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Bedside Cardiac Biomarkers for Respiratory Distress

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Respiratory distress is a common presenting complaint and if left untreated can lead to exhaustion, respiratory failure, and death. Dyspneic patients are fragile, and any intervention, such as handling and routine diagnostics, will increased cardiovascular and respiratory demands and may result in rapid decompensation. Measures should be taken to reduce oxygen demands by administering cardiovascularly sparing sedatives and by administering supplemental oxygen. Often times it becomes necessary to get diagnostics in a step wise fashion, with breaks in between to allow the animal to recover in an oxygen rich environment. Several new biomarkers have recently received a large amount of attention in the literature as potential aids in diagnosing causes for respiratory distress. The ultimate goal of this research is to hopefully find a bedside, inexpensive, easy to administer, and easy to interpret test that may may guide the emergency treatment of the animal while getting these important diagnostics.

NT-proBNP

Natriuretic peptides are proteins that are produced in large quantities in the heart in response to stretch from excess volume. The first discovery of this hormone was in the atria, thus named atrial natriuretic peptide (ANP). The second natriuretic peptide was first found in the brain, but was later determined to be found in higher amounts in the heart, but still maintains its name of brain natriuretic peptide (BNP). There are other natriuretic peptides, but ANP and BNP are the main players when discussing excess volume that occurs with congestive heart failure. Natriuretic peptides act to encourage sodium and fluid loss through the kidneys, thus serves as a modifier of fluid balance. The active portion of the hormone is the C-terminal, but an inactive portion is made in equimolar amounts and is termed the amino terminal (e.g. NT-proBNP). Numerous studies have been performed to determine the usefulness of ANP, NT-proANP, and BNP, but it was NT-proBNP that had the best results and is now the one that is commercially available.

All natriuretic peptides are excreted by the kidneys and renal insufficiency can cause rises in their values. Cats with severe hypertension were also found to have increases in NT-proBNP levels. Dogs were shown to have significant weekly variability; several "normal" individuals would occasionally test in the abnormal range, so all animals may have a certain amount of fluctuation contributing to the imperfection of this test. Furthermore, several human and veterinary studies have shown that multiple conditions, both cardiac and non cardiac in origin, can influence the production of natriuretic peptides and so this test should be interpreted in conjunction with bloodwork and imaging.

Several studies have looked at use of NT-proBNP to distinguish dogs with congestive heart failure (CHF) from non cardiac causes of

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respiratory distress. The largest and newest of the studies showed an area under the curve (AUC) of the receiver operator curve (ROC) of only 0.84 (AUC of 1.0 is a perfect test, 0.5 is the equivalent to a coin toss), indicating that this test's accuracy is less than desirable. Cats, on the other hand, had an AUC of the ROC of 0.94, indicating that NT-proBNP may be fairly accurate in diagnosis of CHF in cats with respiratory distress. Furthermore, another study found that NT-proBNP was significantly higher in cats with pleural effusion secondary to CHF than in cats with pleural effusion from other causes. This study had relatively low numbers of enrolled patients, but found an AUC of the ROC of 1.0.

These studies were all conducted with a quantitative test which gives the clinician a numerical value to track. NT-proBNP has not been evaluated in the literature as a monitoring tool for animals that are being managed long term for CHF, but that may a future use. IDEXX has recently changed the test so it no longer requires the special additive that it once did. Best results are obtained from non-hemolyzed, EDTA plasma (lavender top tube, spin and separate plasma into red top tube). Turn around time is typically 1-2 business days and samples should be kept cold to prevent enzymatic degradation of NT-proBNP.

Recently, a bedside test has become available for feline NT-proBNP. This is a snap test similar to other IDEXX products where the color of the test dot is compared to the color of the reference dot. A test dot that is equal to or darker in color than the reference dot is considered an "abnormal" reading and should be followed up with further diagnostics, preferentially an echocardiogram. At this time, there are no publications in peer reviewed journals to evaluate the bedside test to diagnose CHF in cats with respiratory distress. However, it has been evaluated for cats with moderate to severe occult heart disease and shown to have a sensitivity and specificity of only 87% and 78% respectively for an overall accuracy of only 80%. The reason that the snap test is not as accurate as the send out quantitative test is that when you look at the data in the validation study, a "normal" result translates to a quantitative value of <270 pmol/L while an "abnormal" test equals a quantitative value of >100 pmol/L. Studies looking at the quantitative test showed that a cut-off of 100 pmol/L would be ideal as this was this was the lowest part of the range for cats with significant heart disease. The overlap in the snap test between "normal" and "abnormal" in this particular part of the range is significant enough to affect overall accuracy. Unfortunately at this time, the snap test has not been critically evaluated in cats with respiratory distress. However, a "normal" result makes heart disease severe enough to cause CHF unlikely, but does not rule it out completely. An "abnormal" test should be interpreted with other standard diagnostics, particularly blood pressure, renal values, and thoracic radiographs. When the cat is stable, an echocardiogram should be considered.

Cardiac Troponins

Troponins are proteins that are part of the contractile apparatus in cardiac and skeletal muscle. Cardiac troponins I and T (cTnI and cTnT) have enough differences between their skeletal counterparts that they can be measured in the blood to determine cardiomyocyte damage and have been used for many years in human medicine as part of the criteria to diagnosed an acute myocardial infarction. Cardiac TnI and cTnT are sensitive markers of myocardial injury and will rise quickly after an injury. They do not, however, identify the cause of injury or if it arises from primary cardiac diseases or cardiac damage secondary to systemic disease.

Cardiac TnI appears to be a more sensitive marker than cTnT and so has been evaluated more in the literature. Furthermore , cTnI has

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numerous analyzers, many of which are cost effective point-of-care assays. Although each analyzer has its own reported reference interval, typically these values are very low (< 0.2 ng/mL). However, each company uses a different target on the cTnI protein for their assay. Values obtained on one analyzer cannot be directly compared to values obtained on a different analyzer. In other words, a cTnI value that is used as a cut-off point in a certain study will only have meaning if that same assay is used in clinical practice.

There are two studies looking at use of cTnI to diagnose CHF as the cause of respiratory distress in dogs. One study found a statistical difference between the groups (cardiac causes vs pulmonary causes of respiratory distress) while the other did not, questioning the usefulness of this test in routine practice. In cats, there are also two studies to evaluate cTnI concentration to diagnose CHF as cause for respiratory distress. In one study, AUC of the ROC was determined and found to only be 0.84. Both studies found considerable overlap between the groups and were unable to identify a cut-off point at which a clinician could reliably diagnose cardiac-related dyspnea.

Where cTnI may be more useful in clinical practice is pericardial effusions in dogs. Studies demonstrated that peripheral cTnI concentrations are significantly higher in dogs with pericardial effusion compared to healthy controls. Moreover, those that were diagnosed with cardiac hemangiosarcoma had significantly higher concentrations of cTnI than those with other causes of pericardial effusion (including other neoplasms with reported longer median survival times). However, these studies did not include coccidiomycosis pericarditis and so it is unknown how this regional disease process may affect cTnI concentrations. Splenic and dermal hemangiosarcoma were not associated with increased cTnI concentrations.

Conclusion

Biomarkers are a hot topic and an intense amount of research is being invested into this area. New information is being discovered everyday and will likely continue to change how we practice. At this time, natriuretic peptides and troponins may aid the clinician in guiding therapy, but at this time have not been found to be accurate enough to replace gold standard diagnostics. Although cautionary measures should be practiced so as to not compromise the stability of the patient with respiratory distress, minimum database and thoracic radiographs should still be obtained and a problem based approach pursued on the results obtained from these diagnostics. Abnormal results from NT-proBNP or troponin testing should be interpreted in face of these diagnostics and an echocardiogram should be consider once the patient is stable enough for the procedure.

References

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Arizona Veterinary Specialists

LEADERS IN SPECIALTY CARE

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Dentistry

- Periodontics
- Dental digital radiography
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- Nasal disease treatment
- Oral disease treatment
- Oral surgery
- Orthodontics
- Restoration
- Professional teeth cleaning
- Maxillofacial surgery
- Oral fractures
- Fractured teeth treatment
- Malocclusion treatment
- Crown therapy
- In house lectures
- Telephone radiographic consultation
- Bite evaluation

Arizona Veterinary Oncology, PLLC

Radiation Oncology

- Conventional Radiation Therapy
- Stereotactic Radiosurgery
- I-131 radioactive iodine treatment

Medical Oncology

- Chemotherapy
- Immunotherapy
- Cryotherapy
- Oncologic surgery
- Clinical trials

Desert Veterinary Medical Specialists

Internal Medicine

- Endoscopy
  - Bronchoscopy
  - Bronchoalveolar lavage
  - Colonoscopy
  - Cystoscopy
  - Foreign body retrieval
  - Gastroduodenoscopy
  - PEG tube placement
  - Rhinoscopy
- Endocrine disorders
- Emergency consultations
- Blood and plasma transfusions
- Gastrointestinal diseases
- Genitourinary disorders
- Hepatic diseases
- Infectious diseases
- Intensive care treatment
- Immune-mediated diseases
- Nutrition consultations
- Oxygen therapy
- Pancreatic diseases
- Pulmonary diseases
- Renal disease
- Respiratory diseases
- Second opinion examinations
- Ultrasonography
- Tracheal and urethral stenting

Cardiology

- Echocardiography
- Electrocardiogram (ECG)
- Chest radiographs
- Blood pressure
- Pericardiocentesis
- Cardiology breed certification
- Holter monitoring
- Event monitoring
- Non-surgical PDA repair
- Balloon valvuloplasty
- Pacemaker implantation
- Invasive blood pressure measurements
- Angiography
- Implantable ECG Loop Recording

Radiology

- Outpatient and inpatient ultrasound
- Radiology Rounds
- Digital radiography
- Helical CT scanning
- Fluoroscopic urinary, GI, and tracheal studies
- Nuclear imaging
  - GFR scans
  - Bone scans
  - Thyroid scans
  - Splenic scintigraphy
- Radiographic interpretation
- CT and MRI interpretation

Dermatology for Animals, PC

Dermatology

- Allergy testing (skin testing) and immunotherapy
- CO_2 laser for ablation of skin tumors
- Testing for food allergies and hypoallergenic diets
- Ear disease diagnosis and treatment
- Bacterial and fungal skin disease diagnosis and treatment
- Cytological smears and microbiologic examinations
- Ectoparasite identification and treatment
- Immune-mediated and hormonal skin disease diagnosis and treatment
- Treatments of nail and nail bed disorders
- Skin biopsy sampling and histopathology interpretation

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Southwest Veterinary Surgical Service, PC

Surgery

- ♦ Abdominal surgery
- ♦ Airway surgery
- ♦ Angular limb deformity surgery
- ♦ Arthroscopy
- ♦ CT Scans
- ♦ External skeletal fixation
- ♦ Fracture repair
- ♦ Laparoscopy and Thoracoscopy
- ♦ Neurologic surgery
- ♦ Oncologic surgery
- ♦ Oral surgery, such as maxillofacial surgery and oral fractures
- ♦ Orthopedic surgery
- ♦ Otologic surgery
- ♦ Perineal surgery
- ♦ Reconstructive surgery
- ♦ Ring fixators
- ♦ Soft Tissue surgery
- ♦ Thoracic surgery
- ♦ Tibial Plateau Leveling Osteotomy (TPLO)
- ♦ Triple Pelvic Osteotomy (TPO)
- ♦ Total Hip Replacement (THR) both cemented and cementless procedures available
- ♦ Tracheal Stenting
- ♦ Tibial Tuberosity Advancement (TTA)

Anesthesia and Pain Management

- ♦ Anesthetic management of high risk and critical care patients
- ♦ Extensive anesthesia monitoring
  - • Blood pressure, both direct and indirect
  - • Pulse oximetry
  - • Electrocardiogram
  - • Capnography
  - • Body temperature
  - • Ventilator therapy
- ♦ Pain patches
- ♦ Chronic pain management consultations

BluePearl Veterinary Partners, PLC

Emergency and Critical Care

- ♦ In house diagnostic tests
  - • STAT laboratory blood tests
    - * Complete Blood Count (CBC)
    - * Serum biochemical analysis
    - * Blood gas analysis
    - * Urinalysis
    - * Blood lactate measurement
    - * Coagulation testing
    - * Ethylene glycol (Antifreeze) testing
    - * Parvovirus testing
  - • Digital x-rays
    - * Radiologist interpretation
  - • Scanning ultrasound
  - • Gastrointestinal endoscopy
- ♦ Specialized Therapies
  - • Intravascular volume expansion/shock therapy
  - • Blood component therapy
  - • Rattlesnake antivenom therapy
  - • Oxygen
  - • Short and long term ventilator therapy
  - • Anesthetic ventilator
  - • Pain medication delivery via constantrate infusion
  - • Nutritional support
  - • Feeding tube placement
  - • Peritoneal dialysis
  - • Continuous suction for chest and other drains
  - • Central and peripheral IV catheter placement
  - • CPR with advanced life support
  - • Electrical defibrillation & emergency cardioversion
  - • Anesthesia for high-risk critical patients
- ♦ Soft tissue emergency surgical procedures performed by our emergency veterinarians (included, but not limited to):
  - • Wound repair
  - • Emergency tracheostomy
  - • Chest tube placement
  - • Abdominal surgeries
  - • Gastric Dilatation Volvulus (GDV) or bloat surgery
  - • GI foreign body removal
  - • C-section
  - • Splenectomy
  - • Bladder stone removal
- ♦ Intensive monitoring
  - • Electrocardiogram (EKG)
  - • Blood pressure (direct arterial and indirect)
  - • Urinary catheter placement and measurement of urine output
  - • Pulse oximetry (Oxygen saturation)
  - • Capnography (End Tidal CO2)
  - • Central venous pressure
  - • Arterial and venous blood gas measurement

Eye Care for Animals, dba

Ophthalmology

- ♦ Biomicroscopy
- ♦ Indirect ophthalmoscopy
- ♦ Electroretinography
- ♦ Ultrasonography
- ♦ Applanation tonometry
- ♦ Fluorescein angiography
- ♦ Glaucoma treatment
- ♦ Cataract surgery
- ♦ Corneal reconstructive surgery
- ♦ Treatment of eyelid abnormalities

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