# Panel discussion

*The symposium that formed the basis for this supplement included the following panel discussion in which the faculty fielded questions and comments from the audience.*

Question from audience: What is the mechanism for progressive renal failure in patients who have persisting heart failure?

Dr. Domenic Sica: This is an interesting question and one with several possible answers.

First, heart failure and renal disease can have a common disease-state origin. For example, diabetes, diabetic nephropathy, and heart failure often coexist; if renal failure progresses in that setting, it can be on the basis of the diabetic nephropathy.

Second, urinary protein excretion tends to increase in the setting of advanced heart failure, and the degree of proteinuria accelerates the rate of renal functional decline.

**Age-related GFR decline is accelerated in the presence of heart failure.**
***—Dr. Domenic Sica***

A third consideration is that many heart failure patients have macrovascular disease, microvascular disease, or both. The impact of occlusive disease on renal perfusion, particularly at the low blood pressures seen in systolic forms of heart failure, can prove significant in patients prone to ischemic nephropathy.

Fourth, the cytokine and growth factor excess that marks heart failure also has the potential to act on the kidney; in so doing, it can promote glomerular and/or interstitial disease.

Advancing age is an additional determinant of a decline in kidney function. The rate of glomerular filtration rate (GFR) decline with aging in a patient with heart failure proves to be greater than the age-related decline in GFR in a person without heart failure. This is an important consideration in light of our ability to keep many heart failure patients alive for a longer period of time.

Question from audience: Although a reduction in cardiac output is proposed as the source for a reduced perfusion of the kidney, isn't elevation in central venous pressure and renal vein pressure at least as important?

Dr. Sica: I would agree that this is not simply a matter of reduced perfusion.

The role of an increase in renal vein pressure in determining the state of renal function and/or sodium retention is a complicated one in that it interplays with multiple other sodium-retaining stimuli. Renal venous pressure may prove to have its greatest applicability in preserved systolic forms of heart failure, in which the usual signals heralding salt and water retention (such as a reduction in cardiac output and a fall in blood pressure and renal perfusion) are not present. This is a fertile area for future investigation.

Dr. Mihai Gheorghiade: The model described by Dr. Sica implicates low cardiac output and/or systemic vasodilatation in reduced renal perfusion. However, the majority of patients admitted with heart failure do not have low cardiac output or vasodilatation. Nevertheless, their renal perfusion is diminished. Recently it has been demonstrated that high venous pressure may contribute independently to reduced renal perfusion. For this reason, I would emphasize the importance of treating a high venous pressure in itself, even in patients without low cardiac output.

Question from audience: What is the appropriate route of administration for diuretic therapy?

Dr. Steven Goldsmith: When patients are severely congested, you should give diuretics intravenously. We cannot tell from the Acute Decompensated Heart Failure National Registry (ADHERE) database whether there was a big difference in the response between intravenous (IV) or oral diuretic therapy, but the neurohormonal and electrolyte effects have been shown to occur with IV therapy.

Question from audience: What is your first choice of loop diuretic, and to which agent might you switch following a decline in renal function?

Dr. Goldsmith: My own bias is to use IV furosemide because it is inexpensive and it

usually works, but once the creatinine clearance declines to 30 or 40 mL/min, IV or oral torsemide may be preferable. I personally switch to torsemide when the renal function is down or for oral therapy if the patient is grossly congested because absorption is much better with torsemide.

Dr. Gary Francis: We do not have bumetanide on the formulary at the Cleveland Clinic, because it is too expensive. We do use a lot of torsemide, though.

Dr. Sica: Oral torsemide is an excellent choice in the treatment of volume overload in heart failure. First, not only is it almost completely absorbed but it is also quickly absorbed. This distinguishes it from furosemide, which is quite erratically absorbed on a day-to-day basis. Second, torsemide appears to have a modest anti-aldosterone effect. This is not seen with the other loop diuretics. The clinical significance of this property is unclear.

Question from audience: There is a concern that although vasopressin antagonism is beneficial because it will reduce volume, it does not reduce total body salt. Do you share this concern?

Dr. Goldsmith: Like anything else in heart failure, one size probably does not fit all. We give loop diuretics because they move salt out and water out with it. If the patient is hyponatremic, though, the sodium level drops further, so there is no question that the group at highest risk, based on everything we know, are volume-expanded hyponatremic patients. These are the patients in whom a vasopressin 2 receptor antagonist, with or without a vasopressin 1 receptor antagonist, would be likely to show the greatest benefit.

The other mechanisms come into play in patients with a normal level of serum sodium. We should have an answer to these questions once the results of the Efficacy of Vasopressin antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) are released. Whether or not the net balance in a normonatremic patient is positive or negative is going to be interesting to see. My guess is that if tolvaptan proves beneficial in EVEREST, even in the low- or normal-sodium patient, it will coincide with less loop diuretic use. If we could reduce the amount of loop diuretic by one half to three fourths and replace it with an effective aquaretic, we would remove some of the neurohormonal activation associated with loop diuretics.

Dr. Gheorghiade: In patients with a high wedge pressure, lowering the wedge pressure is important clinically. A drug, independent of its mechanism, that safely reduces the wedge pressure will be beneficial clinically. The discussion about the relative importance of reducing total body water and total body sodium is interesting, but from a clinical point of view the goal is to reduce the filling pressure and body weight.

Dr. Francis: I agree. It's about decongestion and not necessarily about improving forward flow.

Question from audience: A small segment of patients is receiving cardiac resynchronization therapy. What is the effect of that on deterioration or preservation of renal function in heart failure?

Dr. Francis: We have put in about 800 cardiac resynchronization devices, and about one third of patients improve, one third show no improvement, and one third get worse.

Improvement has been much more consistent now that we've been able to identify who is going to respond to biventricular pacing. So, if anything, I think that cardiac resynchronization tends to forestall the worsening of renal function, and there is now a demonstrated mortality benefit.

Question from audience: What role do hemodynamics play in the acute cardiorenal syndrome? Studies have shown that in advanced heart failure, renal blood flow correlated best with hemodynamics (ie, wedge pressure, pulmonary artery pressure, and right atrial pressure), not with cardiac output. Clinical observation indicates that acute deterioration of renal function in heart failure reflects hemodynamics. For example, the serum creatinine declines when acute mitral regurgitation or excessive bradycardia are corrected. Also, acute correction of severe anemia leads to a reduction in the creatinine level by 24 hours. Another probable factor is a diuretic response; for example, ultrafiltration, despite removal of

**$V_2$ receptor antagonism is is likely to show the greatest benefit in volume-expanded patients with hyponatremia.**
***—Dr. Steven Goldsmith***

the same amount of fluid, does not change kidney function unless the patient becomes hypovolemic. Third, hypotension that occurs during treatment, either from excessive diuresis or from some other mechanism, will lead to a decreased GFR. Correction of the hypotension, such as by removing a vasodilator, will lead to an improvement in serum creatinine, particularly if the patient has chronic kidney disease, because the autoregulation curve is shifted to the right.

Dr. Francis: You are correct in that low blood pressure has predicted a poor outcome in every study of this syndrome. If blood pressure is marginal, you can expect the worst. What's more curious is that some patients present with normal systolic function, normal ejection fraction, and normal cardiac output, and yet develop severe congestion and the cardiorenal syndrome, as best as we can define it. Therefore, it seems that it is not solely inadequate flow to the kidney that is the cause. Inadequate renal perfusion clearly can contribute when the cardiorenal syndrome develops, but not all patients have it. I don't think we understand this syndrome at all.

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Dr. Gheorghiade: Our data in patients admitted with heart failure, soon to be published, found that blood urea nitrogen and not creatinine clearance is an important marker for postdischarge mortality and hospitalization. These data suggest that often we are dealing with a vasomotor nephropathy related to further activation of neurohormones and an increase in venous pressure. This vasomotor nephropathy is not an irreversible process and may improve with neurohumoral modulation and/or a decrease in venous pressure.

Question from audience: Do you believe that a low serum sodium is not the problem, but rather that total body water is massively elevated? Do patients who are hyponatremic in fact have an elevated total body sodium? If patients with heart failure, despite being hyponatremic, are massively overloaded with sodium in their body, it suggests that removal of both water and salt is needed if we are to achieve full decongestion.

Dr. Francis: I agree that, generally, the hyponatremia in the cardiorenal syndrome is a dilutional hyponatremia. The total amount of sodium in the body, which must be measured using pretty exotic techniques, can be either normal or increased. It is clear that there is too much water. It is also quite clear that congestion is playing a major role. It is not just the cardiac output or ejection fraction.

I agree with Dr. Gheorghiade that the cardiorenal syndrome is reversible. These patients can sometimes be rescued. The treatment is inconsistent from hospital to hospital, and there is clearly a lot to learn.

Dr. Gheorghiade: We have seen from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) that patients with hyponatremia have the best clinical and hemodynamic response during admission. Those were the patients who had a significant decrease in body weight and the greatest increase in cardiac index. In spite of the huge clinical and hemodynamic improvement, and a decrease in body weight, their serum sodium level did not change during hospitalization. More important, there was a threefold increase in mortality in those patients who had hyponatremia. These data show that outcome is not entirely related to fluid because the patients who were hyponatremic had the best response in terms of diuresis.

Question from audience: Conivaptan has some significant drug interactions, along the cytochrome P450 pathway. Is that a problem with all drugs in this class?

Dr. Wilson Tang: Both conivaptan and tolvaptan are metabolized via the CYP3A4 pathway. I think that the main reason that conivaptan has been developed as an intravenous drug is because the oral form had drug interactions, but clinical trials to date have shown good tolerability with oral tolvaptan.

Dr. Sica: Conivaptan proved to be both a substrate for and an inhibitor of CYP3A4. When given orally, the consistency of its pharmacokinetics was somewhat unpredictable, at least partly because of variable absorption. Its intravenous administration still carries a significant drug-drug interaction potential for compounds metabolized by CYP3A4.

Question from audience: Are there any effects of vasopressin antagonists on the QT interval?

Dr. Gheorghiade: I am not aware of any increase in the QT interval with either tolvaptan or conivaptan.

Question from audience: It seems that we have discovered several parallel mechanisms that promote the congested state and that we have been able to block activation of some of these mechanisms with angiotensin-converting enzyme inhibitors and beta-blockers. Does blocking one of these pathways activate other pathways so that we are destined to keep chasing the next pathway that comes into play pathologically in this state?

Dr. Francis: Yes, as a short answer. It's a very complicated question, but it is theoretically and practically the case.

Dr. Tang: We also have an inability to tell which pathways are more activated than others in certain patients. We do not know because our ability to accurately quantify congestion and renal insufficiency, and to measure renal hemodynamics, is not very good and hasn't evolved.

Question from audience: Does anyone on the panel buy into the concept of a diuretic holiday with procedures such as ultrafiltration, in which the diuretic is eliminated completely to try to restore diuretic sensitivity? In this way, once patients are ambulatory, we can restore sensitivity to the diuretics that kept them well compensated for the months prior to their admission.

Dr. Gheorghiade: It's a valid concept. Theoretically, diuretic therapy may be a contributor to the cardiorenal syndrome that contributes to postdischarge mortality and hospitalization. Breaking this vicious cycle (the use of high-dose diuretics) by ultrafiltration or other means may be beneficial.

Dr. Sica: Restoring diuretic sensitivity by providing a diuretic holiday is an interesting concept and one that has been anecdotally described from time to time. If it holds true, it could possibly relate to a downturn in neurohumoral activation and/or regression of distal tubular cell hypertrophy.

**Blood urea nitrogen, but not creatinine clearance, is an important marker for postdischarge mortality and hospitalization.**
***—Dr. Mihai Gheorghiade***