UNIVERSIDADE DE LISBOA

Faculdade de Medicina Veterinária

USE OF THE SHORT FORM GLASGOW COMPOSITE MEASURE PAIN SCALE IN THE ASSESSMENT OF CANINE PATIENTS PRESENTING IN SHOCK

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DISSERTAÇÃO DE MESTRADO INTEGRADO EM MEDICINA VETERINÁRIA

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"Um homem tem de estar preparado para se queimar na sua própria chama: como se pode renovar sem primeiro se transformar em cinzas?"

Assim falou *Zaratustra,*
Friedrich Nietzsche

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USE OF THE SHORT FORM GLASGOW COMPOSITE MEASURE PAIN SCALE IN THE ASSESSMENT OF CANINE PATIENTS PRESENTING IN SHOCK

Abstract

The short form of Glasgow Composite Measure Pain Scale (CMPS-SF), a previously validated decision-making tool is increasingly used in practice for the assessment of pain in dogs. However, few studies have considered the application of a pain scoring system in patients presenting in emergency situations.

This study aimed to evaluate if pain scoring with the Glasgow CMPS-SF was effective in identifying pain in patients in shock.

A prospective study (November 2014 to January 2015), within a first opinion and specialty intensive care service was developed. A total of 31 client-owned dogs (16 females and 15 males) that presented as primary emergencies or transfers. When admitted to the study, all dogs were examined by a veterinarian or registered veterinary nurse. Patients were classified and grouped as Shock (S) or Not Shock (NS) on basis of their shock index (SI). The shock status was defined a priori if the SI was higher than 1.0. Regardless of group, all patients had their pain assessed with the Glasgow CMPS-SF and by a Board Eligible Internist or a Emergency and Critical Care specialist, blinded to both pain score and SI values.

Dogs in shock numbered 18/31 dogs within the not shock group numbered 13/31. Mean age of dogs in the S group was 4.6 years (0.2 – 10) and in the NS group was 8.3 years (1 – 16); a significant difference existed in age between groups (p-value<0.05). Median pain score of the S group was 5 (0 – 17) and on the NS group was 3 (1 – 15). There was no significant difference on pain scores between the groups (p-value>0.05) and between the clinicians' perception of pain between groups (p-value>0.05). A significant difference was present between pain scores and the clinicians' opinion on pain (p-value=0.014), including within the shock group (p-value=0.0021). Cohen's kappa statistic within the shock group was 0.47, which can be interpreted as weak to moderate agreement between the Glasgow CMPS-SF and the clinician opinion on pain. Within the NS group the differences between the pain scores and the clinician' opinion on pain were not statistically significant (p-value>0.05).

These results do not support an acceptable agreement between the Glasgow CMPS-SF and an experienced veterinarians evaluation of pain in patients presenting in shock. Therefore, further investigation into the relevance of the used pain assessment tool in emergency and shock patients is recommended before use in the objective monitoring of this subset of patients.

Keywords: dogs, pain, pain score, CMPS-SF, shock, shock index.

USO DA FORMA ABREVIADA DA ESCALA COMPOSTA DA DOR DE GLASGOW EM CÃES COM APRESENTAÇÃO DE CHOQUE

Resumo

O reconhecimento e avaliação de dor em doentes veterinários pode ser desafiante, especialmente nos que se encontram em estado crítico. A já validada forma abreviada da Escala Composta da Dor de Glasgow (CMPS-SF) é, cada vez, mais utilizada em ambiente clínico na avaliação da dor aguda em cães. Contudo, poucos estudos têm considerado a aplicação de um sistema de avaliação de dor em doentes que se apresentam em situação de emergência. Foi desenvolvido um estudo experimental com o propósito de avaliar se a pontuação obtida com a CMPS-SF seria capaz de identificar dor em doentes que se apresentassem em choque.

O estudo prospetivo desenvolveu-se numa clínica de primeira opinião e com serviço de cuidados intensivos (entre Novembro de 2014 e Janeiro de 2015). Foram incluídos no estudo 31 cães, admitidos em situação de emergência ou como referências, tendo sido examinados por um médico veterinário ou uma enfermeira veterinária. Os doentes foram classificados como estando em choque (S) ou não (NS) com base no seu índice de choque (IC). O estado de choque foi definido quando IC>1.0. Todos os doentes foram avaliados quanto à dor pela utilização da CMPS-SF e através de um exame físico realizado por um candidato a Internista ou um especialista em Emergências e Cuidados Intensivos, desconhecedores da pontuação obtida com a escala de CMPS-SF e do IC. O nível de significância estabelecido foi de 0.05.

O grupo de cães em choque incluiu 18 cães e o grupo de não choque incluiu 13. A idade média dos animais no grupo S foi de 4.6 anos e no grupo NS foi de 8.3. As diferenças de idade observadas entre os grupos foram consideradas estatisticamente significativas (p-value<0.05). A pontuação média de dor no grupo S foi 5 e no grupo N.S. foi 3. As diferenças observadas na pontuação de dor entre os dois grupos grupos não foi considerada significativa (p-value>0.05). A perceção da dor pelos médicos veterinários nos dois grupos também não foi considerada significativa (p-value>0.05). Considerou-se significativa a diferença observada entre as pontuações de dor e a perceção de dor dos médicos veterinários (p-value=0.014), incluíndo no grupo S (p-value=0.0021). No grupo S, a concordância entre métodos foi de 0.47, interpretada como fraca a moderada.

Face aos resultados obtidos, sugerem-se mais estudos relativos à precisão da utilização de escalas de dor em doentes que se apresentem em emergência e em condições de choque, antes que estas escalas possam ser recomendadas neste tipo de doentes.

Palavras-chave: Cães, dor, pontuação de dor, CMPS-SF, choque, índice de choque.

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List of abbreviations

ABP – Arterial blood pressure
ACE – Angiotensin converting enzyme
AcH – Acetylcholine
ACTH – Adrenocorticotrophic hormone
ADH – Antidiuretic hormone
AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP – Adenosine triphosphate
BDNF – Brain-derived neurotrophic factor
Bid – Administer two times a day
BP – Blood Pressure
Ca^{2+} – Calcium
$CaCO_2$ – Total arterial oxygen content
cAMP – Cyclic adenosine monophosphate
CGRP – Calcitonin Gene Related Peptide
Cl^- – Chloride
CMPS-SF – Short Form Composite Measure Pain Scale
CNS – Central nervous system
CO – Cardiac output
COX – Cyclooxygenase
CRF – Corticotrophin releasing factor
CRI – Constant Rate Infusion
CRT – Capillary refill time
CTZ – Chemo-trigger zone
CVP – Central Venous Pressure
DO_2 – Oxygen delivery to tissues
E – Epinephrine
ECC – Emergency and critical care
ECG - Electrocardiogram
ER – Emergency room
GABA – Gamma-aminobutyric acid
GCMPS – Glasgow Composite Measure Pain Scale
GH – Growth hormone
GI - Gastrointestinal
H^+ - Hydrogen
HPA – Hypothalamic-pituitary-adrenal
HR – Heart rate
IASP – International Association for the Study of Pain
ICU – Intensive Care Unit
IL-1– Interleukin-1
IL-6 – Interleukin-6
IL-8 – Interleukin-8
IM – Intramuscular
IR – Ischemia-reperfusion
IV – Intravenous/intravascular
K^+– Potassium
LA – Local anaesthetic
LC – Locus ceruleus
LOX – Lipoxygenase
MAP – Median Arterial Pressure
NS – Not Shock
NE – Norepinephrine
NMDA – N-methyl-D-aspartate
NO – Nitric oxide
NRS – Numerical Rating System
NSAID – Nonsteroidal Anti-inflammatory drug

NY – Neuropeptide Y
O_2 – Oxygen
p – statistical significance value
pK_a – acid dissociation constant
PAC – Pulmonary Artery Catheter
PAG – Periaqueductal Gray
PaO_2 – Partial pressure of oxygen
PAT – Pain assessment tool
PGE_2 – Prostaglandin E_2
PGI_2 – Prostaglandin I_2/Prostacyclin
PGs - Prostaglandins
PO – Per os
q - every
QID – Administer four times a day
QOL – Quality of life
RAAS – Renin-Angiotensin-Aldosterone-System
RAS – Reticular Activating System
S – Shock
SaO_2 – Oxygen saturation of hemoglobin
SBP – Systolic blood pressure
SC – Sub cutaneous
SDS – Simple Descriptive System
Se – Sensitivity
SI – Shock index
Sid – Administer one time a day
Sp – Specificity
SV – Stroke volume
TCA – Tricyclic Antidepressant
TID – Administer three times a day
TNF-α – Tumour necrosis factor alpha
TSH – Thyroid stimulating hormone
UMPS – University of Melbourne Pain Scale
VAS – Visual Analogue System
VIP – Vasoactive Intestinal Peptide

List of symbols

%	percentage
α	alpha
β	beta
γ	gamma
δ	delta
μ	mu
μg	microgram
mg	milligram
kg	kilogram
ml	millilitre
<	less than
>	more than
=	equal to
±	more or less

Glossary

Allodynia – pain caused by a stimulus that normally does not cause pain.

Analgesia – loss of sensitivity to a stimulus that would normally produce pain

Distress – condition in which stress negatively affects biologic functions critical to the animal's well-being. Distress also means to cause pain or suffering or to make miserable.

Hyperalgesia – an increased response to a stimulation that is normally painful (a heightened sense of pain) at the site of injury or in surrounding undamaged tissue.

Primary hyperalgesia – increased sensitivity to a stimulus that is normally painful at the site localized to the area of tissue damage or inflammation.

Secondary Hyperalgesia – increased sensitivity to a stimulus that is normally painful in uninjured or inflamed tissues in areas around and beyond the site of primary site of tissue injury.

Hyperesthesia – increased sensitivity to touch.

Nociception – the physiologic process that leads to the perception of pain.

Noxious stimulus – A stimulus that is damaging or threatens damage to normal tissues.

Hypoalgesia – decreased sensitivity to a noxious stimulus.

Pain Threshold – the least amount of pain that an animal can recognize.

Sensitization – an increase in the excitability of neurons, leading to greater sensitivity to stimuli or sensory input.

Suffering – a state of emotional distress associated with events that threaten the biologic and/or psychosocial integrity of the individual.

Wind-Up – sensitization of nociceptors and peripheral and central pain pathways in response to a barrage of afferent nociceptive impulses resulting in expanded receptive fields and an increased rate of discharge.

Part I - Externship Report

As part of the 6th year of the Integrated Masters in Veterinary Medicine, and held under the Erasmus+ Program, I performed a 4 month training period, starting on October 6th until January 16th, at Village Vet Hampstead (Vet24 London), London, United Kingdom.

My training period was supported under the supervision of Adam Mugford BVetMed MVetMed DACVECC MRCVS (Village Vet Hampstead) and co-supervised by Prof. Dr. Berta São Braz (FMV-UL).

All the procedures and activities I enrolled were performed under the supervision of one of the veterinarians, veterinary nurses or patient care assistants and by the end of this time period, I carried out approximately 700 hours (698h) of training.

The majority of the hours were spent in wards and intensive care unit (Chart I and II); here, I was able to follow and monitor the patients admitted to the practice and many of emergency and critical care cases I came across in this training period. Further information is displayed on annex I.

Chart 1 - Percentage of time in different clinical areas

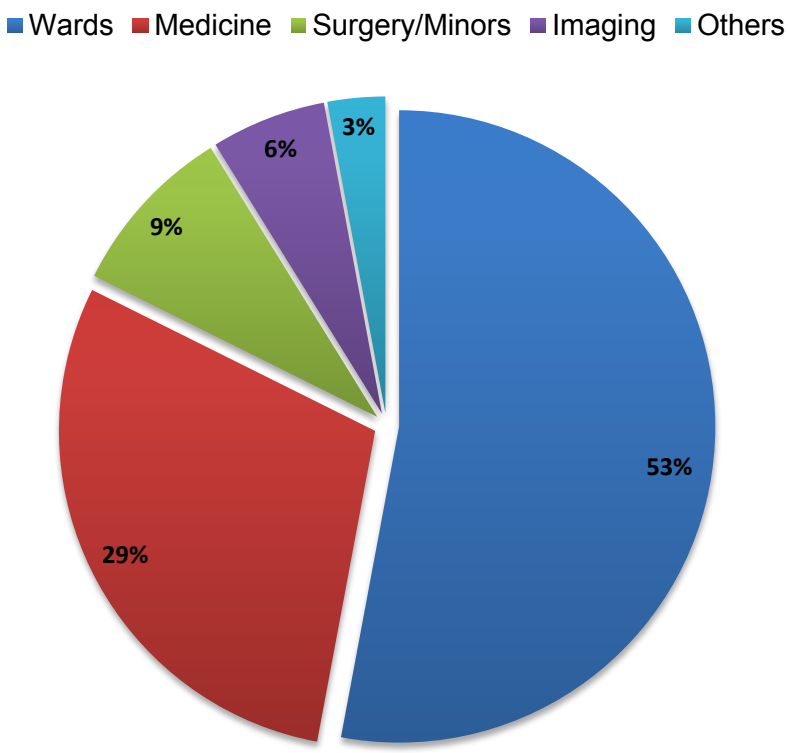
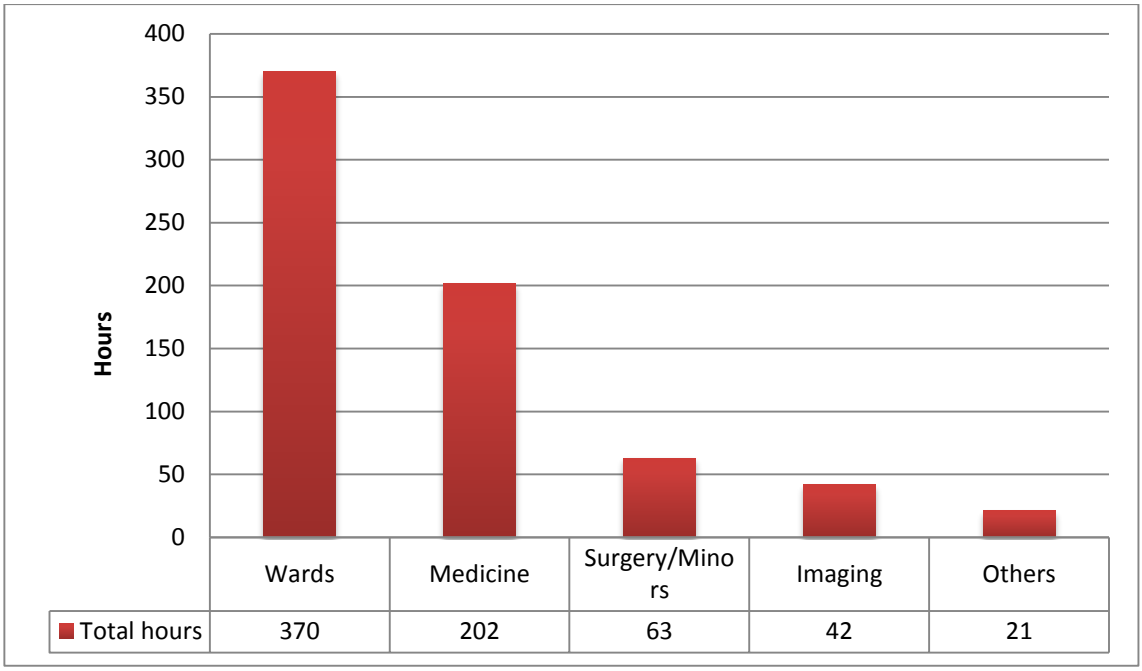


Chart 2 – Distribution of hours in each clinical area



The routine in wards would start with morning rounds, where all the clinical information about the in-patients was transmitted and discussed by the night-shift veterinarian to the veterinarians on the day rota. After distribution of patients through veterinarians, my role was to assist them and veterinary nurses with their tasks, including: physical examinations, patient restraining, intravenous (IV) catheter checks, IV catheterisation and removal, placing and changing bandages, monitoring of critical care patients, taking blood samples, preparation and administration of medications, set fluid therapy systems and bags, perform scheduled brief major body system examinations (Temperature, Pulse and Respiratory rate - TPR) and non-invasive blood pressure (NIBP) monitoring, pain assessment and general patient welfare, feeding the patients, changing bed and cleaning kennels, and *Tender Loving and Care*.

In Medicine I had the opportunity to assist consultations, and by doing so I was able to improve my knowledge on how to conduct a conversation with clients in order to get a complete clinical history. I was also present on morning and late ward rounds, where all in-accommodation cases were discussed regarding clinical history, patient condition and medical or surgical management.

My part in Surgery included all aspects of the perioperative period (pre, intra and post-operative). Pre-operatively I helped with patient's admission, pre-medication preparation and administration, and with the patient's preparation to surgery (IV placements, clipping and cleaning). In intraoperative care, I helped with the patient's anaesthesia and vital signs monitoring. In the postoperative phase, I would help with monitoring the patient's recovery. In some occasions I was allowed to scrub-in with the surgeon and watch the procedures and

assist in surgery (e.g. perform feline castrations and participate on female spays, watch and assist arthroscopies, splenectomies or mammary gland removals, among others). I was also able to watch and assist veterinarians and veterinary nurses with procedures such as endoscopies (upper and lower tract), central catheterization and urinary catheter placements, naso- and oesophageal feeding tube placements, observe and assist with pleural effusion aspiration, among others.

The Imaging area consisted of radiography and ultrasound, and I was able to participate in both, where I helped the veterinarians and veterinary nurses in the positioning of patients and could discuss the imaging findings with the clinicians.

Regarding other tasks, I was able to help in the laboratory with procedures such as packed cell volume reading, blood film examinations and cytology, urine and urine sediment analysis; whenever possible I would read books or scientific papers about several medical subjects of interest or regarding cases present at the hospital.

During this training period, I was able to perform a prospective study project for my masters' degree dissertation, regarding the assessment of pain and shock in dogs presenting in emergencies, while using the Glasgow's short form Composite Measure Pain Scale and the shock index, respectively. The interest on the topic for this dissertation was supported by a small number of data on the evaluation of pain in veterinary patients upon arrival to the clinical environment in emergency situations, with a validated pain scoring system.

As result of this study, an abstract entitled "A Prospective Study Of The Utility Of The Short Form Glasgow Composite Measure Pain Scale (CMPS-SF) In Canine Patients In Shock**"** (Annex II) was accepted and presented as an oral communication at the 14th Congress of the European Veterinary Emergency and Critical Care Society (EVECCS) held in Lyon and published on the Journal of Veterinary Emergency and Critical Care (JVECC), volume 25, issue S1 (Annex III).

PART II – Literature review

2.1 Introduction

As stated by Colin Allen (1998), “scientific attitudes are, in large measure, a product of education” and in Veterinary Medicine the attitudes towards pain in animals have changed dramatically over the past two decades (Weary, Niel, Flower & Fraser, 2006; Reid, Scott, Nolan & Wiseman-Orr, 2013). For many years the subject of pain had been a neglected area in the veterinary field, since it was common belief that animals would not experience pain as humans do because they do not express it in the same way (Mathews, 2000; Morton, Reid, Scott, Holton & Nolan, 2005; Lockhead, 2010; Mathews et al, 2014). Currently, pain is recognised as a complex sensation that is universally shared by all mammals (Mathews et al, 2014) and it is now well defined in veterinary medicine that the provision of optimal patient care includes the management of pain (Mathews, 2000; Hansen, 2005; Lockhead, 2010; Mathews et al, 2014; Epstein et al, 2015). Regardless of the frequency of situations in which it is encountered, both in human and veterinary medicine, pain is a highly subjective, multidimensional and individual experience. As a consequence, the recognition and assessment of pain in small animal practice is particularly challenging and furthermore complicated by the many limitations in communication that veterinarians experience with their patients, as animals are nonverbal and unable to self-report pain (Muir III & Woolf, 2001; Gogny, 2006; Schnakers, 2012; Sharkey, 2013; Mathews et al, 2014; Perkowski, 2014; Epstein et al, 2015). The consequences of pain, especially when unmanaged, are serious threats to the animal’s well being; it causes both physical and psychological damages; increase the metabolic rate, delays healing, suppresses the immune system and can increase the metastatic rate of some cancers (Downing, 2014). For these reasons, ethical principles of beneficence and nonmaleficence should oblige professionals to provide pain management and comfort to all patients, including those less likely or able to display pain such as critically ill animals (Hansen, 2005; Shaffran et al, 2005; Herr, 2006); those animals in pain may not demonstrate overt signs of distress, and failure to manage pain in these patients can compromise their recovery and contribute to patient mortality (Hansen, 2003; Shaffran et al, 2005; Lockhead, 2010; Mathews et al, 2014). Shock is considered a life-threatening condition often found in the emergency rooms and intensive care units (ICU), frequently associated with pain (Shaffran et al, 2005; Lockhead 2010). In fact, acute pain, in conjunction with blood loss has been shown to be an important factor to increase mortality risk associated with traumatic shock, compared with mortality risk for simple hemorrhagic shock (Wiese, Muir & Wittum, 2004). Although there is no gold standard for pain assessment in veterinary medicine, it is recognized that behavioural signs may be more useful in the identification of abnormal processes as pain and also, the use of a pain scoring system is

beneficial in the assessment and quantification of pain (Lockhead 2010; Sharkey, 2013; Rooney, 2014; Mathews et al, 2014; Epstein et al, 2015). Given that many of the pain assessment tools developed focus on the evaluation of post-operative pain, and that few studies considered the assessment of pain of veterinary patients presenting as emergencies or requiring critical care assistance, it is the purpose of this dissertation to evaluate the use of pain scoring in the identification of pain in canine patients presenting in shock.

2.2 Pain

2.2.1 Definition

Pain is a complex experience and for that reason, defining it can be equally challenging (Sawyer, 1998). Pain is not just a physical impression ("how it feels"); it involves both a physiologic sensation and an emotional component associated to that sensation ("how it makes you feel") (Lamont, Grimm & Tranquili, 2000; Muir III & Woolf, 2001; Wiese et al, 2004; Mathews et al, 2014), and it is this emotional charge that causes the suffering commonly associated with pain (Mathews et al, 2014). The International Association for the Study of Pain (IASP) (1979) defines it as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage". However, as veterinary patients cannot self-report their experiences verbally, Molony, Kent, Hosie and Graham (1997) suggest an alternative definition: "an aversive, sensory experience representing awareness by the animal of damage or threat to the integrity of its tissues". Additionally, the IASP also states that the inability to communicate verbally the experience of pain, cannot exclude the possibility that it is present and analgesia is required (Muir III & Woolf, 2001; Meintjes, 2012; Mathews et al, 2014; Epstein et al, 2015). These definitions also recognize the importance of an unpleasant emotional experience, such as fear, in triggering homeostatic responses similar to those induced by noxious stimuli (Muir III & Woolf, 2001).

2.2.2 Pain classification

At simplest, pain can be classified based on its duration as either acute or chronic (Mathews et al, 2014) but there are several proposed classifications. Some authors consider pain either as adaptive (pain that contributes to survival) or as maladaptive (pain as a disease) but despite slight variations on its categorization, it can be classified as physiologic, pathologic, neuropathic, inflammatory or visceral (Lamont et al, 2000; Hellyer et al, 2007; Gaynor & Muir III, 2014; Mathews et al, 2014; Epstein et al, 2015).

2.2.2.1 Physiologic pain

Physiologic pain (also termed nociceptive pain) is considered an adaptive, protective and survival-oriented response quite distinct from the one resulting from overt damage to tissues or nerves (Lamont et al, 2000; Muir III, Wiese & Wittum, 2004). This type of pain occurs after most types of noxious stimulation and initiates self-protective escape and avoidance behaviors and activates a variety of hierarchical homeostatic autonomic responses (stress responses) designed to maintain and restore normal body functions (Muir III et al, 2004). Physiologic pain is only elicited when intense noxious stimuli threaten to injure tissue, and is characterized by a high stimulus threshold, well localized and transient, and demonstrates a stimulus-response relationship similar to those of the other somatic sensations (Lamont et al, 2000).

2.2.2.2 Pathologic pain

Pathologic pain can also be termed as maladaptive or clinical (Lamont et al, 2000; Epstein et al, 2015). It is usually associated with tissue injury incurred at the time of surgery or trauma (Lamont et al, 2000; Gaynor & Muir III, 2014) but can also occur when pain is uncoupled from the noxious stimulus or healing process (Muir III et al, 2004). It is pain as disease and it has been attributed to a variety of pathologic processes as hyperalgesia, allodynia, expansion of the painful field beyond its original boundaries and pain protracted beyond the expected time of inflammation and healing (Muir III, et al 2004; Gaynor & Muir III, 2014a; Epstein et al, 2015).

2.2.2.3 Acute pain

Acute pain has been defined as the one that exists following injury and during the expected time of inflammation and healing. It's usually self-limiting and should resolve in less than 3 months (Gaynor & Muir III, 2014a; Epstein et al, 2015).

2.2.2.4 Chronic pain

It can be described as pain that lasts beyond the expected time of healing (more than 3 months) (Meintjes, 2012; Gaynor & Muir III, 2014a; Epstein et al, 2015) or as persistent pain caused by conditions where healing did not occur or has recurred (Mathews et al, 2014).

2.2.2.5 Neuropathic pain

Defined as the pain arising from injury or involvement of the peripheral or central nervous system and is possibly associated with motor, sensory or autonomic deficits (Gaynor & Muir III, 2014a). After nerve injury, some changes occur in the sensory transmission of pain, including modifications in the expression of neurotransmitters, neuromodulators, receptors, ion channels and structural proteins. Examples of neuropathic pain in veterinary patients include the one induced by lumbosacral lesions, intervertebral disc herniation and other

spinal cord injuries and discospondylitis, among others (Meintjes, 2012).

2.2.2.6 Inflammatory pain

Inflammatory pain is the most common type (Lemke, 2004). This type of pain is a result of tissue damage and activation of the immune system and release of inflammatory mediators, such as prostaglandins, hydrogen ions and histamine. Usually, inflammatory pain decreases along with the reduction of inflammation (Gaynor & Muir III, 2014a; Epstein et al, 2015). Although it may be seen as pathological by some authors (Lamont et al, 2000), it can also be described as adaptive, in the sense that it contributes to survival by limiting or preventing contact or movement of the affected part, until healing is complete (Gaynor & Muir III, 2014a).

2.2.2.7 Visceral Pain

As the name suggests, visceral pain arises from distension or inflammation of the viscera. The noxious input arising from internal organs is processed by the same nociceptive fibres (Aδ and C fibers) that accompanies sympathetic and parasympathetic pathways (Gaynor & Muir III, 2014a), and therefore the pain emerging from the viscera can be accompanied by typical signs of sympathetic stimulation (tachycardia and tachypnea) and typical behavioural signs. It is usually described as deep, cramping, aching or gnawing and diffuse (without a good localization) (Lamont et al, 2000; Gaynor & Muir III, 2014a).

2.2.2.8 Phantom pain

Phantom pain is described as perceived sensations related to a limb or organ than is not physically part of the body and may be associated with the development of neuromas in amputated limbs (Meintjes, 2012).

2.2.2.9 Cancer pain

Cancer pain can be acute, chronic or intermittent and may be related to the disease itself or to the treatment (Gaynor & Muir III, 2014a).

2.2.3 Pain mechanisms

Pain is the perception of the sensory experience induced by a noxious stimulus (Muir III & Woolf, 2001). Although pain responses are singular to each individual, the pain mechanism and sensory components are similar in all mammals (despite some individual variation in pain sensitivity and response to analgesics within species) (Lamont et al, 2000; Lemke, 2004; Viñuela-Fernandez, et al, 2007). Pain is a sensory event that involves the peripheral and central nervous systems, arising from and reciprocally affecting processes of higher consciousness (Lamont, 2008).

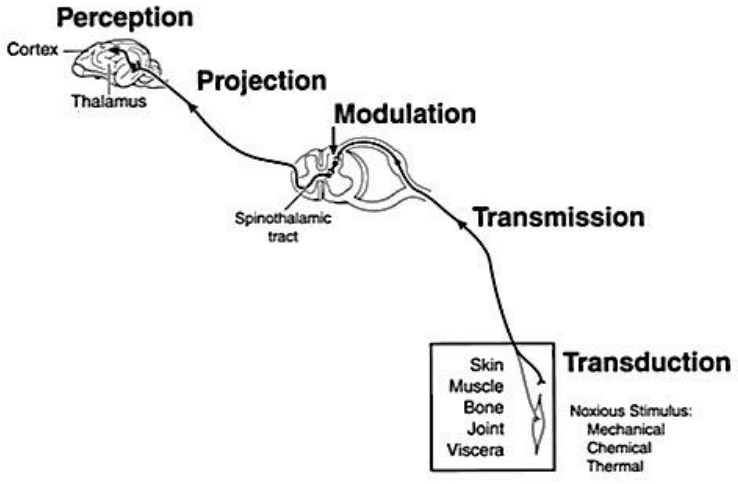
2.2.3.1 Nociception vs Pain

Nociception is the unconscious sensory component of pain - the recognition and neural processing of high intensity noxious stimuli captured by specialized peripheral nerve endings called nociceptors (Lamont et al, 2000; Lemke, 2004; Epstein et al, 2015). As mentioned, this process plays an integral adaptive role as part of the body's normal defence mechanisms, warning of contact with potentially damaging environmental insults and initiating behavioural and reflex avoidance strategies (Lamont et al, 2000; Meintjes, 2012; Valtolina & Goggs, 2012;). Pain is the endpoint of nociceptive input and processing at higher neural structures and can only occur in a conscious animal (Epstein et al, 2015).

2.2.3.2 Nociceptive processing

Nociception comprises a sequence of processes: transduction, transmission, modulation and perception of the neural signs generated in response to external noxious stimuli (Figure 1). Exemplifying this process as a chain, a first neuron (1st order neuron), originating in the peripheral tissues, is the primary afferent neuron responsible for the recognition, transduction – the transformation of various environmental stimuli into electrical signs (action potentials) – and transmission of the signals from its origin to the dorsal horn of the spinal cord. A second neuron (2nd order neuron), also named projection neuron, receives information from the primary afferent neuron, encodes it (modulation) and projects it to neurons in the medulla, pons, midbrain, thalamus and hypothalamus. Finally, a third neuron in chain (3rd order neuron), also named supraspinal neuron, integrates signals from the lower order neurons and projects them to the subcortical and cortical areas, where pain is finally perceived (Lamont et al, 2000; Lemke, 2004; Wiese & Yaksh, 2014). Though it is possible to describe it through a three-neuron chain, the pain pathway involves much more complexity. Accompanying the ascending pain pathway, from stimulus to its cognitive perception, there is also a descending path – descending inhibitory neurons from the midbrain that modulates afferent transmission of painful stimuli (Lamont et al, 2000; Meintjes, 2012).

Figure 1 - Pathway and physiologic processes involved in pain sensation (from Muir III & Woolf, 2001)



2.2.3.2.1 Transduction

Nociceptors respond to high-intensity stimuli that have potential to cause cell damage, such as heat, pressure, vibration and chemicals. Once the nociceptor is triggered, the process of transduction is mediated by membrane bound receptors activated by these stimuli and lead to an influx of sodium and calcium ions along a diffusion gradient, which results in depolarisation of the plasma membrane and generation of an action potential (Meintjes, 2012). These nociceptors are the free endings of afferent nerve fibers that are composed of different populations of axons, including large myelinated, small myelinated and unmyelinated axons. Accordingly to their associated afferent nerve fibers and stimulus sensitivities, pain receptors can be generally classified as A- or C-fibers nociceptors, and as unimodal (sensitive to only one type of stimulus) or polymodal (reactive to several different types of painful stimuli), mechanical, thermal or silent (activated by chemicals and inflammatory mediators) (table 1) (Lemke, 2004; Lamont, 2008; Meintje, 2012; Wiese & Yaksh, 2014).

Table 1 – Primary afferent fibres (Adapted from Handbook of Veterinary Pain Management, Gaynor & Muir III, 3rd Edition, 2014)

Fibre Class	Axon Diameter	Conduction Velocity	Effective stimuli
Aβ (large myelinated)	12-20 µm	>40-50 m/sec	Low-threshold mechanical (tactile or joint position)
Aδ (small myelinated)	1-4 µm	10<x<40 m/sec	Low-threshold mechanical or thermal High-threshold mechanical or thermal (specialised nerve endings)
C (small unmyelinated)	0.5-1-5 µm	<2m/sec	High-threshold thermal, mechanical, chemical (polymodal nociceptors)

The large myelinated and rapidly conducting Aβ fibers respond to nonnoxious low-intensity mechanical stimuli (touch, pressure) but not to noxious stimuli directly. The small myelinated Aδ fibres respond to low and high-intensity thermal or mechanical stimuli and carry the nociceptive input responsible for the fast, sharp pain (first pain) that occurs immediately after injury. The small unmyelinated C fibres typically respond to high-intensity thermal, mechanical and chemical products and are responsible for the prolonged, dull pain (second pain) that occurs after injury (Lemke, 2004; Wiese & Yaksh, 2014). Silent nociceptors are activated by chemical stimuli (inflammatory mediators) and respond to mechanical and thermal stimuli only after they have been activated. These nociceptors also have small, unmyelinated C fibers that conduct impulses at a velocity of less than 3 m/s (Lemke, 2004).

2.2.3.2.2 Transmission

The cell bodies of both types of afferent nociceptive nerve fibers are contained in the dorsal root ganglia and extend axons to synapse with dorsal horn neurons (2nd order neurons) within the grey matter of the spinal cord (Lamont et al, 2000). The primary synaptic transmitter present in all types of primary afferents is glutamate, although these fibres corelease other neuropetptides (substance P, neurokinin A, calcitonin gene related peptide) that bind to receptors on dorsal horn neurons (Lemke, 2004; Lamont, 2008). With normal afferent input, glutamate bind to alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and neuropeptides bind to neurokinin receptors. The activation of AMPA receptors is responsible for the generation of fast postsynaptic potentials that last a few miliseconds, while the activation of neurokinin receptors is responsible for generating slow synaptic potentials that last several seconds, and reinforce the effects of AMPA receptor activation. In addition to having a prolonged duration of action, neuropeptides diffuse away from the synapse and activate neurons outside of the immediate area, and with intense afferent input, prolonged activation of AMPA and neurokinin receptors lead to progressive cellular depolarization and activation of additional types of glutamate receptors (N-methyl-D-aspartate [NMDA]) on dorsal horn neurons (Lemke, 2004). The dorsal horn represents the first relay point for somatic sensory information. Primary afferent axons may form direct or indirect connections with one of three functional populations of dorsal horn neurons: 1) interneurons, excitatory or inhibitory, 2) propriospinal neurons, which extend over multiple spinal segments and are involved in segmental reflex activity and interactions among stimuli acting at separate sources; 3) projection neurons, which participate in rostral transmission by extending axons beyond the spinal cord to terminate in supraspinal centers such as the midbrain and the cortex.

2.2.3.2.3 Projection

Output from the spinal cord arises from the superficial dorsal horn and this information is projected by the second-order neurons to supraspinal sites (Wiese & Yanksh, 2014). The most prominent ascending nociceptive pathway is the spinothalamic tract and it is divided into two components: medial and lateral. The medial component projects to medial thalamic nuclei and then (via 3rd order neurons) to the limbic system and is involved with the affective-motivational aspect of pain. The lateral component projects to the lateral thalamic nuclei and then to the somatosensory cortex and is responsible for transmission of nociceptive input involved with the sensory-discriminative aspect of pain. The spinoreticular pathway projects to the reticular formation (essential to the integration of nociceptive input) in the medulla and pons, to the thalamic nuclei, and then to the somatosensory cortex. The spinomesecephalic tract projects to the reticular formation and to the periaqueductal grey matter (PAG), which has a central role in the integration and modulation of nociceptive input at supraspinal level

(Lamont et al, 2000; Lemke, 2004). These pathways reflect the underlying dichotomy that pain may be considered to have. In fact, these supraspinal systems can be also be described as somatosensory or affective-motivacional pathways. The somatosensory pathway projecting through the somatosensory thalamus to the somatosensory cortex serves to encode stimulus localisation and intensity (sensory-discriminative), whereas the affective-motivational pathway projects to more medial aspects of the thalamus and others regions such as the anterior cingulate and insula, which are classically associated with emotions and affects (Wiese & Yaksh, 2014).

2.2.3.2.4 Perception

The recognition and processing of sensory information (perception) occurs in multiple specific areas of the brain, which communicate via interneurons to produce an integrated response that reflects the coordinated contributions of arousal, somatosensory input, and autonomic and motor output. The reticular activating system (RAS), located in the brainstem, mediates motor, autonomic and endocrine responses and is a critical center for the integration of these sensory experiences and the subsequent affective and emotional aspects of pain through projection to the medial thalamus and limbic system. Nociceptive information arriving from the dorsal horn is processed in regions such as the pons and medulla, midbrain, PAG and thalamus. The PAG and thalamus serve as relay centers for sensory information transfer; the PAG transfers information to the thalamus and hypothalamus whereas the thalamus transfers information to the cerebral cortex (Wiese & Yaksh, 2014). The thalamus relays information to the somatosensory cortex, which projects information to other cortical regions involved with input association, such as the limbic system. In turn, the limbic system includes several regions such as the cingulate gyrus (responsible for behavior and emotion), amygdala (conditioned fear, anxiety), hippocampus (memory), hypothalamus (sympathetic autonomic activity) and locus ceruleus (arousal, vigilance, behavior). The caudal extension of the limbic system, the PAG, receives descending information from the cortex, amygdala and hypothalamus and descending projections from the medulla, medullary reticular formation (including locus ceruleus) and spinal cord, and is of great importance in the antinociceptive pathway (Valtolina & Gobbs, 2012; Wiese & Yaksh, 2014).

2.2.3.2.4.1 Antinociceptive pathways

Accompanying the ascending nociceptive pathways there are descending antinociceptive pathways that modulate the nociceptive input (Lamont, 2008; Lemke & Creighton, 2010; Valtolina & Gobbs, 2012; Wiese & Yaksh, 2014). These antinociceptive pathways refer to the pain-inhibitory mechanisms that can either reduce the probability of nociceptive stimuli to be perceived as painful or reduce the perceived intensity of pain (Argoff, 2011). The descending

antinociceptive pathways originate at supraspinal level and project to neurons in the dorsal horn of the spinal cord (Lemke & Creighton, 2010). Structures such as the PAG, locus ceruleus and medulla are all particularly important in the modulation of nociceptive input (Lamont, 2008; Lemke & Creighton, 2010; Argoff, 2011). Especially, the PAG is considered to be one of the most important relay points for descending facilitative and inhibitory modulation of nociceptive input (Wiese & Yaksh, 2014). Endogenous opioids (β-endorphins, enkephalins, dynorphins), serotonin and norepinephrine are the main transmitters in the descending antinociceptive pathway (Lamont et al, 2000; Lamont, 2008; Lemke & Creighton, 2010; Argoff, 2011).

2.2.3.3 Neuroplasticity and memory of pain

Neuroplasticity refers to the capacity of the nervous system to modify or adapt its biochemical and physiologic functions in response to different environmental (internal and external) stimuli (Lemke & Creighton, 2010; Wiese & Yaksh, 2014). Neuroplasticity implies that multiple minor sensory events or a single major one can change the stimulus-response characteristics of the nervous system. Several aspects, including the animal's behaviour pattern, the environment, the expectation of pain and the intensity of previous painful events form the memory of pain, but it is the peak intensity of pain that is the single most important factor in determining the real memory. Additionally, animals that have an inherent memory of pain or of a significant painful event are more difficult to manage, and those in which pain has been persistent (days to weeks) are less responsive to treatment (Wiese & Yaksh, 2014). As result of the neuroplasticity, peripheral and central sensitization occur in response to the barrage of nociceptive input that accompanies tissue trauma and play a central role in the development of pathological pain (Lemke, 2004). This phenomenon occurs as a result of severely altered nervous system function, with dynamic changes both peripherally (peripheral sensitization) and centrally (central sensitization) (Lamont et al, 2000; Lamont, 2008; Argoff, 2011).

2.2.3.3.1 Peripheral sensitization

Peripheral sensitization occurs as a direct consequence of tissue trauma and inflammation and generally reverts after treatment and healing (Viñuela-Férnandez et al, 2007; Lamont, 2008; Lemke & Creighton, 2010; Argoff, 2011; Toth, 2013). Tissue trauma leads to the release of inflammatory mediators such as hydrogen ions (H^+), potassium (K^+), bradykinin, serotonin, histamine and cytokines (Lemke & Creighton, 2010; Argoff, 2011; Moffat & Rae, 2011; Toth, 2013). The damage to cell membranes also activates the arachidonic acid pathway, which leads to the production of prostaglandins and leukotrienes. Some inflammatory mediators activate nociceptors directly (bradykinin), while others sensitize nociceptors (prostaglandins). Stimulation of nociceptors also leads to antidromal activation of

nociceptive nerve terminals and release of substance P and calcitonin gene related peptide, which causes mast cell degranulation, vasodilation and edema, leading to further sensitization and activation of nociceptors (neurogenic inflammation). Additionally, sympathetic nerve terminals can also contribute to the activation and sensitization of nociceptors by releasing norepinephrine and prostaglandins. The final result is what is commonly named, a “sensitizing soup” of chemical mediators that act synergistically to lower the nociceptors threshold (Lemke & Creighton, 2010; Toth, 2013).

2.2.3.3.2 Central sensitization

In the same way that the peripheral nociceptors can become sensitized, dorsal horn nociceptive neurons can also exhibit increased excitability (Lamont et al, 2000; Lamont, 2008). Central sensitization emphasizes the large plasticity of the somatosensory nervous system in response to activity, inflammation and neural injury. Its occurrence is characterized by a functional improvement of neural circuits in nociceptive pathways, which result from an increase in membrane excitability and a decreased synaptic inhibition. This central sensitization leads to a state of facilitation, potentiation, augmentation or amplification of action potentials (Latremoliere & Woolf, 2009) and therefore it manifests itself as pain hypersensitivity – particularly allodynia, secondary hyperalgesia, aftersensations and an heightened temporal summation (Woolf, 2011). Incessant stimulation of peripheral nociceptors leads to sustained release of glutamate and neuropeptides from afferent nerve fibres. As consequence, continuous activation of AMPA and neurokinin receptors on dorsal horn projection neurons lead to progressive cellular depolarization and further activation of other types of glutamate receptors (NMDA) (Lemke, 2004).

In general, many of the alterations underlying central sensitization are similar to those that produce peripheral sensitization. Numerous intracellular signaling pathways are activated in the dorsal horn by the neurotransmitter glutamate in addition to other neuromodulators (such as substance P and brain derived neutropic factor [BDNF]) (Lamont, 2008). Furthermore, there has been some evidence that glial cells are key players in the formation and maintenance of pathologic pain states. Glial cells (Schuman cells, microglia, astrocytes and oligodendrocytes) are now known to have an important role in the initiation and facilitation of the development of central sensitization (Lamont, 2008; Lemke & Creighton, 2010; Argoff, 2011). Microglia and astrocytes normally are also activated by glutamate and neuropeptides released from primary afferent fibers and are capable of releasing several nociceptive sensitizing agents such as adenosine triphosphate (ATP), nitric oxide (NO), TNF-α, IL-1 and other cytokynes, which directly increase nerve excitability, indicating a role for these cells in the initiation and maintenance of enhanced pain states, including neuropathic pain (Lamont, 2008; Lemke & Creighton, 2010; Argoff, 2011).

2.2.4 Consequences of pain

Animal welfare, well-being and contentment are all key-aspects of animal quality of life (QOL), which has been defined as "a multidimensional, experiential continuum" and should include the "five freedoms": 1) freedom from thirst, hunger and malnutrition; 2) freedom from discomfort; 3) freedom to express normal behaviour; 4) freedom from fear and distress; 5) freedom from pain, injury and disease. Acute and chronic pain states produce stress and activate defensive biologic responses that result in serious physiologic and behavioural alterations. Generally, the pain phenotype clinically observed results from one or more clinical pathologies and produces multiple neuroendocrine responses (table 2) (Wiese & Yaksh, 2014). Furthermore, stress can change the whole pain experience by causing changes in the brain chemistry, affecting the level of alertness, learning performance and memory, which lead to behavioural adjustments in addition to interdependent autonomic, endocrine and immune alterations (Muir III, 2014a).

Table 2 – Pathophysiologic consequences of pain (Adapted from Handbook of Veterinary Pain Management, 3rd Edition, Gaynor & Muir III, 2014)

Source of pain	Symptoms
Cardiovascular	Tachycardia, hypertension, vasoconstriction, increased cardiac work and oxygen consumption
Pulmonary	Hypoxia, hypercarbia, atelectasis, decreased cough, ventilation/perfusion mismatch, predisposition to pulmonary infection
Gastrointestinal	Nausea, vomiting, ileus
Renal	Oliguria, urine retention
Extremities	Skeletal muscle pain, limited mobility, thromboembolism
Endocrine	Vagal inhibition, increased adrenergic activity, increased metabolism, increased oxygen consumption
Central nervous system	Anxiety, fear, sedation, fatigue, depression
Immunologic	Impairment, "sickness syndrome"

2.2.4.1 Stress response in pain

Stress triggers a response that prepares the animal for emergency situations (the "fight or flight" response). Regardless of cause, the pain response induces activation of the sympathetic nervous system, secretion of glucocorticoids, hypermetabolism, sodium (Na^+) and water retention and altered carbohydrate and protein metabolism (Muir III, 2014a). If untreated, the consequences of pain may extend well beyond unnecessary suffering (Hansen, 2005). In fact, severe or persistent stress can stimulate self-sustained neuroendocrine and immune cascades that degrade homeostatic mechanisms, leading to self-mutilation, immune-incompetence and a "sickness syndrome". This "sickness syndrome" occurs when animals are intermittently or constantly exposed to factors that activate the immune-inflammatory response and the animals generally demonstrate clinical signs of

hyperalgesia, depression, inappetence and somnolence, or may actually display signs of hyper-vigilance such as anxiety, restlessness and an over-sensitivity, that interfere with the animal's ability to rest or sleep (Muir III, 2014a).

2.2.4.1.2 Neuroendocrine axis

External stimuli (auditory, visual and somatosensory information) are transmitted to the thalamus or directly to the amygdala, activating the hypothalamic-pituitary-adrenal (HPA) system. This will further stimulate the secretion of CRF and vasoactive intestinal peptide (VIP), which in turn stimulates the pituitary gland to release ACTH, melanocortin, prolactin, vasopressin and thyroid-stimulating hormone (TSH), and growth hormone (GH). The metabolic consequences of these hormonal changes are increased catabolism, the mobilization of substrates to provide energy for tissue repair, and salt and water retention to maintain fluid volume and cardiovascular homeostatis. Additionally, acetylcholine (ACh) released from preganglionic descending sympathetic nerves during the stress response triggers secretion of NE, epinephrine (E) and neuropeptide Y (NPY, a vasoconstrictor) into systemic circulation. E and NE bind to adrenergic receptors, producing a general systemic arousal and prepares the animal for "fight or flight", increase heart rate and breathing, activate muscles, or dilate blood vessels (muscle, brain, lungs, heart), and increase blood supply to organs involved in fight or flight. The release of CRF in the brain is one of the major components of the stress response, if not the most important. CRF acts synergistically with vasopressin to stimulate the production of ACTH and β-endorfins, thereby enhancing survival and producing analgesic effects, respectively. CRF also stimulates the adrenomedullary release of ACTH and catecholamines. CRF is an excitatory neurotransmitter in the brain, producing increased cortical NE release and excitation (Muir III, 2014a).

2.2.4.1.3 Effects on metabolism

As result of this neuroendocrine response, there is increased secretion of catabolic hormones and thus, a catabolic state succeeds. Generally, pain states are responsible for hyperglycaemia, lipolysis and proteolysis. Hyperglycaemia is due to stress-induced production of glucagon and cortisol (and insulin resistance), and is associated with higher incidence of wound infection, morbidity and mortality. Cortisol, catecholamines and GH stimulate the lipolytic activity, and ultimately, the resultant glycerol is a source for additional gluconeogenesis in the liver. Likewise, protein catabolism is also increased and the resultant amino acids from its breakdown can be used to form new proteins, glucose and other substrates (Muir III, 2014a).

2.2.4.1.4 Effects on the immune system

The immune system can also be perceived as a sensory organ communicating injury-related information to the brain, where the messengers are cytokines (such as interleukin 1 [IL-1],

interleukin 6 [IL-6] and tumour necrosis factor alpha [TNF-α]). In chronic pain states sustained increases of cortisol, norepinephrine, epinephrine and glucagon can suppress the humoral and cellular immune responses. Additionally, the systemic release of endogenous opioids, such as endorphins and encephalin, may contribute to immunosuppression (Muir III, 2014a).

2.2.5 Pain recognition and assessment

Pain assessment presents many challenges. In veterinary medicine there is a struggle to effectively recognise, measure and manage pain as part of ongoing efforts to address the issue of quality of life in companion animals. Pain is a subjective and an individual experience. Considering that and even humans (who can self-report pain) struggle to accurately describe their discomfort and pain quality, this issue is amplified in veterinary medicine, as veterinary patients are unable to verbally express themselves with their caretakers. Therefore, the burden of pain assumption, recognition and assessment rests within veterinary professionals (Morton et al, 2005; Lockhead, 2010; Sharkey, 2013; Perkowski, 2014; Epstein et al, 2015;). In this regard, assessing pain in dogs can be similar to the neonatal and paediatric fields of human medicine, and with the cognitively impaired or nonverbal human patients, where pain assessment depends upon an observer interpretation (Sharkey, 2013).

There are several factors that can affect the observer's assessment, including both observer and patient related factors. Observers' age, gender, personal health and clinical experience can introduce bias (Perkowski, 2014). Environmental factors, such as hospital setting and confinement, may alter the likelihood of an animal to display characteristic pain behaviours, and thereby confounding the evaluator's assessment. Breed and temperament influence the display of pain behaviour as well; some breeds are more stoic and less prone to exhibit pain related behaviour, whereas small toy breeds tend to be more open to showing pain (Lockhead, 2010; Wiese, 2014). Age may also play a role in pain perception. According to Lockhead (2010), paediatric and neonatal patients tend to be more vocal and possibly more communicative about their pain or discomfort, while adults or geriatric patients have a tendency toward stoicism and therefore may tolerate painful states without much complaint. Yet, this subject is still a matter of debate since there have been studies with mixed results, reporting increased, decreased or no change in pain sensitivity with increasing age (Wiese, 2014). Also influencing the recognition of pain in clinical practice are temporal restrictions, as often the staff is unable to perform frequent and whole evaluations of each patient (Lockhead, 2010). Nevertheless, an effort should be made to have all patients evaluated for pain on admission and at regular intervals throughout the hospitalization period (Shaffran et al, 2005).

2.2.5.1 Physiologic signs

Physiologic manifestations of pain are largely related to activation of the sympathetic nervous system. As result, the animal may show increased serum cortisol and catecholamine concentrations, hyperventilation or tachypnea, tachycardia, hypertension, hyperthermia, pale mucous membranes, salivation and pupil dilation. Despite their potential value as indicators of pain, physiologic parameters should not be the only method used to identify or assess pain because the sympathetic nervous system and the stress response can be triggered by non-painful conditions such as disease, fear and anxiety (Lockhead, 2010; Crompton, 2014; Wiese, 2014; Perkowski, 2014).

2.2.5.2 Pain behaviour

As mentioned, it is currently accepted that observation of pain related behaviour is preferred when assessing pain in animals (Sharkey 2013; Wiese, 2014; Mathews et al, 2014; Epstein et al, 2015). Becoming familiarized with normal behaviour in a particular animal and species is the first step in learning to assess abnormal or painful behaviour, as behaviour modification is one of the most import signs of pain in veterinary species (Lockhead, 2010). History taking and the owner's judgement can also be a valuable aid. Common behaviours displayed by animals in pain can include anxiety, depression, inappetence, reluctance to move and changes in body posture, reclusion and aggression. Further common behavioural changes associated with pain in dogs and cats are briefly described in table 3, but as mentioned the key-factor in pain awareness is the ability of the observer to recognize a change in the behavioural pattern of the animal in pain (Wiese, 2014).

Inappropriately, many people tend to focus on vocalisation and agitation as signs of pain but these behaviours are the least specific (Lockhead, 2010; Wiese, 2014). When the caretaker requires animals to show dramatic signs of pain, the patients are forced to prove to that they are in pain. However, many animals may instinctively resist to a change in behaviour, for reasons such as 1) a way to mask injury (as they would in the wild), 2) because they may be too ill or injured to commit to behavioural change 3) it may be a learned response in some. In regard to critical illness and debilitating disease, these conditions limit the options for coping and the pain related behaviours that an animal would normally show; some patients may not move, stand, shift position, withdraw, vocalise, or show other recognizable responses to pain. They may lose their ability and motivation to care for themselves and may not groom, eat, drink, or ask to be let out and urinate and defecate. Therefore, when assessing an animal for pain a range of factors should be considered, including the type, anatomical location and duration of surgery, medical problem or extent of injury and it should be assumed that pain is present in animals whose condition puts them at risk (Hansen, 2005; Shaffran et al, 2005; Perkowski, 2014).

Table 3 – Behavioural and Physiologic Signs Associated with pain in dogs and cats (Adapted from Handbook of Veterinary Pain Management, Gaynor & Muir III, 3rd Edition, 2014)

Abnormal Posture • Hunched-up guarding and tensing of abdomen • "Praying" position for dogs, "sphinx" position for cats • Sitting or lying in an abnormal position • Not resting in a normal position • Statue-like appearance • Abnormal body positioning
Abnormal Gait • Stiff • Partial or no weight bearing on injured limb • Lameness, slight to obvious limp • Reluctance to move
Abnormal Movement • Thrashing • Restlessness • Circling • Continuous activity
Vocalisation • Screaming, howling, barking, meowing • Whining (Intermittent, constant or when touched) • Crying (Intermittent, constant or when touched)
Miscellaneous • Looking at, licking or chewing the painful area • Hyperesthesia or hyperalgesia • Allodynia

2.2.5.3 Pain Assessment Tools (PATs)

Validated pain scales offer reliable methods for clinicians to assess pain and quantify changes in pain intensity. There are many different pain scoring or assessment systems in human medicine (over 80 different pain and quality of life questionnaires have been described) and many of them are designed for non-communicative patients such as demented elderly and new-borns or preverbal children (Matthews, 2000; Schnackers, 2012; Sharkey, 2013). Over the last decades, the increasing interest on the subject of pain in veterinary medicine intensified the research for better pain assessment methods as means to

a more effective pain management and as result, many of these human medicine assessment systems have been employed and adapted to veterinary medicine. However, as an inherent issue to pain itself, there is no gold standard for its assessment (Mathews et al, 2014) and no scale is capable of accurately measure all of its dimensions (Matthews, 2000; Shaffran et al, 2005; Sharkey, 2013; Crompton, 2014, Wiese, 2014). Due to the subjective and observational nature of many PATs, validated and reliable pain scales are essential to assure the usefulness of the measure to indicate pain or predict a dog's function or quality of life. Many PATs differ in the specific signs and types of tools used to generate the pain assessment (Sharkey, 2013). Despite certain limitations these systems may present, the American Animal Hospital Association/American Association of Feline Practitioners (AAHA/AAFP) recommends the use of pain scoring tools both for acute and chronic pain in dogs and cats, as its use can decrease observer subjectivity and bias and improve pain management responses (Epstein et al, 2015).

2.2.5.3.1 Subjective unidimensional scales

2.2.5.3.1.1 Simple Descriptive Scale (SDS)

Analogous to the Subjective Verbal Pain Scale used in human medicine, one of the simplest pain scoring systems used in veterinary medicine is the Simple Descriptive Scale (SDS) (figure 2) (Wiese, 2014). It uses a simple approach of assigning descriptors to qualify the level of pain (no pain, mild, moderate, severe). The descriptors are often assigned a number that is used for calculating the patient's pain score. This method is attractive for its simplicity and minimal training required for use, but demonstrate potential for significant interobserver variability and the small number of categories reflects poor sensitivity, leading to potential underestimation or overestimation of pain severity (Lockhead, 2010, Wiese, 2014, Perkowski, 2014).

Figure 2 – Representation of a simple descriptive scale

Simple Descriptive Scale (SDS)	
0	No pain
1	Mild pain
2	Moderate pain
3	Severe pain

2.2.5.3.1.2 Numerical Rating Scale (NRS)

The numerical rating scale (NRS) is very similar to the SDS. This scale consists of multiple categories (ranging from 1 to 4, 1 to 6 or 1 to 10) that list descriptors about each category in an attempt to quantify a gradual increase in pain intensity (figures 3 and 4). These

descriptors are assigned a numeric value analogous to increasing intensity, however the individual scores are not weighted by importance (each descriptor is treated equally). One advantage over the SDS is the inclusion of multiple categories, allowing a more critical assessment of the severity of the animal's pain. Disadvantages include difficulty in applying this scale to multiple species because of species-specific behavioural categories and lack of robustness (Lockhead, 2010; Wiese, 2014).

Figure 3 – Representation of a numerical rating scale (NRS). (Adapted from Handbook of Veterinary Pain Management, Gaynor & Muir III, 3rd Edition, 2014)

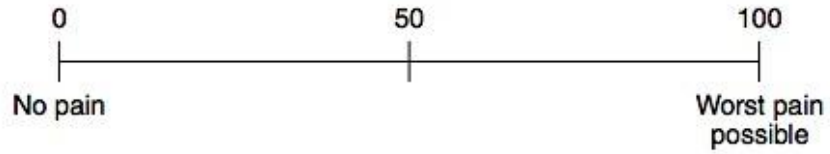
Figure 4 – Different representation of the NRS (Adapted from http://www.animalpain.com.br/en-us/escalas-unidimensionais.php)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

2.2.5.3.1.3 Visual Analogue Scale (VAS)

One of the most commonly used pain scoring systems in human and veterinary medicine is the Visual Analogue Scale (VAS) (figure 5). There are numeric and non-numeric versions of this scale but ultimately the VAS consists of a horizontal line of predetermined length, usually 100 mm long, with a vertical line border at both ends. The beginning of the line is assigned the value "0" to "no pain" and the end is assigned "100" to "very severe pain". The observer will assess the patient and mark a vertical line along the horizontal scale, believed to represent the patient's pain level (Lockhead, 2010; Wiese, 2014). Advantages of the VAS are its simplicity of use as a semi-quantitative means for assessing pain; however, interobserver variability is quite high, which limits its accuracy. Also, in similarity to the SDS, the VAS does not provide objective quantitation of pain (Wiese, 2014).

Figure 5 – Representation of the visual analogue scale (VAS). ((Adapted from Handbook of Veterinary Pain Management, Gaynor & Muir III, 3rd Edition, 2014)



The scales that have been described are referred as one-dimensional scales, as they can only assess the suspected intensity of the animal's pain. Although these semi-objective scales are of easy use and practice-friendly application, they have high observer variability

(the observer's judgement can be affected by factors such as age, gender, personal health and clinical experience) (Lockhead, 2010; Coutinho, 2012; Sharkey, 2013) and seem to be an inadequate means to assess acute pain in dogs and cats. With purpose of increasing the accuracy of pain assessment, numerous efforts have been made in veterinary medicine to develop and validate composite, specie-specific and behaviour descriptive pain scales of which multidimensional pain scales serve as an example (Lockhead, 2010; Sharkey, 2013; Mathews et al, 2014).

2.2.5.3.2 Multidimensional pain scales

2.2.5.3.2.1 University of Melbourne Pain Scale (UMPS)

The University of Melbourne Pain Scale (UMPS) (Annex IV) was developed to assess postoperative pain in dogs and is based on the assessment of six categories that include both physiologic and behavioural data such as respiratory rate, pupil dilation, salivation and rectal temperature, response to palpation, activity, mental status, posture and vocalisation. Each of these six categories is further divided into subcategories that are assigned individual numerical weights. The observer is meant to select a descriptor that approximates the animal's behaviour in each category, making possible pain scores from 0 to a high of 27 (Sharkey, 2013; Wiese, 2014).

2.2.5.3.2.2 Colorado State University Acute Pain Scale for Dogs

The Colorado State University Medical Centre (CSUVMC) has actually developed scales for assessment of acute pain in both canine (Annex V) and feline patients. These scales incorporate many features of previously described scales; they are single-paged, user friendly, practical and include multidimensional descriptors of pain. The scale describes five levels of pain and includes psychological and behavioural signs of it and palpation and body tension responses. The scale also includes a vertical VAS with a 0-4 level range (instead of a 100mm scale) and a colour system regarding to pain severity. Additionally, for each level of pain depicted the scale includes representations of the animals' characteristic posturing and expressions. This scale has been shown to increase awareness of behavioural changes associated with pain, yet further validation studies are to be conducted regarding the use of this pain scale (Wiese, 2014; Mathews et al, 2014; Perkowski, 2014).

2.2.5.3.2.3 Glasgow Composite Measures Pain Scale

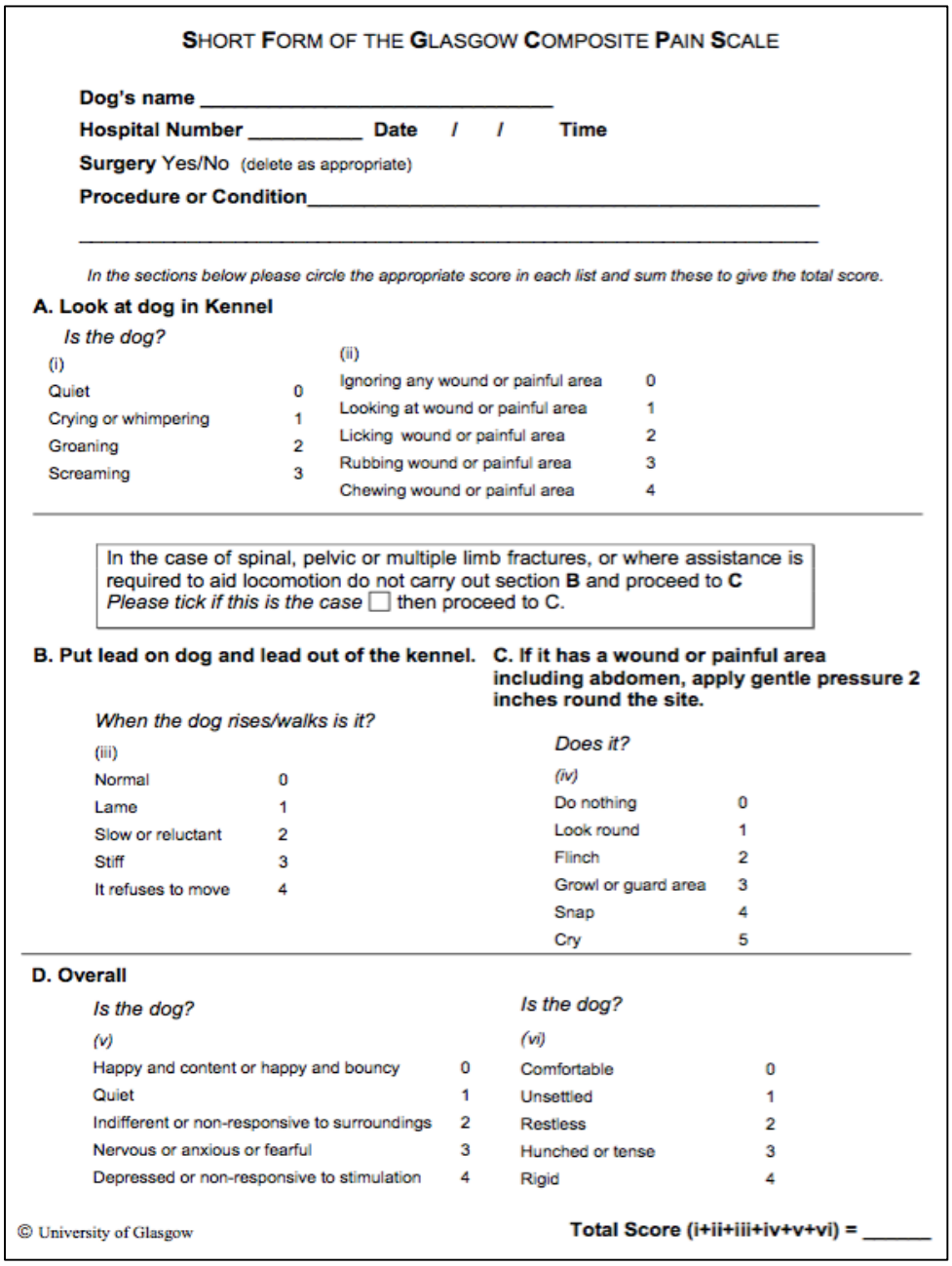
The Glasgow Composite Measures Pain Scale (GCMPS) is a multidimensional pain scale designed to assess acute post-operative pain in canine patients in a hospital setting. This tool takes the form of a questionnaire, and the behavioural assessment included in the scale fall into seven categories (posture, comfort, vocalisation, attention to wound, demeanour, mobility and response to touch) with associated descriptors; the specific descriptors identified

for each category comprise 47 words selected from a collection of 279 to describe pain behaviours. As the categories are divided into equal intervals, the scale enables to quantify the severity of pain based on a total score of the weighted categories (Morton et al, 2005; Sharkey, 2013; Wiese, 2014). The development of this scale was based on the same psychometric methodology employed in the McGill Pain Questionnaire used in human medicine, which provides a composite score based on seven behavioural categories with precise definitions of the descriptors. Although originally oriented to assess of post-operative pain, there are suggestions that the scale could be used in the assessment of acute pain of various medical conditions (Morton et al, 2005; Sharkey, 2013; Mathews et al, 2014).

2.2.5.3.2.4 Short Form of the Glasgow Composite Measure Pain Scale

In order to increase the practicality of the GCMPS in a clinical setting, a shortened form was developed. The simplified short form (CMPS-SF) is a questionnaire based on six behavioural categories that evaluate the dog's spontaneous behaviour, interactive assessment of mobility and response to touch, and the observer's overall impression of the dog's posture and activity (Figure 6). This scoring system provides a clear, repeatable format that the observer may use to identify specific behaviours using set definitions and thereby reducing bias, interpretation and interobserver variability. In addition to its use as a means to quantify individual pain and assess pain management, the CMPS-SF provides an intervention score, which defines when additional analgesia should be considered: scores equal to or higher than 5/20 or 6/24 are suggestive for analgesia implementation. As the CMPS-SF is used in more clinical studies, more insight about its practical use will be further elucidated (Sharkey, 2013; Wiese, 2014). Another advantage of this scale is the fact that it is available in 7 different languages: English, French, German, Italian, Spanish, Swedish and Norwegian.

Figure 6 – Glasgow Short Form Composite Measure Pain Scale (CMPS-SF) for assessment of acute pain in canine patients



SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name _____

Hospital Number _____ **Date** / / **Time**

Surgery Yes/No (delete as appropriate)

Procedure or Condition_____

_____

In the sections below please circle the appropriate score in each list and sum these to give the total score.

A. Look at dog in Kennel

Is the dog?

(i)		(ii)	
Quiet	0	Ignoring any wound or painful area	0
Crying or whimpering	1	Looking at wound or painful area	1
Groaning	2	Licking wound or painful area	2
Screaming	3	Rubbing wound or painful area	3
		Chewing wound or painful area	4

In the case of spinal, pelvic or multiple limb fractures, or where assistance is required to aid locomotion do not carry out section **B** and proceed to **C**
Please tick if this is the case ☐ then proceed to C.

B. Put lead on dog and lead out of the kennel.

When the dog rises/walks is it?

(iii)	
Normal	0
Lame	1
Slow or reluctant	2
Stiff	3
It refuses to move	4

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.

Does it?

(iv)	
Do nothing	0
Look round	1
Flinch	2
Growl or guard area	3
Snap	4
Cry	5

D. Overall

Is the dog? *(v)*		*Is the dog?* *(vi)*	
Happy and content or happy and bouncy	0	Comfortable	0
Quiet	1	Unsettled	1
Indifferent or non-responsive to surroundings	2	Restless	2
Nervous or anxious or fearful	3	Hunched or tense	3
Depressed or non-responsive to stimulation	4	Rigid	4

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Total Score (i+ii+iii+iv+v+vi) = _____

2.2.5.3.2.5 Further pain assessment tools

There are several other relevant acute pain scoring systems in veterinary medicine. The 4A-Vet pain scale (annex VI) is a composite measure pain score for dogs, developed by the French Association for Animal Anaesthesia and Analgesia (Mathews et al, 2014) and although less biased by sedation, it has been reported to have higher interobserver variability than the Glasgow CMPS-SF (Epstein et al, 2015). For feline patients, a currently validated assessment tool is the UNESP-Botucatu multidimensional composite pain scale for assessing postoperative pain in cats has been validated and can be applied in the clinical setting as a useful tool (Brondani et al, 2013; Sousa, 2013; Mathews et al, 2014; Batista, 2015; Epstein et al, 2015) and is available in English and Brazilian Portuguese (Brondani et

al, 2013; Sousa, 2013). Additionally, there are pain assessment tools and questionnaires oriented to the assessment of chronic pain in canine patients such as the Canine Brief Pain Inventory and the Helsinki Chronic Pain Index or the Liverpool Osteoarthritis in Dogs (Sharkey, 2013; Mathews et al, 2014). At the moment, there are no validated instruments available for the assessment of chronic pain in cats, although it is suggested to conduct continuous behavioural assessments including general mobility, activity, eating and drinking, grooming, rest, social interaction and temperament (Mathews et al, 2014).

2.3 Pain management

Preventing and managing pain is a fundamental part of quality and compassionate patient care in veterinary medicine, not only due to its moral implications but also because pain has serious deleterious effects on animal well-being, recovery and outcome. Therefore, as advocates for veterinary patients, the veterinary team has the responsibility to actively prevent, assess and treat pain (Shaffran et al, 2005; Hellyer et al, 2007; Lockhead, 2010; Crompton 2014; Mathews et al, 2014; Epstein et al, 2015).

2.3.1 Multimodal analgesia

There are several approaches to pain management, including pharmacological and non-pharmacological options, although drug therapy remains the cornerstone in pain management. Treatment of pain may be directed at any or all of the steps in the nociceptive pathway and should be tailored to the cause, severity and duration (acute or chronic) of pain (Hansen, 2005; Gaynor 2008; Muir III, 2014b). A balanced or multimodal strategy, where two or more classes of drugs are used, is often preferred to ensure an effective pain management. This approach aims to target multiple sites in pain pathways, allowing the use of lower doses of each drug and minimizing the potential for side effects (Hansen, 2005; Gogny, 2006; Mathews et al, 2014; Epstein et al, 2015). The major classes of drugs that are useful in the treatment of acute pain and stress include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), α2-agonists and local anaesthetics (LAs). Additionally, the use of other adjunctive drugs such as anticonvulsants, NMDA-receptor antagonists and tricyclic antidepressants (TCAs) has proven to be helpful in pain management (Gogny, 2006; Lemke & Creighton, 2010; Mathews et al, 2014; Muir III, 2014b; Tomlinson, 2014; Epstein et al, 2015). Although sedation is no substitute for analgesic therapy, it can also be considered complementary to analgesia when patients present failure to sleep, behavioural manifestations of distress, intense vocalization and/or pacing (Hansen, 2005).

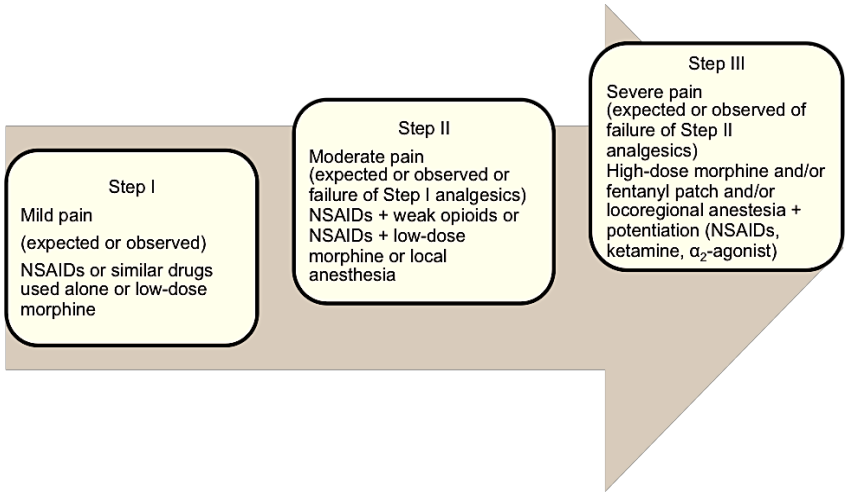
2.3.2 Treatment strategy

Ideally, anticipatory analgesia (preemptive) provided prior to pain onset is more effective than analgesia provided once pain has occurred. However, this is not always possible and therefore pain management protocols should be tailored to the patient and to the source and

type of pain (Gogny, 2006; Gaynor, 2008; Epstein et al, 2015). Some insight of the pharmacology of analgesic drugs in each species should be considered, since factors such as age, breed and physical status may influence drug pharmacology and, consequently, the efficacy and dosing regimen of analgesic drugs (Gaynor, 2008; Mathews et al, 2014).

The World Health Organization (WHO) proposed a three-step ladder model for the classification and management of pain (figure 7), and although it was originally designed for the management of cancer pain in human medicine, it has been transposed and accredited to veterinary medicine. This model suggests a certain drug hierarchy depending on drug potency and its benefit/risk ratio (Gogny, 2006; Gaynor, 2008). Nonetheless, regardless of the type of drug or combination of drugs used, patients should be reassessed frequently to ensure that the analgesic regimen is adequate and appropriate (Quandt & Lee, 2014).

Figure 7 – WHO ladder pain management approach (Adapted from Gogny, 2006)



2.3.3 Drug therapy

2.3.3.1 Opioids

The term opiate used to designate drugs derived from opium such as morphine and codeine; however, with the development of synthetic drugs with morphine-like actions, the term opioid is currently applied to designate all exogenous substances that bind to opioid receptors (Sawyer, 1998). Opioids are considered the most effective drug class for management of moderate to severe acute pain in humans and companion animals (Hansen, 2005; Gaynor, 2008; Beckman, 2013; Epstein, 2014; Mathews et al, 2014; Epstein et al, 2015). Opioid agents bind to different opioid receptors – μ (mu), κ (kappa), δ (delta) and nociceptine (table 4) – that can be found in the central and peripheral nervous systems and act by inhibiting the presynaptic release and postsynaptic response to excitatory neurotransmitters, limiting the input of nociceptive information to the CNS (Mathews et al, 2014; Quandt & Lee, 2014).

2.3.3.1.2 Mechanism of action

Although the ultimate response of opioid receptor activation is a an enhanced postsynaptic efflux of potassium that causes neuronal hyperpolarization of the spinal cord projection neurons and blockade of substance P release (inhibiting the ascending nociceptive pathways) (Mathews et al, 2014), inhibition mechanisms vary with opioid receptors (Epstein, 2014).

Table 4 – Opioid receptors, distribution and effects (Adapted from Handbook of Veterinary Pain Management, Gaynor & Muir III, 3rd Edition, 2014)

Opioid Receptor	Distribution	Effect
μ (μ_1, μ_2, μ_3)	Brain, spinal cord, periphery sensory neurons, immune cells, amygdala, endothelial cells	Supraspinal analgesia, respiratory depression, bradycardia, physical dependence, euphoria; hyperpolarization of peripheral nerves induced by inflammation or immune response
κ (κ_{1a}, κ_{1b}, κ_{2a}, κ_{2b}, k_3)	Brain, spinal cord, peripheral sensory neurons	Analgesia, sedation, miosis
δ (δ_1, δ_2)	Brain, peripheral sensory neurons	Analgesia, euphoria CNS depression, dysphoria, respiratory depression
Nociceptin	Brain, spinal cord	Anxiety, depression, appetite stimulation

Opioids have different receptor specificity, potency and efficacy, which result in different clinical effects. For instance, the analgesic effect of κ-receptor activation is relatively subtle and short-lived in comparison with μ-receptor activation (Epstein, 2014). Overall, opioids can be divided in four classes of agents: full agonists, partial agonists, agonist-antagonists and antagonists (Gaynor, 2008; Mathews et al, 2014; Quandt & Lee, 2014). Full agonists [morphine, methadone, fentanyl and its derivatives (pethidine, meperidine, *etc.*)] produce a strong analgesic effect through complete stimulation of agonist receptors, whereas partial agonists (buprenorphine) bind at the same receptor but have a less pronounced effect. Agonist-antagonists (butorphanol and nalbuphine) act at different types of receptors and have mixed effects; these agents have an agonist effect at one receptor (producing an analgesic response) and an antagonist effect at a different receptor (resulting in a weaker analgesic response or no effect). Opioid antagonists (naloxone, naltrexone, *etc.*) bind to the

same receptors as agonists but generally are devoid of agonist activity, causing no effect and compete with the agonists for the same receptor, which enables to reverse the agonist effect (Gaynor, 2008; Quandt & Lee 2014). Annex VII lists commonly used opioids in veterinary medicine. Most opioids produce species-dependent minimal to moderate CNS effects that generally result in sedation, however opioids can cause hyperexcitability or agitation in cats (Beckman, 2013; Muir III, 2014b; Quandt & Lee, 2014). The sedative properties of opioids might be considered positive when these agents are used in the perioperative setting as part of multimodal and/or preemptive analgesic protocols (Beckman, 2013). Opioids are also widely administered in emergency and critical care patients (particularly full μ agonists) because they have a rapid onset of action and are reversible (Mathews et al, 2014; Quandt & Lee, 2014).

2.3.3.1.3 Tramadol

Tramadol is considered an atypical opioid that produces analgesia through activation of μ opioid receptors and selective inhibition of serotonin and norepinephrine (Gaynor & Muir III, 2014b). The opioid effect of tramadol is believed to be related to its major metabolite O-desmethyltramadol, which is more potent that the parent compound, and there is also suggestion that the analgesic effect may be due to inhibition of serotonin uptake (Gaynor & Muir III, 2014b; Mathews et al, 2014). Tramadol is used for the treatment of mild to moderate pain and as part of a multimodal analgesic protocol. It has been used in association with NSAIDs to alleviate pain associated with chronic conditions such as osteoarthritis and chronic pain (Gaynor & Muir III, 2014b).

2.3.3.1.4 Contraindications and side effects

These agents are considered to be safe, as side effects usually result from excessive dosing. For instance, the partial agonist buprenorphine and mixed agonist-antagonist butorphanol have a maximum effect at the upper end of the dose range. Whenever pain is severe or the analgesia seems inadequate, additional doses of these agents are unlikely to be effective and potential adverse effects may occur. Using a pure μ agonist such as methadone or fentanyl would be more effective because there is no upper limit to the analgesia provided by this class of opioids. However, at the higher doses of pure μ agonists adverse effects such as respiratory depression and bradycardia may occur. Additional adverse effects of μ agonists (morphine and pethidine) include histamine release, which is of particular concern when these agents are given IV administered because this can lead to hypotension due to vasodilation (Quandt & Lee, 2014). However, clinically important reductions in blood pressure in response to proper doses of opioids are uncommon in conscious dogs and cats unless the animal is hypovolemic (Hansen, 2005). More commonly, opioids are responsible for diarrhea (initially), gastroparesis and ileus (with prolonged use), nausea, vomiting,

dysphoria, panting and urinary incontinence or retention (Gaynor, 2008; Beckman, 2013; Muir III, 2014b; Mathews et al, 2014).

Any of these adverse effects can be reversed with naloxone (Mathews et al, 2014). Still, higher doses of opioid agents should be used cautiously in the critically ill and in geriatric or debilitated patients (Gaynor, 2008). Overall the clinician should balance the benefits and disadvantages of opioid administration, as some adverse effects may be clinically irrelevant when pain management is a priority (Mathews et al, 2014).

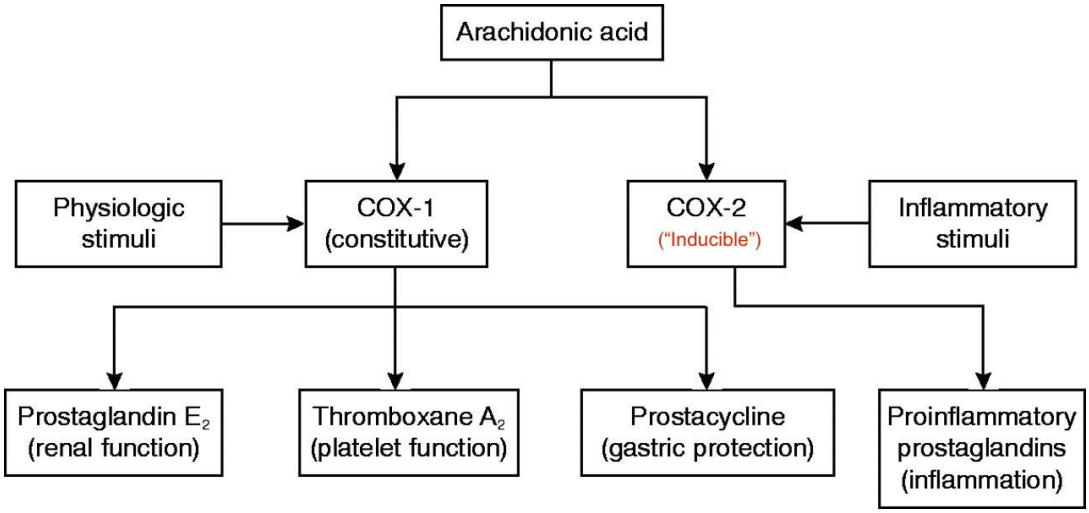
2.3.3.2 Nonsteroidal Anti-Inflammatory Drugs

Shortly termed NSAIDs, these drugs are extensively used in both human and veterinary medicine and represent a heterogeneous group of chemical compounds that produce analgesia, anti-inflammatory and antipyretic effects (Khan & Mclean, 2012). Chemically most NSAIDs are substituted organic acids and although these compounds differ widely in their chemical structure and properties, they share similar therapeutic and adverse effects associated with their use. NSAIDs do not modify the animal's level of consciousness or behaviour and act both peripherally as well as on the CNS level (Khan & Mclean, 2012; Budsberg, 2014). Usually NSAIDs are most effective in the perioperative period, in the treatment of pain caused by tissue damage and treatment of mild to moderate pain associated with osteoarthritis (chronic pain), but are relatively ineffective for treating severe pain and are frequently administered as part of a multimodal pain therapy program (Budsberg, 2014; Mathews et al, 2014). Annex VIII lists some of the most commonly used NSAIDs in veterinary medicine.

2.3.2.1 Mechanism of action

NSAIDs exert their function through the inhibition of the cyclooxygenase synthetase (COX) enzymes, which enable the synthesis of prostaglandins that mediate inflammation and fever (figure 8) (Khan & Mclean, 2012; Budsberg, 2014; Muir III, 2014b; Tomlinson, 2014).

Figure 8 – COX-1 and COX-2 enzymes and NSAID action (Adapted from https://www.jaaos.org/content/12/3/139/F1.expansion)



The COX enzyme has distinct forms: COX-1, COX-2 and COX-3 (which is an alternative splice of COX-1 with higher expression at the brain) (Budsberg, 2014). COX-1 and COX-3 are considered constitutive enzymes and are involved in cell signalling and maintenance of tissue homeostasis. For instance, the COX-1 enzyme is present at tissues such as the stomach, kidney, platelets and reproductive tract, and is responsible for basal prostaglandin production for homeostasis in these tissues. COX-2 has been labelled as an inducible enzyme, since it is the primary enzyme responsible for the overproduction of prostaglandins after acute injury or infection. However, there is evidence that COX-2 is expressed constitutively in several tissues including the brain, kidney, reproductive system and the eye (Budsberg, 2014).

NSAIDS can limit the nociceptive input to the CNS by fighting peripheral and central hypersensitivity (Lemke & Creighton, 2010; Quandt & Lee, 2014). Peripherally, NSAIDs act on COX-2 enzymes to block the formation of prostaglandins such as PGE_2 and PGI_2, responsible for arteriolar dilation and sensitization of peripheral nociceptors to the action of histamine and bradykinin. Centrally, the activation of glial cells and microglia within the CNS by proinflammatoy cytokines and lymphokines is suspected to be responsible for COX-2 mediated prostaglandins (such as PGE_2) and tumour necrosis factor alpha (TNF-α) production. PGE_2 lowers the threshold for neuronal depolarization, thus leading to increases in the number of action potentials and repetitive spiking (Budsberg, 2014; Muir III, 2014b). Therefore, the selective inhibition of certain prostaglandins essentially produced by COX-2 enzymes should allow for more efficient analgesic and anti-inflammatory effects while lessening unwanted side effects caused by inhibition of the COX-1 enzyme (Budsberg, 2014).

2.3.2.2 Contraindications and adverse effects

The nonsedating, analgesic and low-toxicity of newer NSAIDs has helped to decrease traditional concerns. However, given the potential for serious side effects, veterinarians should consider cautiously the NSAID agent or even its administration (Muir III, 2014b). The most common adverse effects associated with NSAID use in dogs and cats involve the gastrointestinal (GI) tract and the renal system. GI toxicity associated with NSAID use may be caused by inhibition of endogenous prostaglandins and signs range from vomiting and diarrhoea (including hematemesis and melena), to silent ulcers that may result in perforation (Muir III, 2014b; Mathews et al, 2014). Similarly, renal injury is due to blockade of homeostatic prostaglandins that are involved in auto regulation of renal blood flow and tubular function (Muir III, 2014b). NSAIDs with selective COX-1 antagonism have been reported to cause inhibition of coagulation via anti-thromboxane activity. This class of NSAIDs should be avoided preoperatively and should only be administered postoperatively when adequate clot formation has occurred (usually upon completion of surgery). While there

is no clear evidence stating that the use of NSAIDs in patients with hepatic disease is an absolute contraindication, GI ulceration is known to be more frequent in animals with hepatic disease (Mathews et al, 2014). For these reasons, NSAIDs are contraindicated in situations such as animals receiving any type of systemic corticosteroids or with concurrent NSAIDs, animals with active GI disease, in animals with renal or hepatic insufficiency or dysfunction, animals with any clinical syndrome involving a decrease in the circulating blood volume (shock, dehydration, hypotension or ascites), animals with known or suspected significant active haemorrhage or blood loss and animals with any type of confirmed or suspect coagulopathies (Budsberg, 2014, Muir III, 2014b).

2.3.3 α_2-adrenergic agonists

Alpha$_2$ (α_2)-adrenergic agonists cause sedation, peripheral vasoconstriction, bradycardia, respiratory depression, diuresis, muscle relaxation and analgesia (Lemke & Creighton, 2010; Quandt & Lee, 2014; Mathews et al, 2014). Common α_2 agents used for anaesthesia and analgesia include xylazine, medetomidine, dexmedetomidine, romifidine and clonidine (Pypendop, 2014), although the most common agents used are medetomidine and dexmedetomidine (Annex IX). Medetomidine is supplied as a racemic mixture of 2 optical enantiomers; dexmedetomidine is the active enantiomer, while levomedetomidine is apparently pharmacologically inactive. Thus, dexmedetomidine is about twice as potent than medetomidine. The clinical effects of both drugs are similar at equivalent doses and they are both approved for use in dogs and cats (Lemke & Creighton, 2010). Both of these α_2-adrenergic agonists have a rapid onset of action, although the sedative effects of medetomidine have longer duration than the analgesic effects (30-90 minutes). At higher doses, medetomidine can be used for sedation of distressed animals and for use in minor procedures. Similarly to opioids, these agents can be reversed with a α_2-receptor antagonist such as atipamezole or yohimbine (Mathews et al, 2014).

2.3.3.1 Mechanism of action

α_2-adrenergic agonists bind to different receptors in the CNS to produce their effects and they present different receptor specificity and potency (Mathews et al, 2014). α_2 agonists activate presynaptic and postsynaptic α_2 receptors in the CNS and periphery, leading to anxiolysis, sedation and analgesia. Sedation in dogs and cats is attributed to activation of CNS α_{2A} receptors in areas of the brain that are responsible for awareness, arousal and vigilance. Activation of presynaptic α_2 receptors inhibits the release of excitatory neuropeptides (noradrenaline) and substance P, and activation of postsynaptic α_2 receptors hyperpolarizes neurons, thereby decreasing the activity of nociceptive neurons. In the spinal cord the analgesic effect of α_2 agonists is likely related to activation of descending medullospinal noradrenergic pathways or to the reduction of spinal sympathetic outflow at

presynaptic ganglionic sites (Muir III, 2014b).

2.3.3.2 Side effects and contraindications

Because α_2 agonists bind to their receptors in the vascular endothelium they cause peripheral vasoconstriction, with increases in systemic and pulmonary vascular resistance while decreasing cardiac output (CO) in a dose-dependent manner. Consequently, bradycardia and bradyarrhythmias (first and second degree atrioventricular block) may occur. α_2-agonists produce dose dependent decreases in respiratory rate and volume that parallel the degree of CNS depression. Pronounced CNS depression is associated with an increase in the threshold to PCO_2 resulting in significant respiratory acidosis and hypoxemia in older or sick animals (Muir III, 2014b). Other common side effects include vomiting or nausea, hyper and/or hypotension, hypothermia, decreases in GI motility, transient hypoinsulinaemia and hyperglycaemia (α_2 receptors modulate the release of insulin by pancreatic β-cells) and glycosuria (Mathews et al, 2014; Muir III, 2014b). In general, α_2-agonists are contraindicated in animals with cardiopulmonary disease with or without arrhythmias or conduction disturbances, significant systemic disease, preexisting hypo/hypertension, diabetes mellitus and liver/renal failure. Caution should be exercised when using in patients with trauma. Anticholinergic agents and α_2-agonists should not be used together or administered to animals with pre-existing ventricular arrhythmias, myocardial contusion, heart failure or any other cause of ventricular electrical instability (Muir III, 2014b).

2.3.4 Local anaesthetics

Local anaesthetics (LAs) are drugs that reversibly bind to Na^+ channels and block impulse conduction in nerve impulses (Lemke & Creighton, 2010; Mathews et al, 2014) and are the only class of drug that renders complete analgesia (Lemke & Creighton, 2010; Epstein et al, 2015). LAs can be either amino-esters (tetracaine, procaine, benzocaine) or amino-amides (lidocaine, bupivacaine, ropivacaine, mepivacaine, prilocaine) (Becker & Reid, 2006; Muir III, 2014b; Mathews et al, 2014). The potency of these agents is mainly influenced by lipid solubility while the onset of action is inversely associated with the acid dissociation constant (pK_a) and lipophilic features, increased protein binding and potency (Becker & Reid, 2006; Mathews et al, 2014).

2.3.4.1 Mechanism of action

All LAs produce analgesia as a direct result of Na^+ channel blockade and membrane stabilization. LAs block the initiation and conduction of action potentials in nerves and usually, small diameter, unmyelinated (Aδ, C) nerve fibers are blocked first in preference to large myelinated fibers (Aβ), thereby producing a loss of sensation (analgesia) and varying degrees of paralysis (Mathews et al, 2014; Muir III 2014b). LAs are most frequently administered at specific sites (topical, local) or on nerves (regional) to produce analgesia but

can also be infused perioperatively to reduce anaesthetic and opioid requirements (Lemke & Creighton, 2010; Muir III, 2014b; Epstein et al, 2015).

2.3.4.2 Local anaesthetics in veterinary medicine

The most common LAs used in cats and dogs are lidocaine, bupivacaine and mepivacaine (Hansen, 2005; Lemke & Creighton, 2010). Lidocaine is often used in critical care because it is well suited for procedural pain and may control ventricular arrhythmias (Hansen, 2005; Lemke & Creighton, 2010); it may be administered by local infiltration for short procedures such as IV catheterization (at a maximum safe dose of 4mg/kg), topically as 2% gel for oral, nasal and urinary procedures (Hansen, 2005). Lidocaine can also be used as an IV CRI (up to 3 mg/kg/h) to provide systemic analgesia to dogs (Hansen, 2005; Lemke & Creighton), reducing the inhalant anaesthetics requirements up to 30% (Lemke & Creighton, 2010).

Table 5 – General characteristics of most commonly used LAs in veterinary medicine

Drug	Observations
Lidocaine	Lidocaine has a fast onset (10 minutes) but a short duration of action (1-2 hours). The total dose of lidocaine should not exceed 8mg/kg. IV loading doses of 1-2 mg/kg are appropriate for most dogs. Intraoperatively, the IV infusion dose range for dogs is 4-6 mg/kg/h. Postoperatively, a lower IV infusion dose range of 2-3 mg/kg/h is used to provide analgesia and to improve GI motility (Lemke & Creighton, 2014).
Bupivacaine	Bupivacaine 0.5% is frequently used for local infiltration and local nerve block and is particularly useful when used perioperatively for surgical wound pain (Hansen, 2005). Bupivacaine is about 4 times more potent than lidocaine and mepivacaine, has a slow onset (20 minutes), a longer duration of action (4-6 hours) and it is used for most surgical procedures (Lemke & Creighton, 2010). Typical dose is 1–2mg/kg (Hansen, 2005; Quandt & Lee, 2014).
Mepivacaine	Mepivacaine is similar to lidocaine in potency and onset, but has a longer duration of action (2-3 hours). Mepivacaine causes less tissue irritation, and also has a higher therapeutic index (Lemke & Creighton, 2010).

2.3.4.3 Contraindications and adverse effects

Some amino-esters anesthetics (prilocaine, benzocaine) may cause allergic reactions in some animals and methaemoglobinaemia in cats (Mathews, 2014). Because amino-amide LAs are highly protein-bound and are metabolized by the liver (Lemke & Creighton, 2010; Mathews et al, 2014) anemic and hypoproteinemic patients may be more vulnerable to

toxicity (Lemke & Creighton, 2010). Administration of an excessive dose and accidental intravenous administration are the most common causes of systemic toxicity in small animals. It is possible that toxicity occurs with higher doses of lidocaine (>10–20 mg/kg) and bupivacaine (>4mg/kg) including seizures, cardiac arrhythmias, tachycardia and cardiovascular collapse as clinical signs (Quandt & Lee, 2014). However, LAs are relatively safe if used correctly (Lemke & Creighton, 2010). The use of LAs is not advised at sites of skin infection and neuro-axial blockades are not advised in the presence of coagulation disorders, spinal cord trauma, hypovolemia and septicemia (Mathews et al, 2014).

2.3.5 Adjunctive Drugs

Common adjunctive drugs include anticonvulsants such as gabapentin, NMDA receptor antagonists as ketamine and amantadine, and TCAs like amitriptyline. These drugs do not fall into major traditional classes of analgesic agents and usually are not meant for single use, however they can be associated with the previously mentioned drugs to improve pain management. Although glucocorticoids are not primary analgesic agents, they may also be associated to other agents, such as opioids, in a multimodal pain management protocol (Mathews et al, 2014). Other drugs that have potential in multimodal pain management protocols may include serotonin reuptake inhibitors such as duoloxetine (Mathews et al, 2014), maropitant (Mathews et al, 2014) and cannabinoids (Gaynor & Muir III, 2014b) but given that there is yet uncertain evidence of their efficacy in pain management these agents are not to be addressed at this moment.

2.3.5.1 Anticonvulsants

Gabapentin is a structural analogue of γ-aminobutiric acid (GABA) and was originally introduced as an antiepileptic drug (Mathews et al, 2014). Gabapentin works by inhibiting calcium flow to halt release of excitatory neurotransmitters as glutamate and substance P (Gaynor & Muir III, 2014b; Tomlinson, 2014). Gabapentin may be useful as part of a multimodal approach to cancer pain and as an adjunctive to NSAIDs in controlling chronic (osteoarthritic) pain (Gaynor & Muir III, 2014b; Mathews et al, 2014; Tomlinson, 2014) and although there is encouraging evidence for its use in human postsurgical pain, there is not enough evidence in dogs and cats (Epstein et al, 2015). This drug is also effective in managing neuropathic pain, hyperalgesia and allodynia. Side effects include sleepiness, muscle weakness, fatigue and weight gain (chronic use) (Gaynor & Muir III, 2014b).

2.3.5.2 N-Methyl-D-Aspartate Receptor Antagonists

NMDA receptor antagonists block multiple binding sites at the NMDA receptor, leading to analgesic, amnestic and psychomimetic effects as well as neuro-protection. Examples of such drugs are ketamine and amantadine. Ketamine is a non-competitive NMDA receptor antagonist that can reverse central hypersensitivity by preventing exaggerated response,

wind-up activity and central sensitization of WDR neurons in the dorsal horn of the spinal cord (Quandt & Lee, 2014). Ketamine is recommended as part of a multimodal perioperative pain management plan for major surgery, in trauma patients or as part of a desensitization treatment for chronic pain patients (Lemke & Creighton, 2010; Mathews et al, 2014). IV or intramuscular (IM) dose-dependent administration of ketamine produces dissociative anaesthesia with poor muscle relaxation in both dogs and cats. The cardiovascular effects are limited and ventilation is better maintained than with other anesthetic drugs and dysphoria and seizures may occur after administration of high doses of ketamine. The anesthetic effects last for approximately 30 minutes, although the motor effects are usually prolonged (Lemke & Creighton, 2010). Amantadine is usually suggested to aid dogs with osteoarthritic pain refractory to treatment with NSAIDs and in patients with other chronic pain conditions with a neuropathic component (Mathews et al, 2014; Tomlinson, 2014).

2.3.5.3 Tricyclic antidepressants (TCAs)

Substances such as amitriptyline and imipramine block the reuptake of catecholamines, enhancing adrenergic transmission. In addition, amitriptyline also has NMDA receptor antagonist properties (Mathews et al, 2014), interacts with opioid receptors and blocks sodium channels (Tomlinson, 2014). Although there is suggestion that these agents may be effective as adjunctive analgesics for a variety of neuropathic conditions in association with other environmental modifiers for treatment of cats with inflammatory bowel disease and interstitial cystitis (Mathews et al, 2014; Tomlinson, 2014), in dogs there is only a single case report where amitriptyline was used for neuropathic musculoskeletal pain (Epstein et al, 2015).

2.3.5.4 Glucocorticoids

Glucocorticoids have an important role in the treatment of many conditions and diseases, including immune-mediated diseases, inflammatory conditions of various tissues, spinal cord compression, raised intracranial pressure, hormonal replacement or cancer, but can also be used to stimulate appetite, suppress nausea, and alleviate fatigue (Vyvey, 2010; Papich, 2014). Glucocorticoids have their primary effect on metabolism, glucose and inflammatory properties; these agents bind to intracellular receptors, translocate to the nucleus and ultimately lead to modulation of genes, altered protein synthesis and cell function; and as anti-inflammatory agents, they inhibit the production of many inflammatory mediators by acting in early steps of the inflammatory cascade (phospholipase A_2). Despite that many painful conditions often have an inflammatory component and that, in fact, glucocorticoids are the most effective drugs available for the treatment of many forms of inflammation in animals, their use in pain management is debatable because their potent anti-inflammatory and immunosuppressive effects must be balanced by their multiple side effects and adverse

effects. These unwanted effects might be gastrointestinal ulceration, immunosuppression and opportunistic infections, anti-insulin effects, behavioural changes, hypoadrenocorticism, electrolytic imbalances, decreased growth, among others (Vyvey, 2010; Papich, 2014).

PART III - SHOCK

3.1 Defining shock

The term “choc” was first employed by Henri François Le Dran, a French surgeon, in “A Treatise of Reflections Drawn from Experience with Gunshot Wounds” (1731) to describe a “sudden impact or jolt”. However, the English physician Clare mistranslated it and introduced the term “shock” into the English language to describe a sudden deterioration of a patient’s condition following major trauma (Sethi, Sharma, Montal & Tyagi, 2003; Manji et al, 2009; Carcillo, et al, 2009). The term was widely popularized by physicians, being described in numerous terminologies such as “a sudden vital depression”, “a final sinking of vitality”, or as Edwin A. Morris described in 1867: “a peculiar effect on the animal system, produced by violent injuries of any cause, or from violent mental emotions” (Manji et al, 2009).

Although the mentioned and many other descriptions may be appropriate, today shock is commonly defined as a clinical state characterized by an inadequate delivery of oxygen and metabolic substrates to meet the metabolic demands of the cells and tissues of the body, leading to impaired cellular function, cellular death and organ failure, and if sufficiently severe or prolonged, this discrepancy between oxygen delivery and cellular oxygen consumption can be life threatening (Barton, 2002; Sethi et al, 2003; Boag & Hughes, 2005; Boysen, 2007; Carcillo et al, 2009; Butler, 2010; Jasani, 2012; Keefe, 2012).

It should be noted that shock is not a disease or a true diagnosis; shock is a complex state with multiple underlying causes and its complexity results not only from the initial insult but also from the host systemic response to that insult (Boysen, 2007; Boller & Otto, 2010; Butler, 2010). Additionally, although shock states are commonly associated to tissue hypoperfusion (from low or unevenly distributed systemic blood flow), shock may occur with normal tissue perfusion (Boller & Otto, 2010; Laforcade & Silverstein, 2014).

3.1.1 General considerations in shock pathophysiology

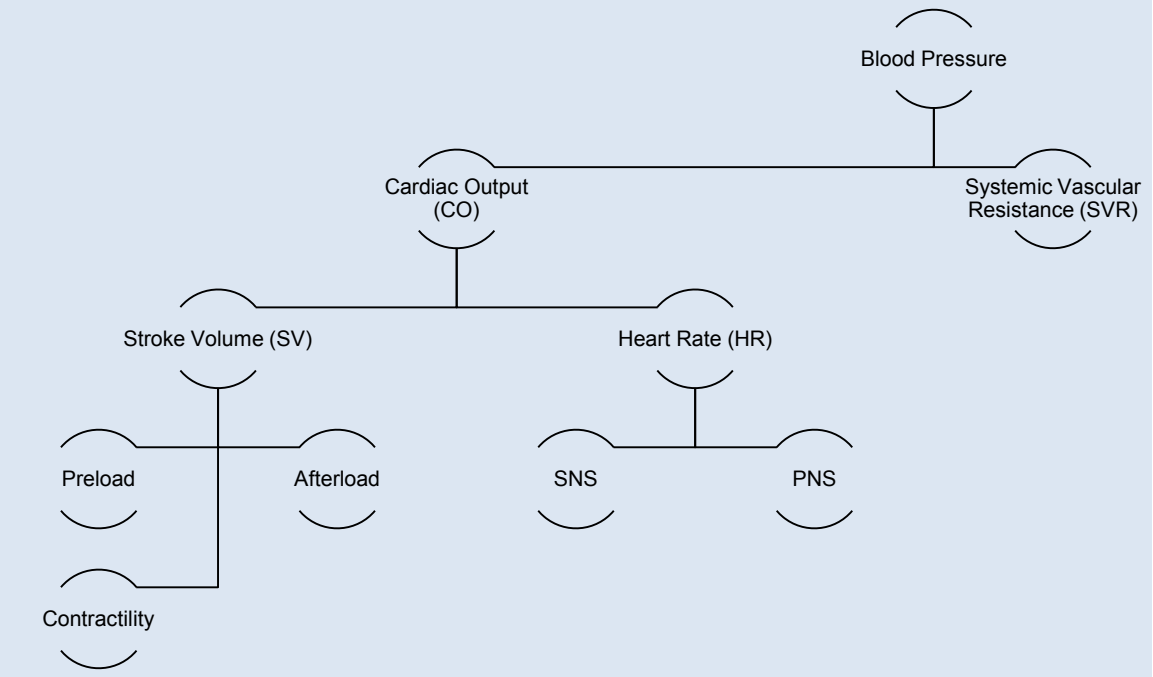
3.1.1.1 Cardiovascular considerations

Ultimately, all forms of shock share a common underlying pathophysiology: inadequate oxygen delivery to the tissues to meet tissue demand, and in all forms of shock the body responds with many compensatory mechanisms as efforts to increase oxygen delivery to the tissues and vital organs (Barton, 2002; Prittie, 2006; Boysen, 2007).

Considering oxygen delivery as the most important factor in the development of shock, any factor that significantly decreases oxygen delivery can result in shock (Boysen, 2007). The two major components determining oxygen delivery to the tissues (DO_2) are cardiac output (CO) and total arterial oxygen content of blood (C_aO_2). In turn, cardiac output depends both on stroke volume (SV) and heart rate (HR). The relation between these parameters is shortly presented in Figure 9. Shortly described, stroke volume is influenced by heart contractility

(force of ventricular contraction), preload (stretching of the ventricles after contraction) and afterload (force needed to overcome aortic pressure and achieve left ventricular outflow). SV is directly related to preload and contractility and inversely related to afterload. Thus, having a decrease in SV may lead to tissue hypoperfusion (Boysen, 2007; Cooper, 2014). The HR is controlled primarily through the sympathetic and parasympathetic nervous systems (Cooper, 2014).

Figure 9 – Schematic representation of parameters involved in Cardiac Output and Blood Pressure maintenance (Adapted from Cooper, 2014)



The total arterial oxygen content of blood (C_aO_2) is influenced by haemoglobin levels, oxygen saturation of haemoglobin (S_aO_2), and partial pressure of oxygen (P_aO_2). With severe pulmonary contusions or acute respiratory distress syndrome, P_aO_2 and S_aO_2 may be markedly decreased, subsequently impairing oxygen delivery to the tissues. However, the greatest contribution to arterial oxygen content tends to be haemoglobin concentration, which emphasizes the importance to maintain blood volume at normal levels. Together, CO and Systemic Vascular Resistance (SVR) are major determinants of arterial blood pressure (ABP) and therefore, abnormalities in these parameters will have repercussions on blood pressure. If a fall in blood pressure is detected, a reflex increase in HR and SVR rapidly occurs such that a normal blood pressure is maintained. This response is very effective and it has been found that animals can preserve a normal blood pressure with up to a 30% loss of blood volume (Hopper, 2011; Peterson, Hardy & Hall, 2013). Therefore all factors that may contribute to decreased oxygen delivery must be considered in an effort to improve or correct each contributing factor (Boysen, 2007).

3.1.1.2 Cellular injury

All forms of shock involve common cellular metabolic processes that typically end in cell injury, organ failure and death (Sethi et al, 2003). Prolonged hypoperfusion states lead to cellular injury mainly through mitochondrial dysfunction and loss of cellular membrane integrity. One of the first consequences of cellular hypoxia is the decrease in mitochondrial ATP production, which leads to a shift in the energetic pathway and balance. Under aerobic conditions, cellular energy production (mostly ATP) is achieved via glycolysis, the citric acid cycle and oxidative phosphorylation or the electron transport chain; however, in anaerobic conditions the only option available is glycolysis. Although this aerobic process still allows energy production to continue under low O_2 concentration, the energy output via anaerobic conditions is much poorer. As a by-product of this anaerobic energy process, lactate and hydrogen ions are generated. Lactate is a normal metabolic end product of glycolysis and is produced in low concentrations throughout the body. Although all body tissues can produce lactate, skeletal muscle, brain, and erythrocytes are responsible for most lactate production, while the liver and kidneys are responsible for most of its metabolism. Excessive production of lactate or its impaired metabolism, ultimately leads to organic metabolic acidosis. Tissue hypoxia, cellular energy depletion, and acidosis lead to disturbed ionic homeostasis across cell membranes, loss of membrane potential, abnormal intracellular signalling and reduced cellular functional capacity and integrity (Sethi et al, 2003; Boag & Hughes, 2005; Pang & Boysen, 2007; Patchinger & Drobtaz, 2008).

Generally, bacterial endotoxins trigger an inflammatory cascade but bacterial antigens, cellular hypoxia and injury itself can promote macrophage and neutrophil releases of proinflammatory cytokines such as TNF-α, IL-1, IL-6, interleukin 8 (IL-8), thromboxanes, eicosanoids, complement and platelet activating factor. These agents lead to systemic inflammation, vasodilation, increased vascular permeability, platelet activation as well as additional neutrophil chemotaxis and adhesion. The neutrophil chemotaxis and adhesion at sites of tissue injury can contribute to local radical oxygen species and proteolytic enzyme production, exacerbating hypoxic tissue damage and ischemia-reperfusion (IR) injury. Also, physical obstruction of capillaries by neutrophil, platelet and fibrin thrombi and swollen endothelial cells may exacerbate maldistribution of flow (Cheatham, Block, Smith & Promes, 2003; Sethi et al, 2003; Mello, Sharma & Dellinger, 2004; Rudloff, 2006; Shell, 2007). Ultimately, patient outcome after an episode of systemic hypoperfusion is related to the severity and duration of hypoperfusion and the degree of impairment in oxygen metabolism and resultant cellular damage (Boag & Hughes, 2005).

3.1.2 Shock classification

There are many underlying disease processes that can lead to tissue hypoperfusion, and therefore there have been several different suggestions of shock classifications. In 1972, Hinshaw and Cox proposed a classification scheme for shock that may be still considered today (Sethi et al, 2003). This common classification scheme includes four aetiologies of shock: 1) hypovolemic (shock as consequence of inadequate circulating volume), 2) cardiogenic (primary pump failure) 3) distributive (caused by maldistribution of the circulating volume), 4) obstructive (due to obstruction to blood flow). Additionally, other causes of shock such as metabolic, hypoxic are also recognized. It should be mentioned that many patients experience more than one type of shock simultaneously (Boag & Hughes, 2005; Shell, 2007; Butler, 2010; Boller & Otto, 2010; Jasani, 2012; Keefe, 2012; Laforcade & Silverstein, 2014). For instance, cardiogenic shock can cause hypoxemic shock when complicated by pulmonary oedema, and any animal with inadequate intestinal perfusion may develop bacterial translocation and sepsis (Boller & Otto, 2010).

Although these classification schemes may be oversimplifications of the complex processes taking place at cellular level (Aldrich, 2007), schemes such as the one described may provide valuable information to guide appropriate treatment.

Table 6 describes a functional classification and common causes of shock in small animals.

Table 6 - Functional Classification and causes of shock (Adapted from Laforcade & Silverstein, 2014)

Classification of shock

Hypovolemic
• Haemorrhage
  ○ Trauma
  ○ Coagulation disorders
• Severe dehydration
• Severe polyuria[1]
• Vomiting and diarrhea
• Third spacing
• Neoplasia[1]
• Burns[1]

Cardiogenic • Congestive heart failure • Cardiac arrhythmia • Cardiac tamponade • Drug overdose (anaesthetics, β-blockers, calcium channel blockers)
Distributive • Sepsis/Systemic Inflammatory Response Syndrome (SIRS) • Anaphylaxis • Catecholamine excess (pheocromocytoma, extreme fear) • Gastric dilation-volvulus • Pancreatitis[1] • Neurogenic
Obstructive* • Heartworm disease • Pericardial effusion • Tension pneumothorax[2] • Thromboembolic disease[2] • Tumours[2] • Gastric dilation-volvulus[2]
Metabolic • Hypoglycemia • Cyanide toxicity • Mitochondrial dysfunction • Cytopathic hypoxia of sepsis
Hypoxemic • Anaemia • Severe pulmonary disease • Carbon monoxide toxicity • Methemoglobinemia

*Some authors consider obstructive shock as cardiogenic and gastric dilation-volvulus as distributive (Laforcade & Silverstein, 2014); [1]Boag & Hughes, 2005; [2]Adapted from Boller & Otto, 2010.

3.1.2.1 Hypovolaemic shock

Hypovolaemic shock is the most common form seen in human medicine and in small animal veterinary practice and is described as a life-threatening decrease in the intravascular circulating fluid volume (Shell, 2007; Cheatham et al, 2003; Boller & Otto, 2010; Keefe, 2012). It leads to inadequate delivery of oxygen and nutrients to tissues and accumulation of

byproducts of cellular metabolism given the insufficient circulating blood volume. Loss of intravascular volume can result from haemorrhage (internal or external), nonhaemorrhagic fluid losses (gastrointestinal, urinary, third spacing), or decreased intake of fluid (Boller & Otto, 2010). Hypovolemic shock can be categorised in three classes based on the degree of circulating volume loss (table 7). It should be noted that a patient who can compensate well for hypovolemia might display tachycardia as the only objective clinical abnormality, even when faced with a considerable reduction of circulating blood volume (Cheatham et al, 2003; Reineke, 2014).

Table 7 – Clinical parameters at different levels of hypovolemia (Adapted from Boag & Hughes, 2005)

Parameter	Mild hypovolemia	Moderate hypovolemia	Severe hypovolemia
Heart rate (bpm)	130-150	150-170	170-220
Mucous membrane colour	Normal to pinker than normal	Pale pink	Grey, white or muddy
Capillary refill time	<1 second	Normal (1-2 seconds)	Prolonged (> 2 seconds) or absent
Pulse amplitude	Increased	Mild to moderate increase	Severe decrease
Pulse duration	Mildly reduced	Moderately reduced	Severely reduced
Metatarsal pulse	Easily palpable	Just palpable	Absent

3.1.2.2 Cardiogenic shock

Cardiogenic shock results mostly from failure of adequate forwards blood flow and maintenance perfusion and oxygen delivery (Shaffran, 2004; Boller & Otto, 2010; Butler, 2010). The dysfunction can occur in either the diastolic or systolic phase (Shaffran, 2004; Boller & Otto, 2010). Systolic flow failure results from contractility failure or severe tachyarrhythmias. Diastolic failure can result from primary cardiac disease such as hypertrophic or restrictive cardiomyopathy (Boller & Otto, 2010). Cardiac dysrhythmias are another source of cardiogenic shock. In addition to malignant dysrhythmias such as ventricular fibrillation, other dysrhythmias may lead to hypotension in patients with coexisting myocardial disease (Cheatham et al, 2003).

3.1.2.3 Distributive Shock

The classic example of this (commonly referred as vasodilatory shock) is sepsis and septic shock. However, other vasodilatory states can also lead to distributive shock, such as systemic inflammatory response syndrome (SIRS), adverse drug reactions, anaphylaxis, heat stroke and neurogenic shock (Shell, 2007; Cheatham et al, 2003; Boller & Otto, 2010). The hallmark of distributive shock is extreme peripheral vasodilation and vascular pooling

and this type of shock is often seen in a hyperdynamic profile (high cardiac output and systemic hypotension). Still, there may also be regional vasoconstriction and endothelial dysfunction that causes sluggish blood flow and arteriovenous shunting, both of which are forms of maldistribution of blood flow (Aldrich, 2007; Butler, 2010; Boller & Otto, 2010). Inherent to septic shock, is its complex immunologic sequence. TNF-α and IL-1 are the dominant cytokines released in response to bacterial endotoxins and cell injury, stimulating the release of further mediators of acute inflammation. Increased TNF-α levels are also seen in heart failure and haemorrhagic shock. These mediators activate the coagulation and complement systems, decrease myocardial contractility, and lead to vasodilation through inducible nitric oxide synthase activation (which is the major mediator of vasodilation and hypotension in septic shock) (Mello et al, 2004). The combined effects of these mediators result in the complex hemodynamic pattern characteristic of septic shock. Despite elevated cardiac output, myocardial depression in sepsis may be demonstrated through decreased ejection fraction, right ventricular dysfunction and left ventricular dilation. Cardiac function usually deteriorates further in later stages of septic shock and the patient's clinical signs mimic other types of shock (Cheatham et al, 2003).

3.1.2.4 Obstructive shock

Obstructive shock occurs when there is a mechanical obstruction to blood flow. Some authors consider this as a form of cardiogenic shock, once that to cause a global deficit in DO_2 it must occur in a vessel close to the heart (Shell, 2007; Aldrich, 2007; Butler, 2010; Laforcade & Silverstein, 2014). Although uncommon in veterinary medicine, this type of shock may be seen in animals with massive pulmonary thromboembolism or pericardial effusion (Aldrich, 2007). In cardiac tamponade, the inadequate heart filling leads to decreased cardiac output and blood pressure, reflex vasoconstriction and elevation of intracardiac pressures despite inadequate filling. Massive pulmonary embolism leads to obstruction of the pulmonary vessels by clot and release of vasoconstrictive agents. Elevation of right-sided pressures with a normal pulmonary artery occlusion pressure and low cardiac output reflects right ventricular failure due to increased pulmonary resistance (Mello et al, 2004). Other causes may include tension pneumothorax, tumours or distended organs (Boller & Otto, 2010).

3.1.2.5 Hypoxemic shock

Hypoxemic shock is caused by low blood oxygen content. Anaemia, metahemoglobinemia, carbon monoxide poisoning, hypoventilation and pulmonary parenchymal disease are examples of diseases associated with hypoxemic shock. Despite normal blood volume and blood pressure, an animal can display key signs of shock secondary to severely decreased blood oxygen content (Boller & Otto, 2010).

3.1.2.6 Metabolic shock

Metabolic shock results from deranged cellular metabolism that, as in all shock states, leads to decreased cellular energy production. Examples include cyanide and bromethalin toxicity (both cause direct interference with mitochondrial function and ATP production), severe hypoglycaemia, relative adrenal insufficiency and severe pH derangements (Boller & Otto, 2010).

3.1.3 Compensatory Mechanisms

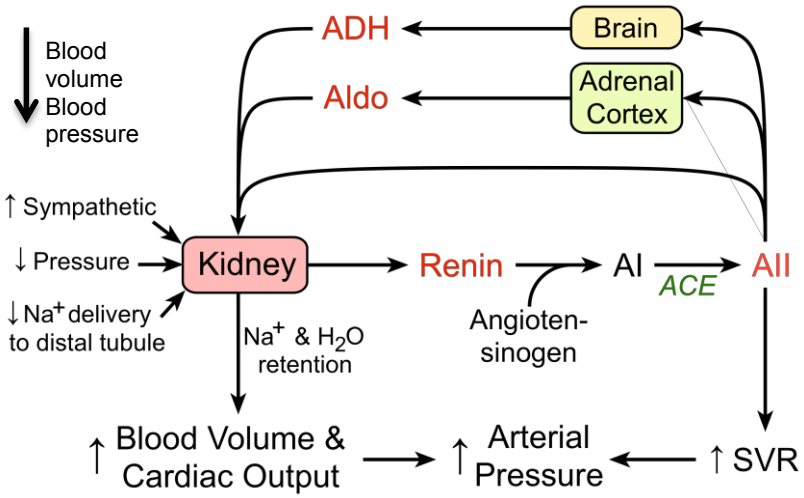
In all forms of shock the organism adopts compensatory mechanisms to offset the decrease in oxygen delivery by increasing cardiac output (Barton, 2002; Prittie, 2006; Shell 2007). These mechanisms are based on an increase of sympathetic stimulation and release of epinephrine and norepinephrine from the adrenal medulla, in order to increase stroke volume, and vasoconstriction to maintain blood pressure and shunt blood to vital organs (Prittie, 2006; Boysen, 2007).

Considering a hypovolemic scenario, after an initial drop on blood pressure, the decreased firing of baroreceptors in the blood vessels in the aortic arch and carotid sinus and mechano- and volume receptors within the heart and kidneys, trigger an intense neuroendocrine response, responsible for an increase in sympathetic stimulation. Attempts are made to re-establish immediate normal blood pressure and preserve perfusion and oxygen delivery to vital organs as the brain, heart and lungs. As mentioned, sympathetic stimulation aims to improve systemic vascular resistance and cardiac output through activation of α-1 and β-1 adrenergic receptors, which cause vasoconstriction, increased heart rate and increased cardiac contractility.

The decreased renal blood flow also leads to activation of the renin-angiotensin-aldosterone-system (RAAS) which results in further vasoconstriction and Na^+ and water retention, helping to increase circulating plasma volume and improve stroke volume (figure 10) (Barton, 2002; Boller & Otto, 2010; Keefe, 2012). The RAAS is activated by the release of renin from the juxtaglomerular apparatus of the afferent renal arterioles, leading to increases in renal tubular Na^+ concentration and triggering β-adrenergic stimulation, which promotes an increase in cardiac output further by increasing the heart rate and cardiac muscle contractility. Renin and angiotensin-converting enzyme (ACE) convert angiotensin I to angiotensin II (a powerful vasoconstrictor), also stimulating the secretion of adrenocorticotropic hormone (ACTH), aldosterone, and antidiuretic hormone (ADH). ACTH triggers the adrenal cortex to release cortisol, which works synergistically with epinephrine and glucagon to induce a catabolic state and stimulating gluconeogenesis. Aldosterone contributes to the increase in intravascular volume by reabsorbing Na^+ and water (while secreting potassium and hydrogen for Na^+ within the kidneys), and ADH, which is also a potent vasoconstrictor, increases water permeability and reduces water and Na^+ losses,

preserving intravascular volume (Otte & Spier, 2009; Keefe, 2012).

Figure 10 – Representation of RAAS as compensatory mechanism in shock (Adapted from http://www.cvphysiology.com/Blood%20Pressure/BP015_RAAS.png)



Note: ADH (Anti-diuretic hormone), Aldo (Aldosterone), AI (Angiotensin I), AII (Angiotensin II), SVR (Systemic vascular resistance).

3.1.4 Stages and clinical signs of shock

Shock is a dynamic state and, therefore, clinical conditions can change quickly. Although the compensatory mechanisms act to immediately increase the intravascular volume, the initial clinical signs of shock are often subtle. Generally, three stages of shock can be described – compensated, early decompensated and late decompensated or irreversible shock (table 8) (Rudloff, 2002; Prittie, 2006; Boller & Otto, 2010; Keefe, 2012).

The early compensatory mechanisms are responsible for the compensatory stage of shock, and patients in this stage may present normal to mild or moderate decreased mentation, normal, pale or hyperaemic mucous membranes, tachycardia with normal or prolonged capillary refill time, tachypnea, strong pulse quality, normal blood pressure and cool extremities. Often, tachycardia is the only clinical sign of compensated shock (Boller & Otto, 2010; Laforcade & Silverstein, 2014).

When endogenous responses are exhausted and therapeutic intervention is inadequate or delayed, shock progresses to the decompensatory stage and clinical signs accentuate. Early decompensatory clinical signs of this phase include tachycardia, weak pulses, hypotension, pale mucous membranes, prolonged capillary refill time, hypothermia and decreased mentation. The late decompensatory phase is the final and terminal stage of all forms of shock, and clinical signs include bradycardia, severe hypotension, pale to cyanotic mucous membranes, undetectable capillary refill time, weak to absent pulses, hypothermia and stuporous to comatose mentation. Ultimately, if left untreated, reduced organ perfusion and systemic inflammation lead to (multiple) organ failure and death (Prittie, 2006; Boller & Otto, 2010; Keefe, 2012; Laforcade & Silverstein, 2014).

Table 8 – Perfusion parameters during compensatory and decompensatory stages of shock
(Adapted from Rudloff, 2002; Butler, 2010; Hopper, 2011)

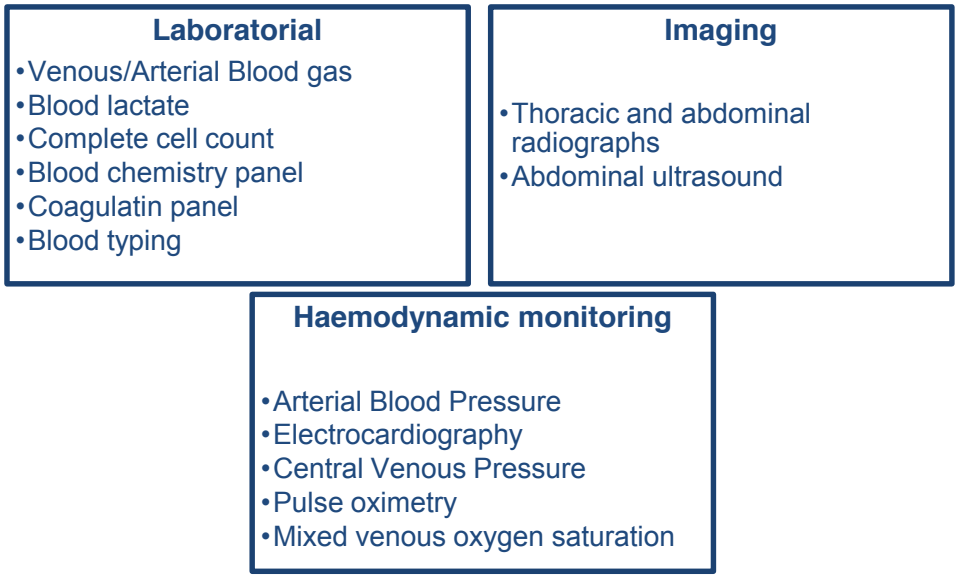
Parameter	Compensatory state	Early Decompensatory state	Late Decompensatory state
Mental state	Normal or Depressed	Depressed	Stuporous or Comatose
MM colour	Normal, Pale or Pinker	Pale	Pale or Cyanotic
CRT	<2s	>2	Prolonged or Absent
HR (bpm)	Dogs: >120	Dogs: >120	Dogs: <120
	Cats: >180	Cats: <200	Cats: <180
Pulse quality	Strong, "bouncing"	Weak	Weak or absent
BP (mm Hg)	MAP >70	*	MAP<70
	SBP >100	*	SBP<100
Rectal Temperature	Normal, Hyper- or Hypothermia	*	Hypothermia

* Imprecise parameters

3.1.5 Recognition and clinical assessment of shock

The ability to recognize and characterize patients in shock continues to be a challenge for veterinarians (Peterson et al, 2013). Shock is primarily a clinical diagnosis and requires a high index of suspicion. The diagnosis is relatively straightforward at later stages of shock; however, at this point intervention is unlikely to be successful (Carcillo et al, 2009). Initial assessment should review the patient clinical history, and a careful evaluation focusing on cardiovascular, respiratory and neurologic systems may provide valuable information regarding systemic perfusion (Mello et al, 2004; Boag & Hughes, 2005; Felice et al, 2011). Furthermore, some complementary tests should be performed in order to assess the degree of organ injury and to identify the aetiology of the shock state (figure 11) (Sethi et al, 2003; Mello et al, 2004; Laforcade & Silverstein, 2014).

Figure 11 – Physical examination and complementary tests for diagnostic and monitoring of shock and perfusion



3.1.5.1 Physical examination

A complete and methodical physical examination and clinical finding interpretation is the first (and sometimes, the only) mean in assessing global perfusion status in veterinary emergency patients. Physical examination does not need expensive equipment and can be repeated multiple times (Boag & Hughes, 2005). The initial assessment should include mental state, mucous membrane colour, capillary refill time (CRT), respiratory rate and manner, heart rate, cardiac auscultation pulse quality and the gradient between extremity and core body temperature (Boag & Hughes, 2005; Patchinger & Drobtaz, 2008). With the exception of early distributive shock, clinical signs of shock are similar regardless of the type or its aetiology (table 9).

Table 9 – Haemodynamic parameters in different types of shock (Adapted from Aldrich, 2007)

Parameter	Hypovolemic shock	Cardiogenic/Obstructive shock	Distributive shock
Mental state	Normal or Depressed	Normal or Depressed	Normal or Depressed
Cardiac Output	Decreased	Decreased	Increased*
Vascular tone	Vasoconstriction	Vasoconstriction	Vasodilation*
Peripheral Vascular Resistance	Increased	Increased	Decreased*
MM colour	Pale	Pale	Hyperaemic*
CRT (s)	>2	>2	<1s
HR (bpm)	Initial tachycardia	Initial tachycardia	Initial tachycardia
	Late bradycardia	Late bradycardia	Late bradycardia
Pulse quality	Weak	Weak	Strong*
RR	Tachypnea	Tachypnea	Tachypnea
Temperature	Hypothermia	Hypothermia	Increased

*Features of distributive shock

In contrast to other types of shock, the hallmark of the distributive shock is the failure of effective vasoconstriction secondary to circulating mediators (nitric oxide, NO) that interfere with vascular tone (vasodilation). This failure leads to relative hypovolemia (most commonly seen with distributive shock secondary to sepsis) (Boller & Otto, 2010). Consequently, the clinical signs often include depressed mentation, red mucous membranes, rapid CRT (<1 second), tachycardia, tachypnea, bounding pulses, hypotension, and normal or increased rectal temperature. As septic shock progresses signs similar to hypovolemic shock listed above predominate (Boysen, 2007; Boller & Otto, 2010). Additionally, patients with hypoperfusion secondary to cardiogenic shock can present with cardiovascular signs that prompt suspicion of a cardiogenic cause, such as heart murmur or gallop rhythm, or arrhythmias with or without pulse deficits. If the cardiac disease is significant enough to cause global hypoperfusion, the patient may also show some degree of respiratory compromise (dyspnoea secondary to pulmonary oedema or pleural effusion). Despite arterial hypotension, many of these patients actually have increased intravascular volume secondary to chronic neurohormonal responses to impending cardiac failure (Boag & Hughes, 2005).

In regards to specie, cats present a special challenge since they do not always display the classic signs of shock like dogs do. The cat in shock often presents with bradycardia, hypothermia and hypotension, even in the early stages of shock. The causes for this are unknown, although it is documented that cats have species-specific alterations in vascular

tone and in vascular response to injury (Boysen, 2007; Butler, 2010).

3.1.5.2 Assessing tissue perfusion

Additional monitoring techniques that are essential in the diagnosis and assessment of tissue perfusion include arterial blood pressure (ABP) measurement, pulse oximetry and blood lactate concentration (Boag & Hughes, 2005; Laforcade & Silverstein, 2014). Ultimately, the placement of a pulmonary artery catheter (PAC) and measurement or calculation of indices of systemic oxygen transport (cardiac output, central venous and arterial pressure, mixed venous blood gases) and mixed venous oxygen saturation can be done, although these methods are not practical in most clinical veterinary practices (Cheatham et al, 2003; Patchinger & Drobtaz, 2008; Carcillo et al, 2009; Laforcade & Silverstein, 2014).

3.1.5.2.1 Arterial Blood pressure

As previously illustrated in Figure 9, blood pressure is a combination of the effects of various elements, including heart rate, stroke volume and systemic vascular resistance, and therefore may be useful in global tissue perfusion assessment (Patchinger & Drobatz, 2008; Cooper, 2014). Systemic arterial blood pressure provides the hydraulic force that drives blood flow, thus affecting tissue perfusion. Depending on the phase of cardiac cycle, arterial blood pressure fluctuates, and different blood pressure measurements can be obtained: systolic, mean and diastolic. The difference between systolic and diastolic blood pressure is the pulse pressure, which determines the height (amplitude) of the palpated arterial pulse. Mean arterial pressure (MAP) is calculated as follows: MAP = diastolic BP + 1/3 (systolic pressure – diastolic pressure) (Boag & Hughes, 2005); and for being more reflective of tissue perfusion, and less variable with peripheral measurement, MAP values are usually preferred (Cooper, 2014). Table 10 illustrates normal arterial blood pressure intervals. In dogs and cats, hypotension could be considered when the MAP is below 80 mmHg. Admitting the limitations where MAP is not available, a systolic blood pressure of less than 90 to 100 mmHg could also be considered reflective of hypotension (Cooper, 2014). Although a low ABP (systolic <80 mm Hg, mean <60 mm Hg) implies severe hypoperfusion and requires urgent treatment, blood pressure may be an insensitive indicator of mild to moderate hypoperfusion due to the body's physiologic response mechanisms to maintain blood pressure within a narrow range (by changing heart rate, stroke volume, and systemic vascular resistance). Additionally, patients with a low cardiac output but intense peripheral vasoconstriction may have a normal blood pressure but dangerously low tissue blood flow (Boag & Hughes, 2005).

Table 10 – Arterial blood pressure ranges for dogs and cats (adapted from Brown & Waddel, 2014)

Arterial Blood Pressure (mm Hg)	Dogs	Cats
Systolic	150±20	125±10
Mean	105±10	105±10
Diastolic	85±10	90±10

ABP measurement can be performed by invasive or and noninvasive methods. Invasive (or direct) arterial pressure is the accepted gold standard in veterinary medicine for blood pressure measurement (Bosiack, Mann, Dodam, Wagner-Mann & Branson, 2010). It uses an arterial catheter, femoral or dorsopedal, and a pressure transducer. In addition to being more accurate than noninvasive (indirect) methods, invasive blood pressure provides continuous reporting of systolic, diastolic and mean pressures. Furthermore, the catheter can be used for arterial blood sampling to monitor acid-base status and blood gas parameters in critically ill patients. However, invasive blood pressure monitoring can be costly and requires advanced technical skills and specialised equipment. Also, obtaining arterial access can pose some risks, including infection, embolus formation and haemorrhage (Haberman, Morgan, Kang & Brown, 2004; Haberman, Morgan, Kang & Brown, 2006; Boag & Hughes, 2005; Bosiack et al, 2010, Cooper, 2014).

Indirect methods of blood pressure measurement include Doppler ultrasonography and oscillometric sphygmomanometry. These methods are generally less invasive, less expensive, less technically challenging and more readily available when compared with direct blood pressure monitoring. Frequently, these methods are often used and the initial, if not only, mean to obtain the patients blood pressure. In many clinical circumstances they can provide useful information to guide diagnosis and clinical decision-making, but it is important to be aware of their limitations. The accuracy of indirect methods is less than direct measurement, with general tendency to overestimate blood pressure in hypotension and underestimate in hypertension (Cooper, 2014).

3.1.5.2.2 Pulse oximetry

Pulse oximetry is a common, noninvasive, method of monitoring the saturation of hemoglobin with oxygen (Farry, 2012). It functions by sensing the difference between light absorption during pulsations (which are assumed to be arterial) and the background tissue. The pulse-oximeter probe emits red (940 nm) and infrared (660 nm) light several times per second by two light emitting diodes. Oxyhemoglobin and deoxyhemoglobin absorb red and infrared light at different wavelengths. The amount of light absorbed at each wavelength is measured, and the absorbance is expressed in percentage of oxygenated total hemoglobin (SpO_2). Normal oxygen saturation should be above 95%. Less than 90% may be associated with a large decrease in partial pressure of oxygen in arterial blood (PaO_2) (Farry, 2012). Sites for probe

placement include the tongue, ear, lip folds, toe pads, axillary or inguinal skin fold, or prepuce/vulva. Some potential limitations in pulse oximetry include difficulty in obtaining a value or inaccurate values in some darkly pigmented patients or patients with markedly compromised perfusion or large increases in central venous pressures. For instance, anaemic patients may display low SpO_2 but have a normal PaO_2. Likewise, an anaemic patient may have significantly decreased ability of the blood to carry oxygen (CaO_2) and therefore a decrease in DO_2 but a normal SpO_2 (Proulx, 1999; Farry, 2012). In humans, hypothermia, icterus and severe anaemia may also compromise pulse oximetry readings. Additionally, the pulse oximeter is not able to distinguish abnormal forms of haemoglobin such as methemoglobin or carboxyhemoglobm (Proulx, 1999).

3.1.5.2.3. Blood lactate

During periods of oxygen deficiency, cells undergo anaerobic glycolysis and as a by-product, lactate is produced from pyruvate (Boag & Hughes, 2005; Prittie, 2006; Patchinger & Drobtaz, 2008). Blood lactate increases when its production in hypoxic tissues overcomes its elimination by the liver (main organ responsible for lactate clearance) and the kidneys. Therefore, tissue hypoperfusion and resultant hypoxia are an important cause of hyperlactatemia. The utility of blood lactate concentration in the indirect assessment of tissue O_2 balance in critically ill shock patients has received much attention (Prittie, 2006). In fact, lactate is commonly accepted as a strong biomarker of shock, and is proven be a useful marker for both diagnostic and as a reliable prognostic indicator in both human and veterinary emergency settings (Boag & Hughes, 2005; Prittie, 2006; Porter et al, 2013). In veterinary medicine, plasma lactate levels <2.5 mmol/L are considered normal in dogs, while a concentration >5 mmol/L is considered a moderate increase and >7 mmol/L is considered a severe increase in lactate (Boag & Hughes, 2005; Porter et al, 2013).

However, even though the most clinically significant cause of increases in plasma lactate is systemic tissue hypoxia - type A hyperlactatemia - the presence of hyperlactatemia is not specific for a global oxygenation defect. In fact, increased plasma lactate can occur without tissue hypoperfusion and hypoxia, as secondary to other illnesses - type B hyperlactatemia - (Table 11) (Boag & Hughes, 2005; Prittie 2006; Porter et al, 2013). Also, lactate is a late marker of hypoperfusion and since the liver, and other tissues in the body have a large capacity to oxidize lactate, it's possible to exist regional hypoperfusion with normal serum lactate concentration (Boag & Hughes, 2005). Additionally, the same severity of hypoperfusion in different patients may reflect different levels of hyperlactatemia and it is possible that in a small proportion of patients, lactate may not rise, despite reduced tissue perfusion (Jasani, 2012). Furthermore, it is possible that this substance may be sequestered from regional tissues where it accumulates during the period of hypoperfusion and are only released with the restoration of blood flow ("wash-out" phenomenon) (Prittie, 2006).

Table 11 – Types and causes of hyperlactatemia (Adapted from Jasani, 2012)

Type A Hyperlactatemia	Absolute oxygen deficiency	Generalised systemic hypoperfusion (shock)
	Local Hypoperfusion	Aortic (or other) thromboembolism, Splanchnic ischaemia, Gastrointestinal necrosis
	Severe hypoxemia	P_aO_2 less than 30-40 mm Hg
	Severe anaemia without hypoperfusion	PCV less than 10-15%
	Relative O_2 deficiency	Increased glycolysis, extreme muscle activity
Type B Hyperlactatemia	Underlying diseases	Sepsis, Severe liver disease, Neoplasia (lymphoma), Diabetes Mellitus, Phaeocromocytoma
	Drugs and toxins	Paracetamol (acetaminophen), Ethanol, Ethylene glycol, Glucose, Insulin, Morphine, Propylene glycol, Salicylates, Terbutaline
	Congenital metabolic defects	Mitochondrial myopathy, defects in gluconeogenesis
	Miscellaneous	Alkalosis/Hyperventilation Hypoglycaemia

3.1.6 Shock Index

In early stages of shock (well compensated), many patients may present with apparently normal or stable vital signs, allowing it to be unrecognized until it progresses into a more advanced stage (Prittie, 2006; Porter et al, 2013). At this period, vital signs such as heart rate, respiratory rate and blood pressure are poor predictors of shock, as they lack sensitivity and specificity when evaluated individually (Peterson et al, 2013). The use of a shock index (SI), defined as the ratio of heart rate to systolic arterial blood pressure (figure 12), was first employed in human medicine by Allgower and Bury in 1967, who observed that the SI would increase following gastrointestinal haemorrhage and therefore assumed this index to be a sensitive guide to the degree of hypovolemia following haemorrhage (Rady, Nightingale, Little & Edwards, 1992).

Figure 12 – Shock index

$$Shock\ Index\ (SI) = \frac{Heart\ Rate\ (HR)}{Systolic\ Blood\ Pressure\ (SBP)}$$

Over the last decades there have been numerous studies with the SI in human medicine, and it has been employed in several clinical conditions. In human medicine, normal values range between 0.5-0.7 (Birkhan et al, 2005; Prittie, 2006; Peterson et al, 2013) and a value of greater than 0.9 is indicative of serious illness (Prittie, 2006; Porter at al, 2013). The proposed advantage of the SI is that it allows identification of derangements in perfusion status (early hypovolemia or occult hypoperfusion) in the face of outwardly normal cardiovascular parameters. Additionally, it is suggested that this calculation may provide a more objective measure of shock than HR and SBP alone, especially in patients with compensated or early hypovolemic shock (Peterson et al, 2013; Chan, 2013).

Recent studies have introduced the SI to veterinary medicine as a triage tool for early identification of shock in canine patients, thus contributing to a better understanding of this parameter in veterinary medicine (Table 12). These studies (Peterson et al, 2013; Porter et al, 2013) managed to demonstrate how this index could be used to discriminate patients with and without shock, and therefore this tool offers an opportunity to re-evaluate the clinicians approach to early patient assessment (where treatment is more likely to be successful) (Chan, 2013; Porter, 2013). Costa (2014) evaluated the relationship of the SI and the patient's mortality rate; however, despite the impression of higher SI was associated with higher mortality rates, these findings were inconclusive.

Table 12 – Comparison between shock index findings in veterinary medicine

<table>
<tr><th colspan="2">Peterson's et al (2013)</th><th colspan="2">Porter's et al study (2013)</th></tr>
<tr><td colspan="2">Median SI, (range)</td><td colspan="2">Median SI, (range)</td></tr>
<tr><td colspan="2">Healthy group
0.91 (0.57 – 1.53)</td><td colspan="2">Healthy group
0.78 (0.37 – 1.30)</td></tr>
<tr><td colspan="2">Shock group
1.37 (0.78 – 4.35)</td><td colspan="2">Shock group
1.37 (0.87 – 3.13)</td></tr>
<tr><td colspan="2">Cut-off: SI >0.9</td><td colspan="2">Cut-off: SI >1.0</td></tr>
<tr><td colspan="2">Healthy dogs VS Dogs in shock</td><td colspan="2">Healthy dogs VS dogs in shock</td></tr>
<tr><td>Sensitivity (Sn)</td><td>Specificity (Sp)</td><td>Sensitivity (Sn)</td><td>Specificity (Sp)</td></tr>
<tr><td rowspan="4">92%</td><td rowspan="4">50%</td><td>89%</td><td>90%</td></tr>
<tr><td colspan="2">Dogs in shock VS ER dogs not in shock</td></tr>
<tr><td>Sensitivity (Sn)</td><td>Specificity (Sp)</td></tr>
<tr><td>89%</td><td>95%</td></tr>
</table>

PART IV – Experimental study

4.1 Introduction and objectives

Awareness of pain in animals remains a challenging task and it can be quite difficult to quantify, particularly in critically ill patients (since these are less prone or able to demonstrate pain behaviours) (Hansen, 2005; Crompton, 2014; Perkowski, 2014). Muir, Wiese and Wittum (2004) managed to evaluate the pain prevalence of both canine and feline patients presenting to a veterinary teaching hospital and reported that 56% of dogs and 54% of cats showed signs of pain. However, the pain assessment did not use a validated PAT. Although there isn't a single, objective and pathognomonic indicator of pain and the ideal PAT still doesn't exist, validated PATs may help the practitioners pain assessment, as their use decreases subjectivity and bias by observers (Sharkey, 2013; Mathews et al, 2014; Epstein et al, 2015). The Glasgow Short Form Composite Measure Pain Scale (CMPS-SF) has been previously validated to evaluate acute post-operative pain in canine patients and is suggested to be able to assess acute pain in several other conditions (Reid et al, 2007; Lockhead, 2010; Scott, Tait, Reid, Firt & Nolan, 2011; Crompton, 2014; Mathews et al, 2014; Epstein et al, 2015). More recently, Moran and Hoffmeister (2013) developed a study intended to determine the prevalence of pain in veterinary ICU patients and used the VAS, NRS and the Glasgow CMPS-SF. The study described 22% of patients as being painful and additionally reported that it is possible that they underestimated the prevalence of pain in their study population. Individual factors, such as the patient's stoicism were reported as possible causes of patients being misidentified as being comfortable when not showing outward signs of distress (Moran & Hoffmeister, 2013). This suggestion relates to the hypothesis of this study – the possibility that patients with emergency and critical conditions may not be able to demonstrate the pain-related criteria within a pain scale, reducing the overall severity of the score and giving a false impression on the degree of pain and reducing the sensitivity of the scale. Considering that shock commonly occurs in patients presenting in emergency, and is potentially life threatening, the study aimed to evaluate if pain scoring with a validated system such as the Glasgow CMPS-SF is effective in identifying pain in canine patients in shock (and emergencies in general).

4.2 Material and methods

4.2.1 Study population

The study was conducted over a three-month period, from November 2014 to January 2015, at Village Vet Hampstead (a Royal College of Veterinary Surgeons Tier III Small Animal Hospital). A total of 31 patients were eligible for inclusion in the study.

4.2.2 Selection criteria

In order to enrol the study, patients had to obey the following inclusion criteria:
1) be of canine species (*canis familiaris*); 2) be admitted to the practice as a primary emergency or transfered as in need of critical care supervision; 3) have a heart rate (HR) and systolic blood pressure (SBP) measurement at the moment of admittance (in order to calculate the SI); 4) have two pain assessments performed at admittance: one with the Glasgow CMPS-SF and one done by two specific veterinarians (a Board Eligible Internist or a Diplomate by the American College of Veterinary Emergency and Critical Care [DACVECC]), unaware of the Glasgow CMPS-SF score and the SI value.
Exclusion criteria comprised failure to meet one or more of the listed conditions, or having patients being medicated with any kind of analgesia or fluid therapy prior to admission or collection of a HR, SBP and pain assessment.

4.2.3 Assessment of shock status

As means to decide on patient's perfusion derangements and detection of early shock states, the SI was calculated for each patient by dividing the heart rate by the systolic blood pressure (SI = HR/SBP). A SI cut-off of 1.0 was defined *a priori* as means to discriminate patients in shock (SI > 1.0) from patients not in shock (SI < 1.0). Nevertheless, vital signs, such as mucous membranes (MM) colour, capillary refill time (CRT), respiratory rate (RR) and rectal temperature (ºC), glucose and lactate measurements were to be taken, although were not considered essential criteria for inclusion in the study. The data collection was performed by the author or by a veterinary nurse at admission and was registered in an individual form developed for the study (annex X). The heart rate was determined by auscultation and femoral or metarsal pulse palpation, and, in some occasions, via ECG monitoring. In order to measure systolic blood pressure, Doppler Ultrasonography was used (figure 12), and the equipment employed was a Doppler Flow Detector model 811-B (Parks Medical Electronics, Inc., USA). Accordingly to the literature recommendations, the cuff size intended for blood pressure measurement was

chosen based on the width of the cuff approximating 40% of the circumference of the measured limb. A specific site of cuff placement wasn't defined due to the unpredictability of clinical presentations.

Figure 13 – Doppler Ultrasonography equipment used in the measurement of systolic blood pressure (original photo)

4.2.4 Pain assessment

Regarding the patients' pain assessment, two examinations were performed at admission: one using the Glasgow CMPS-SF and the other through observation, interaction and physical examination performed by a Board Eligible Internist or a DACVECC blinded to both the SI and the Glasgow CMPS-SF score.

The pain assessments with the Glasgow CMPS-SF were performed either by the author (with scrupulous supervision of the clinical staff) or, whenever the author was absent, by a registered veterinary nurse familiar with this pain scoring system.

The assessments performed by the two clinicians (Board Eligible Internist/DACVECC Specialist) translated to a "Yes"/"No" answer and was labelled "Vetpain". Accordingly to the Glasgow CMPS-SF, scores ≥5/20 or 6/24 suggest that the patient may be in pain and requiring analgesic intervention. For the purposes of this study, the Glasgow CMPS-SF pain scores obtained were adapted into a "Yes" or "No" answer to the question "Is the animal in pain?"; scores <5 would mean "No" and all scores ≥5/20 or 6/24 were converted into "Yes", and this parameter was named "Scalepain".

4.2.5 Analgesia

In order to guarantee the welfare of every patient, analgesia was given anytime the veterinarians considered the patient was in pain or likely to be uncomfortable. The analgesic protocol was tailored individually for each patient and its clinical condition;

nonetheless the leading analgesic drugs used were opioids: methadone (0.1-0.3 mg/kg IV/IM) and buprenorphine (0.005-0.02 mg/Kg IV/IM/SC).

4.2.6 Statistical treatment of data

All data documented in the form developed for the study was transferred to a Microsoft® Excel:mac 2011 (Microsoft Office – Microsoft Corporation©, USA) sheet, where it was properly disposed in a table (Annex XII). Descriptive and inferential statistical analysis was performed with the "R" software (version 3.1.2; Copyright© 2014 The R Foundation for Statistical Computing). Normality of the data was assessed with the Shapiro Wilk normality test. Statistical analysis of non-normally distributed data was performed with: 1) the Spearman rank correlation test, used to assess the relationship of the SI with age and with the Glasgow CMPS-SF pain scores; 2) the Kruskal-Wallis test, to assess differences between gender and the Glasgow CMPS-SF scores in all patients and 3) the non-parametric Wilcoxon rank sum test with continuity correction, to assess the following: i) the relation between age and the patients group; ii) the relation between the patients group and the Glasgow CMPS-SF scores (considering all patients and each subset of patients individually); iii) the relationship between the Glasgow CMPS-SF scores and the veterinarians perception of pain - "Vetpain" (also performed considering all patients and each subset of patients individually). The chi-square test for independence was used to evaluate the association between the patients group and "Vetpain".

Lastly, Cohen's kappa for inter-rater agreement was used to test the agreement between the Glasgow CMPS-SF "Yes" or "No" pain score readings ("Scalepain") and "Vet pain". The *kappa* agreement is a mean to measure quantitatively the magnitude by which two examiners or procedures agree among themselves and it is often considered a more robust measure than simple percent agreement calculation since it takes into account that observers will sometimes agree or disagree simply by chance (Banerjee, Capozzoli, McSweeney & Sinha, 1999; Viera & Garnett, 2005; Uebersax, 2015). The *kappa* test for agreement requires that two raters or procedures use the same rating categories (Uebersax, 2015), and that is why the Glasgow CMPS-SF scores were converted into a "Yes" or "No" response. *Kappa* values may vary from -1 to 1, but are generally described from 0 to 1 (Viera & Garnett, 2005; McHugh, 2012). The obtained *kappa* values assume different interpretations (table 13). All tests were performed assuming a 95% confidence interval and with a p-value of <0.05 being considered significant.

Table 13 –Interpretation of kappa values

Cohens' classic interpretation (1960)		*McHugh (2012)*	
Kappa	*Agreement*	*Kappa*	*Agreement*
<0	None	<0.20	None
0.01 – 0.2	Slight	0.21 – 0.39	Minimal
0.21 – 0.40	Fair	0.40 – 0.59	Weak
0.41 – 0.60	Moderate	0.60 – 0.79	Moderate
0.61 – 0.8	Substantial	0.80 – 0.90	Strong
0.81 – 0.99	Almost perfect	>0.90	Almost perfect

4.3 Results

4.3.1 Sample characteristics

Sample characteristics are summarily described on table 14.

Table 14 – Sample summary characteristics

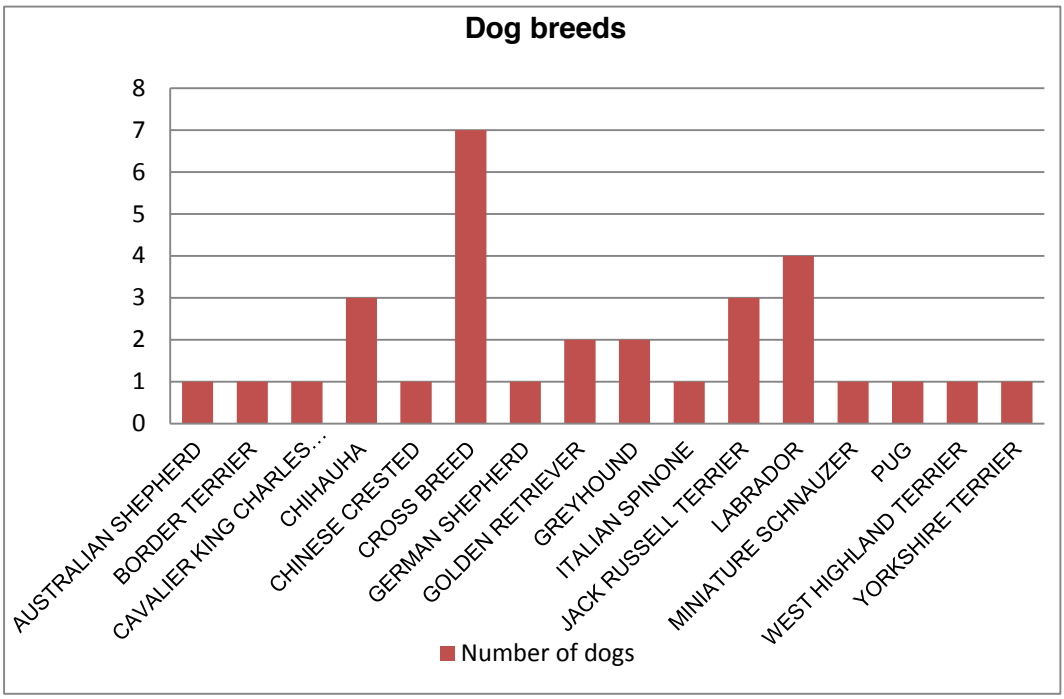
Sample summary characteristics (n=31)			
Gender	**Female**	**Male**	
	Spayed	Intact	Neutered
	16	6	9
	Mean±sd	**Minimum**	**Maximum**
Age (years)	6.1 ± 4.64	0.2	16
Heart Rate (bpm)	142 ± 32.16	80	205
Systolic Blood Pressure (mm Hg)	129 ± 40	50	220
	Median	**Minimum**	**Maximum**
Shock Index	1.2	0.36	3.53
CMPS-SF Pain Score	4	0	17
Patients in shock	**Yes**		**No**
	18		13

Note: Normally distributed data is presented as mean±standard deviation (sd); non-normally distributed data is presented as median and range (minimum and maximum).

4.3.1.1 Gender and breed

Regarding patients' gender, the study included 16 females (all neutered) and 15 male dogs (9 neutered and 6 intact). Dog breeds participating in the study included 7 crossbreed and 14 pure-breed dogs. Crossbreed dogs were the most representative type in this sample (7 animals), followed by Labrador Retriever (4 animals), Jack Russell Terriers and Chihuahua (both with 3 animals), Golden Retriever and Greyhound (both with 2 animals). Australian Shepherd, Border Terrier, Cavalier King Charles Spaniel, Chinese Crested, Italian Spinone, Miniature Schnauzer, Pug, West Highland Terrier and Yorkshire Terrier only had 1 representative (chart 3).

Chart 3 – Dog breeds included in the study



4.3.1.3 Admission motives

The patient's admission motives and underlying disease conditions are displayed on table 15. The majority of admissions were due to GI disorders (38.71%); other causes included toxic associated disorders (19.36%), abnormal neurologic or mental states (12.90%), trauma (12.9%), haemorrhages (9.68%) and pericardial disease (6.45%).

Table 15 – Patient admission motives

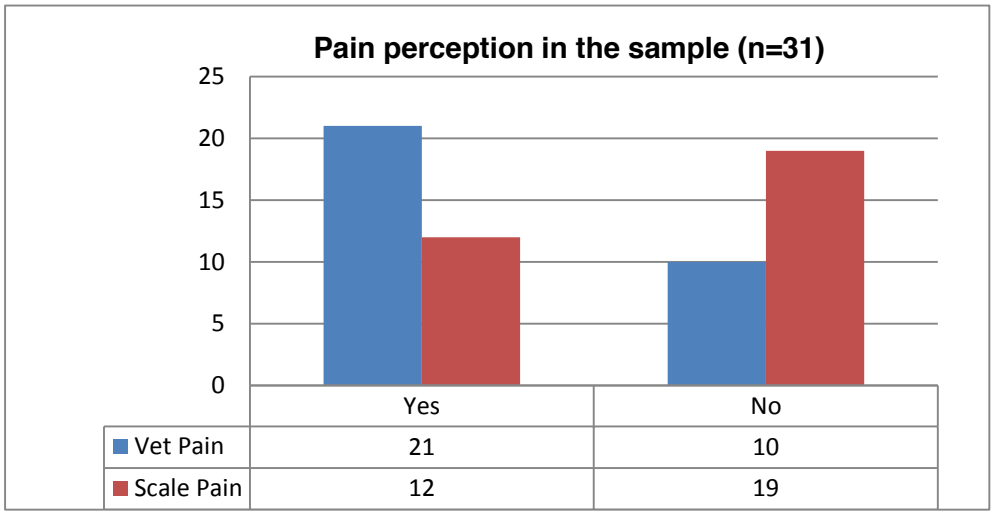
Admission motives	n	(%)
Gastrointestinal	**12**	**38.71**
Haemorrhagic Gastroenteritis (HGE)	5	16.13
Gastrointestinal Foreign Body	2	6.45
Acute Gastroenteritis	2	6.45
Pancreatitis	2	6.45
Abdominal Dilation	1	3.23
Toxicities	**6**	**19.36**
Chocolate toxicity	3	9.68
NSAID toxicity	2	6.45
Raisin toxicity	1	3.23
Trauma - Road Traffic Accidents (RTAs)	**4**	**12.90**
Mental/Neurologic conditions*	**4**	**12.90**
Haemorrhage	**3**	**9.68**
Haemoabdomen	1	3.23
Eye haemorrhage	1	3.23
Splenic mass rupture	1	3.23
Pericardial Disease	**2**	**6.45**
Cardiac mass	1	3.23
Pericardial effusion	1	3.23

*No diagnostic reached

4.3.2 Pain assessments by the veterinarians and with the Glasgow CMPS-SF

Regarding the pain assessments of canine patients presenting in emergencies (chart 4), the veterinarians that performed the physical examination and pain assessments considered that 21 patients were in pain (67.7% were in pain at admission) and the other 10 patients (32.7%) were not.

Chart 4 – Pain perception in the sample with the CMPS-SF (Scale Pain) and the clinicians' perception of pain (Vet Pain)



Considering the use of the Glasgow CMPS-SF to assess pain in these canine patients, 12 patients were classified as being in pain (38.7% were in pain at admission) and 19 were classified as not being in pain (61.3%). Furthermore, the selected Glasgow CMPS-SF descriptors classified 71% of canine patients to be quiet at admission, 84% ignoring any wound or painful area, 52% of dogs capable of marching normally at presentation, 23% as reluctant to move, 35% not reacting to palpation, 58% as being generally quiet, 16% depressed or non-responsive to stimulus, 13% as fearful, nervous or anxious, and described 35% of dogs as comfortable and other 32% as unsettled (table 16).

Table 16 – Summary of the Glasgow CMPS-SF selected descriptors

	Scale parameter	Sample					
		All patients (n=31)		Not Shock Group (n=13)		Shock Group (n=18)	
		n	%	n	%	n	%
A. Look at dog in kennel	*(i)* Quiet	22	71	11	85	11	61
	Crying/whimpering	7	23	2	15	5	28
	Groaning	2	6	0	0	2	11
	Screaming	0	0	0	0	0	0
	(ii) Ignoring any wound/painful area	26	84	11	85	15	83
	Looking at (...)	5	16	2	15	3	17
	Licking (…)	0	0	0	0	0	0
	Rubbing (…)	0	0	0	0	0	0
	Chewing (…)	0	0	0	0	0	0
B. Put lead on and lead out of kennel (When the dog rises/walks)	*(iii)* Normal	16	53	7	*58	9	50
	Lame	1	3	1	8	0	0
	Slow/reluctant	7	23	3	25	4	22
	Stiff	2	7	1	8	1	6
	Refuses to move	4	13	0	0	4	22
C. Wound inspection (…)	*(iv)* Do nothing	11	35	4	31	7	39
	Look around	9	29	4	31	5	28
	Flinch	7	23	4	31	3	17
	Growl/Guard area	2	6	0	0	2	11
	Snap	0	0	0	0	0	0
	Cry	2	6	1	7	1	6
D. Overall (Is the dog…)	*(v)* Happy and content/bouncy	1	3	0	0	1	6
	Quiet	18	58	10	77	8	44
	Indifferent/non-responsive to surroundings	3	10	2	15	1	6
	Nervous/anxious/fearful	4	13	0	0	4	22
	Depressed or non-responsive to stimulation	5	16	1	8	4	22
	(*vi*) Comfortable	11	35	6	46	5	28
	Unsettled	10	32	4	31	6	33
	Restless	2	6	1	8	1	6
	Hunched or tense	7	23	2	15	5	28
	Rigid	1	3	0	0	1	6

* Unable to assess in one case (% in this parameter sum up to 99%)

4.3.2.1 Not Shock (N.S.) group

This group featured thirteen patients (n=13), including 8 females (all neutered) and 5 males (4 neutered and 1 intact). Characteristics of the not shock group are summarized on table 17. Dog breeds within this group included 3 Cross-breeds, 2 Golden Retrievers and 1 each of the following: Australian Shepherd, German Shepherd, Labrador, Cavalier King Charles Spaniel, Miniature Schnauzer, Italian Spinone, Chinese Crested, West Highland Terrier.

Table 17 – Not Shock group summary characteristics

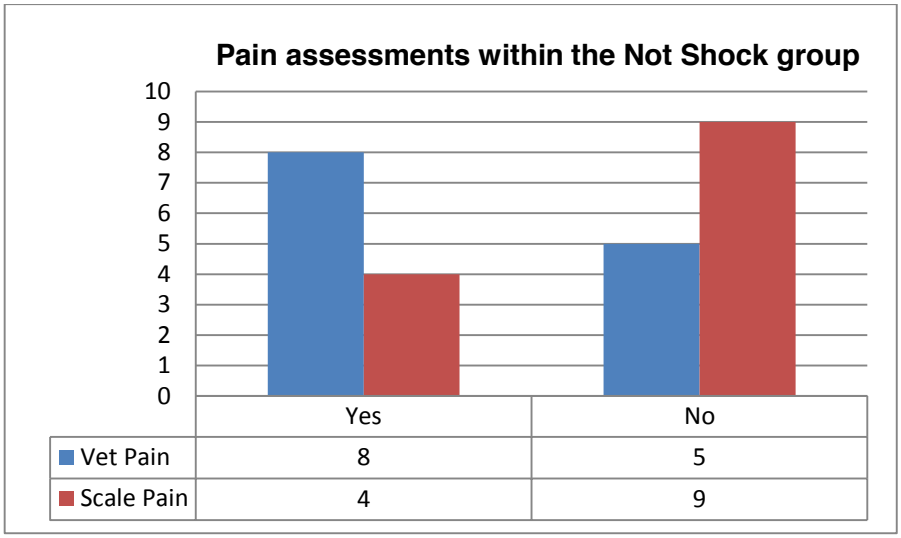
N.S. group summary characteristics (n=13)			
	Mean±sd	**Minimum**	**Maximum**
Age (years)	8.3 ± 5.04	1	16
Heart Rate (bpm)	120.15 ± 26.04	80	160
Systolic Blood Pressure (mm Hg)	164.69 ± 28.83	120	220
	Median	**Minimum**	**Maximum**
Shock Index	0.79	0.36	1
CMPS-SF Pain Score	3	1	15

Underlying disease conditions included 2 neurologic or altered mentation cases, 2 cases of pancreatitis and one case of the following: acute gastroenteritis, haemoabdomen, ocular haemorrhage, HGE, RTA, abdominal dilation, GI foreign body, chocolate toxicity and raisin toxicity.

4.3.2.1.1 Pain assessment within the not shock group

Within the not shock group, the veterinarians that performed the pain assessments considered that 8 patients were in pain (61.5%) while considering the other 5 patients were not (38.5%). With the use of the Glasgow CMPS-SF, 9 patients were classified as not in pain (69.2%) and only 4 patients were classified as being in pain (30.8%) (chart 5). Additionally, the use of the Glasgow CMPS-SF described 85% of the patients as quiet at admission, 85% ignoring any wound or painful area, 58% with normal locomotion, 31% of the patients did not react to wound inspection but 31% looked around and 31% flinched at palpation and overall, 77% of the patients were described as quiet and 46% as comfortable, and 31% as unsettled.

Chart 5 – Pain assessments within the not shock group with the CMPS-SF pain scale and by the veterinarians



4.3.2.2 Shock Group (S)

This group was composed of eighteen patients (n=18), including 8 females and 10 males (5 intact and 5 neutered). Discrimination of shock group parameters are summarized on table 18. Regarding dog breeds, this group included 4 cross-breeds, 3 Labradors, 3 Jack Russell Terriers, 3 Chihuahua and 2 Greyhounds, and 1 each of the following: Pug, Yorkshire Terrier, Border Terrier. Underlying disease conditions within the shock group included 4 haemorrhagic gastroenteritis, 3 road traffic accidents, 2 chocolate toxicities, 2 NSAID intoxications, 2 abnormal mental states and one of each of the following: GI foreign body, acute gastroenteritis, cardiac mass, pericardial effusion and splenic mass rupture.

Table 18 – Shock group summary characteristics

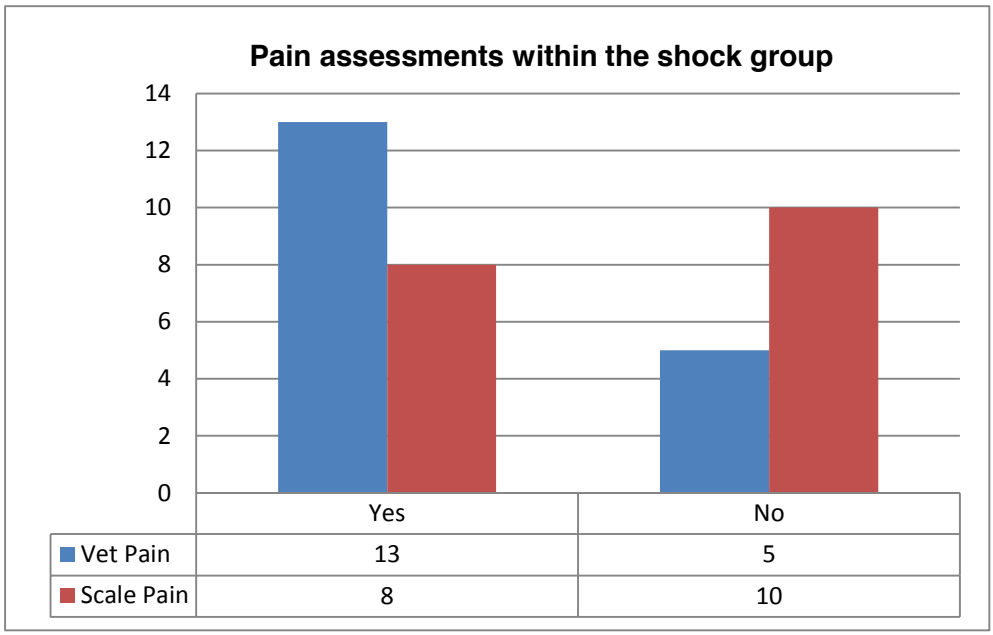
S group characteristics (n=18)			
	Mean±sd	**Minimum**	**Maximum**
Age (years)	4.6 ± 3.72	0.2	10
Heart Rate (bpm)	158.6 ± 26.27	120	205
Systolic Blood Pressure (mm Hg)	103.33 ± 23.99	58	150
	Median	**Minimum**	**Maximum**
Shock Index	1.5	1.09	3.53
CMPS-SF Pain Score	5	0	17

4.3.2.2.1 Pain assessment within the shock group

Within the shock group, the veterinarians who conducted pain assessments considered that 13 canine patients were in pain (72.2%) and 5 as not having pain (28.8%). The Glasgow CMPS-SF classified 8 patients as being in pain (44.4%) and

the remaining 10 patients as not having pain (55.6%) (chart 6). The selected CMPS-SF descriptors showed that 61% of canine patients were described as quiet at admission, 28% were crying or whimpering, 83% of the dogs ignored any wounds or painful areas, 50% of the patients were able to move, 22% of patients were slow or reluctant to move and other 22% refused to move; 39% of the patients did not react to wound inspection; overall 44% of the patients were described as quiet, other 22% were described as being nervous, anxious or in fear and also 22% were depressed or non-responsive to stimuli, and 33% of patients as unsettled.

Chart 6 – Pain assessment within the shock group with the CMPS-SF pain scale and by the veterinarians



4.3.3 Statistical analysis

4.3.3.1 Spearman rank correlation test results

Spearman correlation test (table 19) showed no relation between the patients' shock index and age (p-value=0.07) or CMPS-SF score (p-value=0.2).

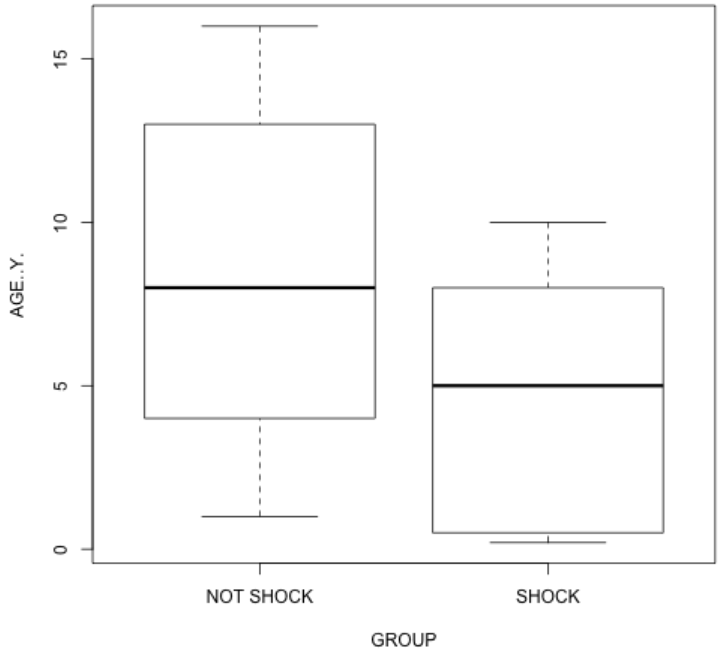
Table 19 – Results of the Spearman rank correlation testing SI with Age and Glasgow CMPS-SF score

Parameter	Spearman correlation coefficient	p-value
SI - Age	-0.3267	0.07276
SI - CMPS-SF score	0.2202	0.2338

4.3.3.2 Testing differences in age between groups

Mean age of patients within the shock group was 4.6 ± 3.72, while mean age of the patients within the not shock group was 8.3 ± 5.04 (chart 7). Using the Wilcoxon rank sum test with continuity correction, a p-value = 0.0445 was found, and for that reason these differences were considered as statistically significant.

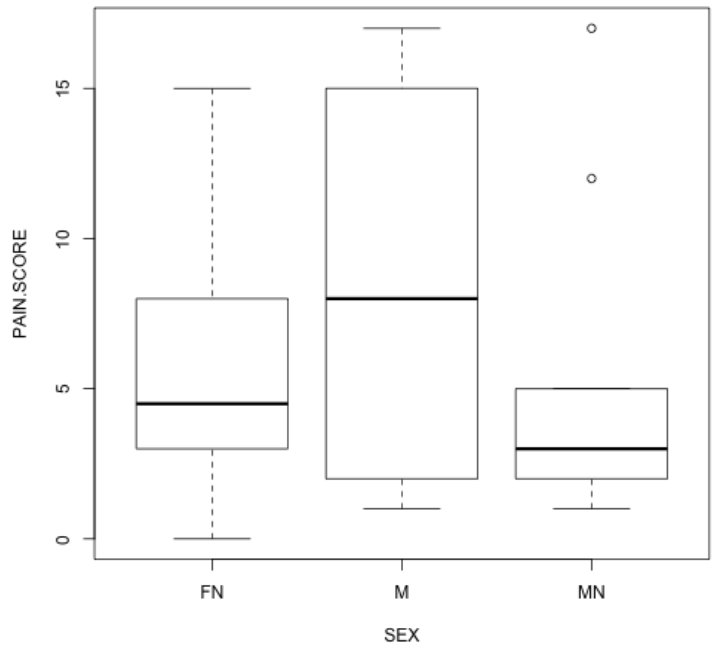
Chart 7 – Comparison of patient's age between groups



4.3.3.3 Testing the patients' gender and Glasgow CMPS-SF pain scores

The pain scores were compared between female (neutered), intact and neutered male dogs. Intact male dogs appear to have higher median pain scores (chart 8). However, the Kruskal-Wallis test indicated a p-value=0.562 which suggests that the differences observed in pain scores between genders are not statistically significant.

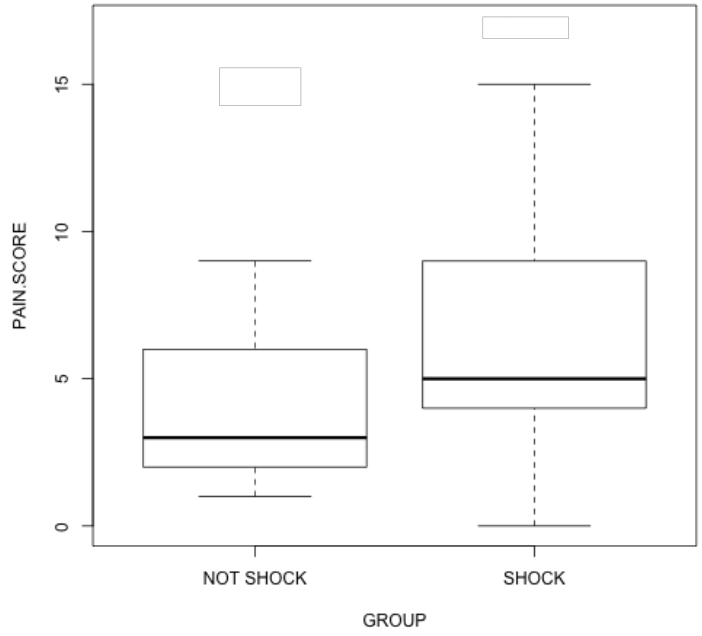
Chart 8 – Comparison of gender and Glasgow CMPS-SF scores



4.3.3.4 Comparing patients Group and Glasgow CMPS-SF scores

Within the S group, median pain score with the CMPS-SF was 5 (minimum of 0 and maximum of 17); while in the NS group median pain score was 3 (minimum of 1 and maximum of 15) (chart 9). The Wilcoxon rank sum test with continuity correction revealed a p-value=0.1311, and for this reason the differences in pain scores between groups were considered as non-statistically significant.

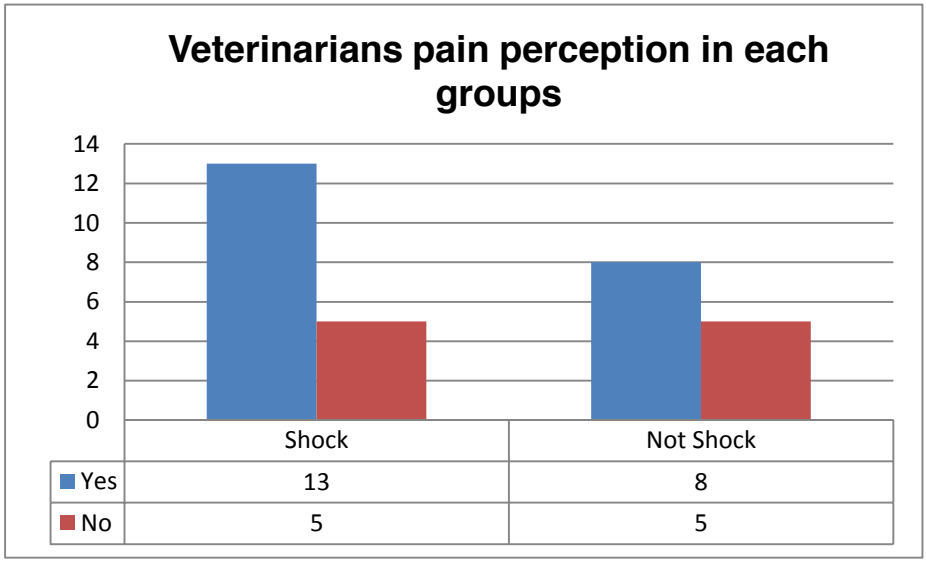
Chart 9 – Comparison of CMPS-SF scores between the two groups



4.3.3.5 Testing the Veterinarians' perception of pain ("Vetpain") between the two groups

As mentioned, in the S group, the veterinarians considered 13 patients to be in pain and 5 other as not in pain. In the NS group, the veterinarians considered that 8 patients were in pain and did not recognise it in the other 5 (chart 10). A p-value=0.5301 was obtained with use of a Chi-square test, suggesting that the differences observed are not statistically significant.

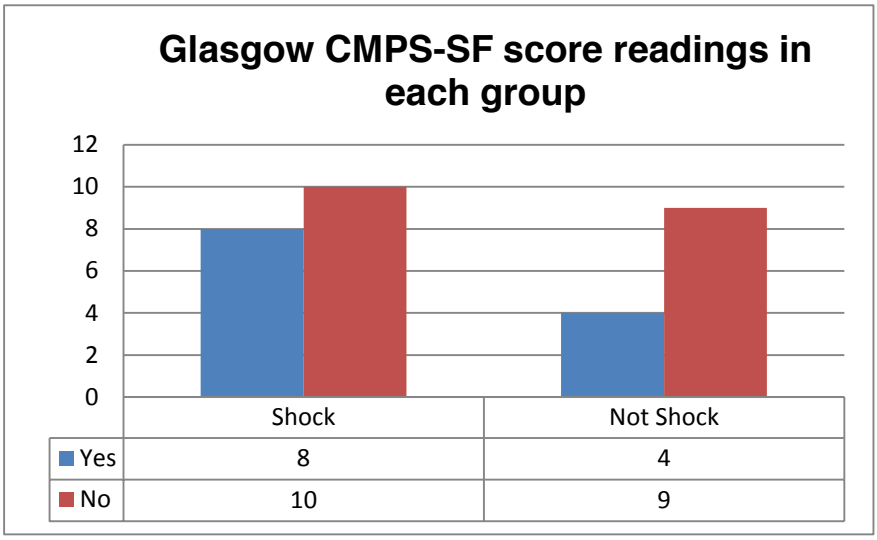
Chart 10 – Comparison of the veterinarians' perception of pain in the two groups



4.3.3.6 Testing the Glasgow CMPS-SF pain score readings ("Scalepain") in the two groups

As previously mentioned, in the S group, the Glasgow CMPS-SF scores classified 10 patients to be in pain and 8 as not. In the NS group, the scale scores classified 4 patients as being in pain and the remaining 9 as not having pain (chart 11). A Chi-square test was applied and a p-value=0.7 was found, suggesting that the differences observed are not statistically significant.

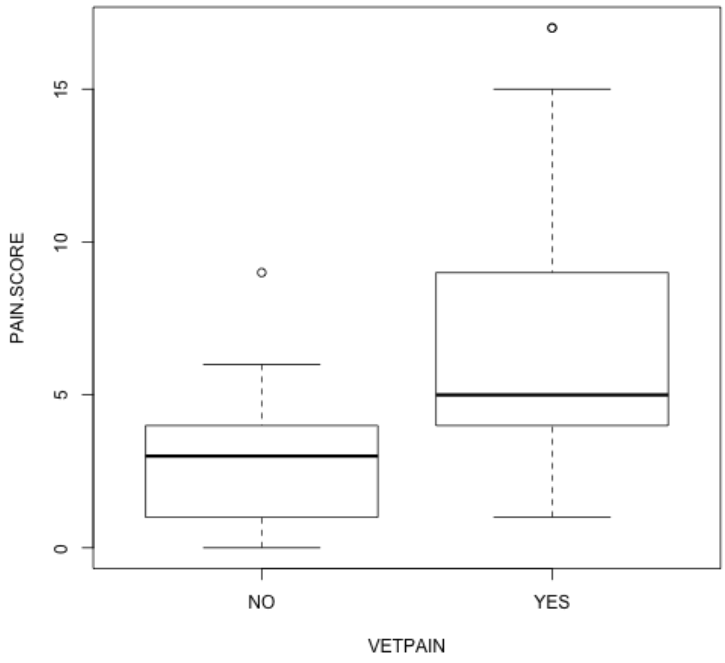
Chart 11 – Comparison of CMPS-SF score readings between the two groups



4.3.3.7 Testing the Glasgow CMPS-SF pain scores and the Veterinarian's perception of pain ("Vetpain")

Regarding the veterinarians perception of pain, 21 patients were considered to be in pain and had median Glasgow CMPS-SF scores of 5, while the remaining 10 dogs were considered as not being in pain had median Glasgow CMPS-SF scores of 3 (chart 12). A Wilcoxon rank sum test with continuity correction revealed a p-value=0.01455, which allowed to consider that the differences observed were statistically significant.

Chart 12 – Comparison of CMPS-SF scores and the veterinarians' perception of pain



4.3.3.8 Agreement between Glasgow CMPS-SF score readings ("Scalepain") and the Veterinarians perception of pain ("Vetpain")

The previously mentioned differences on pain assessments with the Glasgow CMPS-SF and by the veterinarians can be reviewed on table 20. Cohen's kappa for agreement between the two evaluations was 0.2, indicative of slight agreement.

Table 20 - Pain evaluation with the Glasgow CMPS-SF and by the Veterinarians ("Vetpain")

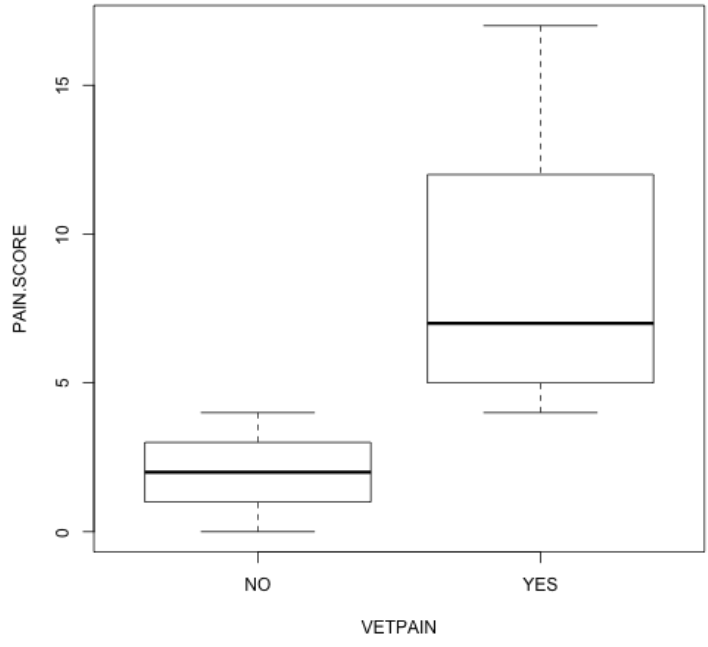
Pain assessment results		
	Yes	**No**
"Vetpain"	21	10
Glasgow CMPS-SF	12	19

4.3.3.9 Shock Group

4.3.3.9.1 Testing the Glasgow CMPS-SF pain scores and the Veterinarians perception of pain ("Vetpain") within the shock group

Within the shock group, median pain score was 7 (minimum of 0 and a maximum of 17). Within this group, the veterinarians acknowledged that 13 patients were experiencing pain (median CMPS-SF score of 7) and that the other 5 were not (median CMPS-SF score of 2) (chart 13). With use of the Wilcoxon rank sum test with continuity correction a p-value=0.0021 was found, and so the differences observed were considered statistically significant.

Chart 13 – Comparison of CMPS-SF scores and the veterinarians' perception of pain within the shock group



4.3.3.9.2 Testing the agreement between the Glasgow CMPS-SF score readings ("Scale Pain") and the Veterinarians perception of pain ("Vetpain") within the shock group

The differences on pain assessment results with the Glasgow CMPS-SF and by the veterinarians can be reviewed on table 21. Cohen's kappa for agreement between the two assessment methods was 0.47, indicative of moderate agreement.

Table 21 – Pain evaluation with the Glasgow CMPS-SF and by the Veterinarians within the shock group

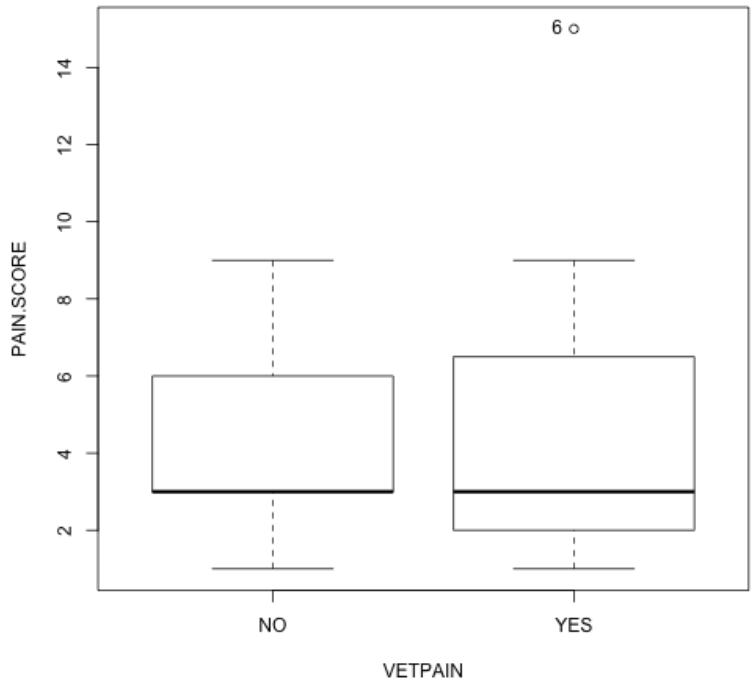
Shock Group: Pain assessment results		
	Yes	**No**
"Vetpain"	13	5
Glasgow CMPS-SF	8	10

4.3.3.10 Not Shock group

4.3.2.10.1 Testing the the Glasgow CMPS-SF pain scores and the Veterinarians perception of pain ("Vet pain") within the not shock group

Within the N.S. group, median pain score was 3 (minimum of 1 and maximum of 15). Veterinarians considered that 8 patients were in pain and 5 as not (chart 14). With use of a Wilcoxon rank sum test with continuity correction a p-value=0.9406 was found, which allows considering the differences observed as not statistically significant.

Chart 14 – Comparison of the CMPS-SF scores and the veterinarians' assessment of pain within the Not Shock group



4.3.3.10.2 Testing agreement between the Glasgow CMPS-SF score readings ("Scale Pain") and the Veterinarians perception of pain ("Vetpain") within the not shock group

Table 22 describes the number of patients that were identified as being in pain with both CMPS-SF and the by the veterinarian in the Not Shock group. Cohen's kappa for agreement between the two pain assessments was -0.13, which states no agreement.

Table 22 - Pain assessment with the Glasgow CMPS-SF and by the veterinarians within the Not Shock group

Not Shock group: Pain assessment results		
	Yes	**No**
"Vetpain"	8	5
Glasgow CMPS-SF	4	9

4.4 Discussion

The sample, composed of a total of 31 canine patients, was represented by an approximately similar number of patients from both genders, from various breeds and with a large age spectrum (ranging from 2.5 months to 16 years).

A total of 18 patients were classified as being in shock (SI>1.0), while 13 were classified as not being in shock (SI ≤ 1.0). Regarding the shock assessment, the SI is simple ratio of HR/SBP that can be calculated soon after admission of a patient and may be considered as a triage tool for ER clinicians in the evaluation of perfusion derangements (Peterson et al, 2013). As a normal response mechanism, the body can maintain normal cardiovascular parameters in response to fluid losses. For instance, the body maintains normal HR and SBP in response to acute haemorrhage until about 15-30% of blood volume is lost (Gutierrez, Reines & Wulf-Gutierrez, 2004). Due to individual patient variation, in early stages of shock HR and SBP may be altered from what is considered the patient's baseline, but still appear to be within the normal reference interval for the population and only become actually abnormal at advanced stages (Peterson et al, 2013; Porter et al, 2013). Therefore, the proposed advantage of this ratio is that by comparing these two parameters together, subtle changes in HR and SBP can be detected and early stages of shock identified (Chan, 2013; Peterson et al, 2013; Porter et al, 2013). In this study, a SI cut-off >1.0 was used to discriminate patients in early shock stages from those not in shock. This cut-off value is based on the study by Porter et al (2013), which reported that a SI>1.0 holds a high sensitivity and specificity in the discrimination of shock patients

from both healthy (Se 89%;Sp 90%) and ill dogs not in shock (Se 89%, Sp 95%). Regarding the patients' age, mean age of the dogs classified as being in shock was lower than the mean age of the patients classified as not being in shock, and these differences were considered statistically significant. However, the Spearman correlation test showed that age and SI are not related. In Petersons' et al (2013) study, age was shown to be associated to SI and it was suggested that it could influence SBP. They also suggested than young canine patients may have a normal SI value different from adult canine patients. However, this subject has not been extensively studied in veterinary medicine and there is not a consensual validity (Bodey & Michel, 1996; Sanan & Arslan, 2007; Porter et al, 2013). One possible consideration is that older patients may have simultaneous disease processes that may alter cardiovascular parameters such as HR and SBP, affecting the SI (Peterson et al, 2013). Yet, the real significance of these age differences between the two groups is uncertain.

Regarding the different Glasgow CMPS-SF pain scores between male and female canine patients, intact male dogs had higher median pain scores than females or castrated dogs, however, the differences weren't statistically significant. This finding may reflect the mentioned pain related variability between genders, breeds and individual temperament (Lockhead, 2010; Mathews et al, 2014).

Despite of group, the two veterinarians who performed the pain assessments consistently classified more patients as being in pain than the assessment and pain scoring with the Glasgow CMPS-SF. In this sample, this PAT classified 38.7% of the patients as being in pain – this is, patients with pain scores equal or higher than 5/20 or 6/24. The veterinarians described 67.7% of canine patients presenting in emergencies to be in pain, which is a higher value than the 56% described in the study by Muir et al in 2005. This percentage may be influenced by the lower sample size, to the environment in which it was performed (private practice) and to the clinical expertise of the veterinarians.

When comparing the Glasgow CMPS-SF pain scores and "Vetpain" between the groups, despite the fact that overall the Shock group had higher pain scores and more patients identified as being in pain by the veterinarians than in the Not Shock group, these findings were not considered statistically significant. Therefore, one group cannot be described as more painful that the other, whether using the Glasgow CMPS-SF or by the veterinarians. Additionally, no correlation was found between SI and the Glasgow CMPS-SF scores. This result may reflect the comprehension that physiologic parameters (such as HR and SBP) are not evident

indicators of pain and may be altered due to other conditions (Lockhead, 2010; Crompton, 2014; Mathews et al, 2014).

When considering all patients and comparing the Glasgow CMPS-SF pain scores with the veterinarians' opinion on pain, overall dogs with higher pain scores were recognized as being in pain and these results were considered statistically significant. However, the veterinarians did classify patients as being in pain when the Glasgow CMPS-SF scored lower than 5/20 or 6/24. A similar result was found within the Shock group, where the veterinarians considered that dogs that had higher pain scores were in pain, and this outcome was considered to be statistically significant. The same did not occur within the Not Shock group. This was an unexpected finding, as it would be assumed that the results would resemble the ones described for the shock group. In this subset of patients the veterinarians classified dogs as painful at pain scores as low as 1 and classified patients as non-painful with pain scores of 9. Possible reasons for this occurrence can be the group size, the patients clinical presentation or to the inherent subjectivity of a pain assessment. These results can be furthermore enlightened with regard to the agreement between the two pain assessments. As mentioned, in order to evaluate the agreement between the veterinarians' opinion on pain ("Yes" or "No") and the relationship with the Glasgow CMPS-SF scale readings ("Yes" or "No" pain), the Cohen's *kappa* for inter-rater agreement was used. Regarding the *kappa* values obtained in the study the agreement can be described as none to slight between the Glasgow CMPS-SF and the veterinarian's opinion on pain (k=0.2), weak to moderate within the Shock group (k=0.47) and no agreement within the Not Shock group. Generally any *kappa* values below 0.60 are indicative of inadequate agreement among raters or procedures (McHugh, 2012). These results are explained by the previously mentioned occurrences with pain assessments, the subjectivity of pain responses and assessments, resulting in veterinarians assuming the patient was in pain when the Glasgow CMPS-SF score was lower than the proposed score for analgesia intervention. One other way of reading these *kappa* values is interpreting kappa as the level of disagreement between methods and in this sense, lower values represent higher disagreement (McHugh, 2012). Since the Glasgow CMPS-SF was designed measuring (acute) pain on a post-surgery setting, there is the possibility that the pain scores stated to reflect pain might not be the same in emergency patients. As mentioned, many dogs were described to be quiet, ignoring painful areas, with normal locomotion, not reactive to wound inspection or palpation and overall quiet and comfortable, which have a low or zero value in pain scoring. Another consideration might be the weight of the assessments performed by the

veterinarians; it is demonstrated that gender, personal and professional experience, may influence this assessment. For instance, women are more likely to score higher and give analgesia (Hugonnard, Leblond, Keroack, Cadre & Troncy, 2004; Ellingsen, Zanella, Bjerkas & Indrebo, 2010), and continuous and advanced veterinary education of the clinicians might influence their assessments (Doohoo & Doohoo, 1996). In this case, both genders were equally represented (one male and one female) and it is suggested that these professionals may tend to be more reluctant to classify patients as non-painful. Eventually, these findings may be a reflection that patients presenting in emergencies or in critical conditions may not appropriately demonstrate the criteria that the pain scoring systems describe. And in fact, there were few circumstances where the dogs were described to be simultaneously quiet and unsettled or as depressed or non-responsive to stimuli and comfortable or restless. Therefore, the agreement between pain assessments was not ideal and cannot be considered acceptable. Although not explored in this dissertation, the suggestion of a different pain score level to reflect pain in emergency patients could lead to higher agreement between the two assessments.

4.4.1 Study limitations

There are some limitations to this study that can be considered and described. An additional group to compare SI values and other parameters such as age or SBP should be present. This study was based on the SI values proposed by Porter et al (2013), but a healthy control group could have been elucidative of a SI range for healthy patients and its relation to age or SBP. Regarding the animals in the study, the possibility of having erroneously classified canine patients as being in shock based solely on the SI cannot be excluded. Factors such as stress, anxiety and pain can influence HR and SBP and thus, the shock index (Peterson et al, 2013; Porter et al, 2013). Additionally, it is suggested that classic objective parameters used to identify shock may have drastic variations between breeds and individuals within breed. For instance, tachycardia can exclude dogs from large breeds, while including small, anxious breeds that are not in shock (Porter et al, 2013). The use of a biomarker such as lactate could have helped in this issue. As previously described, concentrations increase with prolonged, unmanaged states of poor tissue perfusion. Therefore, high lactate concentrations could be beneficial in the detection of shock. However, hyperlactatemia is a late indicator of hypoperfusion. In fact, lactate concentration does not rise until decompensation occurs and there is an absolute or relative tissue oxygen deficiency. Additionally, increased plasma lactate concentration may not be due to primary hypoperfusion but to concurrent or

secondary illnesses (Hughes, 2011; Rosenstein & Hughes, 2014). Although the mean arterial pressure is most reflective of tissue perfusion the shock index is calculated with the SBP, and therefore Doppler Ultrasonography was selected because it measures this factor. Also, there is some suggestion that Doppler Ultrasonography may be more reliable in low perfusion conditions such as shock (Cooper, 2014). Regarding pain assessments with the Glasgow CMPS-SF, although the author made the majority of evaluations, having other observers with different levels of expertise in the assessment of pain with the CMPS-SF could possibly have introduced some score flexibility. Nonetheless, the Glasgow CMPS-SF is designed for an observer to select specific descriptors of pain related behaviour thus decreasing variability between observers. One other consideration to the avoidance of bias is that the veterinarians who performed the pain assessments were blinded to both SI and CMPS-SF scores. Also, a second pain assessment tool could have been used in addition to the Glasgow CMPS-SF and serial assessments of pain could have been performed. However, due to the busy dynamics of the practice this was not possible.

5. Conclusions and future perspectives

Pain assessment in veterinary patients is a challenging and demanding task, particularly when assessing pain at admission of emergency and in critically ill patients. The use of pain scoring systems may be helpful in supporting the veterinarians judgement on whether the animal is in pain and on how much pain the animal may be experiencing. Nevertheless, these instruments should not be used only as diagnostic tools and every case should be considered by its singularities. In this study, the shock group patients scored higher pain scores and a statistical significance was found between these scores and the veterinarians' opinion on pain. However, the agreement between the two pain assessments in emergency patients was not strong enough. Therefore these results suggest that further investigation into the correctness of the use of pain scoring tools in emergencies and in shock patients is required before these tools can be used in the objective monitoring of this subset of patients.

This learning period allowed me to better understand all aspects of emergency settings, fundamental aspects of pain processing and analgesia, and the importance of keeping a solid and motivated team while working under stressful environments.

In the future it would be interesting to continue this study with the use of a larger sample and in a longer timeframe, while using simultaneous validated pain assessment tools with sequential scoring over time with the purpose of monitoring

the progression of recovery, changes in pain score and catalogue common descriptors associated to each stage of illness. Eventually, this slightly different approach would be more effective in defining a better method to identify and treat pain in emergency settings.

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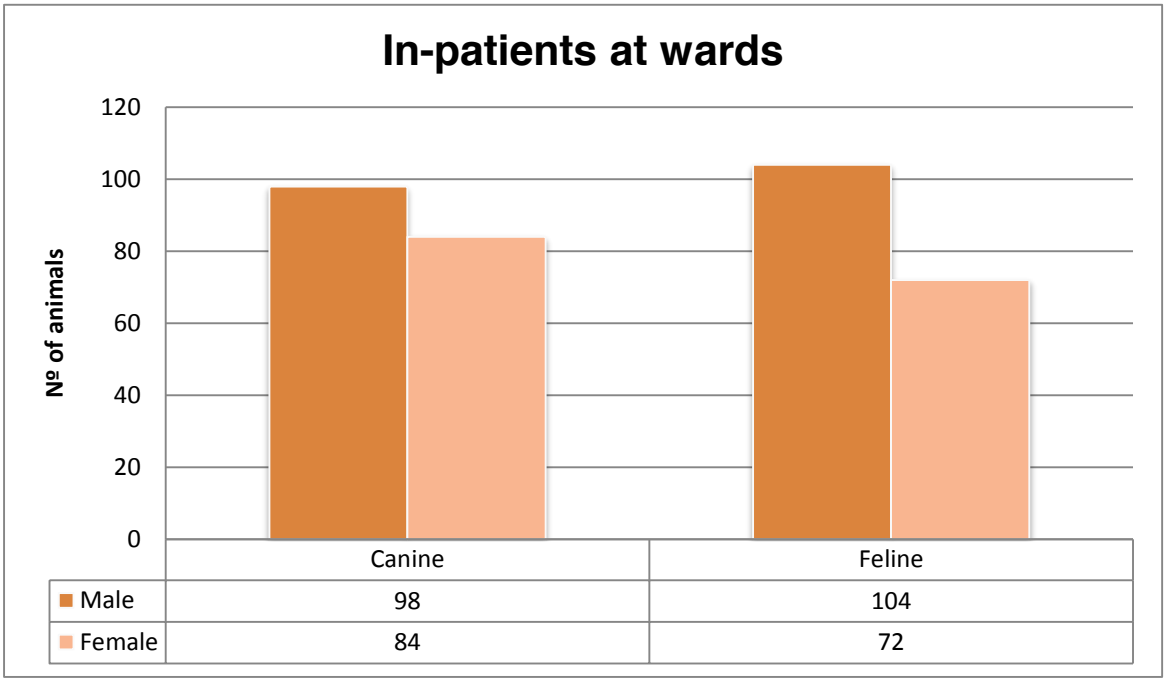
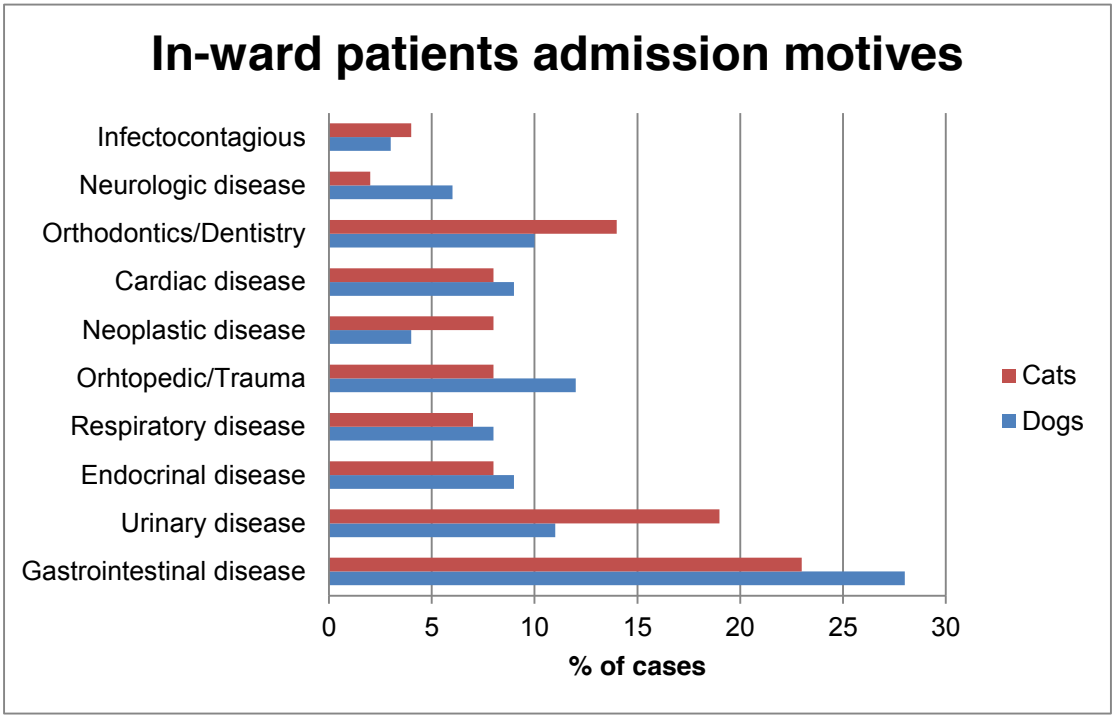
ANNEXES

Annex I – Externship features





Annex II – EVECCS Abstract

14th EVECCS ANNUAL MEETING LYON 2015

ORIGINAL STUDY - LONG VERSION

A PROSPECTIVE STUDY OF THE UTILITY OF THE SHORT FORM GLASGOW COMPOSITE MEASURE PAIN SCALE (CMPS-SF) IN CANINE PATIENTS IN SHOCK

Type : Veterinarian

Presentation : Oral

COUCELO J [1] ; BRAZ B [1] ; NUNES T [1] ; LAM A [2] ; MUGFORD A [2]

[1] Faculty of Veterinary Medicine, University of Lisbon, Lisbon, Portugal
[2] Vet24/Village Vet Hampstead, London, United kingdom

amugford4@hotmail.com

Introduction

The short form of Glasgow Composite Measure Pain Scale (CMPS-SF), a previously validated decision-making tool[1] is increasingly used in practice for the assessment of pain in dogs. However, few studies have considered the application of a pain scoring system in patients presenting in emergency situations. This study aims to evaluate if pain scoring with the Glasgow CMPS-SF is effective in identifying pain in patients in shock.

Material and Methods

Thirty one client-owned dogs (25 females and 6 males) that presented as primary emergencies or transfers. A prospective study (November 2014 to January 2015), within a first opinion and specialty intensive care service. At admission all dogs presenting as emergencies or transfers from other clinics were examined by a veterinarian. Patients were classified and grouped as Shock (S) or Not Shock (NS) on basis of their shock index (SI) Heart Rate/Blood Pressure. The shock status was defined a priori if the SI was higher than 1.0[2]. Regardless of group, all patients had their pain assessed with the Glasgow CMPS-SF and by a Residency trained clinician or Critical Care Specialist, blinded to both pain score and shock index values. (Significance p=0.05)

Results

Dogs in shock numbered 18/31 dogs within the Not Shock group numbered 13/31. Median age of dogs in the group S was 5 years (0.2 – 10) and of the NS group was 8 years (1 – 16); a significant difference existed in age between groups (P-value < 0.05). The S group had a median SI of 1.5 (1.09 – 3.53) and the NS group had a median SI of 0.79 (0.36 – 1) (P-value < 0.0001). Mean pain score of the S group was 7 (0 – 17) and on the NS group was 3 (1 – 15). There was no significant difference between pain scores and the groups (P-value > 0.05) and between the clinicians' perception of pain and group (P-value > 0.05). A significant difference was present between pain scores and the clinicians' opinion of pain within the shock group (P-value = 0.014). Cohen's kappa statistic of the shock group was 0.47, indicating moderate agreement between the Glasgow CMPS-SF and the clinician opinion. Within the NS group there were no significant differences between the pain scores and the clinician' opinion on pain (P-value > 0.05).

Discussion - Conclusion

These results may suggest only moderate agreement between the Glasgow CMPS-SF and an experienced veterinarians evaluation of pain in patients presenting in shock. Further investigation into the accuracy of pain scales in emergencies and shock patients is recommended before they are used in the objective monitoring of this subset of patients.

References :

[1] Reid J, et al. Development of the short-form Glasgow Composite Measure Pain Scale (CMPS- SF) and derivation of an analgesic intervention score. Animal Welfare 2007; 16, 97-104

[2] Porter AE, Rozanski EA, Sharp CR, et al. Evaluation of the shock index in dogs presenting as emergencies. J Vet Emerg Crit Care 2013; 23(5):538–544.

*Correction: 16 female and 15 male dogs. The p-value of the test between the Glasgow CMPS-SF pain scores and the clinicians' opinion on pain within the shock group is 0.0021.

EVECCS Abstracts presented June 12–14, 2015 in Lyon, France At EVECCS Annual Congress

Listing of Small Animal EVECCS Abstracts (in alphabetical order of presenter)

Oral Presentations

IN VITRO EFFECTS OF 6% HYDROXYETHYL STARCH 130/0.42 SOLUTION ON FELINE ROTATIONAL THROMBOELASTOMETRY

Albrecht N, Kovacevic A, Howard J, Adamik KN
Small Animal Clinic, Department of Veterinary Clinical Medicine, Vetsuisse Faculty Bern, Bern, Switzerland

Introduction: The aim of the study was to assess the effects of in vitro hemodilution of feline blood with hydroxyethyl starch (HES) 130/0.42 by rotational thromboelastometry (ROTEM) in healthy cats. A second aim was to develop feline reference intervals for ROTEM at our institution.
Methods: A 1:6 dilution of the feline blood was prepared with HES and Ringer's acetate (RA). Clotting time, CT (s); clot formation time, CFT (s); alpha-angle (°); and maximal clot firmness, MCF (mm) with ROTEM using ExTEM, InTEM, and FibTEM assays were studied in undiluted and diluted samples. Reference intervals, based on the robust method, and coefficients of variation of duplicate measures were calculated.
Results: Twenty-four cats were included in the study. Reference intervals were established for CT, CFT, MCF and alpha, respectively in InTEM (109–219 s, 22–88 s, 53–82 mm, 71–87°), ExTEM (36–70 s, 38–78 s, 61–74 mm, 74–82°) and FibTEM (39–66 s, not applicable, 6–25 mm, 52–81). The dilution with both HES and RA led to significantly ($P<0.05$) prolonged CT (InTEM), CFT (ExTEM, InTEM), and significantly reduced MCF (ExTEM, InTEM, FibTEM) and alpha (ExTEM, InTEM). Compared to RA, HES led to a significant ($P<0.05$) prolongation of CT (FibTEM) and CFT (ExTEM, InTEM), as well as a significant reduction of the MCF (InTEM and FibTEM) and alpha (ExTEM and InTEM).
Conclusions: In vitro hemodilution of feline blood with both RA and HES causes significant impairment of whole blood coagulation, with HES leading to a significantly greater impairment.

PROSPECTIVE EVALUATION OF THE UTILITY OF THE SHORT FORM GLASGOW COMPOSITE MEASURE PAIN SCALE (CMPS-SF) IN CANINE PATIENTS IN SHOCK

Coucelo J[1], Braz B[1], Nunes T[1], Lam A[2], Mugford A[2]
[1]*Faculty of Veterinary Medicine, University of Lisbon, Lisbon, Portugal*
[2]*Vet24/Village Vet Hampstead, London, United Kingdom*

Introduction: The short form of Glasgow Composite Measure Pain Scale (CMPS-SF) is being increasingly used in practice for the assessment of pain in dogs. However, few studies have considered the application of a pain scoring system in patients presenting in emergency situations. This study aimed to evaluate if pain scoring with the Glasgow CMPS-SF is reliable in identifying pain in patients in shock.
Methods: Thirty-one client-owned dogs that presented as emergencies were evaluated. At admission, patients were classified and grouped as in Shock (S) or Not Shock (NS) on the basis of their shock index (SI). Shock status was defined if the SI >1.0. Regardless of group, all patients had their pain assessed with the GCMPS-SF and by an experienced veterinarian blinded to pain score (PS) and SI values. (Significance $P<0.05$)
Results: There were 18 dogs in the S group; 13 dogs in the NS group. The S group had a median SI of 1.5 (1.09 – 3.53) and the NS group had a median SI of 0.79 (0.36 – 1) ($P<0.0001$). There was no significant difference between PS and the groups or between the clinicians' perception of pain and group. A significant difference was present between PS and the clinicians' opinion of pain within the S group ($P = 0.014$). Cohen's kappa statistic of the S group was 0.47, indicating moderate agreement between the PS and clinician opinion.
Conclusions: Our findings are suggestive that there is only moderate agreement between the GCMPS-SF and an experienced veterinarians evaluation of pain in patients with shock. Further investigation in this subject is recommended.

A PROSPECTIVE OBSERVATIONAL STUDY ON THE EFFECT OF A MENTAL METRONOME ON CHEST COMPRESSION RATES DURING SIMULATED CARDIOPULMONARY RESUSCITATION

Kneba E, Humm K

Department of Clinical Science and Services, The Royal Veterinary College, University of London, North Mymms, United Kingdom

Introduction: The effectiveness of the use of mental metronomes in the instruction of cardiopulmonary resuscitation (CPR) has previously been evaluated, but not with both a control group and over time. If using a mental metronome augments CPR performance then it should be used as a teaching tool. This study was designed to evaluate the effect of a mental metronome on chest compression rate performance at the point of training and 8 weeks later.
Methods: A prospective study was carried out on veterinary students without previous training in CPR. Participants were allocated to 1 of 2 groups based on availability, course, and year of study. Both groups received a short lecture and demonstration of CPR. The 'Song group' (SG) listened to "Stayin' Alive" performed by the Bee Gees and were asked to think about the tempo during chest compressions. The 'No Song group' (NSG) were given no guidance on achieving the correct chest compression rate. Both groups were

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*Correction: The p-value of the test between the Glasgow CMPS-SF pain scores and the clinicians' opinion on pain within the shock group is 0.0021.

Annex IV - University of Melbourne Pain Scale

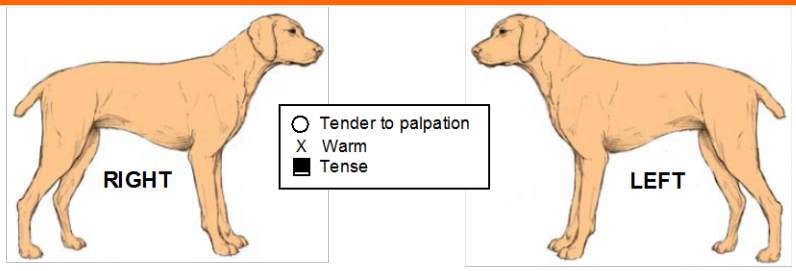
Category	Description	Scale
Biological variables		
	Dilated pupil	2
	Normal pupil	0
	Percentage of increase in Cardiac frequency	
	<20%	0
	>20%	1
	>50%	2
	>100%	3
	Salivation	2
	No salivation	0
Behavior variables		
Response to palpation	No changes	0
	Reaction to touch	2
	Reaction before being touched	3
Motor activity	Resting, sleeping	0
	Semiconscious	0
	Awake	1
	Restless, moving around	3
	Eating	0
Mental state	Submissive	0
	Sociable	1
	Cautious	2
	Agressive	3
Posture	Protects the affected area (fetal position)	2
	Lateral position	0
	Prone position	1
	Sitting or standing	1
	Moving	1
	Abnormal posture	2
Vocalization	Does not vocalize	0
	Vocalizes when touched	2
	Intermitent vocalization	2
	Continuous vocalization	3

Annex V – Colorado State University Canine Acute Pain Scale

Colorado State University

Colorado State University
Veterinary Medical Center
Canine Acute Pain Scale

Pain Score	Example	Psychological & Behavioral	Response to Palpation	Body Tension
No Score		❑ **Animal is sleeping and cannot be evaluated**		
0		❑ **Comfortable** when resting ❑ **Happy, content** ❑ Not bothering wound or surgery site ❑ Interested in or **curious** about surroundings	❑ **Nontender** to palpation of wound or surgery site, or to palpation elsewhere	Minimal
1		❑ **Content to slightly unsettled** or restless ❑ **Distracted easily** by surroundings	❑ **Reacts to palpation** of wound, surgery site, or other body part by **looking around**, **flinching**, or **whimpering**	Mild
2		❑ Looks **uncomfortable** when resting. ❑ May **whimper** or cry and may **lick or rub wound** or surgery site when unattended ❑ Droopy ears, **worried facial expression** (arched eye brows, darting eyes) ❑ **Reluctant to respond** when beckoned ❑ **Not eager to interact** with people or surroundings but will look around to see what is going on	❑ Flinches, whimpers cries, or guards/pulls away	Mild to Moderate **Reassess analgesic plan**
3		❑ **Unsettled, crying, groaning, biting or chewing** wound when unattended ❑ **Guards or protects** wound or surgery site by altering weight distribution (i.e., limping, shifting body position) ❑ **May be unwilling to move** all or part of body	❑ May be **subtle** (shifting eyes or increased respiratory rate) if dog is too painful to move or is stoic ❑ May be **dramatic**, such as a sharp cry, growl, bite or bite threat, and/or pulling away	Moderate **Reassess analgesic plan**
4		❑ **Constantly groaning or screaming** when unattended ❑ May bite or chew at wound, but unlikely to move ❑ **Potentially unresponsive** to surroundings ❑ **Difficult to distract** from pain	❑ **Cries at non-painful palpation** (may be experiencing allodynia, wind-up, or fearful that pain could be made worse) ❑ May react **aggressively** to palpation	Moderate to Severe **May be rigid to avoid painful movement** **Reassess analgesic plan**



Comments _____

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Annex VI – 4A-Vet Pain Scale

The 4AVet grid

Please complete the following pain scale

Subjective overall assessment	Absence of pain	0
		1
		2
	Intolerable pain	3
General behaviour	Among the following symptoms:	
	* shows respiratory alterations	❒
	* moans	❒
	* stoops	❒
	* stays set in analgesic position	❒
	* moves about or is depressed	❒
	* loss of appetite	❒
	* looks, chews, licks operative area	❒
	* limps, moves about with difficulty or is reluctant to move about	❒
	- No sign present	0
	- Only 1 sign present	1
	- 2 to 4 signs present	2
	- 5 to 8 signs present	3
Interactive behaviour	Is attentive and responds to strokes, voice	0
	Responds timidly	1
	Does not respond immediately	2
	Does not respond or responds aggressively	3
Heart rate Initial value	≤ 10 % increase	0
	11-30 % increase	1
	31-50 % increase	2
	> 50 % increase or cannot be assessed	3
Reaction at manipulation of the operative area	No visible or audible response	
	- after 4 manipulations	0
	Visible or audible response(s)	
	- at the 4th manipulation	1
	- at the 2nd and 3rd manipulation	2
	- at the 1st manipulation or non assessable	3
Intensity of this response	No response	0
	Responds easily, tries to escape	1
	Turns its head or vocalises	2
	Tries to escape or to aggress or non assessable	3
TOTAL SCORE	1 to 5: slight pain	
	6 to 10: moderate pain	
	11 to 18: severe pain	

Annex VII – Common opioid agents used in veterinary medicine and respective dosing

<table>
<tr><th>Opioid analgesic</th><th colspan="2">Dose (mg/kg)
Dogs</th><th>Cats</th><th>Observations</th></tr>
<tr><td>Morphine (μ)</td><td colspan="2">0.5 – 2 q2-4h IM, SC, IV
0.5 + 0.1 – 1.0 mg/kg/h CRI</td><td>0.2 – 0.5 q3-4h IM, SC, IV</td><td>Caution when given IV (histamine release)</td></tr>
<tr><td>Oxymorphone (μ)</td><td colspan="2">0.05 – 0.4 q2-4h IM, SC, IV</td><td>0.02 – 0.1 q3-4h IM, SC, IV</td><td></td></tr>
<tr><td>Hydromorphone (μ)</td><td colspan="2">0.05 – 0.2 q1-4h IM, SC, IV</td><td>0.05 – 0.1 q2-6h IM, SC, IV</td><td></td></tr>
<tr><td>Methadone (μ)</td><td colspan="2">0.5 – 1 q3-4h IM, SC, IV</td><td>0.1 – 0.5 q4h IM, SC</td><td>Inhibits NMDA receptors in the spinal cord</td></tr>
<tr><td>Meperidine (μ)</td><td colspan="2">3 – 5 q1-2h IM, SC</td><td>3 – 5 q1-2h IM, SC</td><td>IV use not recommended (histamine release)</td></tr>
<tr><td rowspan="7">Fentanyl (μ)</td><td colspan="2">Loading: 2 – 5 μg/kg IV
2 – 5 μg/kg/h CRI*
10 – 45 μg/kg/h CRI+</td><td>Loading: 1 – 3 μg/kg IV
1 – 4 μg/kg/h CRI*
10 – 30 μg/kg/h CRI+</td><td>CRI is required for sustained effect</td></tr>
<tr><td colspan="3">Transdermal Patches</td></tr>
<tr><td>Cats</td><td>Dose</td><td>Observations</td></tr>
<tr><td>Dogs <5 – 10 kg and cats*</td><td>25 μg/h (2.5 mg Fentanyl)</td><td rowspan="4">*These patients can be dosed with half of a 25μg/h patch; expose only half of the membrane to the patients skin (do not cut the patch in half). Duration of effect lasts about 72h but it may take up to 6h in cats and 12 in dogs to achieve therapeutic concentrations.</td></tr>
<tr><td>Dogs 10-20 kg</td><td>50 μg/h (5 mg Fentanyl)</td></tr>
<tr><td>Dogs 20-30 kg</td><td>75 μg/h (7.5 mg Fentanyl)</td></tr>
<tr><td>Dogs >30 kg</td><td>100 μg/h (10 mg Fentanyl)</td></tr>
<tr><td>Butorphanol (κ agonist/μ antagonist)</td><td>0.1 – 0.4 q1-4h IM, SC, IV
0.5 – 2 q6-8h PO</td><td>0.1 – 0.4 q2-6h IM, SC, IV
0.5 – 1 q6-8h PO</td><td></td></tr>
<tr><td>Buprenorphine (μ agonist/κ antagonist)</td><td>0.005 – 0.02 q 8-12h IM, SC, IV</td><td>0.005 – 0.02 q8-12h IM, SC, IV
0.01 – 0.02 q6-8h PO</td><td>May be difficult to antagonize</td></tr>
<tr><td>Naloxone (μ antagonist)</td><td>0.04 q0.5-1h IM, IV</td><td>0.04 q0.5-1h IM, IV</td><td>Analgesia reversal agent</td></tr>
</table>

Adapted from Handbook of Veterinary Pain Management, Gaynor & Muir III, 3rd Edition, 2014

Annex VIII - Common NSAIDs used in veterinary medicine and respective dosing

Family	Class	Drug	Dosage in dogs	Dosage in cats	Observations
Carboxilic acid	Salicilic acid	**Nonselective agents**			
		Aspirin (acetylsalicylic acid)	10-25 mg/kg, q8-12h PO with food	5-20 mg/kg, q48-72h, PO with food	Not for chronic use or osteoarthritis Antithrombotic in cats
	Acetic acid	Etodolac	10-15 mg/kg, q24h PO	N/A	
	Propionic Acid	Ketoprofen	2mg/kg sid IV/IM/SC then 1mg/kg q24h PO for 3-5 days	2 mg/kg sid PO/SC then 1 mg/kg q24h for 3-5 days	Surgical/chronic pain
		COX-2 Selective agents (COX-1 sparing)			
		Carprofen	2.2 mg/kg q12h or 4.4 mg/kg q 24h PO Perioperative: 4.4 mg/kg sid SC	Perioperative: 4 mg/kg once SC	Not for chronic use in cats
	Fenamic acid	Tolfenamic acid	4 mg/kg q24h PO or SC for 3-5 days	4 mg/kg q24h PO or SC 3-5 days	
Coxibs		Cimicoxib	2 mg/kg q24h PO	N/A	
		Deracoxib	1 – 2 mg/kg q24h PO	N/A	
		Robenacoxib	1 mg/kg q24h PO Perioperative: 2 mg/kg SC once	1 mg/kg q24h PO Perioperative: 2 mg/kg SC once	Cats: 3 – 11 days of administration
		Firocoxib	5 mg/kg q24h PO	N/A	
		Mavacoxib	2 mg/kg on day 1, 14 and 30; then 1 every month	N/A	6 month-limit of continuous administration
Fenamic acid (Oxicams)		Meloxicam	0.2 mg/kg IV,SC 0.2 mg/kg (loading dose), then 0.1 mg/kg PO q24h	0.1 mg/kg SC 0.1 mg/kg PO on day 1, then 0.05 mg/kg PO q24h	
		Piroxicam	0.3 mg/kg PO q24-48h	0.3 mg/kg PO q24-48h	

Adapted from Handbook of Veterinary Pain Management, Gaynor & Muir III, 3rd Edition, 2014

Annex IX - Recommended doses of selected α2-agonists for routine sedation and analgesia

α_2 agonist	Dose (mg/kg)
Dexmedetomidine	Dogs: 0.005-0.01 IM 0.0025-0.005 IV
	Cats: 0.008-0.015 IM 0.005-0.008 IV
Medetomidine	Dogs: 0.01-0.02 IM 0.005-0.01 IV
	Cats: 0.015-0.03 IM 0.01-0.015 IV

Adapted from Handbook of Veterinary Pain Management, Gaynor & Muir III, 3rd Edition, 2014

Annex X – Form developed for the study

Form developed for the study (front)

SI PROJECT SHEET

To be applied in dogs (M/F) admitted or transferred to VillageVet Hampstead, in emergency situations.

PART I – PATIENT IDENTIFICATION (Fill spaces or print and paste a label)

Date _____
Initials
Emergency? Y☐ N☐

Name_____ **Owner**_____

Sex F | FN | M| MN **Age**_____ **Weight**_____

Breed_____

PART II - DATA COLLECTION

Heart Rate_____ **Blood Pressure**_____ **RR**_____ **CRT**_____ **MM** Pink☐ Pale☐ Blue☐ Red☐

Temperature_____ Glucose (if measured)_____ Lactate (if measured)_____

PART III - PAIN SCORING

Apply Glasgow's Short Form Composite Modified Pain Scale (see back)

OBSERVATIONS

RESIDENCY TRAINED CLINICIANS (AND NIGHT VETS)

Pain on physical exam? NO☐ YES☐

Select Analgesia

Methadone 0.1 mg/kg ☐
Methadone 0.2 mg/kg ☐
Methadone 0.3 mg/kg ☐

Form developed for the study (back)

SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

In the sections below please circle the appropriate score in each list and sum these to give the total score.

A. Look at dog in Kennel

Is the dog?

(i)		(ii)	
Quiet	0	Ignoring any wound or painful area	0
Crying or whimpering	1	Looking at wound or painful area	1
Groaning	2	Licking wound or painful area	2
Screaming	3	Rubbing wound or painful area	3
		Chewing wound or painful area	4

In the case of spinal, pelvic or multiple limb fractures, or where assistance is required to aid locomotion do not carry out section **B** and proceed to **C**
Please tick if this is the case ☐ then proceed to C.

B. Put lead on dog and lead out of the kennel.

When the dog rises/walks is it?

(iii)	
Normal	0
Lame	1
Slow or reluctant	2
Stiff	3
It refuses to move	4

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.

Does it?

(iv)	
Do nothing	0
Look round	1
Flinch	2
Growl or guard area	3
Snap	4
Cry	5

D. Overall

Is the dog? (v)		*Is the dog?* (vi)	
Happy and content or happy and bouncy	0	Comfortable	0
Quiet	1	Unsettled	1
Indifferent or non-responsive to surroundings	2	Restless	2
Nervous or anxious or fearful	3	Hunched or tense	3
Depressed or non-responsive to stimulation	4	Rigid	4

Pain Score_____

I. After pain scoring, fold the top of this sheet to match the line above.
II. Fold this section upwards and without mentioning Pain Score, Blood Pressure or Heart Rate ask a Residency Trained Vet (Amy or Adam)/Night Vet to assess pain and analgesia.
III. Place the sheet at the dog's kennel board.

Thank you for your collaboration!

Annex XI – Patients' Individual Glasgow CMPS-SF Scores

Glasgow CMPS-SF Category	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
A1	0	0	0	0	0	1	0
A2	0	0	0	0	0	1	0
B	0	0	0	3	0	2	2
C	0	2	1	2	0	5	0
D1	2	1	1	1	1	4	1
D2	1	0	0	3	0	2	0

Glasgow CMPS-SF Category	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
A1	0	1	0	0	0	0	1
A2	0	1	0	0	0	0	1
B	0	1	0	2	0	0	4
C	0	2	1	1	1	2	5
D1	1	1	1	2	1	1	4
D2	0	3	1	1	0	1	2

Glasgow CMPS-SF Category	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20	Patient 21
A1	0	0	0	0	0	0	1
A2	0	0	0	0	0	0	0
B	0	0	0	0	2	0	0
C	0	0	1	0	1	1	1
D1	3	0	1	1	1	1	1
D2	1	0	0	0	3	3	1

Glasgow CMPS-SF Category	Patient 22	Patient 23	Patient 24	Patient 25	Patient 26	Patient 27	Patient 28
A1	1	1	1	0	0	2	2
A2	0	0	0	0	0	1	1
B	2	0	0	4	0	4	3
C	3	0	0	1	2	2	3
D1	3	3	1	4	1	4	3
D2	3	1	3	0	1	4	3

Glasgow CMPS-SF Category	Patient 29	Patient 30	Patient 31
A1	0	0	0
A2	0	0	0
B	2	4	2
C	0	2	0
D1	1	2	4
D2	0	1	1

Annex XII – Patients' collected parameters

PATIENT	SEX	AGE (Y)	BREED	MM	CRT	RR	TEMP	KG	HR	SBP	SHOCK INDEX	GLUCOSE	LACTATE	PAIN SCORE	SCALEPAIN	VETPAIN	ANALGESIA	ADMISSION
1	FN	13	LABRADOR	PINK	<2	N/A	38,6	N/A	144	170	0,85	N/A	N/A	3	NO	NO	METH 0,1	HAEMOABDOMEN
2	FN	13	GOLDEN RETRIEVER	PINK	N/A	N/A	N/A	36,4	128	162	0,79	N/A	N/A	3	NO	YES	METH 0,2	HEMORRHAGE
3	MN	4	CAVALIER KING CHARLES SPANIEL	PINK	>2	24	38,8	11,5	120	200	0,60	N/A	N/A	2	NO	YES	METH 0,2	GI FOREIGN BODY
4	FN	14	GERMAN SHEPARD	PINK	<2	70	37	N/A	90	160	0,56	8,2	1	9	YES	NO	METH 0,1	NEUROLOGIC CONDITION
5	FN	3	MINIATURE SCHNAUZER	N/A	N/A	N/A	N/A	8,5	100	120	0,83	N/A	N/A	1	NO	NO	METH 0,1	CHOCOLATE TOXICITY
6	M	4	ITALIAN SPINONE	RED	<2	N/A	38,1	51	110	190	0,58	2,3	2,2	15	YES	YES	METH 0,2	ABDOMINAL DILATION
7	FN	13	AUSTRALIAN SHEPARD	PINK	<2	N/A	38,4	14,2	140	146	0,96	N/A	N/A	3	NO	NO	BUP 0,02	RAISIN TOXICITY
8	MN	8	GOLDEN RETRIEVER	PINK	<2	N/A	38,6	29,3	120	164	0,73	N/A	N/A	1	NO	YES	METH 0,3	ACUTE GASTROENTERITIS
9	FN	3	LAB X STAFFORDSHIRE BULL TERRIER	PINK	<2	30	38,3	25	160	164	0,98	5,4	1,6	9	YES	YES	METH 0,2	RTA
10	MN	8	CHINESE CRESTED	PINK	<2	30	39,1	11,8	160	180	0,89	N/A	N/A	3	NO	YES	BUP 0,02	PANCREATITIS
11	FN	1	WHIPPET CROSS BREED	PINK	<2	20	40,2	10,2	120	120	1,00	N/A	<1	6	YES	NO	METH 0,2	SUDDEN LETHARGY
12	MN	8	CROSS BREED	PINK	<2	24	38	39,7	90	145	0,62	N/A	N/A	2	NO	YES	BUP 0,02	HGE
13	FN	16	WEST HIGHLAND TERRIER	PINK	<2	40	40,7	8,1	80	220	0,36	N/A	N/A	4	NO	YES	METH 0,2	PANCREATITIS
14	M	0,6	JACK RUSSEL	PINK	<2	48	38,6	1,9	140	120	1,17	9,9	N/A	17	YES	YES	METH 0,1	RTA
15	FN	4	LABRADOR	PINK	<2	N/A	37,7	N/A	132	75	1,76	N/A	2,1	4	NO	YES	METH 0,2	RTA
16	FN	1	LABRADOR	PINK	<2	36	N/A	20,5	132	110	1,20	N/A	N/A	0	NO	NO	METH 0,2	GI FOREIGN BODY
17	M	0,2	CAVICHON	PALE	N/A	N/A	37,9	1,76	192	120	1,60	4,6	N/A	2	NO	NO	BUP 0,01	ACUTE GASTROENTERITIS
18	M	5	CHIHAUHA	N/A	N/A	N/A	N/A	3,1	200	120	1,67	N/A	N/A	1	NO	NO	METH 0,1	CHOCOLATE TOXICITY
19	FN	10	GREYHOUND	PINK	<2	44	39	33,0	144	100	1,44	5,6	1,6	7	YES	YES	METH 0,1	CARDIAC MASS
20	MN	8	YORKSHIRE TERRIER	PALE	>2	32	37	6,3	200	80	2,50	5,7	5	5	NO	YES	METH 0,1	HGE
21	MN	5	CROSS BREED	PINK	>2	30	38,6	13,4	150	125	1,20	N/A	N/A	4	NO	YES	BUP 0,02	HGE
22	MN	7	BORDER TERRIER	PINK	<2	20	39,1	9,6	160	130	1,23	N/A	N/A	12	YES	YES	METH 0,2	SPLENECTOMY
23	FN	0,5	CHIHAUHA	PINK	<2	44	N/A	1,78	160	104	1,54	N/A	N/A	5	NO	YES	BUP 0,01	NSAID TOXICITY
24	FN	0,5	CHIHAUHA	PALE	<2	N/A	38,9	1,96	160	95	1,68	N/A	N/A	5	NO	YES	BUP 0,02	NSAID TOXICITY
25	M	0,2	LURCHER	RED	<2	30	38,3	3,5	140	110	1,27	N/A	N/A	9	YES	YES	METH 0,2	ABNORMAL LOC
26	FN	7	JACK RUSSEL	PINK	<2	N/A	N/A	5,2	120	110	1,09	N/A	N/A	4	NO	NO	METH 0,1	CHOCOLATE TOXICITY
27	MN	6	GREYHOUND	PINK	>2	60	39,1	34,4	205	58	3,53	6,5	9,1	17	YES	YES	METH 0,2	HGE
28	FN	8	JACK RUSSEL	PINK	>2	30	38,2	5,2	180	150	1,20	7,4	N/A	15	YES	YES	METH 0,2	RTA
29	MN	9	CROSS BREED	PINK	>2	32	37,8	31	160	98	1,63	N/A	N/A	3	NO	NO	METH 0,1	PERICARDIAL EFFUSION
30	FN	10	PUG	PALE	>2	N/A	34,6	5,86	140	60	2,33	15,8	1,5	9	YES	YES	METH 0,1	COLLAPSE
31	M	0,2	LABRADOR	PALE	<2	40	38,8	2,3	140	95	1,47	8,2	0,8	7	YES	YES	BUP 0,01	HGE