Title: HFA 24: Differential Effects of Inter-Atrial Shunt Treatment in HF Patients with Reduced Vs Preserved Ejection Fraction: RELIEVE-HFParticipants: Dr Michael Zile
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"My name is Michael Zile. I'm from the Medical University of South Carolina in Charleston. And today I'm going to talk about the V-Wave RELIEVE HF trial and the structural and functional changes that occur with V-Wave.

Rationale for Interatrial Shunt

So, let's talk about several aspects of this. The first question is, why would you put in an interatrial shunt in any patient with heart failure? Particularly, why would you do it across the ejection fraction spectrum?

And the answer to that really lies in the fact that in all patients who are symptomatic with heart failure, their left ventricular diastolic filling pressures are elevated. That means left ventricular pressure is elevated, left atrial pressure is elevated, pulmonary venous pressures are elevated, and the elevation of these pressures presage and predict and are the cause of decompensations.

So if the target of an interatrial shunt, which is to offload the left side by allowing a small amount of blood to go to the right side, that prevents the elevation in left atrial pressure, like a pop-off valve. And if the pathophysiology of decompensated heart failure is that pressure, then it doesn't matter what your ejection fraction is.

Study Design and Rationale

So, in this particular trial, we chose to study all patients with heart failure with all ejection fractions. However, what we knew was that there are fundamental differences in the structure and function and outcomes in patients with HFrEF, that is, heart failure with a

reduced ejection fraction, compared to patients with heart failure and a preserved ejection fraction.

And we did not know to begin with which group or whether both groups would benefit from this.

Results of the RELIEVE HF Trial

So, if we move to the results of the RELIEVE HF trial, the RELIEVE HF trial was done as one composite study in which all patients with heart failure, regardless of the ejection fraction, were combined. The safety endpoint was positive. The primary effectiveness endpoint was neutral.

However, if you look at the prespecified analyses of HFrEF versus HFpEF, it turns out that the left ventricular ejection fraction determines a positive effect of the shunt. In the HFrEF group, those patients with a heart failure and an ejection fraction less than or equal to 40% had a positive effect. In the HFpEF group, heart failure with an ejection fraction greater than 40% had a negative effect.

Degree and Mechanism of Effect

So the next question becomes, if that's true, to what degree is it true and why is it true? So the degree to which it's true is that in HFrEF patients, the composite endpoint of interest, which is all cardiovascular events, was reduced by 45%. In the HFpEF group, an oppositional effect occurred where there was an increase in all cardiovascular events by 68%.

So a diametrically opposed result, which means that even though this was a single study in which all the patients were pooled together, there's no statistical reason to have done that. In fact, there's every statistical reason to say that they are not poolable and that they should be looked at as two distinct groups. In other words, what we really did was two trials in one.

Structural and Functional Differences

Okay, the next question is, if there's a differential effect in outcomes, why? Why did that occur? What was the mechanistic basis for that? What underlay that finding?

So we thought about the structural and functional differences in the myocardium in these two kinds of heart failure, in these two syndromes of heart failure. And what we knew was a priori, the stiffness of the left ventricle was markedly increased in HFpEF and markedly reduced in HFrEF.

So based on that, we went and looked at all of the data from paired echo studies, baseline versus twelve months, and what we found was that indices of left ventricular diastolic stiffness at baseline were just exactly what I said. The left ventricle was stiffer than the right ventricle, but when you added a shunt, the stiffness in HFrEF fell down the curve in a proportional fashion, and in HFpEF, it got stiffer. Not only is the left ventricle stiffer, but the right ventricle is stiffer.

And when you add a shunt volume in the HFrEF group, there was no change in right ventricular volume, right atrial volume, the size of the inferior vena cava, or pulmonary artery pressures. So there was no increase in right ventricular preload or afterload, because both the right ventricle and the left ventricle had less stiffness, they were more compliant.

That's in HFrEF and HFpEF. On the other hand, after you placed the shunt, right atrial volumes went up. Right ventricular volumes went up, and PA, that is, pulmonary artery systolic pressures, rose. That means that the right ventricle after the shunt had an increase in preload and afterload and could not tolerate that shunted volume because both the right ventricle and the left ventricle were non-compliant.

And as a matter of fact, that increase in PA systolic pressure, which on average was two and a half millimetres of mercury, predicted an increase in mortality. How do I know that? There's been at least two previous studies in which we've examined the relationship between changes in PA pressure and changes in mortality, and whether

you're measuring PA diastolic pressure, PA systolic pressure, or PA mean pressure. One millimetre increase in PA pressure is associated with a five to 7% increase in mortality.

So here we had a two and a half millimetre increase in pressure. And if you look at the V-Wave data, this occurred only in the HFpEF patients and there was an increase in mortality of about 15%. So the prediction of mortality based on the PA pressure was true, and the PA pressure went up because the right ventricle couldn't handle that volume.

Comparison with Other Studies

Now, you might ask the question, well, maybe the volume from the shunt was higher in HFpEF than HFrEF. The answer is nope, it's just the opposite. The volume that was shunted was higher in the reduced ejection fraction patients compared to the preserved ejection fraction patients. And the reason for that was the differences in compliance.

In HFrEF, the compliance was better. In HFpEF, the compliance was worse.

Future Directions

So where do we go from here? What are the next steps that needed to be taken in the studies of interatrial shunting in patients with heart failure?

What I would say is that the evidence to support the use of a shunt in HFrEF is pretty robust. One of the other presentations that were made today was by Stephan Anker, and he demonstrated that if you added cardiovascular events with non-cardiovascular events, the total number of events doubled. So while the total number of patients may be on the margin, in some people's point of view, the number of events wasn't, and the p-value that support the significance in terms of morbidity and mortality was profound.

So I think we all look forward to moving forward in this field and applying shunting to HFrEF.

HFpEF Considerations

What about HFpEF? The Corvia company has sponsored a trial called REDUCE-LAP HF2, in which they demonstrated that in HFpEF there wasn't a reduction in morbidity and mortality with their shunt. However, when they did a subgroup analysis, which they called a responder and non-responder, the responder, obviously because it's called responder, had a better outcome than the non-responders.

And they've now pursued a second trial, which is called the RESponder trial, and other shunt companies like Allay. The Allay study, which is creating an atrial septostomy without leaving a device behind, has copied that same protocol. So the responder characteristic patients will be studied in two studies.

In my opinion, it's critical that those studies get completed and we determine whether there's a reduction in morbidity and mortality in that subgroup of patients with HFpEF. So there may still be a window of opportunity. Jim Udelson always says, what's the strike zone? So the strike zone for HFpEF, I think, is still possible that there is a strike zone.

Differences Between Studies

And then you might ask, what's the difference between the HFpEF patients studied in the Corvia-sponsored study versus the RELIEVE HF-sponsored study? In general, the HFpEF patients in RELIEVE, the V-Wave study, had clearly had more extensive disease, more severe disease. Their levels of NT-proBNP were higher, their comorbidities were higher. There was substantially more evidence that those patients had advanced disease.

The single most important distinguishing feature between RESponder and RELIEVE is the fact that RESponder is requiring a cutoff for pulmonary vascular resistance. So pulmonary vascular resistance is one way to think about how the right ventricle and the

pulmonary artery will receive the shunted blood. And they've limited this to patients under 1.5 pulmonary vascular resistance.

On average, the responder group that they looked at had a PVR of 1.6. The non-responder group had a PVR of 1.9. In the RELIEVE HF trial, the HFpEF patients had a PVR of about 2.1. So you can see the marked difference in pulmonary vascular resistance between the two studies, and you can see where a subgroup of patients with HFpEF might be advantaged by a shunt. But we have to wait for the data.

Conclusion

So I would say the areas of greatest need is to push forward in HFrEF and to keep pushing forward in HFpEF, but in a narrower, highly specific group of patients.