Atrial Natriuretic Peptide and Cardiovascular Diseases in Dogs and Cats

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ABSTRACT

The term biomarker encompasses various biological indicators that objectively reflect a patient's medical status with precision and reproducibility. These indicators range from basic measurements like pulse and blood pressure to more intricate laboratory tests. Cardiac markers are crucial for accurate and prompt diagnosis of heart diseases in animals. Given the challenge of diagnosing cardiac diseases in small animals due to nonspecific clinical signs, cardiac markers provide quantitative indicators of biological processes. These markers include cardiac troponins for myocardial injury, natriuretic peptides for myocardial function, lipoproteins for serum homeostasis, and markers for inflammation of the cardiovascular system. Among natriuretic peptides, atrial natriuretic peptide (ANP) has emerged as a significant tool in diagnosing and monitoring cardiac diseases. ANP, primarily synthesized in cardiac atria, regulates salt and fluid excretion, counteracts vasoconstriction, and inhibits the renin-angiotensin-aldosterone system, contributing to the maintenance of cardiovascular homeostasis. Additionally, it functions as a biomarker for ventricular hypertrophy and congestive heart failure (CHF) in animals. Furthermore, it protects against hypertension and cardiac remodeling by demonstrating antagonism to the same system. This review addresses the definition of biomarkers within the context of molecular biology, elucidates their multifaceted functions in the animal organism in light of integrative physiology, and explores the pathologies correlated with ANP, with an emphasis on its etiopathogenesis and clinical manifestations.

Keywords: Biomarker, Canine, Feline, Heart physiology

INTRODUCTION

According to Barbosa (2022), biomarkers play a crucial role in both the diagnosis and the prognosis of animal pathologies, providing a valuable tool for the clinical evaluation of these conditions. In 1998, the Biomarkers Definitions Working Group of the National Institutes of Health established the definition of a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Strimbu and Tavel, 2010).

Cardiac markers are used to enhance the accuracy and speed of diagnosing heart disease in animals, thereby allowing for early prognosis and therapeutic interventions (Yonezawa et al., 2010). These cardiac markers are quantifiable indices of biological processes executed by a specific organ or system, as noted by Oyama (2015). In the medical field, cardiac markers are categorized into four groups, each associated with distinct clinical conditions. The first category relates to myocardial injury or necrosis, typically indicated by cardiac troponins. The second category pertains to myocardial function represented by natriuretic peptides. The third involves serum lipoprotein homeostasis including high-density lipoprotein (HDL) and low-density lipoprotein (LDL). The fourth category, concerns the inflammation of the cardiovascular system (Yonezawa, 2010). In the contemporary scientific landscape, natriuretic peptides (NPs) have been recognized as pivotal instruments in the diagnostic evaluation and therapeutic monitoring of cardiac pathologies. Empirical evidence indicates that the quantification of N-terminal pro-brain natriuretic peptide (NT-proBNP) in the serum and plasma of canine and feline species serves as the sole biomarker facilitating the identification and monitoring of congestive phenomena as well as indirectly, assessing myocardial function in small animals (Lima and Ferreira, 2017). ANP has demonstrated clinical utility in various scenarios. For instance, in patients with heart failure, ANP levels are often elevated as a compensatory mechanism to counterbalance volume overload and increased cardiac workload (Felker et al., 2017). ANP also shows promise in managing acute kidney injury due to its ability to dilate renal vasculature and increase renal blood flow, underscoring the importance of biomarkers in identifying subclinical acute kidney injury before the onset of renal failure (Pinto, 2023). These examples highlight the clinical relevance and potential therapeutic applications of natriuretic peptides in various medical conditions (Felker et al., 2017).

When evaluating patients with comorbidities in veterinary medicine using cardiac markers, it is crucial to consider species differences, the impact of concurrent medical conditions, and the complexity of interpreting results to ensures an accurate and comprehensive assessment of the animal's cardiac health. Baseline values for cardiac markers can vary among animal species, implying that normal reference ranges can vary between them (Mendes et al., 2019). The presence of comorbidities, such as renal, hepatic, or endocrine diseases, can alter cardiac marker levels, resulting in falsely elevated or reduced values, such as kidney failure, which can affect BNP levels in dogs and cats (Mendes et al., 2019) and heart failure, in which the evaluation of plasma levels of ANP and its molecular precursors has proven fundamental for diagnosis in small animals (Freire et al., 2024).

In this context, the present review aims to address cardiac markers by analyzing cardiovascular physiology, with a particular focus on atrial natriuretic peptide (ANP). It explores ANP's functions in canine and feline organisms, its non-physiological behavior, and its applications in veterinary medicine.

METHODOLOGY

This study was conducted through a bibliographic review, with emphasis on literature available on the internet relevant to ANP. A total of 78 academic articles were examined using databases such as Scopus, Web of Science, Google Scholar, SciELO, PubMed, and journals provided by CAPES. The inclusion criteria for articles in the review were the presence of specific keywords, the origin of the research sources, and the analysis of the titles and summaries of the articles. On the other hand, the exclusion criteria were the irrelevance of the content to the topic of the study, the type of publication, and the date of publication. The strategies for finding appropriate articles included the identification of keywords related to ANP (Biomarker, Canine, Feline, Heart physiology), applying publication date and type filters, analyzing titles and abstracts, and cross-referencing. The research was carried out systematically and comprehensively to ensure the consideration of all the relevant literature.

BIOMARKER OF MYOCARDIAL FUNCTION: NATRIURETIC PEPTIDE

Natriuretic peptides have been studied for several decades to understand their role in various physiologically important processes (Rao et al., 2021). Initially, they were recognized for regulating salt excretion and blood pressure volume (Maack, 2006). Atrial Natriuretic Peptide is a peptide consisting of 28 amino acids with a cysteine-cysteine disulfide bridge (Volpe, 2014). Primarily found in the cardiac atria and stored in secretory granules, ANP is a significant marker of ventricular hypertrophy and congestive heart failure (Maack, 2006). This peptide, the most important among circulating natriuretic peptides, plays a crucial role in the regulation of renal function and plasma volume under normal conditions (Maack, 2006; Richards, 2007). The secretion of ANP is directly stimulated by atrial stretch or pressure, as occurs during volume expansion and hypertension (Richards, 2007). In the vasculature, ANP counteracts vasoconstriction, and in systemic capillaries, it increases permeability, facilitating fluid transfer from the intravascular compartment to the interstitial space, a phenomenon known as the "third spacing effect" (Sisson, 2004). Additionally, ANP inhibits the renin-angiotensin-aldosterone system, neutralizes sympathetic effects, and interferes with the synthesis and effects of other hormones or paracrine/autocrine substances that regulate blood pressure and volume, such as endothelin and vasopressin (Gonsalez et al., 2018). This combined action of ANP aims to maintain blood pressure and blood volume within normal physiological ranges, contributing to cardiovascular homeostasis (Gonzalez et al., 2018).

Atrial natriuretic peptide and its N-terminal pro-ANP cleavage product (Figure 1) were the first natriuretic peptides to be studied (Srisawasdi et al., 2010). ANP is one of the primary natriuretic hormones produced and secreted by the cardiac muscle in response to stress or stretching of cardiomyocytes caused by volume overload, hypoxia, and myocardial hypertrophy (Oyama, 2015; Ruaux et al., 2015; Alkhawan et al., 2016; Pelander et al., 2017). It is worth noting that all natriuretic peptides (NPs) are synthesized as pre-pro-hormones (Samad et al., 2023) with long peptide sequences called proANP and proBNP, and stored in granules attached to the membranes of atrial and ventricular tissues, respectively (Del Ry et al., 2014; Cahill et al., 2015; Harris et al., 2017). The physiological effects of the active fractions of natriuretic peptides stimulate, through the ANP receptor, diuresis and natriuresis, increasing the glomerular filtration rate and inhibiting the tubular transport of sodium through the renal collecting duct. These receptors are present in the lungs, heart, kidneys, adrenal glands, blood vessels, and the central nervous system (Cahill et al., 2015; Hezzel et al., 2015; Harris et al., 2017). Various factors can affect ANP concentrations in dogs and cats. Among these, the age of the animal is an important factor, as changes in cardiac function with aging can lead to an increase in ANP levels. Additionally, the breed of the animal can influence plasma ANP levels. Furthermore, concomitant diseases, such as cardiac lesions and renal insufficiency, can also affect ANP levels (Cruz et al., 2017). There are several testing techniques for the measurement of ANP, including immunoassays such as the enzyme-linked immunosorbent assay

(ELISA) and the radioimmunoassay (RIA). ELISA is frequently used for its high sensitivity and specificity, while RIA, although also highly sensitive, involves the use of radioisotopes (Hezzell et al., 2015).
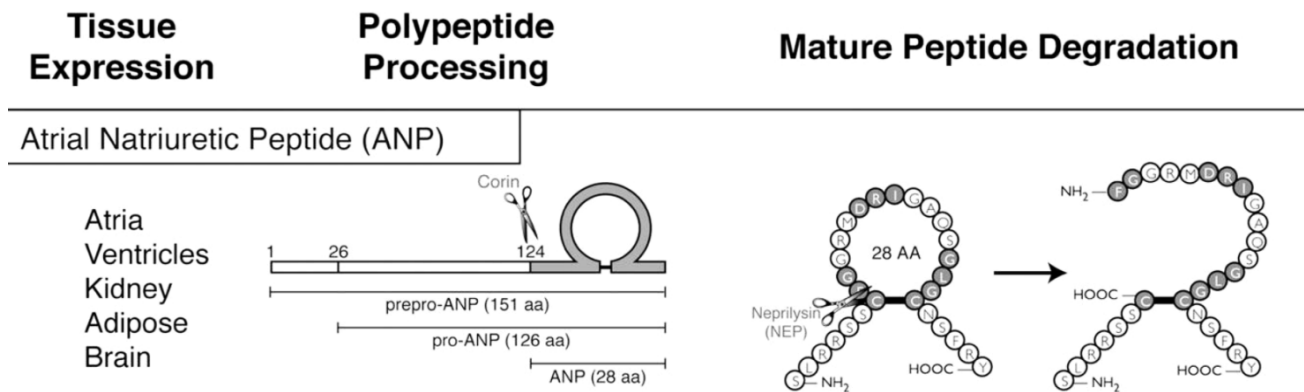

Figure 1. Atrial natriuretic peptide cleavage. (Source: Potter et al., 2009).

Figure 1 illustrates the structure of the pre-prohormone for ANP on the left. The final amino acid sequence and the structure of the mature peptide, along with the main degradation product, are shown on the right, with the cleavage site indicated by scissors. Initially, the ANP gene, located on chromosome 1 in humans, produces a 151-amino acid hormone known as pre-pro-ANP. Then, 25 amino acids are removed from the signal sequence, converting the chain into pro-ANP, which is transported to the Golgi complex. Before secretion, pro-ANP is cleaved again, possibly by membrane proteins, resulting in a functional chain of ANP with 28 amino acids (Potter et al., 2009).

Pro-atrial natriuretic peptide (proANP) is primarily produced by atrial myocytes and, to a lesser extent, by ventricular myocytes (Potter et al., 2009). When the myocardium is subjected to stress or stretch, (such as in response to volume overload, the production of proANP increases, especially in ventricular myocytes (Mahendram et al., 2022). Atrial wall distension or pressure stimulates the release of ANP, which acts as a protective mechanism of the body against cardiovascular volume overload and helps regulate the renal function (Del Ry et al., 2014; Kanno et al., 2016). ANP is valuable for assessing cardiac function, particularly in volume overload situations (Rao et al., 2021). However, its sensitivity and specificity can be influenced by factors such as age, sex, heart rhythm, and renal function. Concurrent diseases like heart failure, renal disease, or hypertension can also affect ANP levels (Kanno et al., 2016; Mahendran et al., 2022). Monitoring variations in ANP levels over time and comparing them to species-specific reference ranges can aid in evaluating cardiovascular health and making therapeutic decisions in dogs and cats (Kanno et al., 2016). Cardiac troponins (TnI and TnT) are highly sensitive and specific for myocardial infarction although their levels can increase in various conditions such as heart failure, pulmonary embolism, septicemia, and renal failure (Mahendran et al., 2022). Brain natriuretic peptide (BNP) is another biomarker, particularly sensitive and specific for heart failure. Additionally, it is useful in distinguishing between cardiac and pulmonary dyspnea (Barbosa, 2022). Each of these three biomarkers has its distinctive advantages in clinical practice: Whereas BNP assesses volume overload, cardiac troponins detect myocardial muscle damage, and BNP evaluates heart failure and distinguishes dyspnea. Clearly, the choice of a biomarker depends on the specific clinical conditions of the patient (Hori et al., 2020).

ANTAGONISM OF ATRIAL NATRIURETIC PEPTIDE HORMONE TO THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

ANP plays a crucial role in regulating blood pressure, exerting an antagonistic relationship with the renin-angiotensin-aldosterone system (RAAS) (Araújo and Ramos, 2022). The RAAS comprises interrelated elements including renin, an enzymatically active hormone, angiotensin peptides with various activities, aldosterone, and a mineralocorticoid (Martyniak and Tomasik, 2022). ANP, circulating through the system, increases natriuresis and diuresis, acting specifically on renal tubules (Araújo and Ramos, 2022). Currently, this hormone is recognized as a potent suppressor of the RAAS (Maack, 2006). Juxtaglomerular cells are responsible for renin production, a key component of the RAAS, which functions to promote salt reabsorption and elevate blood pressure (Rao et al., 2021). Maack (2006) underscores the role of ANP as a physiological equilibrium to salt-retention mechanisms that developed as mammals made the transition from aquatic to terrestrial habitats. ANP secretion adds endocrine characteristics to the heart, obtained by cardiomyocytes, especially in response to atrial volume distension, resulting in atrial cavity expansion and subsequent release of ANP into the systemic circulation (Araújo et al., 2021). Furthermore, it has been observed that ANP presents

relevant antagonism to the RAAS, which can attenuate the physiological mechanism triggered by the release of renin in the kidneys. This release triggers a series of reactions to control blood pressure (Atlas et al., 1986). Additionally, ANP acts as a hypotensive agent, counteracting the effects of angiotensin II and aldosterone, which lead to the increase in systemic blood pressure (Atlas et al., 1986; Atlas and Maack, 1992; Maack, 1996). The stimulating role of angiotensin II in aldosterone release by the adrenal glands is notable, as it increases sodium and water reabsorption, thereby elevating blood pressure and restoring homeostasis (de Oliveira et al., 2019). In molecular terms, ANP inhibits the activity of juxtaglomerular cells in the kidneys responsible for producing renin, an enzyme that catalyzes the conversion of angiotensinogen to angiotensin I (Schettini et al., 2022). Thus, by inhibiting renin release, ANP reduces the production of angiotensin I, which is further converted into angiotensin II by the angiotensin-converting enzyme (ACE), stimulating aldosterone release (Simões et al., 2006). Moereover, aldosterone promotes sodium and water reabsorption in the kidneys and increases blood volume and blood pressure (Wagner, 2014). ANP inhibits aldosterone release and reduces sodium and water reabsorption, leading to decreased blood volume and blood pressure (Freire et al., 2024). These molecular mechanisms enable ANP to regulate blood pressure and fluid balance in the body, counteracting the effects of the RAAS (Bekele, 2023). From a pharmacological standpoint, the use of mineralocorticoid receptor antagonists (MRAs) is a pharmacological intervention that modulates the activity of the RAAS in managing cardiac diseases in animals (Spencer et al., 2020). Spironolactone is the only MRA licensed for veterinary use which is utilized in the treatment of congestive heart failure caused by valvular regurgitation in dogs. Additionally, the combination of spironolactone with benazepril is a therapeutic option for this condition.

CARDIORENAL SYNDROME AND ITS RELATIONSHIP WITH ATRIAL NATRIURETIC PEPTIDE

The cardiorenal syndrome (CRS) in humans is described as 'conditions involving the heart and kidneys where dysfunction, whether acute or chronic, in one of these organs can cause corresponding acute or chronic dysfunction in the other' (Gavazza et al., 2020). This interaction between the two systems involves various mechanisms related to volume regulation and dysfunction (Pouchelon et al., 2015; Athwani et al., 2017; Smyth et al., 2017). Martinelli et al. (2016) highlighted that there are currently no specific biomarkers for cardiorenal syndrome. Assessment of renal function or damage is always performed for the renal part, while atrial natriuretic peptide and troponin I are used for the cardiac component (Martinelli et al., 2016).

ARTERIAL HYPERTENSION

Systemic arterial hypertension (SAH) is a pathological condition of significant relevance in the clinical management of dogs and cats, given that this condition is defined by the continuous increase in systolic or diastolic blood pressure, which can result in harmful effects, primarily affecting the kidneys, heart, eyes, and the central nervous system (Pellegrino et al., 2010). According to Ware (2006), conditions associated with SAH may include renal diseases, cardiac diseases, hyperadrenocorticism, and hyperthyroidism. Blood pressure (BP) is determined by cardiac output and peripheral vascular resistance; therefore, an increase in cardiac output, peripheral vascular resistance, or both will bring about elevated levels of BP (Athavale and Lewis, 2009).

Blood pressure is controlled by nervous, endocrine, cardiovascular, and renal mechanisms. Thus, conditions that impact these mechanisms can lead to changes in blood pressure, such as hypotension and hypertension (Nogueira and Poggiani, 2013). Hall (2011) and Nogueira and Poggiani (2013) described the function of ANP as inhibiting sodium reabsorption, promoting glomerular hyperfiltration, and halting renin release, acting on renal arterioles, venules, and tubular epithelium. Natriuretic peptides, particularly ANP and BNP, have emerged as effective biomarkers for left ventricular dysfunction and are increasingly utilized as biomarkers in pulmonary arterial hypertension (PAH) and right ventricular (RV) dysfunction (Nogueira and Poggiani, 2013). Notably, ANP and BNP are upregulated in response to hypoxia and exert cardioprotective effects (McMahon and Bryan, 2017). In recent years, the recognition of the importance of systemic hypertension in dogs and cats has led to fundamental changes in understanding the pathophysiology and management of various diseases, including chronic kidney disease and arterial hypertension (Brown et al., 2022).

In humans, pulmonary hypertension has been associated with increased levels of cardiac troponin and ANP (Rolph & Cavanaugh, 2022). While studies have evaluated cardiac biomarkers in dogs with pulmonary hypertension, reports on cats with this condition are, thus far, limited (da Silva et al., 2012; Rolph and Cavanaugh, 2022). Although cardiac biomarkers have been rigorously assessed for their use in heart pathologies, many are influenced by various respiratory or systemic diseases (Smith et al., 2015). Several cardiac biomarkers show elevated levels in cases of pulmonary

hypertension (PH). However, distinguishing between congestive heart failure (CHF), PH, or a combination of both is challenging when relying solely on biomarkers (Smith et al., 2015).

CHRONIC KIDNEY DISEASE

Chronic Kidney Disease (CKD) is a metabolic disease characterized by progressive and irreversible loss of renal function due to a decrease in the number of functional nephrons (Tavares, 2021). According to De Nicola et al. (1997), high concentrations of ANP are observed in patients with CKD, a condition characterized by irreversible kidney lesions that progress over months to years. Although more common in elderly dogs, CKD can occur at any age (McGrotty, 2008; Polzin, 2011; Bartges, 2012). As nephrons are lost, there is a decrease in the glomerular filtration rate (GFR), resulting in azotemia due to increased concentration of nitrogenous compounds in the blood. Additionally, substances that are typically reabsorbed by the renal tubules, such as proteins, may be excreted, leading to proteinuria. Therefore, ANP is recognized as a biomarker of renal injury (Polzin, 2011; Bartges, 2012).

Cruz et al. (2017) reported elevated levels of natriuretic peptides in hypertensive cats with CKD, indicating that the release of ANP by cardiomyocytes may increase in response to arterial hypertension, myocardial hypoxia, and ischemia. CKD is a frequently diagnosed condition in dogs and cats. Studies suggest that its prevalence ranges from 0.5% to 7% in dogs and from 1.6% to 20% in cats (Lund et al., 1999; Polzin, 2011). These statistics highlight CKD as one of the most common pathologies in feline species (Polzin, 2011). The disease, which can arise from various causes, is characterized by progressive and irreversible loss of renal function, leading to a range of health complications in affected animals (Lund et al., 1999; Polzin, 2011). Although there is no breed or age predilection (Polzin, 2011), it is known that morbidity and mortality are more prevalent in older dogs and cats (Polzin, 2011).

In CKD, there is often an observed increase in plasma levels of natriuretic peptides (Suda et al., 1988). Although CKD is commonly associated with changes in cardiac hemodynamics, the mechanisms underlying the rise in plasma concentration of natriuretic peptides in patients with renal dysfunction remain undetermined (Tsutamoto et al., 2006). According to Polzin (2011) and Courand and Lantelme (2014), several studies have established that CKD is a leading cause of death in dogs.

CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) occurs when the heart is no longer able to supply the necessary amount of blood to the body (Queiroz et al., 2022). Changes in cardiac muscle or valves result in a chronic decrease in cardiac output and activation of compensatory mechanisms, such as the renin-angiotensin system (RAS) and the sympathetic nervous system (Knight, 1992). These mechanisms induce tachycardia, peripheral vasoconstriction, and retention of sodium and water, leading to an increase in blood pressure and cardiac output, which optimizes tissue perfusion (Awan and Mason, 1996; Camacho, 1996). However, the prolonged activation of these compensatory mechanisms leads to the evolution of the clinical signs observed in CHF, including congestion, ascites, pleural effusion, pulmonary and limb edema, as well as symptoms such as fatigue, exercise intolerance, dyspnea, tachycardia, gallop rhythm, murmurs, and arrhythmias (Calvert, 1991; Camacho, 1996; De Morais, 2000).

ANP is an important biomarker for the diagnosis and monitoring of CHF in dogs and other mammals. It is secreted by cardiac cells in response to stress and volume overload, leading to an increase in plasma concentration in dogs with CHF (Hori et al., 2012). Measurement of ANP levels can be valuable in diagnosing CHF in dogs, especially when clinical signs are nonspecific or when there is uncertainty about the presence of the disease (Hori et al., 2012; Oyama, 2015; Lima and Ferreira, 2017). Kanno et al.'s (2016) study involving 16 healthy dogs and 51 untreated dogs, with some having right-sided heart failure (RHF), demonstrated that plasma levels of ANP in dogs with RHF were significantly higher than those in both the healthy control group and those without RHF.

The connection between ANP and CHF in cats has been the subject of a study by Mendes et al. (2019), which aimed to understand the role of ANP in cardiac conditions in cats. In cases of CHF in cats, there may be an increase in ANP levels, which acts as a compensatory mechanism to regulate fluid balance and blood pressure. Research suggests that plasma ANP levels may vary in cats with cardiac conditions, including congestive heart failure (CHF), where ANP levels fluctuate depending on the severity of heart failure and the stage of the disease (François et al., 2002). However, Khaki et al. (2022) report that ANP is not an effective parameter for diagnosing the subclinical stages of myxomatous mitral valve disease (MMVD). They suggest that serum BNP levels are more accurate across all stages of DMVM.

CONCLUSION

The use of biomarkers has become increasingly common in veterinary medicine, as they not only provide an efficient means of monitoring animal health and identifying diseases in their early stages but are also particularly useful for the diagnosis and monitoring of cardiac, renal, and metabolic diseases. The serum concentration of ANP is useful for diagnosing cardiovascular diseases in dogs and cats. Its crucial function in regulating blood volume and blood pressure makes it a valuable indicator of the animal's cardiovascular health. In the case of chronic kidney disease, it is believed that ANP may play a role in regulating renal function. It is of paramount importance for veterinary medicine to conduct further studies on ANP, given that ANP establishes itself as an indispensable tool for the care and treatment of cardiovascular diseases in dogs and cats. However, there is still much to be discovered about the role of ANP in different animal health conditions and diseases. Thus, additional research in this area can contribute to improving diagnoses and treatments in veterinary medicine.

DECLARATIONS

Authors' contributions

Formal analysis and investigation were carried out by all authors, and the original draft of the manuscript was collectively prepared by them. Additionally, all authors participated in the review and editing process. All authors checked and approved the final version of the manuscript for publication in the present journal.

Funding

No funding was received for conducting this study.

Availability of data and materials

All data generated during the research are relevant and included in this published article.

Competing interests

The authors did not indicate any conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) have been checked by all the authors.

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