA, van der Bij W, van Veldhuisen DJ, et al. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. Eur J Heart Fail. 2007;9(9):872–8.
18. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(7):589–96.
19. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J. 2015;36(23):1437–44.
20. Cottone S, Lorito MC, Riccobene R, Nardi E, Mule G, Buscemi S, et al. Oxidative stress, inflammation and cardiovascular disease in chronic renal failure. J Nephrol. 2008;21(2):175–9.
21. MacFadyen RJ, Ng Kam Chuen MJ, Davis RC. Loop diuretic therapy in left ventricular systolic dysfunction: has familiarity bred contempt for a critical but potentially nephrotoxic cardio renal therapy? Eur J Heart Fail. 2010;12(7):649–52.

22. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham heart study of the national heart, lung, and blood institute. Circulation. 2009;119(24):3070–7.
23. Parikh NI, Hwang SJ, Larson MG, Meigs JB, Levy D, Fox CS. Cardiovascular disease risk factors in chronic kidney disease: overall burden and rates of treatment and control. Arch Intern Med. 2006;166(17):1884–91.
24. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. Drugs. 1990;39 Suppl 4:10–21; discussion 2–4.
25. Carubelli V, Lombardi C, Gorga E, Ravera A, Metra M, Mentz RJ. Cardiorenal interactions. Heart Fail Clin. 2016;12(3):335–47.
26. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, et al. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail. 2007;13(8):599–608.
27. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol. 2006;47(10):1987–96.
28. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, et al. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail. 2008;10(2):188–95.
29. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797–805.
30. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail. 2012;5(1):54–62.
31. Khot UN, Mishra M, Yamani MH, Smedira NG, Paganini E, Yeager M, et al. Severe renal dysfunction complicating cardiogenic shock is not a contraindication to mechanical support as a bridge to cardiac transplantation. J Am Coll Cardiol. 2003;41(3):381–5.
32. Yoshioka D, Sakaguchi T, Saito S, Miyagawa S, Nishi H, Yoshikawa Y, et al. Predictor of early mortality for severe heart failure patients with left ventricular assist device implantation: significance of INTERMACS level and renal function. Circ J. 2012;76(7):1631–8.
33. Sandner SE, Zimpfer D, Zrunek P, Rajek A, Schima H, Dunkler D, et al. Renal function and outcome after continuous flow left ventricular assist device implantation. Ann Thorac Surg. 2009;87(4):1072–8.
34. Butler J, Geisberg C, Howser R, Portner PM, Rogers JG, Deng MC, et al. Relationship between renal function and left ventricular assist device use. Ann Thorac Surg. 2006;81(5):1745–51.
35. Kirklin JK, Naftel DC, Kormos RL, Pagani FD, Myers SL, Stevenson LW, et al. Quantifying the effect of cardiorenal syndrome on mortality after left ventricular assist device implant. J Heart Lung Transplant. 2013;32(12):1205–13.
36. Singh M, Shullo M, Kormos RL, Lockard K, Zomak R, Simon MA, et al. Impact of renal function before mechanical circulatory support on posttransplant renal outcomes. Ann Thorac Surg. 2011;91(5):1348–54.
37. Roehm B, Vest AR, Weiner DE. Left ventricular assist devices, kidney disease, and dialysis. Am J Kidney Dis. 2018;71(2):257–66.
38. Mao H, Katz N, Kim JC, Day S, Ronco C. Implantable left ventricular assist devices and the kidney. Blood Purif. 2014;37(1):57–66.
39. Tromp TR, de Jonge N, Joles JA. Left ventricular assist devices: a kidney's perspective. Heart Fail Rev. 2015;20(4):519–32.
40. Hasin T, Topilsky Y, Schirger JA, Li Z, Zhao Y, Boilson BA, et al. Changes in renal function after implantation of continuous-flow left ventricular assist devices. J Am Coll Cardiol. 2012;59(1):26–36.
41. Lampert BC, Teuteberg JJ. Right ventricular failure after left ventricular assist devices. J Heart Lung Transplant. 2015;34(9):1123–30.

42. Gupta S, Woldendorp K, Muthiah K, Robson D, Prichard R, Macdonald PS, et al. Normalisation of haemodynamics in patients with end-stage heart failure with continuous-flow left ventricular assist device therapy. Heart Lung Circ. 2014;23(10):963–9.
43. Brisco MA, Kimmel SE, Coca SG, Putt ME, Jessup M, Tang WW, et al. Prevalence and prognostic importance of changes in renal function after mechanical circulatory support. Circ Heart Fail. 2014;7(1):68–75.
44. Russell SD, Rogers JG, Milano CA, Dyke DB, Pagani FD, Aranda JM, et al. Renal and hepatic function improve in advanced heart failure patients during continuous-flow support with the HeartMate II left ventricular assist device. Circulation. 2009;120(23):2352–7.
45. Deo SV, Sharma V, Altarabsheh SE, Hasin T, Dillon J, Shah IK, et al. Hepatic and renal function with successful long-term support on a continuous flow left ventricular assist device. Heart Lung Circ. 2014;23(3):229–33.
46. Yoshioka D, Takayama H, Colombo PC, Yuzefpolskaya M, Garan AR, Topkara VK, et al. Changes in end-organ function in patients with prolonged continuous-flow left ventricular assist device support. Ann Thorac Surg. 2017;103(3):717–24.
47. Raichlin E, Baibhav B, Lowes BD, Zolty R, Lyden ER, Vongooru HR, et al. Outcomes in patients with severe preexisting renal dysfunction after continuous-flow left ventricular assist device implantation. ASAIO J. 2016;62(3):261–7.
48. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev. 2016;37(2):85–98.
49. Agostoni PG, Marenzi GC, Pepi M, Doria E, Salvioni A, Perego G, et al. Isolated ultrafiltration in moderate congestive heart failure. J Am Coll Cardiol. 1993;21(2):424–31.
50. Shirakabe A, Hata N, Kobayashi N, Okazaki H, Matsushita M, Shibata Y, et al. Worsening renal function definition is insufficient for evaluating acute renal failure in acute heart failure. ESC Heart Fail. 2018;5(3):322–31.
51. Coffin ST, Waguespack DR, Haglund NA, Maltais S, Dwyer JP, Keebler ME. Kidney dysfunction and left ventricular assist device support: a comprehensive perioperative review. Cardiorenal Med. 2015;5(1):48–60.
52. Ross DW, Stevens GR, Wanchoo R, Majure DT, Jauhar S, Fernandez HA, et al. Left ventricular assist devices and the kidney. Clin J Am Soc Nephrol. 2018;13(2):348–55.
53. Sen A, Larson JS, Kashani KB, Libricz SL, Patel BM, Guru PK, et al. Mechanical circulatory assist devices: a primer for critical care and emergency physicians. Crit Care. 2016; 20(1):153.
54. Hanberg JS, Sury K, Wilson FP, Brisco MA, Ahmad T, Ter Maaten JM, et al. Reduced cardiac index is not the dominant driver of renal dysfunction in heart failure. J Am Coll Cardiol. 2016;67(19):2199–208.
55. Patel AM, Adeseun GA, Ahmed I, Mitter N, Rame JE, Rudnick MR. Renal failure in patients with left ventricular assist devices. Clin J Am Soc Nephrol. 2013;8(3):484–96.
56. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204–12.
57. Alba AC, Rao V, Ivanov J, Ross HJ, Delgado DH. Predictors of acute renal dysfunction after ventricular assist device placement. J Card Fail. 2009;15(10):874–81.
58. Kaltenmaier B, Pommer W, Kaufmann F, Hennig E, Molzahn M, Hetzer R. Outcome of patients with ventricular assist devices and acute renal failure requiring renal replacement therapy. ASAIO J. 2000;46(3):330–3.
59. Topkara VK, Dang NC, Barili F, Cheema FH, Martens TP, George I, et al. Predictors and outcomes of continuous veno-venous hemodialysis use after implantation of a left ventricular assist device. J Heart Lung Transplant. 2006;25(4):404–8.
60. Genovese EA, Dew MA, Teuteberg JJ, Simon MA, Bhama JK, Bermudez CA, et al. Early adverse events as predictors of 1-year mortality during mechanical circulatory support. J Heart Lung Transplant. 2010;29(9):981–8.

61. Demirozu ZT, Etheridge WB, Radovancevic R, Frazier OH. Results of HeartMate II left ventricular assist device implantation on renal function in patients requiring post-implant renal replacement therapy. J Heart Lung Transplant. 2011;30(2):182–7.
62. Welp H, Rukosujew A, Tjan TD, Hoffmeier A, Kosek V, Scheld HH, et al. Effect of pulsatile and non-pulsatile left ventricular assist devices on the renin-angiotensin system in patients with end-stage heart failure. Thorac Cardiovasc Surg. 2010;58(Suppl 2):S185–8.
63. Kihara S, Litwak KN, Nichols L, Litwak P, Kameneva MV, Wu Z, et al. Smooth muscle cell hypertrophy of renal cortex arteries with chronic continuous flow left ventricular assist. Ann Thorac Surg. 2003;75(1):178–83; discussion 83.
64. Ootaki C, Yamashita M, Ootaki Y, Kamohara K, Weber S, Klatte RS, et al. Reduced pulsatility induces periarteritis in kidney: role of the local renin-angiotensin system. J Thorac Cardiovasc Surg. 2008;136(1):150–8.
65. Tank J, Heusser K, Malehsa D, Hegemann K, Haufe S, Brinkmann J, et al. Patients with continuous-flow left ventricular assist devices provide insight in human baroreflex physiology. Hypertension. 2012;60(3):849–55.
66. Sandner SE, Zimpfer D, Zrunek P, Dunkler D, Schima H, Rajek A, et al. Renal function after implantation of continuous versus pulsatile flow left ventricular assist devices. J Heart Lung Transplant. 2008;27(5):469–73.
67. Nadziakiewicz P, Szygula-Jurkiewicz B, Niklewski T, Pacholewicz J, Zakliczynski M, Borkowski J, et al. Effects of left ventricular assist device support on end-organ function in patients with heart failure: comparison of pulsatile- and continuous-flow support in a single-center experience. Transplant Proc. 2016;48(5):1775–80.
68. Kamdar F, Boyle A, Liao K, Colvin-adams M, Joyce L, John R. Effects of centrifugal, axial, and pulsatile left ventricular assist device support on end-organ function in heart failure patients. J Heart Lung Transplant. 2009;28(4):352–9.
69. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361(23):2241–51.
70. Jacobs S, Droogne W, Waelbers V, Bossche KV, Bollen H, Geens J, et al. Evolution of renal function after partial and full mechanical support for chronic heart failure. Int J Artif Organs. 2014;37(5):364–70.
71. Mao H, Giuliani A, Blanca-Martos L, Kim JC, Nayak A, Virzi G, et al. Effect of percutaneous ventricular assist devices on renal function. Blood Purif. 2013;35(1–3):119–26.
72. Sloth E, Sprogoe P, Lindskov C, Horlyck A, Solvig J, Jakobsen C. Intra-aortic balloon pumping increases renal blood flow in patients with low left ventricular ejection fraction. Perfusion. 2008;23(4):223–6.
73. Vecchio S, Chechi T, Giuliani G, Lilli A, Consoli L, Spaziani G, et al. Use of Impella Recover 2.5 left ventricular assist device in patients with cardiogenic shock or undergoing high-risk percutaneous coronary intervention procedures: experience of a high-volume center. Minerva Cardioangiol. 2008;56(4):391–9.
74. La Torre MW, Centofanti P, Attisani M, Patane F, Rinaldi M. Posterior ventricular septal defect in presence of cardiogenic shock: early implantation of the impella recover LP 5.0 as a bridge to surgery. Tex Heart Inst J. 2011;38(1):42–9.
75. Gregoric ID, Loyalka P, Radovancevic R, Jovic Z, Frazier OH, Kar B. TandemHeart as a rescue therapy for patients with critical aortic valve stenosis. Ann Thorac Surg. 2009;88(6):1822–6.
76. Aragon J, Lee MS, Kar S, Makkar RR. Percutaneous left ventricular assist device: "TandemHeart" for high-risk coronary intervention. Catheter Cardiovasc Interv. 2005;65(3):346–52.
77. Smith EJ, Reitan O, Keeble T, Dixon K, Rothman MT. A first-in-man study of the Reitan catheter pump for circulatory support in patients undergoing high-risk percutaneous coronary intervention. Catheter Cardiovasc Interv. 2009;73(7):859–65.
78. Kilburn DJ, Shekar K, Fraser JF. The complex relationship of extracorporeal membrane oxygenation and acute kidney injury: causation or association? Biomed Res Int. 2016;2016:1094296.

79. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351–63.
80. Doll N, Kiaii B, Borger M, Bucerius J, Kramer K, Schmitt DV, et al. Five-year results of 219 consecutive patients treated with extracorporeal membrane oxygenation for refractory postoperative cardiogenic shock. Ann Thorac Surg. 2004;77(1):151–7; discussion 7.
81. Smedira NG, Moazami N, Golding CM, McCarthy PM, Apperson-Hansen C, Blackstone EH, et al. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: survival at five years. J Thorac Cardiovasc Surg. 2001;122(1):92–102.
82. Chung AC, Lan HY. Chemokines in renal injury. J Am Soc Nephrol. 2011;22(5):802–9.

Patient with Severe Right Heart Failure and Preserved Left Ventricular Ejection Function

17

Anaïs Caillard, Benjamin G. Chousterman, and Alexandre Mebazaa

Case Vignette

Mrs. X is a 62 year old woman who was diagnosed with heart failure with preserved ejection fraction several years ago. The diagnosis of pulmonary venous hypertension was confirmed on right heart catheterization. Now, Mrs. X presents at the emergency department because of dyspnea with minimal exercise. She has gained 10 kg in body weight and demonstrates impressive bilateral edema in both legs. Transthoracic echocardiography shows markedly impaired right heart function with severe tricuspid valve regurgitation (4/4). Serum creatinine levels have increased from 1.52 mg/dL 6 months ago to 2.56 mg/dL at the current presentation.

Chapter Key Points

- Incidence of renal dysfunction in patients with primary right-sided heart failure
- Pathophysiology of kidney dysfunction in right-sided heart failure
- Management of patients with primary right-sided heart failure and kidney dysfunction
- Preventing renal dysfunction in primary right-sided heart failure

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Brief Discussion of the Case

This a typical case of worsening of renal function during an episode of decompensated right-sided heart failure (HF) in a patient with a long history of HF with preserved ejection fraction (HFpEF). In the case vignette, Mrs. X is a 62 year old women suffering HFpEF diagnosed with pulmonary venous hypertension several years ago. She is at risk of chronic kidney disease due to both nephron-angiosclerosis and venous congestion. She now presents with global edema and signs of decompensated HF. Global overload may have led to increased tricuspid regurgitation (TR) which in turn aggravates right ventricular (RV) function with elevated right atrial pressure. This venous hypertension aggravated a chronic kidney disease via an episode of acute kidney injury (elevation of serum creatinine with over 50%). This is a severe condition that needs to be aggressively taken care of to prevent dramatic aggravation of renal function.

Incidence of Renal Dysfunction in Patients with Primary Right-Sided Heart Failure

The definitions and subsequent types of HF have been addressed recently by consensus. The definition of "worsening renal function" in heart failure is however not consensual. Therefore, it is difficult to draw clear estimations of the incidence of renal dysfunction after chronic or acute right-sided HF due to the heterogeneity of clinical definitions used. HFpEF is defined as HF with left ventricular (LV) diastolic dysfunction that may be associated with contractile dysfunction despite the preservation of global ejection fraction (EF). It is estimated that 4–48% of the HFpEF patients present with RV dysfunction [1, 2]. The prevalence of RV dysfunction in HFpEF varies widely depending on the study design, definition used, and population characteristics (Fig. 17.1).

It is important to distinguish RV dysfunction from right heart failure. Right heart failure involves hemodynamic decompensation. Right heart failure presents with various associated clinical signs such as hypoxemia, signs of systemic congestion (jugular venous distension, hepatojugular reflux, peripheral edema, pericardial effusion, congestive hepatosplenomegaly, ascites or anasarca) and more specific signs of RV dysfunction such as those associated with tricuspid regurgitation (third heart sound, systemic murmur of tricuspid regurgitation, hepatic pulse, etc.) [3]. Signs of low cardiac output state (hypotension, tachycardia, cool extremities or oliguria) could be present. No specific biomarker of right heart failure has been described yet. Nevertheless, non-specific biochemical markers such as lactate, natriuretic peptides [brain natriuretic peptide (BNP) or N-terminal of the prohormone of BNP (NT-proBNP)], cardiac troponin I or T, but also liver biochemistry or markers of renal function (especially creatinine) [3] could guide the diagnosis and help to evaluate prognosis [4] in primary right heart failure such as for instance in the case of pulmonary arterial hypertension [5].

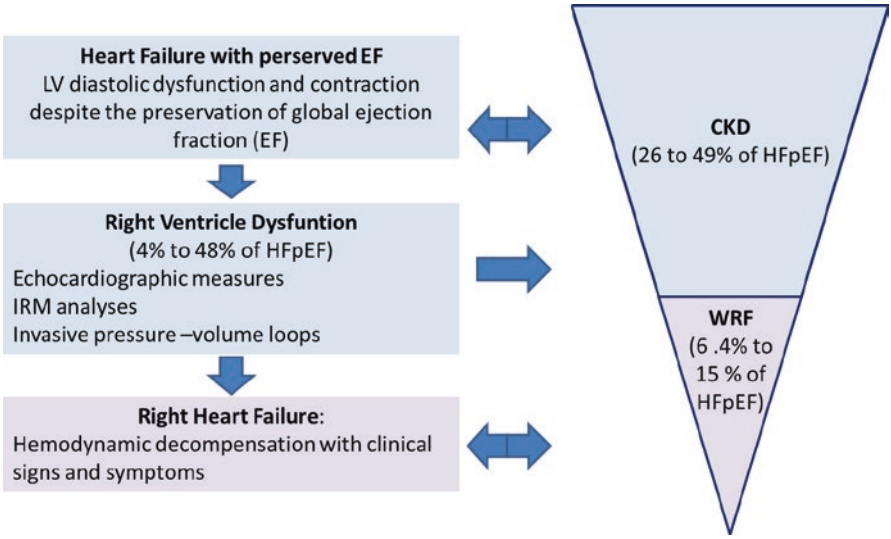

Fig. 17.1 Definition and incidence of renal and right ventricular complications in heart failure with preserved ejection fraction (HFpEF). Blue: chronic features; purple: acute features. CKD, chronic kidney disease defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2; CMR, cardiac magnetic resonance imaging; LV, left ventricular; WRF, worsening of renal function defined as an increase in serum creatinine or decrease in diuresis

A comprehensive definition of right ventricular dysfunction remains elusive. Right ventricular dysfunction is used to characterize RV alteration mainly by imaging. It is based on the monitoring of RV function and is therefore not based on a clinical syndrome. Diagnosis of RV dysfunction could involve echocardiographic or cardiac magnetic resonance imaging analyses with various cut-off values [6]. Finally, a gold standard method to quantify RV dysfunction considers the RV–pulmonary artery coupling and involves invasive pressure measurements and acquisition of volume loops ideally associated with the hemodynamic tracings. Heterogenic cohorts and multiplication of diagnosis methods including echocardiographic criteria such as reduced RV fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular systolic velocity (RV S′) or cardiac magnetic resonance imaging analyses contribute to the complexity of the estimation of RV dysfunction prevalence [7]. A recent meta-analysis found a RV dysfunction prevalence of 18%, 21% or 28% using RV FAC, RV S′ and TAPSE, respectively. TAPSE or RV FAC values are associated with mortality [6].

In parallel, renal dysfunction encompasses several definitions, most of them coming from criteria used for the diagnosis and classification of chronic kidney dysfunction (CKD), worsening of renal function (WRF) or acute kidney injury (AKI). The definition of CKD involves an isolated measurement of the serum creatinine level or/and an estimated glomerular filtration rate (eGFR). Cohorts analyzing CKD by eGFR analysis below 60 mL/min/1.73 m^2 in HFpEF found an incidence of

Table 17.1 Kidney Disease Improving Global Outcomes (KDIGO) score [11]

Stage 1	Serum creatinine: 1.5–1.9 fold increase from baseline within 1–7 days or ≥26.5 μmol/L increase within 48 h Urine output: <0.5 mL•kg−1/h for 6–12 h
Stage 2	Serum creatinine: 2.0–2.9 fold increase from baseline Urine output: <0.5 mL•kg−1/h for ≥12 h
Stage 3	Serum creatinine: ≥3.0 fold increase from baseline or increase >354 μmol/L or initiation of renal replacement therapy Urine output: <0.3 mL•kg−1/h for ≥24 h or anuria ≥12 h

between 26% and 49% [8] which is similar to the rate observed in case of heart failure with reduced ejection fraction (HFrEF) [9]. CKD is also associated with all-cause mortality in patients with HF [OR (95%CI) = 2.34 (2.20–2.50), P < 0.001] [10]. WRF or AKI definitions are based on the increase in serum creatinine or decreased diuresis. Various renal dysfunction score exist including the Acute Kidney Injury (AKIN) classification, the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification or the Kidney Disease Improving Global Outcomes (KDIGO) scores (Table 17.1) and share the same pitfall: the evaluation of the basal creatinine value. WRF and AKI are dynamic and adaptive entities that rely on relative increase of creatinine (or absolute decrease of urine output). Using the abovementioned scores, the incidence of RV dysfunction varies between 6.4% and 15% in HFpEF [10, 12]. As seen for CKD criteria, there is a relationship between RV dysfunction and outcome when using WRF or AKI criteria [10, 13]. Even mild WRF (increase of serum creatinine levels >0.3 mg/dL) is associated with a sensitivity of 81% and specificity of 62% for death [13]. The usefulness of other markers of renal dysfunction such as blood urea nitrogen (BUN) [14], Cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), proenkephaline, liver-type fatty acid-binding protein (L-type FABP), or kidney injury molecule 1 (KIM-1) [15] needs to be further investigated [16].

Pathophysiology of Kidney Dysfunction in Right-Sided Heart Failure

The pathophysiology of kidney dysfunction in right-sided HF remains incompletely understood. It is necessary to differentiate two mechanisms involved in kidney dysfunction: one chronic mechanism, secondary to HFpEF (and associated with the underlying cause of HFpEF (diabetes, hypertension, etc.) versus another acute mechanism related to decreased blood flow (reduced cardiac output) and vascular congestion (elevated central venous pressure) (Fig. 17.2).

Renal Dysfunction Secondary to HFpEF

Compared to HFrEF secondary to direct cardiomyocyte injury (ischemic, infectious or toxic mechanisms for example) with an alteration of calcium

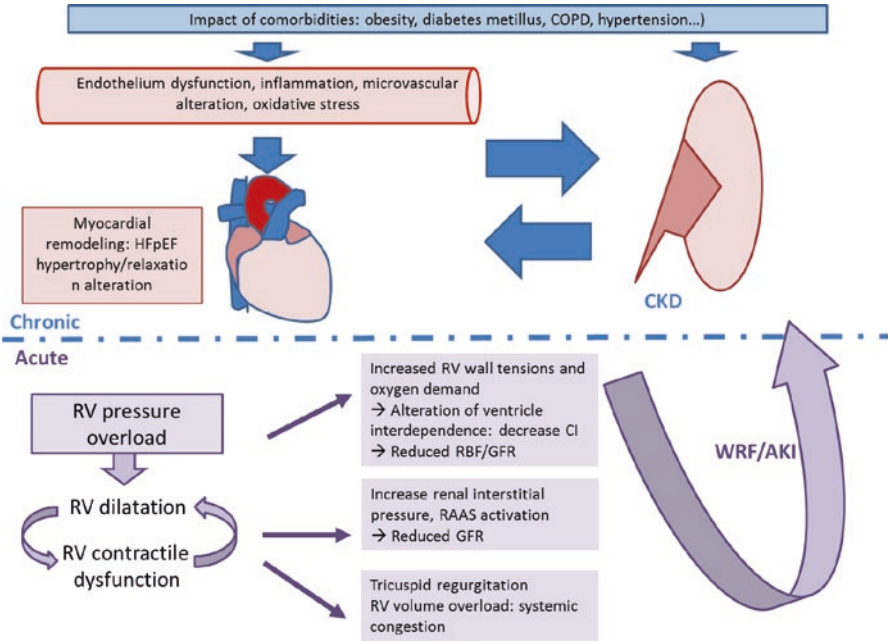

Fig. 17.2 Chronic and acute physiologic mechanisms leading to renal dysfunction in heart failure with preserved ejection fraction (HFpEF). Blue: chronic features; purple: acute features. AKI, acute kidney injury; CI, cardiac index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; RBF, renal blood flow; RAAS, renin-angiotensin-aldosterone system; RV, right ventricular; WRF, worsening renal function

homeostasis and myocardial contraction, HFpEF is secondary to a set of conditions that cause systemic alterations, inflammation and endothelial dysfunction that eventually lead to pathological remodeling of the myocardium [8]. In this context, three pathways could be proposed to link chronic cardiac dysfunction and chronic renal dysfunction: (1) cardiac dysfunction leading to renal dysfunction (cardiorenal syndrome type 2), (2) renal dysfunction leading to cardiac dysfunction (cardiorenal syndrome type 4) and (3) common systemic mechanisms secondary to patients' comorbidities leading to renal and cardiac changes (cardiorenal syndrome type 5).

HF induces CKD. Indeed, in 2013, Paulus et al. proposed a pathophysiological model to describe the relationship between HFpEF and CKD through systemic mechanisms such as inflammation, endothelial dysfunction, oxidative stress and microvascular disorders. Systemic disorders are mainly due to patient's comorbidities [hypertension, diabetes, obesity, chronic obstructive pulmonary disease (COPD), etc.] by altering the protein kinase G pathway involved in cardiac remodeling (hypertrophy and relaxation mechanisms) [17]. The kidney proteome analyzed in an established model of HF in rats, shows an increase in various family proteins such as proteins involved in endothelial function [Von Willebrand factor (vWF), caveolin 1–3, T-kininogen 2], proinflammatory extracellular matrix

activation [Microfibril-associated protein-4 (MFAP-4), collagen-VI, galectin-3, Four and a half LIM domains protein-1 (FHL-1), calponin] or glomerular filtration membrane integrity [Chloride Intracellular Channel-5 (CLIC-5), Zonula Occludens-1 (ZO-1)] [18]. Inversely, CKD is also associated with endothelial, microvascular and inflammatory dysfunctions. Nevertheless, specific mechanisms of CKD appear to be involved such as microalbuminuria, vitamin D deficiency or lack of erythropoietin. Those are all inducers of endothelial dysfunction, oxidative stress or inflammation [8]. Moreover, activation of the sympathetic nervous system in CKD has also been implicated in the development of cardiac failure [8]. In chronic state, distinction between causes and consequences of CKD in patients with HFpEF is not easy. In the context of combined renal and cardiac failure (cardiorenal syndrome type 5), Galectin-3 is a marker of interest that is currently emerging. Initially identified as a marker of cardiac fibrosis, it has been shown in animal models to be involved in the development of renal fibrosis [19] and to promote hypertensive nephropathy. Hypertensive nephropathy develops to a lesser extent after pharmacological inhibition of Galectin-3 [20]. More studies are necessary to confirm these observations.

Acute Kidney Injury Principally Related to Vascular Congestion

In acutely decompensated HFpEF, renal failure is related to decreased cardiac output, but also to venous congestion [21]. Damman et al. analyzed the relationship between venous congestion measured by right heart catheterization and renal dysfunction in a cohort of 51 patients with HF secondary to pulmonary hypertension. They compared the evolution of right atrial pressure (RAP), cardiac index (CI) and GFR as well as renal blood flow (RBF), measured by 125I-Iothalamate and 131IHippuran clearances. In multivariate analysis, RBF and RAP were independently associated with GFR suggesting that if RBF was the main factor determining GFR, venous congestion itself, characterized by increased RAP was also an independent determinant of GFR [22]. Other studies in larger cohorts of various types of HF have shown similar results with increased CVP consistently associated with impaired renal function and independently related to all-cause mortality [23, 24]. Association between an increased in BNP levels and renal dysfunction was observed in a large cohort of patients with chronic HF. The vascular congestion mechanism with elevated CVP has been shown to induce WRF both in HFrEF and HFpEF. The relationship between GFR and venous congestion is not simple. To understand this complex relationship, it must be remembered that the kidney is an encapsulated organ. Increase of central venous pressure will lead to increase of venous volume then interstitial edema that in turn increases hydrostatic pressure in Bowman's capsule and decreases GFR [23]. Elevated central venous pressure potentially causes a reduction of RBF and activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system that cause kidney damage and subsequently decreased GFR [16]. Knowing

this cascade of events enables to introduce specific treatment such as active depletion but also inhibitors of RAAS, or sympathetic nervous system inhibitors such as beta blockers.

Management of Patients with Primary Right-Sided Heart Failure (with Severe Tricuspid Regurgitation) and Kidney Dysfunction

Determining the Volume and Cardiac Function Status

Different hemodynamic profiles are associated with WRF during decompensated HF: congestion and/or decreased RBF. One of the hurdles for choosing the adequate treatment is the evaluation of intravascular volume in these patients with right heart failure preload-dependency but also with important risk of fluid overload. Fluid overload causes cardiac contraction failure, worsening of tricuspid regurgitation, an increase in ventricular interdependency, a LV dysfunction, and finally an impairment of cardiac output. It seems appropriate to advise monitoring to guide fluid loading or depletion tests [3]. Hemodynamic monitoring such as measurement of CVP and/or cardiac output could be recommended in order to evaluate tolerance and efficiency of therapy. Decongestion strategies based on monitoring of total blood volume and plasma volume measurements at admission by using iodine-131-albumin dilution technique are associated with lower 30-day rates of readmission and 30-day and 365-day mortality but longer lengths of stay than control subjects [25]. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) [26] study compared a pulmonary artery catheter (PAC)-guide therapy to usual care to determine if PAC monitoring is safe and improves clinical outcomes. PAC use did not significantly affect prognosis during the first 6 months without increase in mortality related to PAC use. Monitoring and optimization of the intravascular volume status seems interesting but should not be done at the expense of patient safety. Less invasive methods such as CVP measurements, measurements of natriuretic peptides and troponins, as well as echocardiography seem interesting in the first steps of treatment.

Active Decongestion

As previously described, congestion causes both aggravation of HF and renal function. Intravenous diuretics are the first-line therapy to treat volume overload in patients with signs of venous congestion. Intravenous loop diuretics (through intermittent bolus or continuous infusion) are recommended for all patients admitted with signs or symptoms of fluid overload to improve symptoms [3]. The Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure (REALITY-AHF), a prospective, multicenter, observational cohort study, has

suggested an association between early treatment with intravenous loop diuretics and lower in-hospital mortality in patients with acute HF [27]. A post-hoc analysis of the 4953 patients of the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) cohort found no association between diuretic dosing and short-term mortality [28]. Nevertheless, loop diuretics may be associated with increased morbidity [29] and may lead to deterioration of renal function [30]. Chronic infusion of loop diuretics into animals induces increased activity of the thiazide-sensitive Na^+/Cl^--cotransporter (NCC), demonstrated to be an aldosterone-induced protein [30]. Extraction of excess fluid through ultrafiltration has been proposed as an alternative method. Some studies tried to compare the safety and efficacy of ultrafiltration and conventional intravenous diuretic therapy for patients with acute HF and volume overload [31]. A meta-analysis has shown that the weight loss and fluid loss at 48 h was greater in patients who received ultrafiltration compared to diuretics, but the occurrence of WRF (defined as increase in serum creatinine >0.3 mg/dL at 48 h), was similar in the two groups. Actually, no clear recommendation exists regarding the use of ultrafiltration [31]. Moreover, other drugs are currently under investigation to design the optimal diuretic agent or combination of drugs to improve decongestion in acute HF with volume overload. For example, tolvaptan, an oral vasopressin-2 receptor antagonist, added to conventional therapy with loop diuretics achieved more diuresis and relieved dyspnea symptoms in acute HF patients with renal dysfunction [32]. Nevertheless no effect on long-term mortality or HF-related morbidity was observed [33]. Moreover, the Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) trial investigates the carbonic anhydrase inhibitor acetazolamide combined with loop diuretic therapy in acute HF with volume overload [34].

Optimization of Arterial Pressure and Cardiac Output

WRF may be secondary to reduced cardiac output and low arterial pressure. Norepinephrine is primarily indicated to restore hemodynamic stability in RV failure [3]. Restoring blood pressure and cardiac blood flow is necessary to improve cerebral, coronary, kidney and other organ perfusion. In ventilated dog models, norepinephrine infusion decreases biventricular filling pressures and increases stroke volume without major increase of the pulmonary vascular resistance [35].

Monitoring cardiac output could justify the introduction of inotropes if low. Dobutamine improves cardiac contractility and output but may reduces blood pressure through its vasodilatory effect. Association of norepinephrine could therefore be necessary. Levosimendan was shown to have an inotropic effect without worsening of myocardial diastolic dysfunction, nor increase of myocardial oxygen consumption. Levosimendan has vasodilator effects in different organs such as the myocardium, lungs, liver and renal medulla and has anti-inflammatory and anti-apoptotic effects [36]. Compared to dobutamine in a specific group of patients with biventricular failure, levosimendan was shown to offer more beneficial effects on TAPSE, 24-h urine output and serum creatinine levels [37]. Levosimendan may also decrease pulmonary arterial

pressure in acute conditions [38]. Lastly, phosphodiesterase III inhibitors have positive inotropic effects on the RV without increase of the pulmonary vascular resistance.

Mechanic circulatory support like extracorporeal membrane oxygenation (ECMO) could be proposed to support the RV in certain specific clinical situations such as refractory acute pulmonary embolism. Cardiac pump assistance devices need to be evaluated further for this indication.

Manage Causes of Acute Decompensation of HF

Identification and treatment of triggers of decompensation is necessary to resolve decompensated HF. Sepsis, arrhythmias, RV infarction, valvular disorders, drugs or pulmonary embolism should be sought after and treated. Pulmonary hypertension secondary to cardiac or pulmonary disease may also increase RV failure and congestive signs. Alveolar hypoxia, hypercapnia, hypothermia and acidosis promote pulmonary artery vasoconstriction and increase RV overload. Oxygen therapy with or without non-invasive ventilation to decrease hypercapnia and optimize arterial oxygen saturation > 90% could be proposed [3]. Positive pressure ventilation may increase RV overload but decreases LV preload. However, in the case of decompensated HF, it is associated with increased myocardial performance and reduction of pulmonary hypertension.

Increase of tricuspid regurgitation is a common cause of decompensation in chronic HF with right ventricular failure. In a retrospectively study of 5223 patients, it was associated with poor prognosis, independently from age, biventricular systolic function, RV size, and dilation of the inferior vena cava [39]. These data were confirmed by another study suggesting a beneficial effect of more aggressive approaches toward tricuspid repair or replacement [40].

Prevention of Renal Dysfunction in Primary Right Sided Heart Failure

Prevention of renal dysfunction in primary right-sided HF overlaps with the treatment of chronic HF. Current guidelines for patients with chronic HF recommend the use of beta blockers, angiotensin-converting enzyme (ACE) inhibitors, mineralocorticoid receptor antagonists (MRA) and diuretics [4]. Most of these treatments, such as ACE inhibitors and MRA, may induce a decline in GFR. However, this reduction in GFR is usually small and should not lead to treatment discontinuation [4]. In a recent meta-analysis, RAAS inhibitors were shown to induce renal dysfunction in both HFrEF and HFpEF during the acute phase [41]. However, in contrast to patients with HFrEF where the mortality increase with WRF is small, HFpEF patients with RAAS inhibitor–induced WRF have an increased mortality risk, without experiencing improved outcomes with RAAS inhibition. More studies are necessary but the most important conclusion should be that careful assessment of eGFR

during RAAS inhibitor treatment is essential [42]. This also stays true when RAAS inhibitors are prescribed to patients with HFpEF [41].

Prevention of WRF necessitates monitoring of both cardiac and renal function. In the long term, renal function can adequately be monitored using eGFR based on serum creatinine levels. Unfortunately, in the acute situation, reliable tools to evaluate kidney function are lacking and none has proved to be specific of congestion causing WRF. New biomarker strategies based on the pathophysiology of venous congestion or biomarkers of renal injury have been investigated. A recent analysis of 146 patients from the Metabolic Road to Diastolic Heart Failure: Diastolic Heart Failure (MEDIA-DHF) study showed a correlation between mid-regional pro-atrial natriuretic peptide (MR-proANP) (marker of cardiac congestion) and soluble CD146 (expressed by endothelial cells and a potent marker of venous congestion) with echocardiographic features of venous congestion (enlarged inferior vena cava, dilated left and right atria, RV dilation) [43]. Interestingly, in this study, no correlation was observed with BNP. This confirms the interest of using both markers of heart dilation and venous congestion in the management of patient with chronic right ventricular failure (Fig. 17.3).

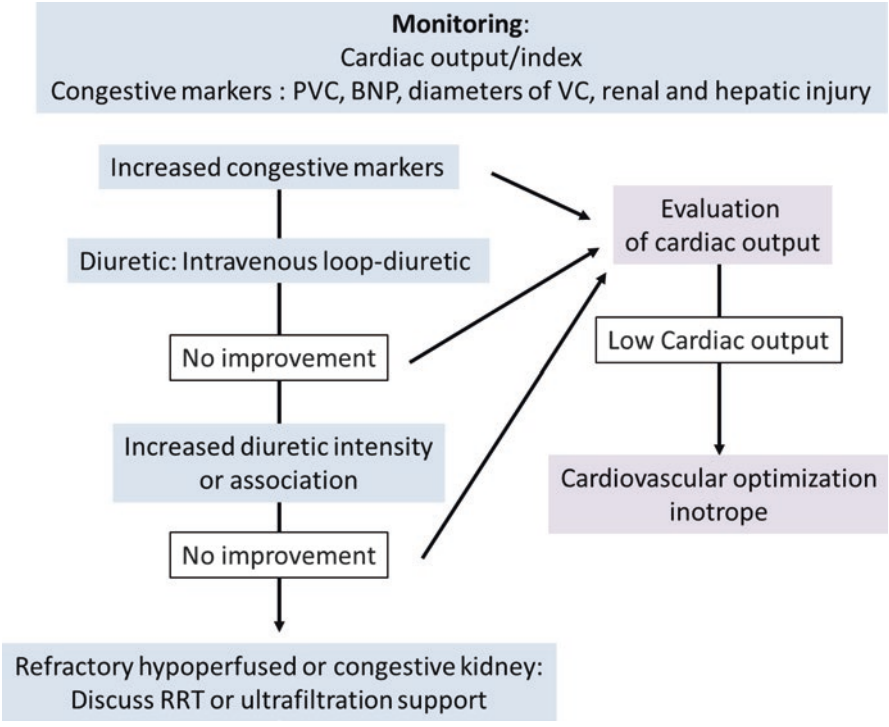

Fig. 17.3 Management of right heart failure. BNP, B-type natriuretic peptide; CVP, central venous pressure; RRT, renal replacement therapy; VC, vena cava

Treatment Pearls for the Case Vignette

On top of invasive hemodynamic monitoring (pulmonary artery catheter or jugular central line with measurement of CVP), this patient needs appropriate decongestion with diuretics together with a control of blood pressure. Echocardiography will guide the treatment, together with serial measurements of troponin (ischemia), BNP and if possible MR-proANP or sCD146. Decrease of TR is a main objective.

References

1. Chatterjee NA, Steiner J, Lewis GD. It is time to look at heart failure with preserved ejection fraction from the right side. Circulation. 2014;130(25):2272–7.
2. Zakeri R, Mohammed SF. Epidemiology of right ventricular dysfunction in heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2015;12(5):295–301.
3. Harjola V-P, Mebazaa A, Čelutkienė J, Bettex D, Bueno H, Chioncel O, et al. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. Eur J Heart Fail. 2016;18(3):226–41.
4. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803–69.
5. Sztrymf B, Souza R, Bertoletti L, Jaïs X, Sitbon O, Price LC, et al. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. Eur Respir J. 2010;35(6):1286–93.
6. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, et al. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(1):16–37.
7. Aschauer S, Kammerlander AA, Zotter-Tufaro C, Ristl R, Pfaffenberger S, Bachmann A, et al. The right heart in heart failure with preserved ejection fraction: insights from cardiac magnetic resonance imaging and invasive haemodynamics. Eur J Heart Fail. 2016;18(1):71–80.
8. Ter Maaten JM, Damman K, Verhaar MC, Paulus WJ, Duncker DJ, Cheng C, et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail. 2016;18(6):588–98.
9. McAlister FA, Ezekowitz J, Tarantini L, Squire I, Komajda M, Bayes-Genis A, et al. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. Circ Heart Fail. 2012;5(3):309–14.
10. Damman K, Valente MAE, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35(7):455–69.
11. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:S1–138.
12. Voors AA, Gori M, Liu LCY, Claggett B, Zile MR, Pieske B, et al. Renal effects of the angiotensin receptor neprilysin inhibitor LCZ696 in patients with heart failure and preserved ejection fraction. Eur J Heart Fail. 2015;17(5):510–7.
13. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail. 2002;8(3):136–41.

14. Schrier RW. Blood urea nitrogen and serum creatinine: not married in heart failure. Circ Heart Fail. 2008;1(1):2–5.
15. Damman K, Masson S, Hillege HL, Voors AA, van Veldhuisen DJ, Rossignol P, et al. Tubular damage and worsening renal function in chronic heart failure. JACC Heart Fail. 2013;1(5):417–24.
16. Damman K, Masson S, Hillege HL, Maggioni AP, Voors AA, Opasich C, et al. Clinical outcome of renal tubular damage in chronic heart failure. Eur Heart J. 2011;32(21):2705–12.
17. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263–71.
18. Melenovsky V, Cervenka L, Viklicky O, Franekova J, Havlenova T, Behounek M, et al. Kidney response to heart failure: proteomic analysis of cardiorenal syndrome. Kidney Blood Press Res. 2018;43(5):1437–50.
19. Sharma UC, Pokharel S, van Brakel TJ, van Berlo JH, Cleutjens JPM, Schroen B, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation. 2004;110(19):3121–8.
20. Frenay A-RS, Yu L, van der Velde AR, Vreeswijk-Baudoin I, López-Andrés N, van Goor H, et al. Pharmacological inhibition of galectin-3 protects against hypertensive nephropathy. Am J Physiol Renal Physiol. 2015;308(5):F500–9.
21. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. Drugs. 1990;39 Suppl 4:10–21; discussion 22–24.
22. Damman K, Navis G, Smilde TDJ, Voors AA, van der Bij W, van Veldhuisen DJ, et al. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. Eur J Heart Fail. 2007;9(9):872–8.
23. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009;53(7):582–8.
24. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(7):589–96.
25. Strobeck JE, Feldschuh J, Miller WL. Heart failure outcomes with volume-guided management. JACC Heart Fail. 2018;6:940–8.
26. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA. 2005;294(13):1625–33.
27. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. J Am Coll Cardiol. 2017;69(25):3042–51.
28. Yilmaz MB, Gayat E, Salem R, Lassus J, Nikolaou M, Laribi S, et al. Impact of diuretic dosing on mortality in acute heart failure using a propensity-matched analysis. Eur J Heart Fail. 2011;13(11):1244–52.
29. Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? J Am Coll Cardiol. 2006;47(1):1–8.
30. Abdallah JG, Schrier RW, Edelstein C, Jennings SD, Wyse B, Ellison DH. Loop diuretic infusion increases thiazide-sensitive Na(+)/Cl(-)-cotransporter abundance: role of aldosterone. J Am Soc Nephrol. 2001;12(7):1335–41.
31. De Vecchis R, Esposito C, Ariano C. Efficacy and safety assessment of isolated ultrafiltration compared to intravenous diuretics for acutely decompensated heart failure: a systematic review with meta-analysis. Minerva Cardioangiol. 2014;62(2):131–46.
32. Matsue Y, Suzuki M, Torii S, Yamaguchi S, Fukamizu S, Ono Y, et al. Clinical effectiveness of tolvaptan in patients with acute heart failure and renal dysfunction. J Card Fail. 2016;22(6):423–32.

33. Konstam MA, Gheorghiade M, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007;297(12):1319–31.
34. Mullens W, Verbrugge FH, Nijst P, Martens P, Tartaglia K, Theunissen E, et al. Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. Eur J Heart Fail. 2018;20:1591–600.
35. Ghignone M, Girling L, Prewitt RM. Volume expansion versus norepinephrine in treatment of a low cardiac output complicating an acute increase in right ventricular afterload in dogs. Anesthesiology. 1984;60(2):132–5.
36. Pierrakos C, Velissaris D, Franchi F, Muzzi L, Karanikolas M, Scolletta S. Levosimendan in critical illness: a literature review. J Clin Med Res. 2014;6(2):75–85.
37. Yilmaz MB, Yontar C, Erdem A, Karadas F, Yalta K, Turgut OO, et al. Comparative effects of levosimendan and dobutamine on right ventricular function in patients with biventricular heart failure. Heart Vessels. 2009;24(1):16–21.
38. Morelli A, Teboul J-L, Maggiore SM, Vieillard-Baron A, Rocco M, Conti G, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. Crit Care Med. 2006;34(9):2287–93.
39. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol. 2004;43(3):405–9.
40. Sadeghpour A, Hassanzadeh M, Kyavar M, Bakhshandeh H, Naderi N, Ghadrdoost B, et al. Impact of severe tricuspid regurgitation on long term survival. Res Cardiovasc Med. 2013;2(3):121–6.
41. Beldhuis IE, Streng KW, Ter Maaten JM, Voors AA, van der Meer P, Rossignol P, et al. Renin-angiotensin system inhibition, worsening renal function, and outcome in heart failure patients with reduced and preserved ejection fraction: a meta-analysis of published study data. Circ Heart Fail. 2017;10(2)
42. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J. 2015;36(23):1437–44.
43. Van Aelst LNL, Arrigo M, Placido R, Akiyama E, Girerd N, Zannad F, et al. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. Eur J Heart Fail. 2018;20(4):738–47.

Refractory Congestion: When to Use Ultrafiltration?

18

Bradley A. Bart

Case Vignette

Mrs. X is a 79 year old woman with an ischemic cardiomyopathy who was admitted to the hospital 4 days ago with signs and symptoms of volume overload. Despite full nephron blockade with intravenous acetazolamide 500 mg daily, intravenous furosemide 120 mg twice daily and metazolone 2.5 mg daily, net fluid loss is only 250 mL during the past 24 h with clinical signs of volume overload still present. The serum creatinine has bumped up from 1.68 mg/dL around admission to 2.59 mg/dL at the current. Blood pressure is 98/62 mmHg in the supine position.

Chapter Key Points

- Indications for ultrafiltration in acute heart failure
- Impact of ultrafiltration in acute heart failure on kidney function
- Practical recommendations on how to prescribe ultrafiltration in acute heart failure
- Upfront use of ultrafiltration instead of diuretics in acute heart failure

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Brief Discussion of the Case

Cases like this are often encountered in clinical practice. Relief from congestion is the primary treatment goal after excluding precipitating factors such as ischemia, arrhythmia, and infection. In addition, a low cardiac output could be contributing to her clinical picture and it is important to assess the adequacy of tissue perfusion by examination and other indirect measures of cardiac output. This patient has persistent signs and symptoms of congestion despite an aggressive diuretic regimen. While clinicians depend on signs and symptoms as a surrogate for elevated cardiac filling pressures, the predictive value is limited. If there is clinical uncertainty about a patient's cardiac filling pressures or cardiac output, further evaluation would be helpful and might include an echocardiogram, lactate levels, mixed venous oxygen saturation, non-invasive devices that estimate cardiac output based on pulse contour analysis or bioimpedance, or a right heart catheterization. For this patient, the combination of refractory congestion and acute kidney injury places her at increased risk of death or rehospitalization. Ultrafiltration is indicated and with proper monitoring and "dose" titration of fluid removal rates, can relieve congestion and improve kidney function. However, these "salvage" cases where treatment has been escalated over the course of several days without clinical improvement are at higher risk for adverse outcomes including renal failure and death. Early treatment with ultrafiltration within the first 24 h of hospital admission may result in better outcomes based on recent clinical trials.

Introduction

The importance of treating congestion is self-evident and has been covered in previous chapters. National guidelines recommend diuretics as the first-line therapy. However, in the setting of refractory congestion, ultrafiltration is recommended as a reasonable alternative. This final chapter will discuss the definitions of congestion and refractory congestion; describe the use of diuretics and ultrafiltration in the treatment of congestion; and review the importance of case selection.

Congestion

Signs and Symptoms

Signs and symptoms of congestion in heart failure are manifestations of ventricular diastolic pressures (Fig. 18.1). However, directly measured filling pressures are rarely available in the clinical setting and surrogates are used to determine whether congestion is present. Jugular venous distention is perhaps the best clinical indicator

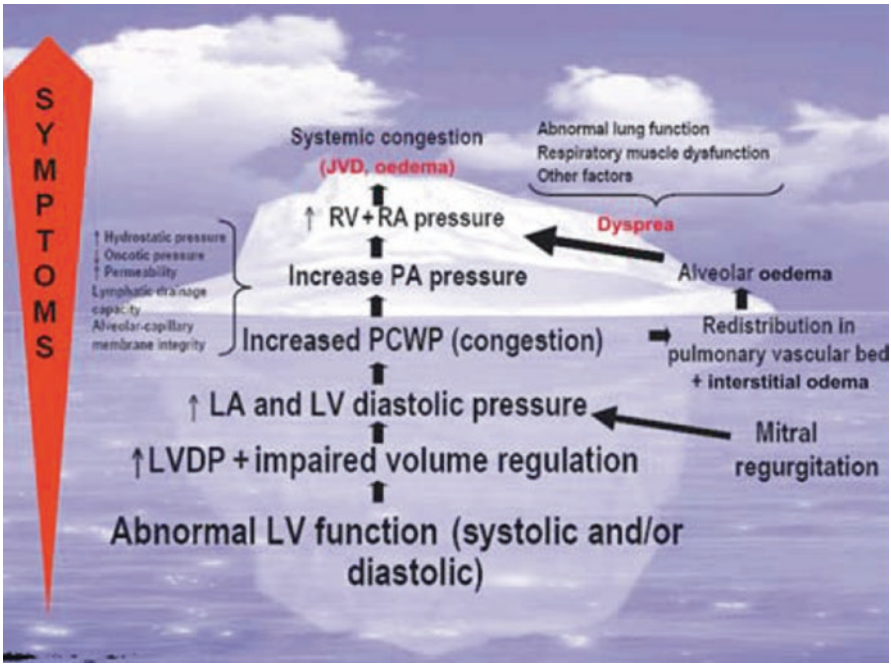


Fig. 18.1 Pathophysiology of congestion. Abbreviations: RV right ventricular, RA right atrial, PA pulmonary artery, PCWP pulmonary capillary wedge pressure, LA left atrial, LV left ventricular, LVDP left ventricular diastolic pressure, JVD jugular venous distension. (From Gheorghiade et al. [1])

of elevated ventricular filling pressures. However, clinical estimates of jugular venous pressure ≥12 mmHg have relatively poor operating characteristics with a sensitivity of 65%, specificity of 64%, and positive and negative predictive values of 69% and 38%, respectively [2]. Other physical and radiographic signs of congestion cannot be reliably used to distinguish patients with from those without elevated ventricular filling pressures [2–4].

Weight Gain

Weight gain has also been used as a surrogate for congestion. A rapid increase in weight can precede decompensated heart failure and greatly increases the risk for hospitalization in patients with heart failure. However, other factors can influence weight and not all weight gain is attributable to decompensated heart failure. In addition, a large number of patients who are hospitalized for decompensated heart failure have little or no weight gain [5, 6].

Clinical Profiles

Clinical profiles of congestion have been used to provide prognostic information and to guide therapy. Characterizing heart failure patients based on the clinical indicators of perfusion and congestion as either warm, cold, wet, or dry is relatively easy to do using information available in the history and physical examination. Patients described as *warm* and *dry* after treatment in the hospital have better clinical outcomes than patients with other clinical profiles [2]. While this framework is useful in the clinical setting, the clinical indicators of congestion are often inaccurate as described above.

Fluid Compartments

While increases in left-sided filling pressures can rapidly occur due to shifts in blood compartments (this occurs largely between the splanchnic venous beds and the effective arterial circulation), this scenario is generally not the primary process in patients with refractory congestion who might be considered candidates for ultrafiltration [7].

Blood Volume

Heart failure is a sodium avid state that often leads to expansion of total body water and total blood volume. For this reason, blood volume analysis using radiolabeled Iodine-131 dilution techniques can be used as another surrogate for congestion. Physical manifestations of congestion are not associated with total blood volume and increased blood volume is significantly associated with elevated left-sided filling pressures [8]. In one study, 65% of heart failure patients who were euvolemic by physical examination were actually hypervolemic when total blood volume was measured. In another study only 37% of patients hospitalized with decompensated heart failure had an increase in total blood volume [9]. While blood volume analysis introduces a more quantitative approach to the assessment of congestion, it is only a surrogate for elevated left-sided filling pressures – increases in blood volume only explain approximately half the variation in measured wedge pressure [8]. Blood volume analysis is rarely used clinically in part because it requires handling radioactive materials and multiple blood draws to create an accurate dilution curve and because its value in directing therapeutic decisions has not yet been demonstrated.

Persistent Congestion

Relief of congestion is the primary treatment goal for patients with decompensated heart failure. Clinicians use a variety of surrogates to diagnose and monitor the regression of congestion during therapy such as physical examination, symptoms,

Table 18.1 Association of persistent congestion with clinical outcomes

	Indicators of persistent congestion	Clinical correlates to persistent congestion
Lucas 2000 [10]	Scoring system including orthopnea, jugular venous pressure, change in weight, edema, and the need for IV diuretics 4–6 weeks after hospital discharge for heart failure	Increased mortality 2 years following hospital discharge
Wattad 2015 [11]	Scoring system including jugular venous pressure, hepatomegaly, edema, rales, third heart sound	Increased mortality, mean follow up 15 months
Aoki S [12]	Diuretic response expressed as weight loss/40 mg furosemide equivalent dose, edema, jugular venous distention	Increased cardiac death and rehospitalization for worsening HF 1 year after hospital discharge
Lala A 2015 [13]	Orthodema score based on presence of orthopnea and degree of edema	Increased rates of death, rehospitalization, or emergency department visits 60 days after hospital discharge
Kociol RD 2013 [14]	Weight loss, net fluid loss, reduction in NT Pro BNP	Increased rates of death, rehospitalization, or emergency department visits 60 days after hospital discharge
Abraham 2011 [15]	Pulmonary artery pressure measured directly by wireless pulmonary artery monitoring system	Increased heart failure related hospitalizations 6 months after randomization
Darawsha 2016 [16]	Scoring system including jugular venous pressure, hepatomegaly, edema, rales, third heart sound	Increased mortality, mean follow up 14 months

radiographs, changes in weight, blood volume analysis, and B-type natriuretic peptide (BNP) levels. As described in the preceding paragraphs, these surrogates for elevated ventricular filling pressures are not particularly accurate [1]. Nevertheless, persistent congestion, as defined by a treating physician is associated with worse clinical outcomes (Table 18.1). Persistent congestion represents a failure to address patient symptoms, physical functioning, and quality of life. In addition, persistent congestion leads to unrelieved and ongoing neurohormonal activation which can ultimately lead to a cascade of pathologic processes including further sodium retention, renal failure, cardiac chamber dilatation, progressive mitral regurgitation, subendocardial ischemia and arrhythmia [17].

Diuretics for the Management of Congestion

Diuretics are first-line therapy for patients with heart failure and congestion [13, 18]. The goal of therapy is to relieve congestion by increasing urine output and removing excess intravascular and extravascular fluid [1]. Loop diuretics such as furosemide exert their action on the thick ascending portion of the loop of Henle to block the sodium-potassium-chloride transporter [19]. This results in an increase in urinary excretion of sodium, chloride, calcium, magnesium, and potassium. In

general, plasma water follows sodium in the nephron resulting in an increase in urine production. Diuretics can sometimes be challenging to use because the dose response between individuals can be highly variable and electrolytes must be closely monitored and replaced. In addition, diuretic resistance is common, often requiring increasing doses to achieve similar degrees of urine output [20].

Diuretics produce hypotonic urine and this reduces the effective removal of excess total body sodium present in patients with heart failure. As a result, these drugs are often ineffective. In one large registry of over 100,000 patients hospitalized with acute decompensated heart failure, more than 90% received intravenous (IV) diuretics yet nearly half failed to lose any weight after treatment with IV diuretics [21]. In a clinical trial of diuretic dosing strategies, clinical decongestion was achieved in less than 20% percent of patients regardless of whether patients received high dose or low-dose diuretics, intermittent boluses or continuous intravenous infusions [22]. Vasodilators, inotropes, and other agents have been added to diuretics in an attempt to preserve renal function and improve outcomes yet these efforts have failed [23–27].

Refractory Congestion

There is no universally accepted definition of refractory congestion. Published guidelines are vague about this and refer to "a failure to respond to diuretics" or "after all diuretic strategies are unsuccessful". Investigators have offered a number of working definitions for refractory congestion with varying degrees of specificity (Table 18.2). Some, but not all describe threshold doses of diuretics that must be

Table 18.2 Definitions of refractory congestion

Ellison 2011 [28]	When moderate doses of diuretics fail to achieve the desired volume reduction
Sackner-Bernstien 2003 [29]	A lack of response to 200 mg of furosemide per day
Simpson 1986 [30]	Persistent edema despite treatment with diuretics, vasodilators, and inotropes
Dormans 1996 [31]	Failure to lose weight or to develop a negative sodium balance despite bedrest, sodium restriction to <80 mmol/day, and high dose furosemide (> 250 mg/day)
Bart 2012 [32]	Worsening renal function in the setting of IV diuretics with (a) pulmonary capillary wedge pressure >22 mm hg and at least 2+ peripheral edema and/or pulmonary edema or pleural effusions on chest x-ray; or (b) at least two of the following: ≥2+ peripheral edema, jugular venous pressure >10 mm Hg, and pulmonary edema or pleural effusions on chest x-ray
ter Maaten 2015 [33]	(1) persistent congestion despite adequate and escalating doses of diuretic with >80 mg furosemide per day and/or (2) amount of sodium excreted as a percentage of fltered load less than 0.2% and/or (3) failure to excrete at least 90 mmol of sodium within 72 h of a 160 mg oral furosemide dose given twice daily
Mentz 2014 [17]	Failure of diuretics to control volume status adequately despite appropriate dose escalation

administered before describing a patient as having refractory congestion. Other authors incorporate specific measures of sodium excretion in their definitions. However, using diuretic doses or urine sodium response to IV diuretics to define refractory congestion is problematic since less than half the variability in urine output following IV diuretics can be explained by the dose or predicted by spot urine sodium assessments [34, 35]. The common theme in all the definitions of refractory congestion is that there are persistent signs or symptoms of congestion despite therapies that include IV diuretics. The lack of a standardized definition of refractory congestion makes it difficult to conduct research and compare findings across published trials.

Ultrafiltration for the Management of Congestion

Ultrafiltration is the mechanical removal of isotonic plasma water directly from the circulation. Blood is withdrawn from a vein and flows across a semipermeable membrane under pressure to separate isotonic plasma water from blood. The plasma water is discarded and the remaining blood is returned to the patient [36]. Simplified ultrafiltration devices can be used in a variety of settings without the need for central venous access. Low blood flow rates are well tolerated even in patients with advanced heart failure and plasma water removal rates can be adjusted across a range from 0 to 500 mL/h. In contrast to diuretics which produces a hypotonic urine, ultrafiltration removes isotonic plasma water which can result in greater overall sodium removal – an important objective in treating heart failure [37]. Ultrafiltration results in rapid and predictable fluid removal, restores responsiveness to diuretics in patients with diuretic resistance, has no direct effect on serum electrolytes, and does not directly stimulate the neurohormonal system [38–41].

Direct Comparisons of Diuretics and Ultrafiltration

Randomized controlled trials comparing ultrafiltration to diuretic-based strategies have been performed in the modern era of heart failure treatment. These trials contribute to a growing database of experience that suggests that ultrafiltration may be superior to diuretic-based strategies in the management of patients who fail to adequately respond to loop diuretics.

RAPID [42]

The Relief for Acutely Fluid Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial was the first randomized controlled trial comparing diuretic-based therapies to ultrafiltration in patients with acute decompensated heart failure using a simplified ultrafiltration circuit. This feasibility study

randomized 40 patients hospitalized with decompensated heart failure to usual care with intravenous diuretics versus a single 8 h course of ultrafiltration performed within the first 24 h of hospitalization. There was a trend for improved weight loss in the ultrafiltration group at 24 h and significantly greater net fluid loss (4650 mL versus 2838 mL, P = 0.001). RAPID-CHF demonstrated that ultrafiltration is well tolerated in patients with acute decompensated heart failure and may be an alternative to diuretic therapy.

UNLOAD [39]

The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial randomized 200 patients hospitalized with decompensated heart failure to usual care versus ultrafiltration within the first 24 h of hospitalization. Patients in the usual care group received IV diuretics at doses equal to or greater than twice their usual outpatient diuretic dose and all diuretics were stopped in the ultrafiltration group, while volume reduction therapy was managed exclusively using ultrafiltration for the first 48 h after randomization. Patients in the ultrafiltration group lost more weight in the first 48 h compared to the usual care group (5 kg versus 3.1 kg, P = 0.001). The average diuretic dose in the usual care group was 181 mg of furosemide per day and the average plasma water removal rate in the ultrafiltration group was 241 mL/h over 12.3 h. There was a slight increase in serum creatinine in the ultrafiltration group but this was not statistically or clinically significant. There was a significant reduction in the prespecified secondary endpoint of heart failure-related hospitalizations at 90 days (Fig. 18.2). While promising, this improvement in clinical outcomes came under question because there was no formal clinical events committee to adjudicate the

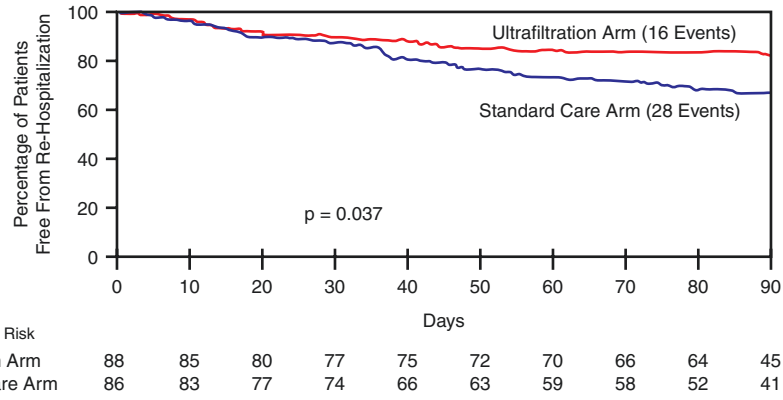


Fig. 18.2 Freedom from heart failure rehospitalization. Kaplan-Meier estimate of freedom from rehospitalization for heart failure within 90 days after discharge in the ultrafiltration (red line) and standard care (blue line) groups. (From Costanzo [39])

endpoints, treatment was not blinded, and more fluid was removed during ultrafiltration raising uncertainty about the potential mechanism of benefit.

ULTRADISCO [43]

The Effects of Ultrafiltration Versus Diuretics on Clinical, Biohumoral and Haemodynamic Variables in Patients With Decompensated Heart Failure (ULTRADISCO) study randomized 30 patients hospitalized with decompensated heart failure and congestion to a continuous IV infusion of furosemide versus ultrafiltration with a conventional renal replacement device using slow continuous ultrafiltration techniques. In the usual care group, the initial rate of furosemide infusion was 250 mg per 24 h and this dose was adjusted according to changes in creatinine, blood pressure, and heart rate. The dose was increased to 500 mg per 24 h if the initial dose did not achieve a negative fluid balance of at least 2000 mL per day. The ultrafiltration group initiated ultrafiltration with a fluid removal rate between 100–300 mL/h and this rate was adjusted according to blood pressure. Both groups achieved similar degrees of weight loss and fluid loss by the end of treatment. However, patients in the ultrafiltration group had significant improvements in cardiac performance when measured noninvasively using pulse contour analysis suggesting a possible advantage to ultrafiltration versus traditional diuretics.

Hanna, et al. [44]

This is the only randomized controlled study of ultrafiltration versus usual care in which all patients underwent invasive hemodynamic monitoring. Thirty-six patients, all with pulmonary arterial wedge pressure ≥24 mmHg were randomized to usual care with IV diuretics at the discretion of the treating physician or slow continuous ultrafiltration using a standard renal replacement device. The primary endpoint was the time required for the pulmonary arterial wedge pressure to fall ≤18 mmHg for at least four consecutive hours. Both groups experienced significant decreases in central venous pressure and pulmonary arterial wedge pressure and there was a trend favoring ultrafiltration for achieving the primary endpoint (22 h versus 34.8 h, $P = 0.081$). Despite more fluid removal in the ultrafiltration group (5213 mL versus 2167 mL, $P = 0.041$), there was no significant change in renal function. Length of hospital stay was lower in the ultrafiltration group (4.53 days versus 9.61 days, $P < 0.001$).

CUORE [45]

The Continuous Ultrafiltration for Congestive Heart Failure (CUORE) study randomized 56 patients hospitalized with decompensated heart failure and significant congestion to usual care involving IV diuretics (average dose of diuretics at

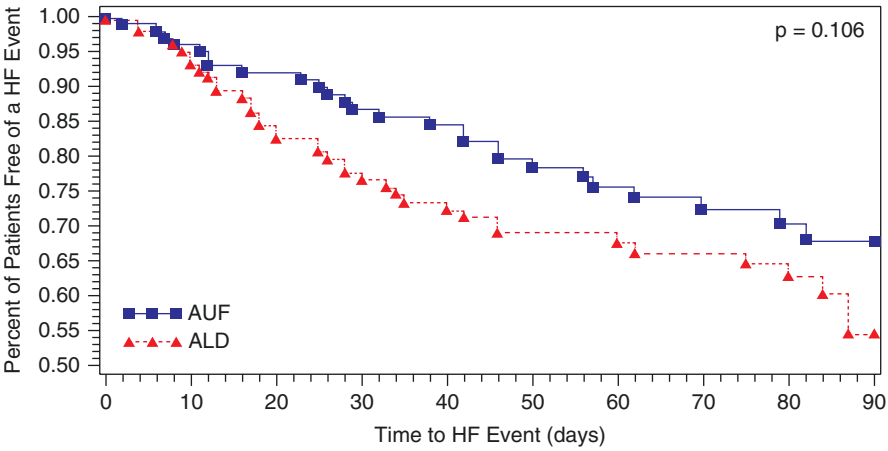
initiation of therapy was 153 mg per day) or ultrafiltration for an average of 19 h with a mean plasma water removal of 4254 mL. Interestingly, diuretics were continued in patients randomized to the ultrafiltration group. There was no significant difference in weight loss achieved in the two groups (7.5 kg for ultrafiltration versus 7.9 kg for usual care, P = 0.75). There was no difference in length of hospital stay. However, 6 months after discharge, patients in the usual care group gained more weight, required higher doses of diuretics, and had higher creatinine compared to the ultrafiltration group. Ultrafiltration patients had fewer heart failure readmissions after 12 months of follow-up compared to usual care (hazard ratio 0.14, P = 0.002).

CARRESS-HF [32]

The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) randomized 188 patients with acute kidney injury and persistent congestion after failing standard treatment with escalating doses of diuretics to a diuretic-based, stepped pharmacologic care treatment protocol designed to achieve 3–5 L of urine output per day or ultrafiltration (average treatment duration 40 h, target plasma water removal rate of 200 mL/h). The primary endpoint was change in weight and change in creatinine measured 96 h after randomization. There was no significant difference in weight loss and a transient increase in creatinine at 96 h which resolved 30 days after discharge. There were no differences in clinical outcomes at 60 days. Due to a significant number of dropouts and crossovers from the ultrafiltration arm of the trial to the diuretic-based arm of the trial, an analysis was performed comparing subjects who actually received their assigned treatment after randomization. In this per-protocol analysis, patients receiving ultrafiltration had significantly greater net fluid loss and weight reduction than patients receiving pharmacologic therapy [46] Ultrafiltration was associated with higher creatinine and blood urea nitrogen values, lower serum sodium concentrations, and increased plasma renin activity; pharmacologic therapy was associated with higher serum bicarbonate. However, there were no significant differences in 60-day outcomes suggesting that transient increases in serum creatinine associated with ultrafiltration are not clinically significant [46].

AVOID-HF [47]

The Aquapheresis versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF) trial randomized patients hospitalized for decompensated heart failure and congestion to IV diuretics or ultrafiltration within 24 h of hospital admission. Both treatment strategies included protocols for adjusting the rate of fluid removal based on response to therapy and other clinical parameters. The primary endpoint was time to heart failure readmission, or treatment with IV diuretics or



	Baseline	30 Days	60 Days	90 Days
AUF	105	80	52	19
ALD	108	74	49	15

Fig. 18.3 Primary endpoint: time to heart failure event after discharge from the AVOID-HF study. Log-rank analysis of the time to first heart failure (HF) event after discharge from index hospitalization up to 90 days in the adjustable ultrafiltration (AUF) (squares) and adjustable loop diuretics (ALD) (triangles) groups. The difference in time to first heart failure event within 90 days after discharge from the index hospitalization was not statistically significant at the 0.05 alpha level (p = 0.106) due to the smaller than originally planned sample size. AQ aquapheresis, LD loop diuretics. (From Costanzo [47])

ultrafiltration during an unscheduled outpatient or emergency room visit. The sample size of 810 patients was based on the ability to detect a 37.5% reduction in 90 day heart failure events with 90% power (Fig. 18.3). Unfortunately, this study was terminated for nonclinical reasons after enrolling 224 patients. Patients randomized to IV diuretics received an average daily dose of 271 mg furosemide during an average of 100 h. Patients randomized to ultrafiltration had an average rate of plasma water removal of 138 mL/h and underwent treatment for an average of 80 h. There was a 37% reduction in the risk of heart failure events with ultrafiltration versus diuretic therapy but this failed to reach statistical significance (hazard ratio 0.663, confidence interval 0.402–1.092). There was a non-significant trend favoring ultrafiltration for time to heart failure event (62 days versus 34 days, P = 0.106). Patients in the ultrafiltration group had fewer heart failure and cardiovascular events at 30 days, and no significant changes in serum creatinine. There were more serious adverse events felt to be related to study therapy in the ultrafiltration group than in the diuretic group (14.6% versus 5.4%, P = 0.026) and more adverse events of special interest including infection, bleeding, hypotension, and acute coronary syndrome (31% versus 17% P = 0.018).

Treatment Pearls for the Case Vignette

Importance of Case Selection

Despite the promising results described in some of the randomized trials above, case selection clearly plays a key role in determining the outcomes of patients undergoing ultrafiltration therapy. Small, uncontrolled case series involving patients with refractory heart failure have been associated with very poor outcomes. In one series of 12 patients treated with vasopressors and high doses of furosemide for 22 days prior to initiating hemofiltration or hemodialysis, the median survival was 24 days [31]. A larger series of 63 patients with advanced heart failure in the intensive care unit were treated with slow continuous ultrafiltration for an average of 3 days. Prior to ultrafiltration therapy, all of these patients had oliguria or worsening renal function with persistent congestion and the majority were receiving high-dose IV loop diuretics and IV vasoactive drugs. The mean pulmonary arterial wedge pressure was 30 mmHg, central venous pressure 20 mmHg, and cardiac index 1.8 L/min/m^2. After ultrafiltration, hemodynamic parameters improved, weight loss occurred, and there was a significant negative fluid balance. However, there were no improvements in renal function and 30% of patients died during the index hospitalization with an additional 10% discharged to hospice care [48].

There is currently no consensus regarding the optimal selection criteria for ultrafiltration. Factors that need to be considered include the patient's volume status, the patient's clinical response to diuretics, and the patient's severity of illness prior to consideration of ultrafiltration therapy. When ultrafiltration is used as *rescue* or *salvage* therapy, it appears that the underlying disease processes involving the heart and the kidneys are so advanced that overall outcomes are poor. The randomized trials of ultrafiltration demonstrating more favorable outcomes targeted patients for early ultrafiltration therapy usually within the first 24 h of hospitalization.

Volume Status

Ultrafiltration effectively removes extracellular volume and can only be recommended in patients with volume overload and congestion. However, the clinical assessment of volume status and filling pressures is challenging even for experienced clinicians. Common elements include symptoms of congestion such as orthopnea; physical exam findings such as edema, jugular venous distention, pulmonary rales, and the presence of a 3rd heart sound; radiographic evidence of pulmonary congestion; direct or indirect measures of elevated filling pressures including central venous pressure, pulmonary artery pressure, pulmonary arterial wedge pressure, and left ventricular diastolic pressure; non-invasive assessments of hemodynamic status using ultrasound, pulse contour analysis, bio impedance; wireless intravascular or intracardiac pressure measurement, and others.

The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial placed

a wireless implantable hemodynamic monitor in eligible ambulatory patients with class III heart failure symptoms and then randomized them to usual clinical care with no hemodynamic data available to guide therapy versus an active treatment group in which the treating medical team had access to hemodynamic data to assist in titration of medications to achieve a prespecified pulmonary artery pressure. Patients in the treatment group had a 28% reduction in heart failure related hospitalizations in 6 months (rate 0.32 versus 0.44, $P = 0.0002$) [15]. This study demonstrates the potential value in accurate measurements of filling pressures and the importance of clinical decongestion on outcomes.

In another study, heart failure medications were titrated to achieve a prespecified total blood volume estimated using an iodine 131 labeled albumin indicator dilution technique. In this retrospective analysis performed at a single community hospital, targeted decongestion based on estimates of total blood volume was associated with improved 30 day readmission rates (12.2% versus 27.7%, $P < 0.001$) and a significant reduction in 30 day mortality (2% versus 11.1%, $P < 0.001$) when compared to propensity score-matched controls from a CMS limited data set.

Response to Diuretics

The above two trials demonstrate improved clinical outcomes by targeting directly measured pulmonary artery pressures and total blood volume. However, not every patient with elevated filling pressures and/or expanded extracellular volume will require or benefit from ultrafiltration therapy. In the CHAMPION trial, ambulatory patients with elevated filling pressures were successfully treated in the outpatient setting with oral medications, especially diuretics, to optimize filling pressures [15]. Therefore, only patients who fail oral medications in the ambulatory setting could be considered candidates for ultrafiltration. IV diuretics are often effective in managing the symptoms of congestion in decompensated heart failure – especially in patients without previous exposure to diuretics or in those who are taking diuretics at lower doses. The threshold at which ultrafiltration therapy is favored over intravenous diuretics has yet to be determined and will likely be defined by clinical outcomes. In the Diuretic Optimization Strategies Evaluation trial in Acute Heart Failure (DOSE-AHF) trial, a threshold of 80 mg of oral furosemide per day was used to define eligibility in a randomized clinical trial testing different dosing strategies of furosemide in patients hospitalized with decompensated heart failure. Clinical outcomes were poor (42% died, were rehospitalized, or had an emergency department visit within the 60-day follow-up period) regardless of the dosing strategy used (high intensity versus low intensity, continuous infusion versus intermittent bolus) [22]. A similar threshold of 80 mg of furosemide was used in the UNLOAD [39] and AVOID [47] trials and in these clinical trials there was a trend towards improved outcomes in patients undergoing ultrafiltration therapy versus IV diuretics.

Table 18.3 Patient selection for ultrafiltration

Hospitalized with decompensated heart failure
Evidence of significant congestion
Failed or inadequate response to IV diuretics equal to at least 80 mg of oral furosemide per day
Treatment initiated within 24–48 h of first dose of intravenous diuretics

Severity of Illness

Severity of illness is another consideration in selecting candidates for ultrafiltration. When ultrafiltration is used as a rescue or salvage procedure in patients with cardiogenic shock, often days or weeks after the initial hospitalization, outcomes are poor. [31, 48–50] Ultrafiltration performed early in the course of therapy in congested patients not requiring vasoactive drugs for support appears to result in improved outcomes compared to diuretics in randomized trials [39, 43, 45, 47, 51]. Based on the above considerations and the results of randomized controlled trials, ultrafiltration may be particularly useful in patients hospitalized with decompensated heart failure and significant congestion with failed or inadequate response to IV diuretics equal to at least 80 mg of oral furosemide per day. The best outcomes following ultrafiltration therapy occur when ultrafiltration is initiated within 24–48 h of the first dose of intravenous diuretics (Table 18.3). Successful ultrafiltration therapy depends on careful and appropriate patient selection. Once the decision to perform ultrafiltration has been made, it should be administered by clinicians with experience using ultrafiltration. The initial rate of plasma water removal should be carefully considered based on blood pressure, creatinine, and degree of left versus right ventricular dysfunction. Patients should be closely monitored during ultrafiltration for clinical response with special attention to heart rate, blood pressure, creatinine, urine output and signs of congestion [52].

References

1. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12(5):423–33.
2. Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail. 2008;1(3):170–7.
3. Chakko S, Woska D, Martinez H, de Marchena E, Futterman L, Kessler KM, et al. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. Am J Med. 1991;90(3):353–9.
4. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA. 1989;261(6):884–8.
5. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation. 2007;116(14):1549–54.
6. Zile MR, Bennett TD, St John SM, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation. 2008;118(14):1433–41.

7. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail. 2011;4(5):669–75.
8. Androne AS, Hryniewicz K, Hudaihed A, Mancini D, Lamanca J, Katz SD. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. Am J Cardiol. 2004;93(10):1254–9.
9. Strobeck JE, Feldschuh J, Miller WL. Heart failure outcomes with volume-guided management. JACC Heart Fail. 2018;6(11):940–8.
10. Lucas C, Johnson W, Hamilton MA, Fonarow GC, Woo MA, Flavell CM, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. Am Heart J. 2000;140(6):840–7.
11. Wattad M, Darawsha W, Solomonica A, Hijazi M, Kaplan M, Makhoul BF, et al. Interaction between worsening renal function and persistent congestion in acute decompensated heart failure. Am J Cardiol. 2015;115(7):932–7.
12. Aoki S, Okumura T, Sawamura A, Kitagawa K, Morimoto R, Sakakibara M, et al. Usefulness of the combination of in-hospital poor diuretic response and systemic congestion to predict future cardiac events in patients with acute decompensated heart failure. Am J Cardiol. 2017;119(12):2010–6.
13. Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, et al. Relief and recurrence of congestion during and after hospitalization for acute heart failure: insights from Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). Circ Heart Fail. 2015;8(4):741–8.
14. Kociol RD, McNulty SE, Hernandez AF, Lee KL, Redfield MM, Tracy RP, et al. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. Circ Heart Fail. 2013;6(2):240–5.
15. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011;377(9766):658–66.
16. Darawsha W, Chirmicci S, Solomonica A, Wattad M, Kaplan M, Makhoul BF, et al. Discordance between hemoconcentration and clinical assessment of decongestion in acute heart failure. J Card Fail. 2016;22(9):680–8.
17. Mentz RJ, Kjeldsen K, Rossi GP, Voors AA, Cleland JG, Anker SD, et al. Decongestion in acute heart failure. Eur J Heart Fail. 2014;16(5):471–82.
18. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):e240–327.
19. Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJ. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med. 1973;288(21):1087–90.
20. Brater DC. Diuretic therapy. N Engl J Med. 1998;339(6):387–95.
21. Gheorghiade M. Reassessing treatment of acute heart failure syndromes: the ADHERE registry. Eur Heart J. 2005;7(Suppl):B13–9.
22. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797–805.
23. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013;310(23):2533–43.
24. Massie BM, O'connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med. 2010;363(15):1419–28.
25. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365(1):32–43.

26. Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med. 2017;376(20):1956–64.
27. Teerlink JR. RELAXin in acute heart failure-2-RELAX-AHF-2. 2017.
28. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology. 2001;96(3–4):132–43.
29. Sackner-Bernstein JD, Obeleniene R. How should diuretic-refractory, volume-overloaded heart failure patients be managed? J Invasive Cardiol. 2003;15(10):585–90.
30. Simpson IA, Rae AP, Simpson K, Gribben J, Boulton Jones JM, Allison ME, et al. Ultrafiltration in the management of refractory congestive heart failure. Br Heart J. 1986;55(4):344–7.
31. Dormans TP, Huige RM, Gerlag PG. Chronic intermittent haemofiltration and haemodialysis in end stage chronic heart failure with oedema refractory to high dose frusemide. Heart. 1996;75(4):349–51.
32. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'connor CM, Bull DA, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367(24):2296–304.
33. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol. 2015;12(3):184–92.
34. Aronson D, Burger AJ. Diuretic response: clinical and hemodynamic predictors and relation to clinical outcome. J Card Fail. 2016;22(3):193–200.
35. Brinkley DM Jr, Burpee LJ, Chaudhry SP, Smallwood JA, Lindenfeld J, Lakdawala NK, et al. Spot urine sodium as triage for effective diuretic infusion in an ambulatory heart failure unit. J Card Fail. 2018;24(6):349–54.
36. Ronco C, Ricci Z, Bellomo R, Bedogni F. Extracorporeal ultrafiltration for the treatment of overhydration and congestive heart failure. Cardiology. 2001;96(3–4):155–68.
37. Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? J Am Coll Cardiol. 2006;47(1):1–8.
38. Ali SS, Olinger CC, Sobotka PA, Dahle TG, Bunte MC, Blake D, et al. Loop diuretics can cause clinical natriuretic failure: a prescription for volume expansion. Congest Heart Fail. 2009;15(1):1–4.
39. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007;49(6):675–83.
40. Guazzi MD, Agostoni P, Perego B, Lauri G, Salvioni A, Giraldi F, et al. Apparent paradox of neurohumoral axis inhibition after body fluid volume depletion in patients with chronic congestive heart failure and water retention. Br Heart J. 1994;72(6):534–9.
41. Marenzi G, Guazzi M, Lauri G, Perego GB, Sganzerla P, Agostoni P. Body fluid withdrawal with isolated ultrafiltration effects persistent improvement of functional capacity in patients with chronic congestive heart failure. Furosemide does not produce the same result. Cardiologia. 1994;39(11):763–72.
42. Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. J Am Coll Cardiol. 2005;46(11):2043–6.
43. Giglioli C, Landi D, Cecchi E, Chiostri M, Gensini GF, Valente S, et al. Effects of ULTRAfiltration vs. DIureticS on clinical, biohumoral and haemodynamic variables in patients with deCOmpensated heart failure: the ULTRADISCO study. Eur J Heart Fail. 2011;13(3):337–46.
44. Hanna MA, Tang WH, Teo BW, O'Neill JO, Weinstein DM, Lau SM, et al. Extracorporeal ultrafiltration vs. conventional diuretic therapy in advanced decompensated heart failure. Congest Heart Fail. 2012;18(1):54–63.
45. Marenzi G, Muratori M, Cosentino ER, Rinaldi ER, Donghi V, Milazzo V, et al. Continuous ultrafiltration for congestive heart failure: the CUORE trial. J Card Fail. 2014;20(5):378–9.

46. Grodin JL, Carter S, Bart BA, Goldsmith SR, Drazner MH, Tang WHW. Direct comparison of ultrafiltration to pharmacological decongestion in heart failure: a per-protocol analysis of CARRESS-HF. Eur J Heart Fail. 2018;20:1148–56.
47. Costanzo MR, Negoianu D, Jaski BE, Bart BA, Heywood JT, Anand IS, et al. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. JACC Heart Fail. 2016;4(2):95–105.
48. Patarroyo M, Wehbe E, Hanna M, Taylor DO, Starling RC, Demirjian S, et al. Cardiorenal outcomes after slow continuous ultrafiltration therapy in refractory patients with advanced decompensated heart failure. J Am Coll Cardiol. 2012;60(19):1906–12.
49. Liang KV, Hiniker AR, Williams AW, Karon BL, Greene EL, Redfield MM. Use of a novel ultrafiltration device as a treatment strategy for diuretic resistant, refractory heart failure: initial clinical experience in a single center. J Card Fail. 2006;12(9):707–14.
50. Ramos R, Salem BI, DePawlikowski MP, Tariq M, Haikal M, Pohlman T, et al. Outcome predictors of ultrafiltration in patients with refractory congestive heart failure and renal failure. Angiology. 1996;47(5):447–54.
51. Siddiqui WJ, Kohut AR, Hasni SF, Goldman JM, Silverman B, Kelepouris E, et al. Readmission rate after ultrafiltration in acute decompensated heart failure: a systematic review and meta-analysis. Heart Fail Rev. 2017;22(6):685–98.
52. Costanzo MR, Ronco C, Abraham WT, Agostoni P, Barasch J, Fonarow GC, et al. Extracorporeal ultrafiltration for fluid overload in heart failure: current status and prospects for further research. J Am Coll Cardiol. 2017;69(19):2428–45.