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New Perspectives on the Management of HFrEF: Iron Deficiency and Cardiac Remodeling

Announcer:
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Dr. van der Meer:
Iron deficiency, independent of anemia status, is common in heart failure with reduced ejection fraction, or also called HFrEF. It's associated with reduced functional status, poor exercise performance, and an increased risk for heart failure hospitalization and cardiovascular mortality. In normal cardiac physiology, contractility increases disproportionally to heart rate, the phenomenon called positive force-frequency relationship. In patients with HFrEF and iron deficiency, cardiac output increases to a lesser extent during exercise. In addition, HFrEF patients with iron deficiency who receive cardiac resynchronization therapy, or CRT, exhibit diminished cardiac reverse remodeling after CRT implantation. So how can we work to improve reverse cardiac remodeling, the force-frequency relationship, and also quality of life in our patients with HFrEF and iron deficiency receiving CRT?

This is CME on ReachMD, and I'm Dr. Peter van der Meer.

Dr. Martens:
Hi, I'm Dr. Pieter Martens.

Dr. van der Meer:
So, Pieter, as I just mentioned in the introduction, iron plays an important role in patients with HFrEF receiving CRT. So what's your take on the underlying pathophysiology of iron deficiency in patients with HFrEF requiring CRT?

Dr. Martens:
So it's important to remember that iron deficiency is common in your HFrEF patients, irrespective of whether they are getting a CRT implant, and it will affect about 50% of your patients. To understand the detrimental effect of iron deficiency in those HFrEF patients, it's important to remember 2 things.

First, that iron is an essential cofactor of the first 3 elements of the electron transport chain, and detrimental cellular effects have actually been nicely illustrated by a paper from your group, in which it took stem cell-derived cardiomyocytes and you incubated them with an iron chelator, deferoxamine, to induce iron deficiency. And what you saw in that paper was that those cardiomyocytes, their mitochondria were less able to produce ATP, and that's the energy that the cell needs for myofilament shortening and relaxation.

Secondly, it's important to remember that iron is an essential cofactor of antioxidative enzymes, and as a result, iron deficiency is implicated in the process of progressive cardiac remodeling. And these 2 elements become clinically relevant to our patients, because if we instituted therapy which normally induces reverse remodeling such as CRT, patients with iron deficiency will manifest with less cardiac reverse remodeling. Secondly, the impact on the energy metabolism, that also becomes clinically relevant to our patients, and they will manifest during moderate or vigorous exercise with exercise limitations. And this is due to the fact that patients with iron

deficiency have lessened ability to increase their cardiac output during exercise. One of the operating mechanisms which regulates the contractility of the heart or the cardiac output during exercise is force-frequency relationship. And this indicates the force-frequency relationship that once your heart rate goes up, normally you will have a disproportionate increase in contractility. This is called a positive force-frequency relationship, when your contractility increases disproportionately to your heart rate.

Now we know that heart failure patients, especially when they have iron deficiency, actually manifest in reverse. They will have either a blunted or a down-sloping force-frequency relationship. And the reason for this was nicely illustrated in a paper out a few years ago in *European Heart Journal*. And they took a mice model of iron deficiency, and when they stimulated the mice with dobutamine, which induced the heart rate to go up, they actually found that contractility, which was measured invasively using DPTT, was actually decreasing.

So those mice had a negative force-frequency relationship, and the reason why this was, was because they measured myocardial energy reserve, and there was actually a drop in the energy measured as a phosphocreatine/ATP ratio. So there was insufficient energy to sustain that increased contractility during higher heart rates.

And given the very important effect of iron on both remodeling and energy metabolism, it's not surprising to see the associations that we see in our clinical practice, that our patients with HFrEF who have iron deficiency, they will manifest with a higher risk to die from cardiovascular diseases, to be admitted for heart failure in the hospital, and also they have a poorer exercise capacity or quality of life.

Dr. van der Meer:
Fully agree with you, Pieter. An excellent point, you raise. I think it's indeed very important to remember that iron is doing much more beyond hematopoiesis. And I think you very nicely pointed out that it's indeed crucial, also, for proper functioning of the mitochondria.

So now, I'm interested in how would you approach the care of such a patient. So let me describe a case which we recently had in our hospital. So it's a 51-year-old woman with nonischemic cardiomyopathy. She's treated with maximal tolerated dose of beta-blockers, bisoprolol 5 mg. She receives ramipril 10 mg; an MRA, spironolactone 25 mg; and she's euvolemic and functioning in New York Heart Association Functional Class III. Her ECG shows sinus rhythm 90 beats per minute, and a left bundle branch block with a QRS duration of 145 milliseconds.

So our therapeutic plan when she was referred to our university hospital consisted of CRTD, adding ivabradine, and switching ramipril for sacubitril/valsartan, and adding an SGLT2 inhibitor. So at 6 months' follow-up, after CRT, the patient unfortunately had only a 0.2% increase in her ejection fraction and similar end systolic and diastolic volumes. When we did additional lab testing, we found that she had a hemoglobin level of 13.4 grams per deciliter, a ferritin concentration of 63 nanograms per milliliter, and a transferrin saturation of 18%.

So my question to you, Pieter: What is the clinical evidence for iron supplementation in patients with HFrEF and iron deficiency, who are receiving CRT, and how does this apply also to this patient?

Dr. Martens:
Think the patient that you highlight is an interesting case, and it's a relevant case. These are the patients that we typically see in our CRT clinic and the literature would label them as "nonresponder." They don't seem to improve that much in terms of ejection fraction. So that always prompts us to think about different metaphysiologic mechanisms that might be contributing to the disease, and the lab work shows that the patient has iron deficiency. So this will prompt us to start the patient on IV iron therapy. So first of all, I think it's important to remember that prescribing oral iron in this patient will not really lead to any benefits, because the IRONOUT-HF trial showed that oral iron doesn't replenish transferrin saturation, so the way to go is probably prescribe an IV therapy.

And this case that you highlight would be a typical patient that could have been enrolled in the IRON-CRT trial. This was a multicentered, randomized, controlled trial that we did in which patients with heart failure with reduced ejection fraction who received CRT as part of their treatment plan – CRT worked adequately as documented by a high percentage by ventricular pacing. Those had iron deficiency and they had still a persistent reduced left ventricular ejection fraction. Those patients were randomized to either intravenous ferric carboxymaltose or to IV placebo. And we measured, after 3 months, the change in left ventricular ejection fraction measured by 3D echocardiography, and this was a primary endpoint. And what we saw was that patients who were allocated to the ferric carboxymaltose arm, they had an improvement in their left ventricular ejection fraction. This was about an absolute 4% improvement in ejection fraction, which was driven by a significant reduction in the left ventricular and systolic volume after 3 months. So iron therapy in this patient could induce incremental reverse remodeling.

Additionally, in the IRON-CRT trial, we looked at some supportive secondary and tertiary endpoints. And one of the secondary endpoints that we looked at was actually measuring the force-frequency relationship. Remember, I alluded to this earlier, but because our patients have a CRT device, we were able to artificially increase their heart rate in a fashioned manner.

And we did this using a validated force-frequency pacing protocol, in which we increased heart rate from 70 to 90 to 110 beats of pacing per minute. And at those time points, we measured the cardiac contractility using a noninvasive cardiac contractility index. And patients in the IRON-CRT trial, as alluded to in the beginning, they have a negative force-frequency relationship. Their contractility goes down at higher heart rates. However, 3 months after treatment with ferric carboxymaltose, what we noticed was that the negative force-frequency relationship in the IV iron-treated patients was transformed to a positive relationship, indicating that there is an improvement in the cardiac performance seen in our patients.

Looking at our tertiary endpoints, this improvement in cardiac contractility was actually associated with improvement in the functional status, measured by the Kansas City Cardiomyopathy Questionnaire, and also an improvement in your maximal exercise capacity of our patients.

Dr. van der Meer:
Thank you, Pieter, for this very clear answer, and also for elaborating on the IRON-CRT trial. Very important data you showed there. And I think it's also very much in line what we observed in the AFFIRM acute heart failure trial, where we also observed improvement in quality of life during follow-up.

For those just tuning in, you're listening to CME on ReachMD. I'm Peter van der Meer, and here with me today is Dr. Pieter Martens. We're discussing the impact of iron deficiency on cardiac remodeling in patients with heart failure with reduced ejection fraction.

So that's indeed how we treated our patient, Pieter. We gave her intravenous iron because she was iron deficient. Her ferritin level was below 100, and the definition of iron deficiency in patients with heart failure is based on 2 components: on one hand, ferritin and on the other hand, transferrin saturation. So when the ferritin is below 100, iron deficiency can be diagnosed in patients with heart failure. But sometimes, ferritin levels may not reflect very well iron status in patients with heart failure because it's an acute-phase reactant ferritin, so it might be elevated while there is still iron deficiency present. So when ferritin levels are between 100 and 300, transferrin saturation needs to be measured, and if transferrin saturation is below 20%, there is – even when ferritin levels are between 100 and 300, patients are considered iron deficient.

This definition is used in many trials, so for example, the FAIR-HF, the AFFIRM and EFFECT-HF, and all these trials showed beneficial effect of intravenous iron, like correcting iron deficiency, improving exercise capacity and quality of life. And I think, recently, we also showed data on hard endpoints from AFFIRM, where we showed what I mentioned previously, a benefit on quality of life but also a significant reduction in heart failure hospitalizations.

So one question, Pieter: So what are your thoughts on heart failure patients with iron deficiency without an initial response of CRT?

Dr. Martens:
I think it shows that heart failure is a complex disease, and very often in the patients, multiple elements contribute to the poor trajectory that we see in our patients. So for patients that we typically see in a CRT clinic because they received CRT, their electromechanical desynchrony as one of the pathophysiologic mechanisms contributing to their heart failure is being alleviated, but I think it also shows that about 50% still have iron deficiency, which is another metaphysiologic mechanism contributing to the overall heart failure in a patient. So it's important, I think, that we screen these patients, and if they have iron deficiency, that they treat that. I think this multilevel intervention with CRT, IV iron, other drugs – combining everything will put the patient on the best possible trajectory, and I think this is always the goal in our CRT clinics. Try to make the patient as good and try to improve their disease in the best possible way.

Dr. van der Meer:
Well, this has certainly been an excellent conversation. But before wrapping up, Dr. Martens, can you share your one take-home message with our audience?

Dr. Martens:
If iron deficiency is common in your CRT patients – 50% has it – and if you treat iron deficiency with intravenous ferric carboxymaltose, this can improve the cardiac function and the structure that you observe in your patients.

Dr. van der Meer:
Fully agree with you, Pieter. Iron deficiency is indeed very common, and we should look further than only hemoglobin. The majority of the patients with heart failure and iron deficiency have a normal hemoglobin value, so it's very important, also, to screen for iron deficiency in patients who are non-anemic, and treatment of iron deficiency improves not only quality of life, but what we've seen also from the AFFIRM study, also reduces heart failure hospitalizations.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in, and thank you, Dr. Pieter Martens, for joining me and for sharing all of your valuable insights. It was really great speaking with you today.

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