THE EFFECTS OF PDE-5 AND DPP-4 INHIBITORS ON TESTICULAR MORPHOLOGY IN A PORCINE MODEL FOR HEART FAILURE

College of Veterinary Medicine
University of Missouri

Damian H. Peyton[1], Craig A. Emter[1], and Tim J. Evans[1]
[1]College of Veterinary Medicine University of Missouri-Columbia

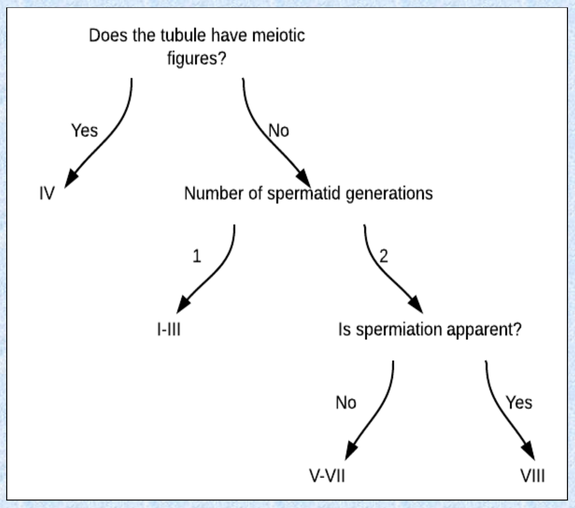
BACKGROUND

- Heart failure affects many Americans, and there have been numerous attempts by researchers and clinicians to find better ways to treat this disease syndrome.
- Studies aimed at evaluating the effects of novel heart medications, including PDE-5 and DPP-4 inhibitors, are currently under way.
- PDE-5 breaks down cGMP, which promotes relaxation of cardiac muscle, along with modulating testosterone production in the testes.
- DPP-4 breaks down incretins, like GLP, and some studies have shown DPP inhibitors to be cardioprotective. These have unknown effects on the testes.
- One of these classes of drugs is used in the treatment of erectile dysfunction (PDE-5 inhibitor), and the other is used in the treatment and control of diabetes (DPP-4 inhibitor).
- Both classes of drugs are thought to have potential as medications for the treatment and control of heart failure.
- However, there is little known about the effects of long-term use of these drugs on spermatogenesis.
- Histopathologic evaluation of the testes and staging of the seminiferous tubules are considered the gold standards for evaluating spermatogenesis, especially when semen is not being collected.

EXPERIMENTAL HYPOTHESIS

Six months of aortic band-induced heart failure, plus or minus oral administration of a PDE-5 or DPP-4 inhibitor, will adversely affect porcine spermatogenesis.

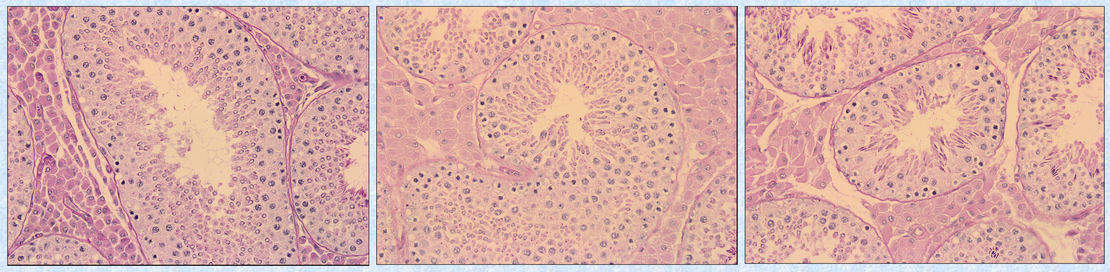
METHOD FOR STAGING SEMINFEROUS TUBULES



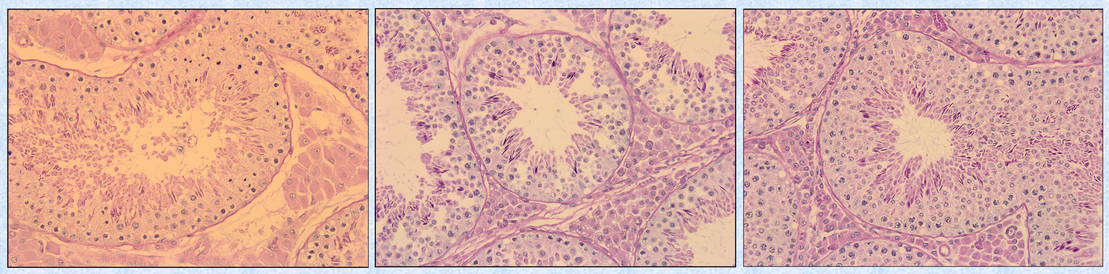
RESEARCH OBJECTIVE

Examine the effects of two novel heart failure medications, both of which are marketed for other purposes, on spermatogenesis in a porcine model for heart failure.

STAGES OF THE SEMINIFEROUS TUBULES



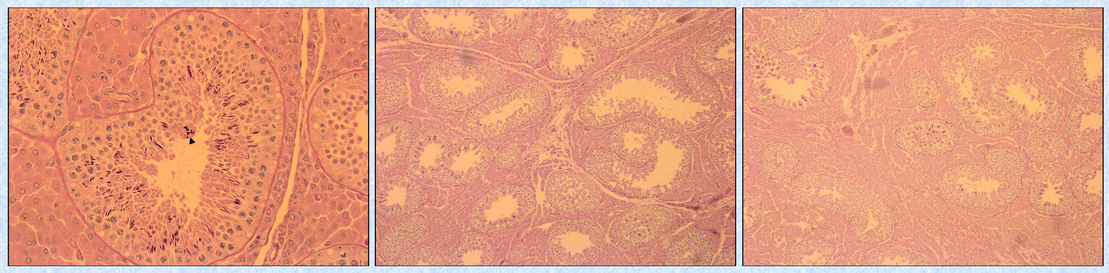
From left: Stage I, Stage II, Stage III



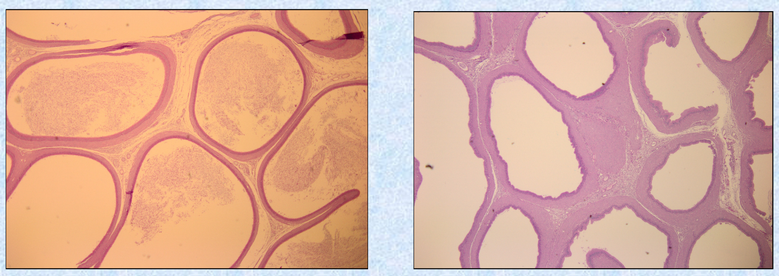
From left: Stage IV, Stage V, Stage VI

From left: Stage VII, Stage VIII, Seminiferous tubule degeneration

OTHER OBSERVED HISTOLOGICAL CHANGES



From left: Giant cell (arrowhead), normal Leydig (interstitial) cells, hyperplastic Leydig cells



From left: Normal and abnormal (spermatozoa absent) caudae of the epididymidies

CONCLUSIONS

Chronic oral administration of a high dosage of the PDE-5 inhibitor, tadalafil, appeared to cause an increased incidence of degeneration of seminiferous tubules and a decreased frequency of spermiation in a porcine model for heart failure.

ACKNOWLEDGEMENTS

- Merck-Merial
- Boehringer Ingelheim Vetmedica
- Bristol Myers-Squibb/AstraZeneca
- University of Missouri College of Veterinary Medicine
- Veterinary Medical
- Diagnostic Laboratory
- Dr. Aaron Stoker
- Dr. Craig Franklin
- Dr. Chris Baines
- Catherine Jones
- Jan Ivey
- Shelly Nail
- Don Connor
- Karen Clifford

MATERIALS AND METHODS

- A total of 30 male Yucatan miniature pigs entered the study at 3 months of age.
- One group (Control) did not have aortic band-induced heart failure and was given vehicle alone (n=6). The remaining three groups had their aortas banded at three moths of age to induce heart failure and received no treatment (vehicle only; n=7) or either a PDE-5 inhibitor, tadalafil (n=8; 2 mg/kg BW, PO, q 12 hours) or a DPP-4 inhibitor, saxagliptin (n=9; 10 mg/kg BW, PO, q 24 hours), for six months.
- The testes were collected under anesthesia at the time of evaluation of heart function, followed by euthanasia, at nine months of age.
- The testes were placed in modified Davison's solution for at least one week, then into 10% neutral buffered formalin for at least one week.
- The testes were measured grossly (length, width, height) before being prepared for histology.
- Three micrometer-thick sections stained with Periodic-Acid Schiff were used for staging and histopathologic evaluation.
- At least 250 seminiferous tubules were staged from each boar using a modified version of a staging scheme first outlined by Swierstra (1968). For uniformity, we grouped the stages as pre-meiotic (I-III), meiotic (IV), post-meiotic (V-VII), and undergoing spermiation (VIII), with an additional option for degeneration.
- Statistical analyses were performed using ANOVA in SigmaPlot®.

RESULTS

Gross Measurements

- There were no statistically significant differences among the means of the lengths (p=0.54), heights (p=0.73), or widths (p=0.90) of any of the groups tested.

Histological Examination

- The tadalafil group differed significantly from the mean of the Control group in both stage VIII (*P*=0.042, Figure 1) and in degenerated seminiferous tubule frequencies (*P*=0.005, Figure 2).
- The other groups displayed no significant differences from the Control group mean (Figures 1 and 2 below).
- Furthermore, other abnormalities were much more apparent in the tadalafil group. Common abnormalities observed included giant cells, vacuolization, hyperplastic Leydig cells, and the absence of spermatozoa in the caudae of the epididymidies.
- In the control group (n=6), one specimen showed slight hyperplasia of the Leydig cells, with limited giant cells and vacuolization.
- In the control with heart failure group, most of the testes displayed vacuolization with two slides showing giant cells.
- The tadalafil group (n=8) showed mostly hyperplastic Leydig cells (six), with low sperm numbers in the epididymis, vacuolization, and giant cells throughout.