Title: HF 22: Ghrelin-HF: Intravenous Ghrelin In Patients with HFpEF
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- My name is Lars Lund, I'm a Professor of Cardiology at the Karolinska University Hospital in Stockholm, Sweden.

Aims of This Study

So, patients with advanced heart failure and reduced ejection fraction, their primary problem is reduced contractility. And we have tremendous treatments today for heart failure with reduced ejection fraction. But what they all do, is that they block the progression, none target the underlying pathology, which is reduced contractility. In extreme settings, we use intravenous inotropes and they do improve contractility, but are otherwise harmful and are recommended only in rare settings.
We've developed a new treatment concept based on the endogenous ghrelin peptide, which we believe has the potential to improve cardiac contractility and improve cardiac output, and thus have a good potential in acute and advanced heart failure. And we believe that this concept, it will not have the same adverse effects that traditional inotropes do, and therefore our treatment concept and our mode of action may be suitable for long term and chronic use.
So, we hope to improve cardiac output, quality of life and symptoms and outcomes in patients with heart failure, reduced ejection fraction of moderate to severe degree.

Mechanism of Action

So, ghrelin is an endogenous peptide. It's secreted by the stomach, and it acts primarily by stimulating appetite. But we and others have shown that it also has vascular and direct cardiac effects. And in preclinical studies, we do have some hints that it might act in a favourable mechanism without inducing calcium, which the traditional inotropes do, but instead by increasing the sensitivity to existing calcium, which would not be associated with ischemia, tachycardia, arrhythmia.

Patient Cohort and Study Design

Yeah, this is a double-blind, placebo controlled, randomised trial of ghrelin given for two hours intravenously, or placebo given for two hours intravenously. Patients were ambulatory in New York Heart three to four, so moderate to severe heart failure but not in the hospital, an eject fraction of less than or equal to 40%. So moderately to severely reduce ejection fraction. And they spent one day in the hospital where we performed multiple investigations before, during and after this treatment.
So multiple biomarkers and PK and PD assessment, of course but with the primary end point measure or primary outcome measure being changed in cardiac output.

Key Findings

The results showed that on this primary endpoint in this randomised trial, ghrelin increased cardiac output from a little above four to above five, it normalised cardiac output to more than five litres per minute, whereas the placebo group remained flat at approximately four litres per minute. So, this is a very clinically meaningful effect, highly statistically significant and provides great promise for this treatment concept to be developed further.

Take-Home Messages

Given this a very positive effect on cardiac output, the immediate worry is number one, is this associated with some harmful effect? But there was no hypotension, no tachycardia, no arrhythmia in our study.
And when we went to the lab and studied in beating ex vivo cardiomyocytes, we showed that the reason there were no clinical side effects is because indeed it does act through calcium sensitization rather than inducing increased calcium transient or calcium concentrations.
So, this explains why in the clinical study, we didn't see side effects. Furthermore, an important mode of action of most inotropes is that they are inodilators.
So, they act to a great extent by dilating vessels, reducing after load, and making it easy to increase cardiac output without increasing the force of contraction. But in our experimental setup, cells are beating in a load independent fashion, and we observed that they increased their fractional shortening. They contracted faster and better, even in the absence of vessels, either as a preload or afterload system.
So, the findings taken together, suggest that we increase the force of contraction, contractility, cardiac output through calcium sensitization, and without being dependent on a reduction in after load. Very promising for clinical future studies and applications.