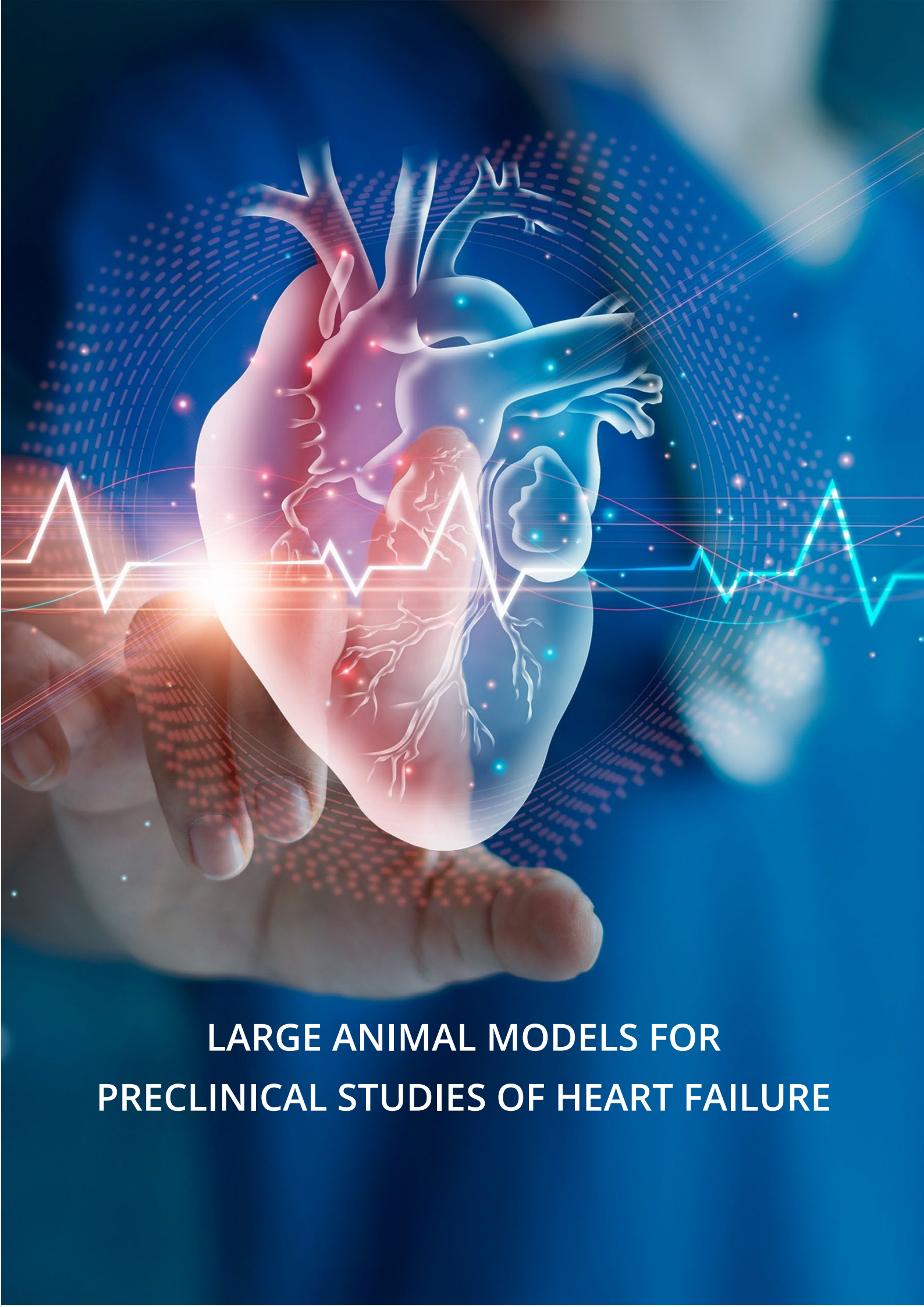

LARGE ANIMAL MODELS FOR PRECLINICAL STUDIES OF HEART FAILURE

WEBINAR SUMMARY: LARGE ANIMAL MODELS FOR PRECLINICAL STUDIES OF HEART FAILURE

A recent emka TECHNOLOGIES webinar, led by Dr. Angel Moctezuma-Ramirez from the Texas Heart Institute, explored several large animal models for heart failure research, focusing on their development, implementation, and significance in preclinical studies. Dr. Moctezuma-Ramirez, an expert in cardiovascular research, discussed innovative therapeutic techniques, mechanical circulatory support, and procedural advancements for minimally invasive treatments.

The Texas Heart Institute provides an advanced research center equipped for extensive preclinical work, including surgical and interventional procedures, device development, regenerative treatment efficacy testing, and training programs. Dr. Moctezuma-Ramirez shared insights into four critical large animal models used to study heart failure, highlighting the role of emka telemetry, IOX software, and ecgAUTO software for detailed monitoring and analysis.

The article below summarizes some of the key points that were presented during the webinar. The presentation was also recorded and is available here.

Watch the webinar

1. ACUTE MYOCARDIAL INFARCTION (AMI) MODEL

The first model discussed was an acute myocardial infarction (AMI) model, designed to replicate heart attacks in porcine subjects. Based on a study by Li *et al.* in 2021, this model aimed to balance low mortality rates with a significant reduction in left ventricular function, measured as a greater than 30% decrease in left ventricular ejection fraction (LVEF). To induce AMI, researchers performed a percutaneous balloon occlusion in the left anterior descending artery for a full 90 minutes, following an initial echocardiogram baseline. Fourteen days later, animals that exhibited the targeted LVEF reduction underwent a secondary echocardiographic evaluation and NOGA electromechanical mapping to assess infarcted and surrounding heart tissue.

To maintain a low mortality rate in this AMI model, the team implemented a prophylactic antiarrhythmic protocol using amiodarone and lidocaine, administered continuously to prevent arrhythmic complications during and after the procedure.

Any ventricular fibrillation that occurred during balloon inflation was managed with electrical cardioversion, epinephrine administration, and compressions as needed. Despite the procedure's complexity, the study achieved an impressive low mortality rate of 4.8%.

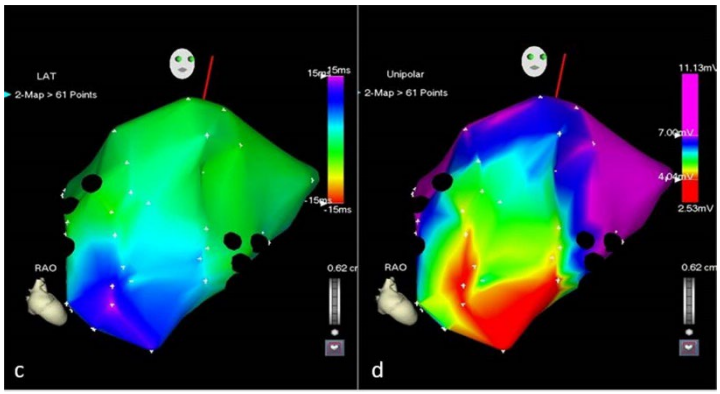

Figure 1: Li *et al* (2021) (c) NOGA mapping of local activation time (LAT) at day 14 shows a delay (blue) around the apex, indicating slower electrical conduction in this area. (d) NOGA velocity mapping at day 14 shows that this delayed LAT area overlaps with the infarction zone.

The NOGA mapping results in Figure 1 showed distinct infarct and border zones, with decreased strain and desynchrony observed in regions beyond the occlusion site. The ecgAUTO software facilitated precise arrhythmia analysis, confirming that the AMI model was effective in producing consistent, measurable functional changes in left ventricular performance.

2. GENE THERAPY FOR HEART FAILURE

Next, Dr. Moctezuma-Ramirez introduced a gene therapy model for heart failure, targeting the Hippo signaling pathway—a pathway known to inhibit cardiomyocyte renewal in adult hearts. Building on the work of Zhang *et al.* (2022), this study used gene therapy to repress Hippo signaling and thereby promote cardiomyocyte regeneration after myocardial infarction.

An AMI was induced in the study animals, and an easyTEL+L telemetry device was implanted for continuous ECG monitoring, with IOX software visualizing cardiac rhythm data. Two weeks after AMI, a viral vector carrying short hairpin RNA (shRNA) was delivered to silence Hippo signaling, and continuous monitoring was maintained for an additional 30 days to assess therapeutic effects. The team focused on PVC and atrial tachycardia as key arrhythmic events.

The shRNA-treated group showed a significant decrease in PVC frequency after treatment compared to the control group, with arrhythmia incidence stabilizing to baseline levels by day 10 (Figure 2). Importantly, no adverse arrhythmogenic effects were observed, unlike some other gene therapies reported in literature.

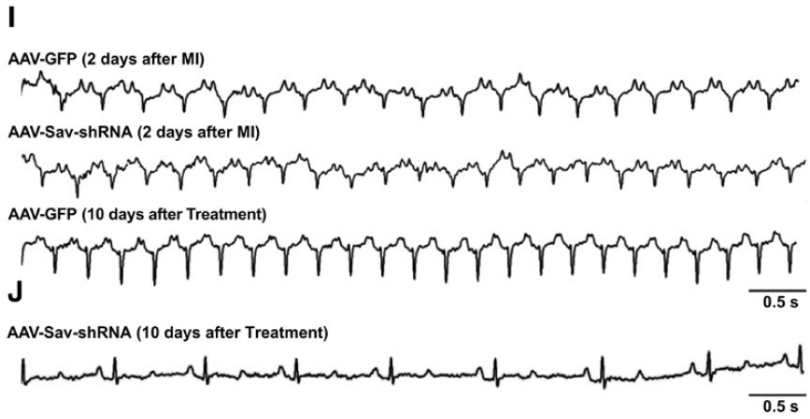

Figure 2: Zhang *et al* (2022). (I) Sample ECG traces showing atrial tachycardia at various times after MI. (J) Sample normal ECG recorded 10 days after AAV-Sav-shRNA injection

The IOX software and ecgAUTO analysis provided valuable insights into how this gene therapy reduced arrhythmic events and promoted functional cardiac recovery in large animal models.

3. HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF) MODEL

Dr. Moctezuma-Ramirez then discussed a heart failure model with preserved ejection fraction (HFpEF), designed to simulate systemic hypertension and metabolic syndrome.

In this model, the team used a combination of aortic occlusion, dietary modifications, and metabolic adjustments. An aortic cuff was surgically implanted in the animals to create pressure overload, and emka telemetry was used to track left ventricular and arterial pressure continuously. Insulin deficiency was induced through streptozotocin injections, and animals were placed on a high-fat, high-salt diet. Progressive inflation of the aortic cuff increased pressure weekly until a target of 80 mmHg was reached, simulating the gradual onset of systemic hypertension often associated with HFpEF. Echocardiography and blood tests conducted weekly revealed substantial changes in glucose levels, LV wall thickness, and left atrial end-diastolic volume (LA EDV) in the experimental group, aligning with HFpEF criteria.

The IOX software provided real-time signal monitoring (Figure 3), while telemetry data allowed for comprehensive, continuous tracking of cardiovascular parameters. However, technical challenges arose, such as cuff leaks and diet adherence difficulties. To address these, the team developed a patented diet and employed additional tools to enhance model reliability.

This HFpEF model serves as a vital tool in understanding how pressure overload and metabolic factors contribute to heart failure with preserved ejection fraction.

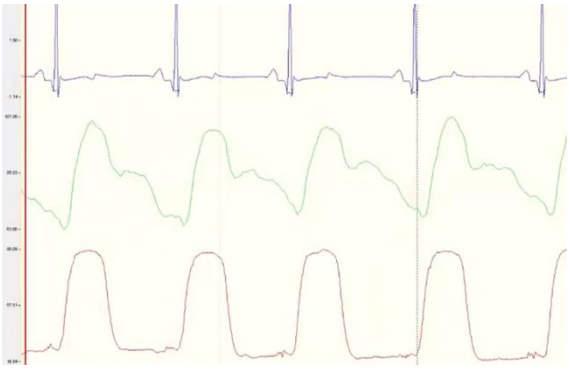

Figure 3: Real-time measurements displayed by IOX software, showing an EKG waveform (top), aortic pressure (middle), and left ventricular (LV) waveform (bottom)

4. TACHYPACING MODEL FOR HEART FAILURE

Lastly, Dr. Moctezuma-Ramirez described a tachypacing model to induce heart failure through controlled, incremental increases in heart rate. In this model, a pacemaker was implanted in the right ventricle, initially set to a baseline rate of 110–120 beats per minute, with weekly rate increases until reaching 150 bpm or an LVEF drop below 35%. This model, monitored using emka telemetry and ecgAUTO software, demonstrated a clear correlation between increased pacing rates and declining LVEF, simulating the progression of heart failure. Each pacing increment led to a gradual reduction in LVEF, which was carefully tracked through continuous telemetry and arrhythmia analysis.

5. CONCLUSION

Dr. Moctezuma-Ramirez's presentation highlighted large animal models' indispensable role in preclinical heart failure studies. By integrating advanced monitoring tools such as emka telemetry, IOX software, and ecgAUTO software, researchers achieved accurate, real-time tracking of cardiovascular events, arrhythmias, and LVEF changes. Each model discussed — from AMI and gene therapy to HFpEF and tachypacing — provided valuable insights into different aspects of heart failure, enhancing the understanding of heart failure progression and response to therapies.

REFERENCES

» A Robust Percutaneous Myocardial Infarction Model in Pigs and Its Effect on Left Ventricular Function. (2021). Li, K., et al. *J Cardiovasc Transl Res. 14(6): 1075-1084*

» Gene Therapy Knockdown of Hippo Signaling Resolves Arrhythmic Events in Pigs After Myocardial Infarction. (2022). Zhang, S., et al. *Circulation, 146(2)*

MORE RESOURCES

» Evaluating large Animal models of Heart Failure with hFpEF Using Clinical Scores
» Accurately Phenotyping Arrhythmia in rodents
» Mitigating transient Arrhythmogenicity in pig following human cardiomyocyte transplantation
» Identifying premature ventricular contractions with ecgAUTO software