Transverse Aortic Constriction:
The Importance of Monitoring Surgical Outcomes

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Topics of Discussion

- Transverse Aortic Constriction – considerations during model development
- Monitoring Surgical Outcomes
- Importance of Stratification of Animals by Severity
TAC – Considerations during model development

- Compensated left ventricle hypertrophy vs. Heart failure outcomes
- Considerations in study design
TAC Model – Left Ventricular Hypertrophy vs. Heart Failure
Transverse Aortic Constriction (TAC)

- Transverse aortic constriction (TAC) was initially developed as a surgical technique to rapidly induce left ventricle cardiac hypertrophy as a model to study the cellular and molecular pathways involved in remodeling.

- This surgical model allowed for the use of a variety of transgenic mice to provide valuable insights, and to study novel therapeutic interventions, for the treatment of cardiac hypertrophy and heart failure.
Cardiac Hypertrophy vs. Heart Failure

• Pressure overload, induced by TAC, initially results in compensation by the left ventricle to maintain cardiac output. Over time, in some animals, this advances to heart failure.

• The increased load on the heart initially causes left ventricle cardiac hypertrophy as the muscle must work hard to maintain a normal cardiac output.

• Heart failure occurs when the myocardium is no longer able to compensate for the increased load; the ventricle ultimately dilates and the heart no longer fills or contracts adequately to maintain its normal output.
TAC Model – Considerations in Study Design
Most measurements and parameters are functions of time, so we need waveforms.

Considerations in Study Design

• **Variability in surgical success** may occur in many forms, from **mortality** to **surgical outcomes**
  
  • Mortality may vary immediately following surgery and over the time course of study
  
  • Surgical outcomes may vary in severity and manifestation of left ventricular cardiac hypertrophy and/or heart failure

• Variability has been shown by many authors to vary based on a number of factors
  
  • Mouse strain
  • Sex
  • Surgical technique
  • Standardization of needle size
  • Percent stenosis of the aorta
  • Time course
Surgical Techniques

- Conventional open chest technique – Rockman et al. 1991
- Minimally invasive technique – Hu et al. 2003
- O-ring aortic banding open chest technique – Melleby et al. 2018
Originally published by Rockman et al. in 1991 the widely accepted transverse aortic constriction (TAC) surgery involved an open chest procedure in which the mice were intubated and a suture along with a 27 gauge needle was used to create a 0.4mm diameter stenosis in the transverse aorta, resulting in 65-70% stenosis on the 8 week old mice.

The goal of Rockman’s original studies was to develop a surgical model to begin investigating the role of specific signalling molecules in the development of hypertrophy and heart failure by making use of the wide variety of transgenic mice models being developed.
The minimally invasive technique was developed to simplify the TAC procedure. In this closed chest technique no ventilator was required as the pleural space was not entered. Similar to the original technique a suture was tied around a 27 gauge needle to create the stenosis.

The goal of Hu’s studies were to develop a more accessible surgical technique that could be used to continue the investigate the cellular and molecular pathways involved in left ventricle hypertrophy.
This open chest procedure utilizes fabricated O-rings with fixed inner diameters (0.71mm, 0.66mm, and 0.61mm) resulting in reproducible and graded levels of stenosis.

The goal of Melleby's studies was to develop a more consistent model of TAC, allowing for the continued investigation into therapeutic options and a continued understanding of the underlying mechanisms of cardiac remodelling.
Needle Size & Percent Stenosis

- One must consider their choice of **needle size** based on the desired outcome, as this will determine the **percent stenosis**. The resulting **pressure gradient** across the band has been found to **correlate with the severity of hypertrophy and progression to heart failure**.  

- If working with transgenic animals one must also consider the **diameter of the aorta** compared to the control animals being used; it may be smaller, and therefore considerations made to maintain the same percent stenosis and resulting pressure gradient rather than applying a standard needle size which may introduce further variability.
Monitoring Surgical Outcomes

- Confirming surgical success – carotid flow velocity
- Determining relative tightness of band - stenotic jet flow velocity, carotid artery flow velocity ratio
- Monitoring cardiac function over longitudinal study
  - Doppler measures of systolic and diastolic function
  - Structural measures of cardiac function (MRI and Ultrasound)
Confirm Surgical Success
Normal flow through aorta and carotid arteries

Surgical technique to create Transverse Aortic Constriction (TAC)

Flow to the right carotid artery is dramatically increased.

Left carotid artery receives little flow.

The flow through the aortic stenosis becomes jet-like and the velocity increases substantially.

Abnormal flow through aorta and carotid arteries post-banding.
To achieve **accurate, reproducible, flow velocity measurements** the **angle** between the Doppler probe and blood flow must be **minimized** – this is possible with the **Doppler Flow Velocity System from Indus Instruments**.

This difference between right and left carotid flow velocity confirms the **location of band is correct**.
Confirming Surgical Success

Tightness of Aortic Band

Peak Flow Velocity Ratio measured:

\[ \text{Ratio} = \frac{\text{Right Peak Flow Velocity}}{\text{Left Peak Flow Velocity}} \]

Stenosis Jet Flow Velocity measured post surgery can be used to approximate the pressure drop across the band using a simplified Bernoulli’s equation:

\[ \Delta P = 4V^2 \]

Where P is reported in mmHg, if V is in m/s

Hartley et al., Ultrasound Med Biol 34, 2008
Confirming Surgical Success

Tightness of Aortic Band

Right Carotid Velocity

No Band
Ratio ≈ 1.0

Loose Band
Ratio ≈ 4.5

Tight Band
Ratio ≈ 6.2

Left Carotid Velocity

Stenosis Jet Velocity

ΔP ≈ 4mmHg

ΔP ≈ 15mmHg

ΔP ≈ 49mmHg

Hartley et al., Ultrasound Med Biol 34, 2008
Monitoring Cardiac Function
Heart failure occurs when the myocardium is no longer able to compensate for the increased load; the ventricle ultimately dilates and the heart no longer fills or contracts adequately to maintain its normal output. At this stage cardiac function drops, the left ventricle dilates, and the walls thin.

The pressure overload caused by TAC increases causes left ventricle cardiac hypertrophy as the muscle must work hard to maintain a normal cardiac output. At this stage cardiac function is normal, however wall thickness increases.
Monitoring Cardiac Function

Doppler Measures

Diastolic Function may be measured through the mitral valve, reported as the E/A ratio, IVRT & IVCT, or simply the peak E flow velocity.

Systolic Function may be measured as peak flow velocity through the aortic valve.

Both systolic and diastolic measures of cardiac function are normal during hypertrophy, both decline with the onset of heart failure.
Structural measures of cardiac function may be measured from either a long or short axis view of the left ventricle using ultrasound.

These measurements can be made with the Prospect T1 system from S-Sharp.
Various measurement techniques are possible, here from a B-mode image the Area Length Measurement:

- End diastolic volume; End systolic volume
- Stroke volume
- Ejection fraction
- Fractional area change
- Fractional shortening
- Left ventricular mass
Monitoring Cardiac Function

Structural Measures - Ultrasound

- Can be done on either the long or short axis **M-mode image**
  - LV mass
  - LV mass index
  - Fractional shortening
  - End diastolic volume; end systolic volume
  - Stroke volume
  - Ejection fraction
  - Cardiac output
Structural measures of cardiac function may also be measured using MRI, the gold standard in soft tissue imaging.

These measurements can be made with the M-Series™ Systems from Aspect Imaging.
Monitoring Cardiac Function

Structural Measures - MRI

- Cardiac function can be measured from a single slice, or collection of short and long axis images

- Measurements could include:
  - Ejection Fraction
  - Volume Measurements – i.e. stroke volume, end-diastolic, and end-systolic volumes
  - Wall Thickness
  - Left Ventricular Mass
Importance of Stratification of Animals by Severity

• When and how to stratify animals
• Improved power and significance of therapeutic response measured
When and How to Stratify Animals

- **Stratification** – is the partitioning of subjects by a factor other than treatment given; i.e. tightness of band, or development of heart failure

- One may choose to stratify animals
  - **Immediately** following surgery based on a functional marker; i.e. stenosis jet flow velocity
  - At a **specified time-point** based on a functional marker; i.e. carotid artery flow velocity ratio
  - Upon **disease progression** meeting a specified level of functional marker; i.e. blood pressure value, cardiac function parameter
Improved Power and Significance of Therapeutic Response Measured

- Stratification ensures that the *variability between animals within a study group is minimized*, specifically with respect to tightness of the band, development of heart failure, or other parameter chosen to stratify by.

- *Therapeutic efficacy* can then be *measured with more power and significance* with respect to the specific target, whether that’s prevention of disease onset, or regression of advanced disease.

If all animals are *grouped together with no monitoring of surgical outcome or disease progression for stratification*, and a therapy given to treat heart failure at a specific time point, then the *therapeutic effects may not be fully understood as some animals may never have had the remodeling the compound was designed to resolve*. 
Top ics of Discussion

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• Importance of Stratification of Animals by Severity
Q&A SESSION:

To ask a question, **click the Q&A Button**, type your question and click send. Any questions that are not addressed during the live webinar will be answered following the event.

Thank you for participating!

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