Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Research in Veterinary Science 152 (2022) 564–568

Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

Elevated angiotensin-converting enzyme 2 (ACE2) expression in cats with hypertrophic cardiomyopathy

Fabian Z.X. Lean [a,*], Simon L. Priestnall [b], Ana Gómez Vitores [a], Alejandro Suárez-Bonnet [b], Sharon M. Brookes [c], Alejandro Núñez [a]

[a] Department of Pathology and Animal Sciences, Animal and Plant Health Agency (APHA), Addlestone, Surrey, UK
[b] Department of Pathobiology and Population Sciences, The Royal Veterinary College, North Mymms, UK
[c] Department of Virology, APHA, Addlestone, Surrey, UK

ARTICLE INFO

Keywords:
SARS-CoV-2
Feline hypertrophic cardiomyopathy
Angiotensin-converting enzyme 2
Immunohistochemistry
ACE2
Hypertrophic cardiomyopathy
RAAS
Cat

ABSTRACT

Angiotensin-converting enzyme 2 (ACE2) is an enzyme within the renin-angiotensin-aldosterone system that plays a role in regulating blood pressure. However, it is also a cellular receptor for infection with SARS coronaviruses. Although most cats develop subclinical or mild disease following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) acquired from human patients, a previous study has suggested hypertrophic cardiomyopathy (HCM) is a potential risk factor for the development of severe disease in the cat. Herein we investigate the ACE2 protein expression in the lung, heart, and kidney from a small subset of cats with (n = 10) and without HCM (n = 10) by immunohistochemistry. The abundance and intensity of ACE2 expression is slightly elevated in alveoli (p = 0.09; 0.07, respectively) and bronchioles (p = 0.095; 0.37, respectively). However, statistically elevated abundance and intensity of ACE-2 expression was only evident in the heart of cats with HCM ($p = 0.032$; $p = 0.011$, respectively). Further investigation did not demonstrate a statistical correlation between the ACE2 expression in the heart in relation to the heart weight to body weight ratio, and the ventricular wall ratio. Current findings suggest an overexpression of ACE2 in HCM cases but follow up study is warranted to understand the pathophysiological process.

1. Introduction

The causative agent for Coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a sustained pandemic since the end of 2019. Throughout the period, numerous spill over events from humans to cats have been documented (Adler et al., 2022; Barroso-Arévalo et al., 2022; Barrs et al., 2020; Jairak et al., 2021; Schulz et al., 2021; van der Leij et al., 2021) and in some rare circumstances from other infected animals to cats or among cats (van Aart et al., 2021). Most of these cases do not present clinical signs or only display with mild upper respiratory clinical signs (Barroso-Arévalo et al., 2022; Hosie et al., 2021; Klaus et al., 2021). Generally, the susceptibility of cats to SARS-CoV-2 infection is thought to be related to the expression of cognate viral receptor ACE2 in the upper respiratory tract (Färber et al., 2022; Gerhards et al., 2021; Krüger et al., 2021; Lean et al., 2021). Similar observations have also been made from *in vivo* modelling of SARS-CoV-2 infection in cats (Bosco-Lauth et al., 2020; Gaudreault et al., 2020).

Feline hypertrophic cardiomyopathy (HCM), a disease condition commonly reported in cats and characterised by increased thickness of the left ventricular wall and/or interventricular septum, has been reported as a comorbidity in some cats found to have SARS-CoV-2 infection (Carpenter et al., 2021; Carvallo et al., 2021; Segales et al., 2020). In several cases, respiratory distress has been reported and was attributed to congestive heart failure from underlying HCM and not related to SARS-CoV-2 infection (Barrs et al., 2020; Carpenter et al., 2021; Rotstein et al., 2022; Segales et al., 2020). However, there is one case which has demonstrated viral infection *in situ* and association with viral-induced pneumonia and myocardial degeneration (Carvallo et al., 2021). Current *in vivo* studies have only utilised young and healthy cats (Bosco-Lauth et al., 2020; Gaudreault et al., 2020). Therefore, the role of underlying cardiac comorbidity contributing to severe COVID outcome in cats is not well understood.

Apart from the respiratory tract, ACE2 is also expressed in the heart and kidney of mammalian species (Hikmet et al., 2020; Lean et al., 2021) and plays a endocrinological function within the renin-

* Corresponding author.
E-mail address: flean22@rvc.ac.uk (F.Z.X. Lean).

https://doi.org/10.1016/j.rvsc.2022.09.024
Received 10 June 2022; Received in revised form 12 September 2022; Accepted 22 September 2022
Available online 27 September 2022

angiotensin-aldosterone system (RAAS) (Bekassy et al., 2021). In humans, underlying cardiovascular disease is associated with poor disease outcome during COVID-19, with evidence suggesting a relationship with an elevated ACE2 expression in the heart (Matsushita et al., 2020; Vukusic et al., 2022). Currently, there is a lack of knowledge regarding the expression of ACE2 in the lung, heart, and kidney in clinically healthy or HCM cats. Here we present the first association between HCM and ACE2 expression in the lung and heart, in the absence of SARS-CoV-2 infection.

2. Materials and methods

2.1. Case materials

Formalin-fixed and paraffin-embedded (FFPE) feline tissues were selected from the pathology archive of the Department of Pathobiology & Population Sciences of the Royal Veterinary College. Hypertrophic cardiomyopathy cases were defined as cats with cardiomegaly (total heart weight > 20 g and/or > 1% body weight) and with cardiac ventricular wall ratio (right ventricle: interventricular septum: left ventricle) of >1:3:3 at necropsy, and with compatible histopathological findings of myofiber disarray and/or degeneration and fibrous replacement. Cats with normal heart and absence of clinical cardiac issues were selected as non-HCM control animals.

2.2. Immunohistochemistry

ACE2 immunolabelling was performed as described previously (Lean et al., 2021). Briefly, this involved antigen retrieval of FFPE sections in pH 6 buffer, immunolabelling with rabbit polyclonal antibody against ACE2 (Abcam) and Envision flex (Dako) and visualisation with DAB chromogen.

Semiquantitative and qualitative assessment were performed by analysing 5 high-power fields at 200× magnification per tissue from each case by veterinary pathologists on a conventional light microscope. The level of protein expression was determined through the abundance and intensity of immunolabelling. The abundance of ACE2 immunolabelling was scored as 0 (no positive staining), 1 (>0 to <25% positive cells), 2 (≥25% to <50% positive cells), 3 (≥50% to <75% positive cells) and 4 (≥75% to 100% positive cells) through estimation of the number of positive cells. The immunolabelling intensity was recorded as 0 (negative), 1 (weak, faint brown), 2 (moderate, brown), 3 (strong, dark brown and saturated). Slides were blind reviewed by two veterinary pathologists, followed by case discussion to achieve consensus results including standardisation of relative intensity.

Bronchiole and alveoli were assessed separately, with the bronchiolar epithelium evaluated for bronchiole, whereas the alveoli included type 1 and 2 pneumocytes and septal vessels. Left and right cardiac ventricular walls were evaluated. In the kidney, the cortical renal

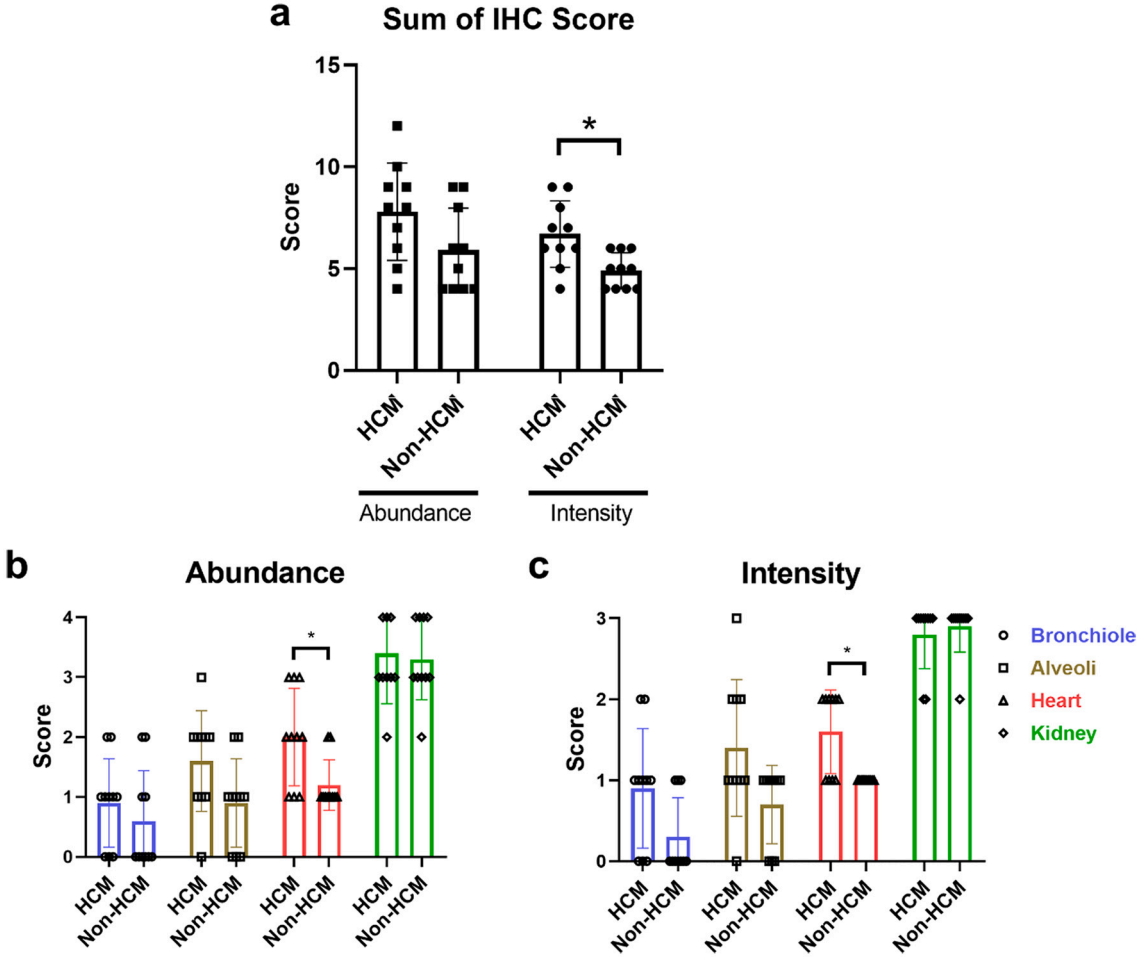

Fig. 1. ACE2 immunohistochemical analysis of the cat lung, heart, and kidneys from hypertrophic cardiomyopathy (HCM) and non-HCM cases. (a) Total score of abundance and intensity of ACE2 immunolabelling, expressed as sum of bronchiole, alveoli, heart, and kidney scores for each animal, were compared between the two groups. (b, c) Semi-quantitative and qualitative assessment were made for the abundance or intensity of ACE2, respectively. Score as follow: abundance - 0 (no positive staining), 1 (0 to <25% positive cells), 2 (≥25% to <50%), 3 (≥50% to <75%) and 4 (≥75% to 100%); intensity 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). Ten cases were reviewed for both HCM and non-HCM. Height of bars (a, b, c) represent the mean value and the error bars represent standard deviation. Mann-Whitney test. *$p < 0.05$.

tubules were assessed.

2.3. Statistical analysis

Data were analysed and graphs generated using GraphPad Prism 8. Two-tailed Mann-Whitney test was used for comparing distribution of populations and the Spearman test for assessing correlation between cardiac parameters.

3. Results

HCM histology cases were derived from cats aged between 2.8 and 13.8 years old, and between 1 month old to 16 years old of non-HCM cats. Generally, there was increased abundance ($p = 0.090$) and intensity ($p = 0.011$) of ACE2 immunolabelling in HCM cats compared to non-HCM cats when scores were assessed at the host level (defined as sum of scores of bronchiole, alveoli, heart and kidney) (Fig. 1a). All kidney samples showed similar levels of ACE2 in the renal tubular epithelium and did not differ between HCM and non-HCM cases. Heart tissue from both groups expressed ACE2. However, the abundance ($p = 0.032$) and intensity ($p = 0.011$) of ACE2 immunolabelling in the heart were statistically greater in the HCM than that from non-HCM cats (Fig. 1b and c). The immunolabelling morphology was suggestive of endothelium of the capillary and medium-sized arteriole (Fig. 2a and b) and occasionally within tunica media of arteriole. Cardiomyocyte labelling was however not detected in either group.

In the lung, ACE2 expression in healthy cats was limited to type I (Fig. 2c; 5 out 10 cats, 50%) and rarely in type II pneumocytes (1 out of 10 cats, 10%). In addition, there was infrequent immunolabelling of the bronchial submucosal glandular cells (5 out of 10 cats, 50%) and absent in bronchiolar epithelium. In contrast, the intensity ($p = 0.07$) and abundance ($p = 0.09$) of ACE2 immunolabelling was greater within the alveoli of the HCM group (Fig. 1b and c), commonly in type I pneumocytes (Fig. 2d; 10 out of 10 cats, 100%) and infrequently in type II pneumocytes (3 out of 10 cats, 30%) and in alveolar septa with morphology suggestive of capillaries (2 out of 10 cats, 20%). Immunolabelling in the bronchioles was limited to the mucosal epithelium and often weak ($p = 0.37$) and relatively infrequent ($p = 0.095$). Mild to moderate immunopositive labelling levels were also detected within the medium-sized arterioles of lung sections from HCM cats (9 out of 10 cats, 90%). This was, however, less frequent and with weaker immunolabelling in the non-HCM lung (7 out of 10 cats, 70%).

Further analysis of the ACE2 expression in conjunction with cardiac parameters showed weak correlation between heart to body weight ratio with ACE2 abundance ($rs = 0.15$, $p = 0.53$) or intensity ($rs = 0.25$, $p = 0.29$), and between ventricular wall ratio with ACE2 abundance (rs =

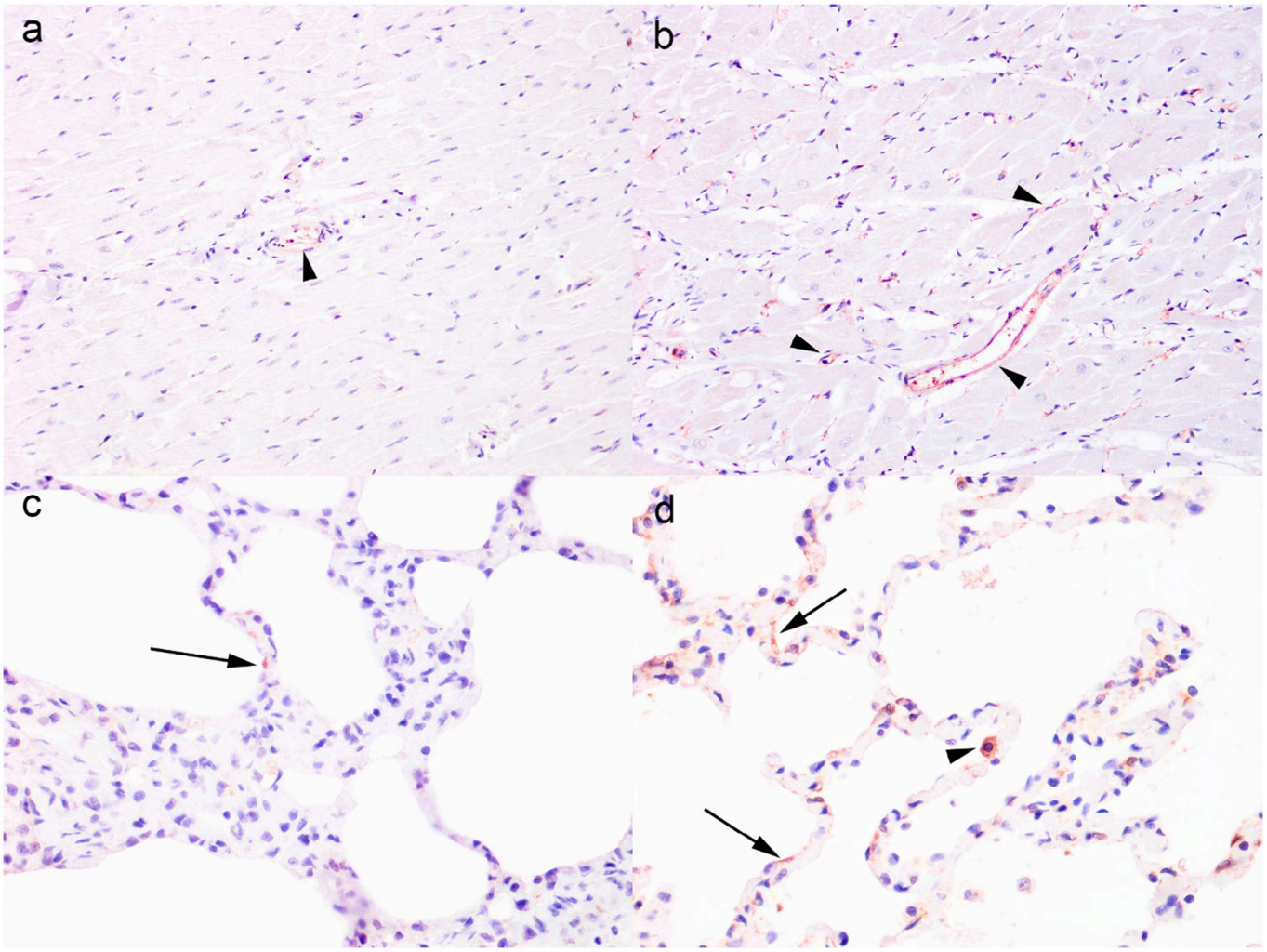

Fig. 2. Immunohistochemical labelling of ACE2 in the heart and lung of cats from non-HCM (a, c) and HCM (b, d) cases. Low levels of ACE2 immunolabelling in the heart and lung of non-HCM cats, limited to the vascular endothelium (arrow head) and type I pneumocytes (arrow), respectively (a, c). ACE2 immunolabelling was more abundant and intense in the vasculature (arrowhead) within the heart (b), and more abundant and intense in the alveoli typically in the type I pneumocytes (arrow) and occasionally in type II pneumocytes (arrowhead) of cats with HCM (d). Images taken with 200× objectives.

0.31, $p = 0.19$) or intensity (rs = 0.28, $p = 0.23$). However, the significance of these relationships was not conclusive ($p > 0.05$).

4. Discussion

Our study demonstrates an overexpression of ACE2 in cats with HCM compared to non-HCM cats, indicating a potential interplay of RAAS locally within the heart but also in the lung. HCM is common in domestic cats and incidence increases with age (Payne et al., 2015). HCM is often subclinical in cats but affected animals can develop congestive heart failure and arterial thromboembolism at compensatory/end stages, leading to morbidity and mortality (Luis Fuentes et al., 2020).

Among clinically healthy humans, there are low to undetectable levels of ACE2 by IHC in the heart (Bos et al., 2020; Nicin et al., 2020; Vukusic et al., 2022; Zhou et al., 2020), with commonly immunolabelled cells being the capillaries (Nicin et al., 2020; Zhou et al., 2020) and infrequently in cardiomyocytes (Hikmet et al., 2020). Human patients with obstructive HCM have overexpressed ACE2 gene and protein which is thought to be counteracting cardiac hypertrophy and fibrosis through negatively regulating RAAS (Bos et al., 2020). In a different study, proteomic screening of patients with heart failure revealed ACE2 as being one of the most abundant proteins and it was particularly expressed in cardiomyocytes and fibroblasts (Vukusic et al., 2022). Indeed, activation of RAAS has been documented for its role in contributing to heart failure (Patel et al., 2016) and ACE2 can provide cardiac protection through attenuation of angiotensin II (vasoconstrictor) (Zhong et al., 2010).

In feline HCM, the cardiac pathogenesis involves the remodelling of the ventricular wall through myofiber disarray, increased interstitial macrophages, replacement with fibrous tissue, but importantly a reduction in myocardial microvascular density and alteration of vascular structure (Kitz et al., 2019; Rodríguez et al., 2022). ACE2 helps to reduce blood pressure by hydrolysing angiotensin II (vasoconstrictor) to angiotensin (1–7) (vasodilator) (Bekassy et al., 2021). A recent clinical trial in cats with cardiomyopathy using a angiotensin II receptor blocker, telmisartan, demonstrated an increase in angiotensin peptides (1–7) (Huh et al., 2021). The increased ACE2 expression in the myocardial vessels in cats with HCM could potentially be a response to counteract increased vascular resistance.

Further, HCM in cats can lead to increased pulmonary venous and capillary pressure (or pulmonary hypertension) following impairment of left atrium emptying. As described previously, ACE2 expression in the lung is relatively low compared to the upper respiratory tract in healthy cats (Krüger et al., 2021; Lean et al., 2021). In this study, we observed increased ACE2 expression in pneumocytes and capillaries within the alveolar wall in cats with HCM. A human clinical trial conducted with administration of recombinant ACE2 into patients with pulmonary arterial hypertension showed reduced pulmonary vascular resistance (Hemnes et al., 2018). Similar to the heart, we propose that an increased in ACE2 expression in the lungs of cats with may be associated with HCM as a response to attenuate pulmonary vascular resistance.

Although most experimental SARS-CoV-2 studies in cats demonstrated subclinical to mild infection, these investigations only evaluated outcomes using clinically healthy and young cats (Bosco-Lauth et al., 2020; Gaudreault et al., 2020). The susceptibility of cats to this upper respiratory tract infection is related to abundance of ACE2 expression (Färber et al., 2022; Krüger et al., 2021; Lean et al., 2021). Underlying cardiac condition such as HCM (Carvallo et al., 2021) could potentially increase the susceptibility of the cat with respect to the development of clinical COVID-like disease. Although only HCM was investigated, endocrinological and renal diseases in cats can also contribute to secondary cardiac hypertrophy and consequently systemic hypertension, with potential implications on ACE2 expression. Cardiovascular conditions such as HCM which is highly prevalent and often subclinical in the cat could potentially serve as a unique comparative model for human disease to understand the influence of underlying cardiovascular disease over the outcome of COVID-19. Nevertheless, further investigation of ACE2 profiles in a wider cat population, as well as incorporation of other molecular techniques for protein (eg. western blot) and genomic (eg. quantitative polymerase chain reaction) detection on fresh tissues, will be needed to better understand the risk factor associated with ACE2-mediated viral infection.

Ethical statement

No ethical approval was required as tissue blocks were derived from histology archives of the Dept Pathobiology & Population Sciences of the Royal Veterinary College.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

Authors declare no conflict of interest.

Acknowledgements

This work was supported by the European Joint Programme One Health EJP COVRIN project funded under the European Union's Horizon 2020 Research and Innovation Programme https://onehealthejp.eu/jip-covrin/ [Grant Number 773830]. The authors would like to thank the pathology scientist at APHA for their laboratory work and support and Dr. Colin Birch from the Department of Epidemiological Sciences for biostatistical consultation.

References

Adler, J.M., Weber, C., Wernike, K., Michelitsch, A., Friedrich, K., Trimpert, J., Beer, M., Kohn, B., Osterrieder, K., Müller, E., 2022. Prevalence of anti-severe acute respiratory syndrome coronavirus 2 antibodies in cats in Germany and other European countries in the early phase of the coronavirus disease-19 pandemic. Zoonoses Public Health 69, 439–450.

Barroso-Arévalo, S., Sánchez-Morales, L., Pérez-Sancho, M., Domínguez, L., Sánchez-Vizcaíno, J.M., 2022. First detection of SARS-CoV-2 B.1.617.2 (Delta) variant of concern in a symptomatic cat in Spain. Front. Vet. Sci. 9, 841430.

Barrs, V.R., Peiris, M., Tam, K.W.S., Law, P.Y.T., Brackman, C.J., To, E.M.W., Yu, V.Y.T., Chu, D.K.W., Perera, R., Sit, T.H.C., 2020. SARS-CoV-2 in quarantined domestic cats from COVID-19 households or close contacts, Hong Kong, China. Emerg. Infect. Dis. 26, 3071–3074.

Bekassy, Z., Lopatko Fagerström, I., Bader, M., Karpman, D., 2021. Crosstalk between the renin-angiotensin, complement and kallikrein-kinin systems in inflammation. Nat. Rev. Immunol. 1–18.

Bos, J.M., Hebl, V.B., Oberg, A.L., Sun, Z., Herman, D.S., Teekakirikul, P., Seidman, J.G., Seidman, C.E., dos Remedios, C.G., Maleszewski, J.J., Schaff, H.V., Dearani, J.A., Noseworthy, P.A., Friedman, P.A., Ommen, S.R., Brozovich, F.V., Ackerman, M.J., 2020. Marked up-regulation of ACE2 in hearts of patients with obstructive hypertrophic cardiomyopathy: implications for SARS-CoV-2–mediated COVID-19. Mayo Clin. Proc. 95, 1354–1368.

Bosco-Lauth, A.M., Hartwig, A.E., Porter, S.M., Gordy, P.W., Nehring, M., Byas, A.D., VandeWoude, S., Ragan, I.K., Maison, R.M., Bowen, R.A., 2020. Experimental infection of domestic dogs and cats with SARS-CoV-2: pathogenesis, transmission, and response to reexposure in cats. P Natl. Acad. Sci. USA 117, 26382–26388.

Carpenter, A., Ghai, R.R., Gary, J., Ritter, J.M., Carvallo, F.R., Diel, D.G., Martins, M., Murphy, J., Schroeder, B., Brightbill, K., Tewari, D., Boger, L., Gabel, J., Cobb, R., Hennebelle, J., Stanton, J.B., McCullough, K., Mosley, Y.C., Naikare, H.K., Radcliffe, R., Parr, B., Balsamo, G., Robbins, B., Smith, D., Slavinski, S., Williams, C., Meckes, D., Jones, D., Frazier, T., Steury, K., Rooney, J., Torchetti, M., Wendling, N., Currie, D., Behravesh, C.B., Wallace, R.M., 2021. Determining the role of natural SARS-CoV-2 infection in the death of domestic pets: 10 cases (2020–2021). J. Am. Vet. Med. Assoc. 259, 1032–1039.

Carvallo, F.R., Martins, M., Joshi, L.R., Caserta, L.C., Mitchell, P.K., Cecere, T., Hancock, S., Goodrich, E.L., Murphy, J., Diel, D.G., 2021. Severe SARS-CoV-2 infection in a cat with hypertrophic cardiomyopathy. Viruses 13.

Färber, I., Krüger, J., Rocha, C., Armando, F., von Köckritz-Blickwede, M., Pöhlmann, S., Braun, A., Baumgärtner, W., Runft, S., Krüger, N., 2022. Investigations on SARS-CoV-2 susceptibility of domestic and wild animals using primary cell culture models derived from the upper and lower respiratory tract. Viruses 14, 828.

Gaudreault, N.N., Trujillo, J.D., Carossino, M., Meekins, D.A., Morozov, I., Madden, D. W., Indran, S.V., Bold, D., Balaraman, V., Kwon, T., Artiaga, B.L., Cool, K., García-

Sastre, A., Ma, W., Wilson, W.C., Henningson, J., Balasuriya, U.B.R., Richt, J.A., 2020. SARS-CoV-2 infection, disease and transmission in domestic cats. Emerg. Microb. Infect. 9, 2322–2332.
Gerhards, N.M., Cornelissen, J.B.W.J., van Keulen, L.J.M., Harders-Westerveen, J., Vloet, R., Smid, B., Vastenhouw, S., van Oort, S., Hakze-van der Honing, R.W., Gonzales, J.L., Stockhofe-Zurwieden, N., de Jong, R., van der Poel, W.H.M., Vreman, S., Kortekaas, J., Wichgers Schreur, P.J., Oreshkova, N., 2021. Predictive value of precision-cut lung slices for the susceptibility of three animal species for SARS-CoV-2 and validation in a refined Hamster model. Pathogens 10, 824.
Hemnes, A.R., Rathinasabapathy, A., Austin, E.A., Brittain, Evan L., Carrier, E.J., Chen, X., Fessel, J.P., Fike, Candice D., Fong, P., Fortune, N., Gerszten, R.E., Johnson, Jennifer A., Kaplowitz, M., Newman, J.H., Piana, R., Pugh, M.E., Rice, T. W., Robbins, I.M., Wheeler, L., Yu, C., Loyd, J.E., West, J., 2018. A potential therapeutic role for angiotensin-converting enzyme 2 in human pulmonary arterial hypertension. Eur. Respir. J. 51, 1702638.
Hikmet, F., Méar, L., Edvinsson, Å., Micke, P., Uhlén, M., Lindskog, C., 2020. The protein expression profile of ACE2 in human tissues. Mol. Syst. Biol. 16, e9610.
Hosie, M.J., Epifano, I., Herder, V., Orton, R.J., Stevenson, A., Johnson, N., MacDonald, E., Dunbar, D., McDonald, M., Howie, F., Tennant, B., Herrity, D., Da Silva Filipe, A., Streicker, D.G., Consortium, T.C.-G.U, Willett, B.J., Murcia, P.R., Jarrett, R.F., Robertson, D.L., Weir, W., 2021. Detection of SARS-CoV-2 in respiratory samples from cats in the UK associated with human-to-cat transmission. Vet. Rec. 188, e247.
Huh, T., Larouche-Lebel, É., Loughran, K.A., Oyama, M.A., 2021. Effect of angiotensin receptor blockers and angiotensin-converting enzyme 2 on plasma equilibrium angiotensin peptide concentrations in cats with heart disease. J. Vet. Intern. Med. 35, 33–42.
Jairak, W., Charoenkul, K., Chamsai, E., Udom, K., Chaiyawong, S., Bunpapong, N., Boonyapisitsopa, S., Tantilertcharoen, R., Techakriengkrai, N., Surachetpong, S., Tangwangvivat, R., Suwannakarn, K., Amonsin, A., 2021. First cases of SARS-CoV-2 infection in dogs and cats in Thailand. Transbound. Emerg. Dis. 69, e979–e991.
Kitz, S., Fonfara, S., Hahn, S., Hetzel, U., Kipar, A., 2019. Feline hypertrophic cardiomyopathy: the consequence of cardiomyocyte-initiated and macrophage-driven remodeling processes? Vet. Pathol. 56, 565–575.
Klaus, J., Meli, M.L., Willi, B., Nadeau, S., Beisel, C., Stadler, T., Eth Sars-Co, V.S.T., Egberink, H., Zhao, S., Lutz, H., Riond, B., Rösinger, N., Stalder, H., Renzullo, S., Hofmann-Lehmann, R., 2021. Detection and genome sequencing of SARS-CoV-2 in a domestic cat with respiratory signs in Switzerland. Viruses 13.
Krüger, N., Rocha, C., Runft, S., Krüger, J., Färber, I., Armando, F., Leitzen, E., Brogden, G., Gerold, G., Pöhlmann, S., Hoffmann, M., Baumgärtner, W., 2021. The upper respiratory tract of felids is highly susceptible to SARS-CoV-2 infection. Int. J. Mol. Sci. 22, 10636.
Lean, F.Z.X., Núñez, A., Spiro, S., Priestnall, S.L., Vreman, S., Bailey, D., James, J., Wrigglesworth, E., Suarez-Bonnet, A., Conceicao, C., Thakur, N., Byrne, A.M.P., Ackroyd, S., Delahay, R.J., van der Poel, W.H.M., Brown, I.H., Fooks, A.R., Brookes, S.M., 2021. Differential susceptibility of SARS-CoV-2 in animals: evidence of ACE2 host receptor distribution in companion animals, livestock and wildlife by immunohistochemical characterisation. Transbound. Emerg. Dis. 69, 2275–2286.
Luis Fuentes, V., Abbott, J., Chetboul, V., Côté, E., Fox, P.R., Häggström, J., Kittleson, M. D., Schober, K., Stern, J.A., 2020. ACVIM consensus statement guidelines for the classification, diagnosis, and management of cardiomyopathies in cats. J. Vet. Intern. Med. 34, 1062–1077.
Matsushita, K., Ding, N., Kou, M., Hu, X., Chen, M., Gao, Y., Honda, Y., Zhao, D., Dowdy, D., Mok, Y., Ishigami, J., Appel, L.J., 2020. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: a systematic review and meta-analysis. Glob. Heart 15, 64.
Nicin, L., Abplanalp, W.T., Mellentin, H., Kattih, B., Tombor, L., John, D., Schmitto, J.D., Heineke, J., Emrich, F., Arsalan, M., Holubec, T., Walther, T., Zeiher, A.M., Dimmeler, S., 2020. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. Eur. Heart J. 41, 1804–1806.
Patel, V.B., Zhong, J.-C., Grant, M.B., Oudit, G.Y., 2016. Role of the ACE2/angiotensin 1–7 axis of the renin–angiotensin system in heart failure. Circ. Res. 118, 1313–1326.
Payne, J.R., Brodbelt, D.C., Luis Fuentes, V., 2015. Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centres (the CatScan study). J. Vet. Cardiol. 17 (Suppl. 1), S244–S257.
Rodríguez, J.M.M., Fonfara, S., Hetzel, U., Kipar, A., 2022. Feline hypertrophic cardiomyopathy: reduced microvascular density and involvement of CD34+ interstitial cells. Vet. Pathol. 59, 269–283.
Rotstein, D.S., Peloquin, S., Proia, K., Hart, E., Lee, J., Vyhnal, K.K., Sasaki, E., Balamayooran, G., Asin, J., Southard, T., Rothfeldt, L., Venkat, H., Mundschenk, P., McDermott, D., Crossley, B., Ferro, P., Gomez, G., Henderson, E.H., Narayan, P., Paulsen, D.B., Rekant, S., Schroeder, M.E., Tell, R.M., Torchetti, M.K., Uzal, F.A., Carpenter, A., Ghai, R., 2022. Investigation of SARS-CoV-2 infection and associated lesions in exotic and companion animals. Vet. Pathol. 0, 03009858211067467.
Schulz, C., Martina, B., Mirolo, M., Müller, E., Klein, R., Volk, H., Egberink, H., Gonzalez-Hernandez, M., Kaiser, F., von Köckritz-Blickwede, M., Osterhaus, A., 2021. SARS-CoV-2-specific antibodies in domestic cats during first COVID-19 wave, Europe. Emerg. Infect. Dis. 27, 3115–3118.
Segales, J., Puig, M., Rodon, J., Avila-Nieto, C., Carrillo, J., Cantero, G., Terron, M.T., Cruz, S., Parera, M., Noguera-Julian, M., Izquierdo-Useros, N., Guallar, V., Vidal, E., Valencia, A., Blanco, I., Blanco, J., Clotet, B., Vergara-Alert, J., 2020. Detection of SARS-CoV-2 in a cat owned by a COVID-19-affected patient in Spain. P Natl. Acad. Sci. USA 117, 24790–24793.
van Aart, A.E., Velkers, F.C., Fischer, E.A.J., Broens, E.M., Egberink, H., Zhao, S., Engelsma, M., Hakze-van der Honing, R.W., Harders, F., de Rooij, M.M.T., Radstake, C., Meijer, P.A., Oude Munnink, B.B., de Rond, J., Sikkema, R.S., van der Spek, A.N., Spierenburg, M., Wolters, W.J., Molenaar, R.J., Koopmans, M.P.G., van der Poel, W.H.M., Stegeman, A., Smit, L.A.M., 2021. SARS-CoV-2 infection in cats and dogs in infected mink farms. Transbound. Emerg. Dis. 69, 3001–3007.
van der Leij, W.J.R., Broens, E.M., Hesselink, J.W., Schuurman, N., Vernooij, J.C.M., Egberink, H.F., 2021. Serological screening for antibodies against SARS-CoV-2 in Dutch shelter cats. Viruses 13.
Vukusic, K., Thorsell, A., Muslimovic, A., Jonsson, M., Dellgren, G., Lindahl, A., Sandstedt, J., Hammarsten, O., 2022. Overexpression of the SARS-CoV-2 receptor angiotensin converting enzyme 2 in cardiomyocytes of failing hearts. Sci. Rep. 12, 965.
Zhong, J., Basu, R., Guo, D., Chow, F.L., Byrns, S., Schuster, M., Loibner, H., Wang, X.H., Penninger, J.M., Kassiri, Z., Oudit, G.Y., 2010. Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. Circulation 122, 717–728 (718 p following 728).
Zhou, L., Niu, Z., Jiang, X., Zhang, Z., Zheng, Y., Wang, Z., Zhu, Y., Gao, L., Huang, H., Wang, X., Sun, Q., 2020. SARS-CoV-2 targets by the pscRNA profiling of ACE2, TMPRSS2 and furin proteases. iScience 23, 101744.