

**Hypertension and Cardiovascular Risk in Small Animals: What We Can Learn From a Human Epidemic**  
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## **INTRODUCTION**

Hypertension is a global epidemic. It is the single largest contributor to the global disease burden<sup>1</sup>. As well as being a clinical end-point for cardiovascular disease (CVD), it is now recognised as a key player in the morbidity and mortality associated with an increasingly longer list of systemic diseases. Not only do these include diabetes mellitus, chronic kidney disease and hyperadrenocorticism, but more recently, immune-mediated diseases as well. Despite the diverse aetiologies of these conditions, there appear to be key common pathways that maintain the hypertensive state, and which have been clarified, through a combination of *in vitro* and *in vivo* techniques, particularly with rodent models. Naturally occurring diseases in small and large animal veterinary patients have the potential to bridge the translational gap between rodent models and people, while, at the same time, providing insight into morbidity and mortality risk in companion animals. Yet, surprisingly little is known about the role of vascular disease and hypertension in common veterinary illnesses. Is this because we hold the traditional view that vascular dysfunction is not a key player in pet diseases, or instead is it because we have not yet developed sufficiently robust diagnostic techniques to identify vascular dysfunction in our patient population?

## **REGULATION OF BLOOD PRESSURE**

Arterial blood pressure (BP) is generated by the expulsion of stroke volume by the left ventricle against the resistance of the arterial tree. In the short term, the autonomic nervous system, in response to central inputs and peripheral baroreceptors, modifies heart rate, cardiac contractility, and arteriolar tone. This ensures adequate perfusion of the vital organs (heart, brain and kidneys), and meets metabolic or survival requirements such as “fight or flight”. Perfusion of organs can be “fine-tuned” at the tissue and capillary level by fluctuations in endothelium- and non-endothelium-dependent arteriolar tone and pre-capillary constriction by pericytes. These are usually in response to autocrine and paracrine agents released as metabolic by-products or inflammatory mediators, and following autonomic stimulation and changes in vascular wall stress. Usually, acute rises and falls in BP are short-lived, whereas, in the state of hypertension, BP is inappropriately elevated over the long-term.

Central to the long-term regulation of BP are the kidneys, which control plasma volume by controlling sodium balance<sup>2</sup>. This has been confirmed through a series of renal transplantation experiments in several rodent models of hypertension. BP in nephrectomised Dahl salt-sensitive (DSS) rats normalises following transplantation of a single kidney from a Dahl salt-resistant (DSR) donor. Similarly, nephrectomised DSR rats become hypertensive following transplantation of a single kidney from a DSS rat donor<sup>3-5</sup>. Thus, the BP phenotype follows the genotype of the kidney donor rather than the genotype of the recipient. Similar results have been reproduced in other hypertensive rodent models, such as the spontaneous hypertensive rat (SHR)<sup>6</sup>.

## **ACUTE PRESSURE NATRIURESIS**

Renal handling of sodium can be influenced by external factors such as the renin-angiotensin-aldosterone system (RAAS). Nephrectomised wild-type (WT) mice, transplanted with a kidney from an AngII receptor knockout (AngII R KO) donor mouse, are protected from hypertension during chronic infusion of AngII<sup>7</sup>. Conversely, nephrectomised AngII R KO mice develop hypertension during AngII infusion when grafted with a WT mouse kidney. However, RAAS can be overridden by the inherent ability of the kidney to handle salt, called acute pressure natriuresis. For example, in the phenomenon of “aldosterone escape”, sustained hypertension from hyperaldosteronism is prevented in people by compensatory downregulation<sup>8</sup> and inhibition of sodium transport<sup>9</sup> that restores natriuresis.

Acute pressure natriuresis is crucial to the kidney’s role in the long-term regulation of BP. The mammalian kidney is incapable of actively secreting sodium into urine, and so urinary sodium and water excretion is dependent on a process of large-scale filtration followed by selective reabsorption. The relationship between renal perfusion pressure (a surrogate marker of arterial BP) and urinary sodium excretion is a sigmoidal one. However, with Western diets, which exceed maintenance salt requirements, the relationship is linear. The mechanism is vasculotubular and activated following ingestion of a meal<sup>10</sup>. Rapid sodium reabsorption from the gastrointestinal tract is accompanied by water ingested following the sensation of thirst. This maintains plasma osmolality at the expense of increased plasma volume. Increased cardiac preload activates the Frank-Starling mechanism, increasing cardiac output and renal artery perfusion. Autoregulation of glomerular filtration rate (GFR) transmits increased renal perfusion through efferent arterioles into the peritubular vascular network, including the medullary *vasa recta*. Increased perfusion through this network increases medullary hydrostatic pressure and, through Starling’s forces, inhibits tubular sodium and water reabsorption, principally from the proximal convoluted tubule (PCT)<sup>10</sup>. Distal sodium transporters such as the sodium-potassium-chloride co-transporter (NKCC2), sodium-chloride co-transporter (NCC) and epithelial sodium channel (ENaC) may also be inhibited by paracrine agents such as nitric oxide (NO), endothelin-1 (ET-1) and adenosine triphosphate (ATP)<sup>11-14</sup>. The result is a diuresis/natriuresis appropriate for the degree of sodium and water ingestion, and that is self-limiting once an appropriate plasma volume has been restored<sup>2</sup>.

## **CIRCADIAN VARIATION IN BLOOD PRESSURE AND CARDIOVASCULAR RISK**

Many consider acute pressure natriuresis to be so important to the long-term regulation of BP, that in order for the state of hypertension to exist, acute pressure natriuresis must also be impaired<sup>10</sup>. Also, impaired acute pressure natriuresis has been identified in diseases, such as Type 1 diabetes mellitus (T1DM), that predispose to hypertension and are associated with increased cardiovascular risk<sup>15,16</sup>. Furthermore, impaired acute pressure natriuresis is associated with enhanced susceptibility to

hypertensive renal injury<sup>17</sup>. Thus, deranged renal salt handling, hypertension and chronic kidney disease are linked. This is exemplified by the high risk of CVD in patients with hypertension or chronic kidney disease (CKD). There is also strong clinical evidence that these relationships disrupt normal circadian variation in BP. Acute pressure natriuresis is activated soon after salt ingestion. Salt excretion varies over a 24-hour period, implying that an intact acute pressure natriuresis response is vital to maintaining a circadian rhythm in BP<sup>18</sup>. In people with salt-sensitive hypertension or T1DM, reduced daytime urinary sodium excretion is tightly linked to increased nocturnal BP and reduced dipping in BP<sup>19</sup>, suggesting a weaker daytime acute pressure natriuresis response has to be maintained during the night at the expense of increased BP<sup>18</sup>.

In essential hypertension, loss of nocturnal dipping is associated with a higher risk of target organ damage<sup>20-22</sup>, suggesting that nocturnal dipping may be necessary for organ recovery from the haemodynamic stresses of the daytime systemic arterial load. The kidney is highly perfused and receives approximately 25% of cardiac output, so, intuitively, elevated nocturnal BP could induce a form of hyperfiltration that initiates glomerular injury. The implication is that there are potential benefits from therapeutic targeting of elevated night-time BP to re-establish nocturnal dipping as well as simply lowering BP. This is the rationale behind the recommendation by the American Diabetes Association to dose anti-hypertensive medication at bedtime<sup>23</sup> and there is already evidence that this may reduce cardiovascular risk<sup>24</sup>. However, the therapeutic goal should be to target the mechanistic basis to impaired acute pressure natriuresis rather than simply treating its effect. Indeed, arteriodilators could potentially exacerbate impairment to acute pressure natriuresis by interfering with the rise in renal medullary blood flow that initiates the natriuretic response. The disconnect between arteriodilation and reduced nocturnal BP has been demonstrated clinically in patients with non-diabetic CKD: arteriodilation with a calcium channel antagonist failed to re-establish nocturnal dipping while the selective endothelin A antagonist, sitaxentan, was successful<sup>25</sup>.

The physiological mechanism underpinning impairment to acute pressure natriuresis could involve suppression of renal medullary perfusion, or inappropriate tubular sodium reabsorption. In several established rodent models of hypertension, suppression of medullary perfusion is a common feature. Investigations into medullary perfusion in a rodent model of T1DM are ongoing, but the effects of insulin on tubular sodium reabsorption in the different forms of diabetes are complex. In T2DM, associated with hyperinsulinaemia, insulin promotes sodium reabsorption through NCC and ENaC, and the development of hypertension<sup>26</sup>. In T1DM, replacement insulin therapy appears to inhibit sodium reabsorption. Thus the aetiologies of hypertension and increased cardiovascular risk may vary in the different forms of diabetes, but for both, targeting medullary perfusion to re-establish acute pressure natriuresis could restore regulation of BP and reduce cardiovascular risk.

In conclusion, studies in humans and rodent models suggest that cardiovascular risk and target organ damage are linked with BP and its circadian regulation, which are linked with acute pressure natriuresis, which is linked with renal vascular function and tubular sodium reabsorption.

## ASSESSMENT OF VASCULAR FUNCTION IN COMPANION ANIMALS

So what does this mean for our veterinary patients? Traditionally, vascular function in companion animals has been distanced from changes to vascular function in people. This is despite the existence of common or similar naturally-occurring diseases in animals that should model, more effectively than rodent species, many of the complexities of diseases that increase cardiovascular risk in people. One justification for this view has been the absence of clinically overt atherosclerosis in our patient population, with notable exceptions, such as hypothyroidism. However, in more recent times, as diagnostics have advanced, it has become apparent that features of macro- and microvascular disease such as stroke, neuropathy, retinopathy and limb ischaemia do indeed have veterinary equivalents. If we extrapolate further, the possibility emerges of subclinical CVD contributing to significant morbidity and mortality that is usually attributed to different, separate diseases of other organ systems. The diagnosis of CVD is implicit within a range of conditions frequently diagnosed in people, such as CKD, T1/T2DM and obesity. Yet data on whether and to what extent it contributes to outcome in dogs and cats with these diseases are limited<sup>27-29</sup>. Long-term epidemiological studies in the veterinary patient population, such as DogsLife in Labrador retrievers<sup>30</sup>, may provide crucial data on not just clinical disease but pre-clinical risk factors.

Broadly speaking, there are two approaches to determining the significance of cardiovascular dysfunction in veterinary medicine. The first is to assess vascular function, which can be performed in small animals *ex vivo*, and, not without difficulty, *in vivo*. Simple *in vivo* methods include measuring agents or their metabolites that mediate vasodilation, such as nitric oxide (NO)<sup>31</sup> or endothelin-1 (ET-1), in plasma or urine. Although suggestive of vascular dysfunction with increasing severity of myxomatous mitral valve disease (MMVD), studies have generated conflicting data<sup>32</sup>, possibly because they are an indirect assessment of function, and measure systemic levels of agents that operate in an autocrine or paracrine manner. More recently, attempts at a direct assessment of vascular function has been applied to dogs<sup>33</sup> and horses<sup>34</sup>. Measurement of flow-mediated vasodilation (FMD) in femoral or brachial arteries by Doppler ultrasound following vessel occlusion and release (reactive hyperaemia) has shown that vascular dysfunction does exist at an advanced stage of MMVD<sup>35</sup>, although the technique is highly specialised and prone to variable results that preclude its use clinically. An alternative method, venous occlusive plethysmography, has not been applied to pets. The technique is relatively straightforward, only mildly invasive, and is routinely performed on human volunteers when, for example, determining the functional properties of novel peptides<sup>36</sup>. Changes in limb volume following local intra-arterial injection of vasoactive agents are measured by a pre-placed strain gauge around a limb during temporary venous occlusion. The agents injected are at concentrations that are orders of magnitude below levels that elicit systemic effects. The major disadvantage of the technique in animals is that general anaesthesia is required, but the influence of anaesthetic agents is minimised by the dynamic nature of the test, which measures relative changes from baseline. However, the ethical considerations of performing such clinical research under general anaesthesia are difficult to overcome. This illustrates the irony of modern clinical veterinary research: while animal research and experimental techniques developed

in animals are routinely applied to human medicine, human research and experimental techniques developed in people are less routinely applied to veterinary patients.

### LIMITATIONS OF INDIRECT BLOOD PRESSURE MEASUREMENT

The second potential approach to assessing cardiovascular risk is the serial measurement of BP, a clinical biomarker of cardiovascular risk. Major advances in in-clinic assessment of BP have been made in small animals using indirect methods. Doppler and oscillometric devices are commonplace in general practice but limitations still exist<sup>37,38</sup>. High definition oscillometry minimises these limitations by high frequency sampling of pressure waveforms over a wide range of pressures. While this increases its reliability for measurement of systolic BP, the reliability of diastolic BP in cats remains in doubt<sup>39</sup>. Although systolic BP may be considered as more applicable to the assessment of hypertension<sup>40</sup>, diastolic BP may have a greater correlation with preload-induced hypertension indicative of failing acute pressure natriuresis<sup>41</sup> and risk of nephropathy in T1DM<sup>42</sup>. Thus, although clear guidelines for risk of target organ damage have been established<sup>38,40</sup>, limitations of Doppler and oscillometric-based methods of BP measurement remain. Furthermore, the “white-coat effect” cannot be entirely removed. Even assuming that an individual pet is calm and relaxed during the period of measurement, trips to the clinic are still associated with changes in routine such as timing of feeding, exercise, car journeys, environmental temperature and other stimuli, all of which can invoke unconscious physiological effects in the short term<sup>43</sup> that could modify one or more serial BP measurements. To overcome these, the pet should, ideally, remain within its “normal” environment and either be unaware that some form of intervention/assessment is taking place or be conditioned to it. In people and laboratory rodents, this can be partly addressed by 24-hour BP measurement. Not only is BP measured outwith a clinical environment but also circadian variation in BP, a predictor of cardiovascular and CKD risk long before in-clinic hypertension develops<sup>44</sup>, can also be determined. Although circadian variation in laboratory cats and dogs has been studied, very little is known about circadian variation in BP in companion animals in home environments, and the effects that disease, pharmacological intervention, and imposition of human daytime routines have upon them. At least, there is common ground between human and veterinary medicine in that the “white-coat effect” cannot be entirely removed from patients undergoing 24-hour BP monitoring because, in people, it is performed indirectly by oscillometry.

### DIRECT BLOOD PRESSURE MEASUREMENT

Direct measurement of BP is the “gold standard” but is limited clinically to intra-operative or ICU monitoring. In laboratory rodents, radiotelemetry has provided a solution. If this could be applied to our patients, it could maximise the utility of BP measurement, including diastolic BP, and determine circadian variation. Not only would this allow assessment of cardiovascular risk in clinical disease, there would be the potential to identify novel risk factors for CVD in pre-clinical disease, and risks associated with metabolic conditions such as obesity. Treatment of hypertension could be tailored to individual needs that not only lower BP, but also re-establish circadian rhythm. Radiotelemetry units are already used routinely in laboratory cats and dogs<sup>45,46</sup>. They are usually surgically placed into the aorta or femoral artery. A transmitter emits data streams at pre-programmed intervals, such as for two minutes in every hour, to one or two remote receivers within the same room. If applied successfully to a clinical situation, BP could be monitored for days to weeks at a time in the home environment for several years. However, transferring this technology to uncontrolled home and outdoor environments will require extensive trialling and validating, and again significant ethical considerations must be overcome. The latter relate to timing of anaesthesia, the invasiveness of the technique, patient safety in the event of haemorrhage at the arteriotomy site, and hardware durability. In the meantime, before making this giant leap, *in vivo* and *ex vivo* data on cardiovascular function within a range of canine, feline and equine disease states are being accumulated.

### CONCLUSION

If we are to learn anything from the human global epidemic of hypertension and CVD, it is that a long-term goal must be to fully characterise naturally occurring risk factors for cardiovascular morbidity and mortality in pets. By bridging the translational gap between animals and people, pets would be beneficiaries. Translational research should be bidirectional: from bench to bedside and from bedside to basket.

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