



# expert roundtable »

## Vasodilators in Acute Heart Failure: Who Needs Them and How Soon?



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Moderated by **W. Frank Peacock, MD<sup>1</sup>**

Discussants: **Alexandre Mebazaa, MD<sup>2</sup>**; **John Teerlink, MD<sup>3</sup>**; **James Udelson, MD<sup>4</sup>**

**DR. PEACOCK:** I'm Frank Peacock, Emergency Physician at Baylor Medical College, and my interest is in heart failure (HF).

**DR. TEERLINK:** I'm John Teerlink, Professor of Medicine at the University of California, San Francisco, and Director of the Heart Failure Program as well as Director of the Clinical Echocardiography Laboratory at the San Francisco Veterans Affairs Medical Center.

**DR. UDELSON:** My name is James Udelson. I'm Chief of the Division of Cardiology at Tufts Medical Center in Boston, and I'm very involved in the care of patients with HF.

**DR. MEBAZAA:** I am Alexandre Mebazaa, Professor of Critical Care Medicine in Paris, and my area of interest is acute HF.

**DR. PEACOCK:** The first question today is "Should all HF patients get vasodilators and when should they be administered?" Dr. Teerlink, would you like to begin with your theories on vasodilation in HF?

**DR. TEERLINK:** I assume we are limiting our discussion to acute decompensated HF or acute HF today. I think the utility of vasodilators and the neurohormonal antagonists in chronic HF has been well established, but it's in the field of acute HF where we're still

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The discussion focused primarily on: (1) The role of vasodilation in heart failure (HF); (2) the ideal patient population for vasodilators; (3) chronic versus acute HF patients; (4) hemodynamic models of acute HF; (5) clinical studies using vasodilators; (6) the role of blood pressure/hypertension; (7) novel vasodilators; (8) guidelines for using vasodilators; and (9) the use of vasoconstrictors. (*Med Roundtable Cardiovasc Ed.* 2014;3(4):278–284) ©2014 FoxP2 Media, LLC

### STUDIES DISCUSSED:

ADHERE, ALARM-HF, ASCEND, EVEREST, Pre-RELAX-AHF, RELAXIN, PRONTO, TRUE-AHF

### COMPOUNDS DISCUSSED:

tezosentan, nitroprusside, furosemide, clevidipine, epinephrine, norepinephrine, tolvaptan, nesiritide, serelaxin, nifedipine, ularitide, natriuretic peptides, riociguat, cinaciguat, tezosentan, cenderitide

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learning about these agents. Initially, our research in this field was a bit stymied as many of the early researchers were involved in transplant centers. The early picture of an acute HF patient was actually a pretransplant patient, and this is usually a patient with low systolic blood pressure (BP) who had chronic HF that had decompensated.

As we've looked forward towards people such as you, Dr. Peacock—professionals who are working in the emergency departments and are taking care of HF outside of the cardiology setting,

per se—we realize that more than 50% of the patients actually present with a normal or elevated BP and that about half of these patients also have normal ejection fractions (EFs). These are appropriate targets for vasodilator therapy, which can decrease the abnormally elevated afterload as well as decrease the abnormally elevated preload through both arterial and venous vasodilation. So, I think this is a very promising area of research, which is why there have been a number of trials and new agents that have been developed to try to address this, as of yet, unmet need.

**DR. PEACOCK:** Yes, your epidemiology comments are quite accurate: we did start in the heart-transplant world, and as the Acute Decompensated Heart Failure National Registry (ADHERE) registry<sup>1</sup> showed us, HF is slightly common in women—just over half of the HF population—and they certainly have more hypertension than we ever expected.

Dr. Udelson, you've been involved in many studies. What are your views on this?

**DR. UDELSON:** I agree that one of the important findings, upon careful examination of these registries, is that there is a completely different understanding of who these patients are from what we might have thought 10 years ago. An example is the finding that most people have high BP, not low BP, and preserved EF when they come in with decompensated HF and shortness of breath. So, it's only by understanding that you can design therapeutic targets, and the fact that many people are hypertensive instead of hypotensive would suggest that there could be a further role for vasodilators beyond current practice. To this point, the trials that have been conducted in the last 8 to 10 years, in which Drs. Teerlink and Mebazaa and others have been involved, have not been beneficial with drugs such as tezosentan or nesiritide. So, the search continues. In addition, the pathophysiology rationale makes sense.

**DR. PEACOCK:** Dr. Mebazaa, you've had some experience with different agents and patient selection. Who do you think should be receiving vasodilators? What patient population is ideal?

**DR. MEBAZAA:** Your question on the population is very interesting because the more we are learning through investigations in acute HF, the more we are discovering that it includes a

wide range of patients with a comorbidity of age. The population goes from frequent flyers and patients with chronic HF who come in regularly with low BP who are often very well treated with many medications, to patients who come in with high BP who are not well treated. It's true that it seems difficult to have one drug that will save all those patients, but maybe vasodilators will help many of those acute HF patients.

One point I would like to mention is that we should rethink the term "vasodilation." Maybe it does not necessarily mean a decrease in BP and maybe we do not necessarily need the decrease in BP to see an improvement in a patient's condition. In one of our last trials,

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*-W. Frank Peacock, MD*

we showed that although dyspnea improved in patients with high BP and low BP, there was a trend toward improved mortality in patients with low BP when they were administered vasodilators.<sup>2</sup> But, maybe we are focusing too much on the role of vasodilators on the arterial side for reducing BP and forgetting about what Dr. Teerlink was mentioning, which is the action of the venous beds: they cause a reduction in central venous pressure and improvement in organ dysfunction. Perhaps, if we improve organ dysfunction, we may save lives more than we would by just reducing blood pressure, per se.

**DR. PEACOCK:** So, it sounds like you're very supportive of some kind

of hemodynamically active drug that builds space within the vasculature, regardless of BP. As long as patients have functional BP, you would add it. Is that your position?

**DR. MEBAZAA:** Yes, BP is very easy to measure. I mean, everyone knows how to measure BP, and when the BP is decreasing, we feel that the drug is working. But maybe, within the organs, there are some special effects of vasodilators and sometimes, we forget that some, or maybe most, of the vasodilators have some local effects. Drugs such as nitrates and ularotide have some biochemical local effects, and we maybe forgetting those effects, which could either potentiate the decrease in BP or have their own positive effect on outcome.

**DR. PEACOCK:** Dr. Teerlink, you and I have talked about the hemodynamic models of acute HF and the variations of how that could work. Can you expand on that a little bit?

**DR. TEERLINK:** Yes, I think Dr. Mebazaa has mentioned a very important point as well, that BP is not necessarily a reliable reflection of what the mechanism of action is for many of these vasodilators. We've had to walk a very careful line here because the early trials with tezosentan and other vasodilators such as nesiritide, cenderitide and cinaciguat were largely hampered by episodes of hypotension during the early development and later development program. So, I happen to agree that vasodilators can be very useful in the setting of patients who have increased afterload but still don't have low BP. In that pathophysiologic state, one can be given an arterial vasodilator that will decrease the afterload, allowing for an increased stroke volume that actually preserves or may even improve systolic BP.

There was a very informative study by Gary Francis and his colleagues,<sup>3</sup>

wherein they administered nitroprusside to patients with aortic stenosis and severe HF, which is supposedly one of the exact examples of the pathophysiologic state where you should not, by traditional teachings, administer vasodilators. Yet, these patients showed significant improvements and achieved multiple beneficial outcome variables. So, I think there is definitely a very important target on the arterial side in patients who have severely reduced cardiac output and markedly elevated afterload, where afterload reduction can be very beneficial.

On the other hand, you have patients with hypertensive crisis. Patients who have this marked and rather sudden ventricular arterial impedance mismatch will also, I believe, benefit substantially from targeted afterload reduction. In between, you have the other pathophysiologic state of pulmonary venous congestion. Such patients clearly benefit from venodilators, and we are reminded of the article from 1931 by Dr. Winton<sup>4</sup> that suggested that much of the renal dysfunction that is associated with acute HF is due to elevation in central venous pressure. So, in terms of end-organ damage, vasodilators that work on the venous side may help improve renal function as well.

**DR. PEACOCK:** Let me direct this question to Dr. Udelson. If we look at the ADHERE data,<sup>1</sup> only about 15% of all HF patients receive any kind of vasodilator in the first 24 hours of their hospitalization. Suppose I am the physician in the emergency department, how do I decide on who receives the vasodilator, and should the number of patients receiving vasodilators be higher?

**DR. UDELSON:** I think for the moment, we're probably on the right track because the previous trials haven't identified a clear benefit of drugs that act that way, although, maybe, we're

missing a subgroup that actually does benefit from it. So, if I were an emergency department physician, I would think that if you have a patient who's short of breath in front of you, they are usually volume overloaded. You start treatment with diuretics, and if I am empirically thinking of who might benefit from the administration of vasodilators, I suppose I would it would be people with very high BP.

I completely agree with everything Drs. Mebazaa and Teerlink have said, that anytime we administer a drug for lower BP, we'd like to think it lowers afterload and increases stroke volume. We usually go back and think very simplistically, but there are many other

**"Even if a drug is shown to be safe in patients with normal or high BP [blood pressure], many experts will still be reluctant to use a drug that will decrease the BP."**

*-Alexandre Mebazaa, MD*

effects. Ultimately, it takes observations and trials to accurately assess the overall clinical effect of such an agent. There are relevant trials underway, but in the absence of that knowledge, I would think, particularly if someone had low EF, that a person with high BP and presumably very high impedance to outflow would benefit from a drug that has some arterial vasodilating effect with or without venodilating effects.

**DR. MEBAZAA:** In the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) database with HF patients, we showed that even in patients with initial systolic BP below 120 mm Hg, and even below 100 mm Hg, administering vasodila-

tors, mostly nitrates, is safe. In fact, we showed that there was a decrease in mortality among patients receiving vasodilators compared with those who did not receive them.<sup>5</sup> Even though they may not point out the beneficial effect of vasodilators, emergency doctors know what they are doing when they are administering these drugs to patients with a BP below 120 mm Hg. They will try to maintain the BP or decrease it a little. I now believe that even in those patients, if you administer vasodilators carefully, they are safe and perhaps even beneficial.

**DR. PEACOCK:** Can you describe the ALARM-HF project a bit?

**DR. MEBAZAA:** The ALARM-HF database was a study originally performed in 10 countries, but unfortunately, we could not show the data from Brazil because there was an issue with the ethics committee, so we reported data from 9 countries from 4 continents. In each country, we had roughly 600 patients, with a total of nearly 5000 patients. We assessed the initial BP and treatment in the initial 24 hours of hospital admission and examined in-hospital outcome.

We showed that close to half of the patients all around the world received vasodilators. The physicians in charge, mostly emergency department physicians, prescribed vasodilators within 30 minutes of patient admission. I think this is an important point because it shows that in our general practice, physicians are administering, within 30 minutes, furosemide and vasodilators.

Then, we looked at in-hospital mortality. When we performed the analysis, we split the initial BP into higher than 120 mm Hg and below 120 mm Hg. In patients with a BP higher than 120 mm Hg, we saw an improvement in dyspnea but no change in mortality, whether they received or did not receive vasodi-

lators. We were surprised to see that in patients with a BP below 120 mm Hg, the survival rate improved with vasodilators. But, again, without pointing out this improvement, I think we can say that it's safe. The European Society of Cardiology, and I'm sure the American College of Cardiology as well, recommend giving vasodilators only when the systolic BP is higher than 120 mm Hg. I believe we can go down to at least 100 mm Hg based on these findings.

**DR. PEACOCK:** I think your experience does not reflect what is common in the published literature. When a patient is enrolled, within 30 minutes, HF is treated more like a myocardial infarction, at least in the United States, than traditionally managed HF. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial,<sup>6</sup> generally considered a negative trial, analyzed patients for as long as 24 hours after a hospitalization and that, I think, misses the point. About 5 years ago, we published data on 35,700 patients from the ADHERE registry and showed that if patients didn't receive a vasodilator in the first 24 hours, there was no mortality benefit.<sup>7</sup> But if they received it within 24 hours, there was a benefit and that benefit increased the sooner they received the drug. This means that the 30-minute cutoff point is apt and then, every minute after that, you lose any kind of benefit you could have obtained from that drug.

Drs. Udelson or Teerlink, do you want to comment on the timing issue?

**DR. UDELSON:** I think that, again, there's such a gap in knowledge on this point. Most physicians would agree with your experience that the initial therapy is diuretics and then the rest follows very empirically. Again, you would think, the sooner the better. There is a published post-hoc analysis of the Efficacy of Vasopressin

Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial database showing a greater benefit from tolvaptan compared to placebo on patient-assessed dyspnea when dosing was done earlier compared to later.<sup>8</sup>

**DR. PEACOCK:** There is a subset analysis from the ASCEND-HF where the patients who received nesiritide less than 9 hours after admission had significant improvements compared with the general cohort of that trial. So, there is some, albeit limited and secondary, analysis data to support that.

**DR. TEERLINK:** This is one of the lessons I think we learned from the early trials where we were enrolling patients later in the course of their hospitaliza-

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tion and subsequently, as we performed the subset analyses. As pointed out in ASCEND, I think it was a 15- or 16-hour cutoff point for the median where they showed improvement. We also saw that with the Relaxin for the Treatment of Patients with Acute Heart Failure (Pre-RELAX-AHF) trial,<sup>9</sup> which was the pilot study for the RELAXin in Acute Heart Failure trial,<sup>10</sup> showing that earlier enrollment helped.

We're battling, of course, with some of the pragmatics of doing a clinical

trial, which is, by its nature, a bit of an artificial setting, but in those trials, we were enrolling patients within 16 hours of presenting to the emergency department, and the median time was 8 hours. So, we were doing better than we did in the other trials and, in fact, if the results of RELAX-AHF confirm what was predicted in the Pre-RELAX study, serelaxin should also provide a significant improvement in dyspnea as well as trends towards improvements in more important outcomes such as worsening HF and even cardiovascular death. So, I think it is important to administer these therapies earlier.

I don't know how we instill in physicians the same sense of urgency for treating acute HF as they have for acute coronary syndrome (ACS). The advantage of the ACS arena has been that there is a clearly defined, specific pathophysiology (the clot in the coronary artery) with a specific biomarker (troponins). In ACS, physicians have a door-to-balloon or door-to-needle time as a mandated measure. For acute HF, we have not developed that same urgency for early treatment. That is something that definitely needs to be addressed.

**DR. PEACOCK:** Yes, I think that is important. The objective nature of a diagnosis in ACS is performing electrocardiography and a troponin test, and these tests are very objective. In contrast, in the HF world, you perform a B-type natriuretic peptide (BNP) test and then you can argue about what the number means. But, it's still better than it was a decade ago when we didn't have BNP. I agree that we need a more specific measure, and some of the trials that are currently underway use chest radiography and BNP only, which I think is probably the best we can do currently.

But the important point of emergency medicine is that when you have to make a diagnosis very early, the misdiagnosis rate is higher than

that when you get more time to think about it. So, that's always a challenge for our drugs. When we administer vasodilators to HF patients, it's quite consistent. In most trials, between 3% and 5% of patients will become symptomatically hypotensive. Although they tend to tolerate that very well, it's not a very thrilling experience for the physician when there's an unstable patient with a pressure below 70 mm Hg. So, the challenge is that the risk/benefit analysis changes from the emergency department as it moves along, which is, I think, historically why we were studying early enrollment, but the newer agents seem to have a margin of safety that's better than the older ones.

**DR. UDELSON:** Dr. Peacock, that's actually a very important point. For emergency physicians to treat patients earlier, the safety data of an agent are very important. It seems compelling on the basis of these subgroup analyses, as flawed as they may be, that earlier treatment may be better. You have to do that with the understanding that you're going to treat some people unnecessarily who probably don't have acute HF and you're not going to know that at that time. If you know that an agent is quite safe, then no harm is done in some ways and you might be doing more good. So, as trials and registries go on, that safety information is really important.

**DR. PEACOCK:** Yes, I think the medicines that have shorter half-lives and easy titration have an advantage here because, as you said, there is a certain percentage of people who derive no benefit from the drug, who may receive it because of diagnostic uncertainty. However, if you can stop the condition and it gets alleviated and doesn't cause any trouble, you haven't hurt them.

In contradistinction with the ACS model, if you administer a lytic to a non-acute myocardial infarction patient who subsequently suffers an

intracranial hemorrhage, that is an awful outcome for a patient who could not possibly have obtained any benefit from the intervention. So, in HF at least, we have some margin of safety compared with the extreme nature of the ACS world.

**DR. UDELSON:** Yes, that's very important.

**DR. MEBAZAA:** Dr. Peacock, there is another issue of BP because even if a drug has been shown to be safe in patients with normal or high BP, many experts will still be reluctant to use a drug that will decrease the BP. The ALARM database seems to suggest that the beneficial effects of vasodilators overcome the harmful effect of decreased blood pressure.

**"It's only by understanding that you can design therapeutic targets, and the fact that many people are hypertensive instead of hypotensive would suggest that there could be a further role for vasodilators beyond current practice."**

*-James Udelson, MD*

**DR. TEERLINK:** Yes, I've seen that in every nitroprusside review published, but it's failed to mention though, is that the patients who had received nitroprusside after 9 hours actually had a survival benefit, and these patients are much more similar to our acute HF patients.

In the same issue of *The New England Journal of Medicine*, there was a report of a trial done in Europe with nitroprusside that was stopped early due to a survival benefit.<sup>11</sup> I think there may be indications that nitroprusside and similar agents can be beneficial and actually improve outcomes in

the setting of acute decompensated HF. It obviously needs to be proven, but if anything, the weight of the evidence is in support of the beneficial outcome rather than an adverse clinical outcome.

**DR. PEACOCK:** I can tell you from the emergency medicine point of view, nitroprusside is a difficult drug. It automatically guarantees a stay in the intensive care unit, and the nurses have to watch patients very carefully. Hemodynamically, it makes good sense. I feel we have agents that are newer and probably safer to use, but nitroprusside is a great drug nevertheless.

**DR. TEERLINK:** Dr. Peacock, you and your colleagues have done some interesting work with an agent called clevidipine.

**DR. PEACOCK:** Yes, we're just wrapping up the Clevidipine in the Treatment of Blood Pressure in Patients with Acute Heart Failure (PRONTO) trial, and the preliminary findings look very good. Clevidipine has a 1-minute half-life similar to Nipride; however, its titration ability and unpredictability seems to be much better. My experience with Nipride is that one minute, you're fine and the next minute, the pressure is 60 mm Hg, and you're not really sure how that happened. I have not had that experience with clevidipine, which seems to be a lot smoother in its management. Otherwise, there are different classes of drugs that seem to have similar hemodynamic effects.

**DR. TEERLINK:** Interesting. I look forward to those results.

**DR. PEACOCK:** They will be coming out shortly. So, the last thing to discuss is what we should do once we have started administering a vasodilator. What's the end game? In the emergency department, when dyspnea gets better, I stop its administration,

but I'm not sure that's right. What kind of guidelines can we give physicians for that procedure?

**DR. UDELSON:** None at this point, to our knowledge. It's a really good question and, in fact, for a lot of the acute HF drugs that have been studied, it is usually not unclear about why a certain duration for intravenous drugs is chosen; there's usually some thinking that goes into it to decide on some things used in the preliminary trials. For a drug, such as Nipride or clevidipine, is it an apt period when the BP is normalized but maybe the patient is still not doing well? Maybe, we could use some reduction of impedance and improved stroke volume? There's very little guidance on this, and I think there's no concrete answer to it question as yet.

**DR. PEACOCK:** That is the answer, I guess. Is there anything else we haven't covered that you feel we should discuss before we wind this up?

**DR. TEERLINK:** I think we should mention the other agents that are under trials, as well. I already mentioned the RELAX-AHF trial with serelaxin, which will be presenting results this year. The TRial of Ularitide's Efficacy and safety in patients with Acute Heart Failure (TRUE-AHF) is a phase III, multicenter, randomized, double-blind, placebo-controlled trial of ularitide (Urodilatin), which is underway as well. There are multiple new, designer natriuretic peptides emerging from labs and entering clinical trials, including a differentially spliced BNP variant. In addition, there are new soluble guanylate cyclase activators and stimula-

tors such as riociguat that are advancing, based on the lesson learned from cinaciguat. All of these have very interesting and unique mechanisms of action. So, I, at least, look forward to these newer agents being established and seeing whether they can inform us about how we can better use vasodilators in the setting of acute HF.

**DR. PEACOCK:** It's going to be a great year because we're going to be constantly busy doing all sorts of studies. Anybody else need to say anything?

**DR. UDELSON:** Yes, I think everyone really looks forward to these well-done studies to see whether there's something that will help these patients. But the naysayers, and I'm not one of them, might say that alleviating acute dyspnea better a bit faster is great, but ultimately, everyone gets to the same place and goes home. New drugs are expensive, and another major problem is what happens to these people after they get discharged—generally, about 30% of them die within 6 months or so. If a vasodilator of any type is having some short-term effect that somehow translates into a somewhat longer-term effect, it's very useful.

We'll learn a lot from these trials. It is possible that in the people with very high BP, if you bring the BP down, there will be less myocardial myocyte necrosis. Maybe that's very good. Many different things could happen. So, the short-term, as well as slightly longer-term, follow-up of these people on these new drugs will be really interesting and potentially really important.

**DR. PEACOCK:** Yes. I think that's very important, especially in the United States where we have trouble with revisits. Dr. Mebazaa lives in a world where people are kept in the hospital longer, but they have benefits from that—at least, that's the way I think. They have much lower revisit rates in

## Clinical Implications

- The fact that many acute heart failure (HF) patients are hypertensive instead of hypotensive would suggest a further role for vasodilators beyond current practice.
- Drugs such as nitrates, serelaxin, and ularitide have some biochemical local effects, which could either potentiate the decrease in blood pressure (BP) or have their own positive effect on the outcome.
- Vasodilators can be very useful in acute HF patients who have increased afterload but not low BP.
- Administering nitroprusside to patients with aortic stenosis and severe HF has been shown to cause significant improvements, contrary to traditional conceptions.
- In acute HF patients with a BP below 120 mm Hg, the use of vasodilators improved the survival rate.
- If acute HF patients do not receive a vasodilator within the first 24 hours, there is no mortality benefit.

the next 30 days than we do in the United States.

**DR. MEBAZAA:** Dr. Peacock, is there time left to talk about the disadvantages of vasoconstrictors? There is not enough evidence today to prove that vasopressors like epinephrine or norepinephrine are beneficial in acute HF. In ALARM-HF, we clearly showed that catecholamines are toxic by a direct effect or because increasing BP is harmful.

**DR. PEACOCK:** I am personally hesitant when I have to use a vasoconstrictor. The mortality isn't good after that, at least when patients present to the emergency department. The probability of them surviving is less than 30%.<sup>12</sup>

**DR. MEBAZAA:** We need to have this information available.

**DR. PEACOCK:** Yes, I would have to agree that using vasoconstrictors means that you're in the last inning of the ballgame.

**DR. MEBAZAA:** Many emergency doctors and physicians think epinephrine can be used in the state just for cardiac arrest. We should use epinephrine only in cardiac arrest.

**DR. PEACOCK:** I can certainly sign on to that. I'd like to thank our participants for being here and adding their wisdom to this topic. As is always the case, it's easier to pose questions than generate answers, but I think we have

been informative on this topic, and I'd like to thank you all once again for joining us.

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