Turkish Journal of Computer and Mathematics Education *Vol.13 No.02 (2022), 717-724*

Research Article

Percolation associated to the Fokker-Planck equationto Modeling the ACE2 effect on the NCX exchanger: COVID-19 and the failing heart

N. Bessai[a], H. Riane[b,c], S.Bahlouli[b], F. Hamdache[b]

[a]Faculté de Physique, Université d'Oran des Sciences et de la Technologie-Mohammed Boudiaf- USTO-MB, Oran, Algeria
[b]Laboratoire de Physique des Plasmas, Matériaux Conducteurs et leurs Applications, Faculté de Physique, Université d'Oran des Sciences et de la Technologie-Mohammed Boudiaf- USTO-MB, Oran, Algeria
[c]Département de Physique, Faculté des Sciences Exactes, Université de Mascara, Algeria

Abstract : Current data on COVID-19 shows that hypertensive patients are the most vulnerable to this virus. These patients have low activation rates of the angiotensin-converting enzyme 2 (ACE2), and angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs) are commonly used in the treatment of hypertension. Unfortunately ACE2 is the ideal receptor of the COVID-19 and this paradoxworries doctors. Our role in this modeling consist on leading the researchers towards a new concept and treatment based on the relationship between the activity of the Na / Ca exchanger (NCX) of the cardiac cell and the activation rate of ACE2. The results obtained of the I_{NCX} exchange current, the calcium transient and the action potential AP are very promising and show the direct effect of ACE2 on the exchanger which influences the cardiac electrical activity.

Keywords: ACE2; NCX exchanger; COVID-19; Fokker-Planck equation, percolation

1. Introduction

Since its discovery in Whuan in China in December 2019, the whole world is suffering from the pandemic of Coronavirus disease 2019 (COVID-19), researches has doubled to find out the causes of the health problems of people affected. In many severe cases, the coronavirus infection caused interstitial pneumonia which may lead to severe acute respiratory syndrome (SARS) and even death (Huang, C.et al. 2020&Wang, D.et al.2020). Epidemiological data has shown that the most threatened persons are hypertensive (Huang, Z. et al.2020&Li, B.et al. 2020), which has led some to make the link between the renin angiotensin system blockers (RAS) and COVID-19(Kai, H. &Kai, M. 2020 &Sommerstein, R.&Gråni, C.2020 &Vaduganathan, M.et al.2020), since these inhibitors are all indicated in the management of high blood pressure, and some of which are indicated in heart failure, post-myocardial infarction, and proteinuric nephropathy of diabetes.

The work of Fang, L. et al. (2020)and several other authors(Rossi, G.P. et al. 2020 &Esler, M &Esleer, D. 2020 &Agata, J. et al. 2006 & Wang, X. et al.2016) have hypothesized that angiotensinconverting enzyme inhibitors (ACEs) and / or angiotensin II receptor antagonists (ARA2, or SARTANS) might increase the expression of angiotensin-converting enzyme 2 (ACE2) on the membrane surface.

The ACE2 is an ideal receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Hoffmann, M. et al. 2020), same as SARS-CoV (-1) (Kuba, k. et al. 2005). The work of Ferrario, CM. et al. (2005) on a rat model shows that lisinopril and losartan increase the expression of ACE2 mRNA in the heart, as well as the activity of the enzyme. We note that ACE2 was increased in failing human heart ventricles and in human idiopathic dilated cardiomyopathy and ischemic cardiomyopathy (Andrew, B.Goulter. et al.2004).

Our work is a contribution to link between the activity of the NCX exchanger, which plays a very important physiological role in the cardiac cells to regulate the intracellular calcium concentration $[Ca^{2+}]_i$, and the activity of ACE2. We use a simple electrical network model associated with the finite difference method and the percolation concept that already proved its efficiency on the pancreatic beta cells activity (Bahlouli, S. et al.2015).The ion transfer through the membrane proteins of a cardiac cell is modeled by a square network of conductances randomly distributed, representing the following channels: K-Ca, K_v, Na_v, Ca_v-L and NCX exchanger. Switches are put in series with the conductance to highlight the activation or inactivation of the channel. The ACE2 is modeled by a controlled and vectorizedswiches. For the NCX exchanger, the conductance is chosen according to the intracellular calcium concentration. Beside, the dielectric property of phospholipids may be represented by a capacity, placed in parallel to the network. In the vicinity of the percolation threshold(Hunt, A.G. 2004), the behavior of the exchanger current, the calcium transient and the action potential shows the effect of the increased activity of ACE2 on health.

2. Statistical model

ACE2 is localized exclusively in cardiac endothelial cells (Donoghue, M. et al.2000), in the endothelial and smooth muscle cells of myocardial vessels as well as in cardiac myocytes (Hamming, I.et al.2007 & Gallagher, P.et al.2008).

Electrical modeling has been used for a long time following the Hodgkin, A.L.& Huxley, A.F (1952) model, but not that of an enzymatic activity since it involves chemical reactions. In this work we were inspired by the article ofEisenberg,R.S. (1990)entitled "Channels as Enzymes: Oxymoron and Tautology" who concludes that a channel is a catalyst for diffusion through membranes and announces "channel is an enzyme". In this case, we can assume that an enzyme is a channel that catalyzes electrical activity.

Many study suggest that impaired ACE2 activity results in excessive amountsof angiotensin II AngII, allowing for unopposed activation of type 1 angiotensin 2 receptor AngIR and subsequentdevelopment of acute respiratory distress syndrome (ARDS)in which they explained the susceptibility of hypertensive patients to COVID-19 (Devaux, C. et al.2020 &Tignanelli, C.J. et al. 2020).

In the RAS (renin–angiotensin system), Ang I (angiotensin I) is cleaved by ACE (angiotensin-converting enzyme) to form AngII (angiotensin II), which has effects on blood pressure, fluid and electrolyte homoeostasis. Although Ang II is hydrolysed very efficiently by ACE2, with a highest catalytic efficiency of *k*cat/*K*m of 2.2×10^{6} $M^{-1}\cdot s^{-1}$

The distribution of ACE2 concentration follows the Fokker-plank (FPE) equation (El Wakil, S.A. et al.2001).After application of the chain rule, the corresponding FPE becomes (Hesama, S. et al. 2012):

$$\partial C/\partial t = -y\,\partial C/\partial x + (2\xi\omega y + x)\,\partial C/\partial y + 2\xi\omega C + D\,\partial^2 p/\partial y^2 \quad (1)$$

In terms of central finite differences, an explicit formulation is obtained for the concentration:

$$C^{m+1}_{i,j} = C^{m}_{i,j} + \Delta t[-y(C^{m}_{i+1,j} - C^{m}_{i-1,j})/2\Delta x + 2\xi\omega C^{m}_{i,j} + (2\xi\omega y)\,(C^{m}_{i,j+1} - C^{m}_{i,j-1})/2\Delta y + D(C^{m}_{i,j+1} - 2C^{m}_{i,j} + C^{m}_{i,j-1})/\Delta y^2] \quad (2)$$

The boundary conditions are given by $Ci,j = 0$ for $i, j = 1, N$. The discretization using central finite differences leads to an explicit scheme, which means that the values $C^{m+1}_{i,j}$ can be calculated directly from values $C^{m}_{i,j.}$

Near the percolation threshold, we impose the linear 2D oscillation of the chemical enzyme reaction(Goldbeter, A. 2013) and the parameters of the oscillator$\xi = 0.05$, $\omega = 1$ and $D = 0.1$ are chosen according to the imposed infinity condition of the concentration(Pichler, L.et al. 2011):

$$C(x,y\ ,\ t) \rightarrow 0\ as\ x,y \rightarrow \pm\infty \quad (3)$$

Owing to simplicity, we assume thatthe relaxation kinetics are first order (Milescu, L.S. et al.2005) and described by time homogeneous Markov process (Hugtenburg, R.P. & Yin, Z.A. 2001 &Venkataramanan, L. &Sigworth, F.J. 2002), where the channel jumps from the open state to the closed state.

The intracellular concentrations have values higher or equal to physiological values such as C_K(100 mmol/l), C_{Na}(10 mmol/l) and C_{Ca}(1 µmol/l). The extracellular concentrations will not be modified and correspond to the physiological values. The values of the different conductances correspond to those usually used in physiology: $\gamma_{K\text{-}Ca}$ = 200 pS/cm^2, γ_K= *300*pS/cm^2, γ_{Na} = 3 nS/cm^2 ,γ_{Ca} =15 pS/cm^2 and γ_{NCX} equals 0 or 44 nS/cm^2(Hill, B. 2001). The biological membrane capacity per unit of area C_m is equal to 1 µF/cm^2. The open or closed switches are randomly distributed on the circuit.

In our computation, we carried out 1500 iterations, in which we controlled the direction of the ion flows, the gradients of concentration and the variations of the membrane potential.

The details of the concentration and the ionic current of the NCX, Cav-L,K-Ca, K_v, are given in our previous work(**Bahlouli, S.et al.2008 &Bahlouli, S.et al.2015**). For the inward rectifier current $I_{Na}$of Na_v channels,we use(Hill, B. 2001):

$$I_{Na} = \gamma_{Na}\,.m^3\,.h\,.\,(V_m - E_{Na}) \quad (4)$$

Where$V_m$is the membrane potential, $E_{Na}$is the reversal potentials (mV), *m* is the probability of the activation gate and *h* is the probability of the inactivation gate

3. Results and discussions

3.1 Percolation threshold

In first, we determine the percolation threshold of our network. It described the depolarization threshold of the membrane at low ACE2 concentrations. Several parameters must be controlled to detect the threshold: the

concentrations, the conductances and the activation probabilities, and it become very difficult to monitor the depolarization. Electrically, the response of the circuit corresponds to a current flowing to either side of the cell and fractally, it corresponds to the generation of the backbone. For this, we use the Tarjan'sdepth-first-search algorithm (Tarjan, R.1972) which runs in time O(N) for a graph of N nodes, provided the number of edges meeting at each node is finite, and the effective-medium theory (Kirkpatrick,S.1973&Nakamura, M.1982)in order to reduce the matrix size from$[L^2 \times L^2]$ to $[L \times (L+1)]$.

We represent the percolation cluster for different concentration and probabilities of activated channel and we chose three morphology, below, near and far the percolation threshold.

- In figure. 1, finite clusters appear but there isn't response of the system because the total conductivity is null. This is for $P_{K\text{-}Ca}$ =0.16, P_K = 0.17, P_{Na} = 0.18, P_{Ca} =0.19, P_{ACE2} =0.10 andP_{NCX} = 0.20.

- For $P_{K\text{-}Ca}$ =0.18, P_K = 0.19, P_{Na} = 0.22, P_{Ca} =0.20, P_{ACE2} =0.05 andP_{NCX} = 0.16,the infinite cluster appears near the percolation threshold in Figure.2, with a backbone of total conductivity equal to 0.093 pS/cm^2.

- The infinite cluster in Figure. 3 is more pronounced and developed by the appearance of blobs and dangling parts. After the percolation threshold the total conductivity is higher and is equal to 1.302pS/cm^2 for$P_{K\text{-}Ca}$ =0.17, P_K = 0.20, P_{Na} = 0.23, P_{Ca} =0.15, P_{ACE2} =0.07 andP_{NCX} = 0.18.

The network near the percolation threshold corresponds to a non-conducting towards conducting transition consists of 18% K-Ca, 19% K_v, 22% Na_v, 20% Ca_v-L, 16% NCX channels and 5% ACE2.

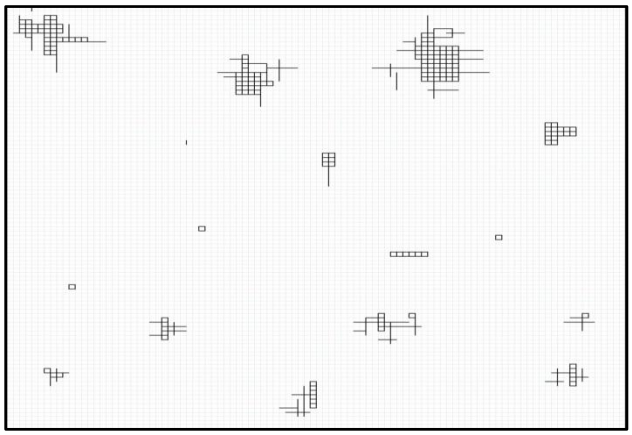

Figure.1. Finite clusters structure of activated Channelsbelow the percolation threshold: $P_{K\text{-}Ca}$ =0.16, P_K = 0.17, P_{Na} = 0.18, P_{Ca} =0.19, P_{ACE2} =0.10 andP_{NCX} = 0.20.

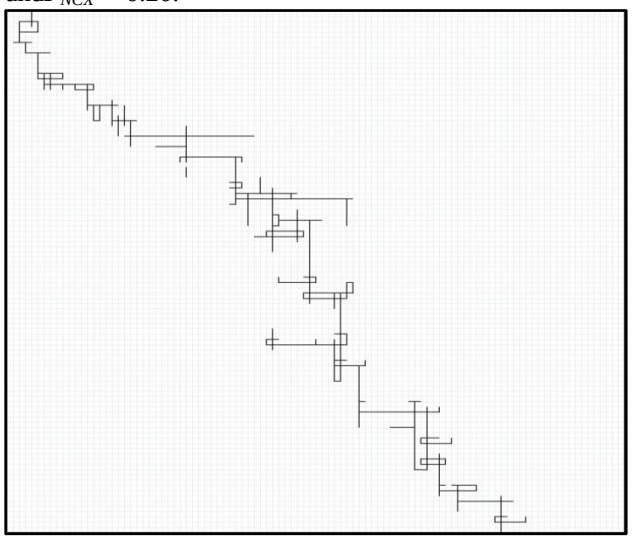

Figure.2. Infinite cluster structure of activated Channelsnear the percolation threshold. The backbone is formed for $P_{K\text{-}Ca}$ =0.18, P_K = 0.19, P_{Na} = 0.22, P_{Ca} =0.20, P_{ACE2} =0.05 andP_{NCX} = 0.16

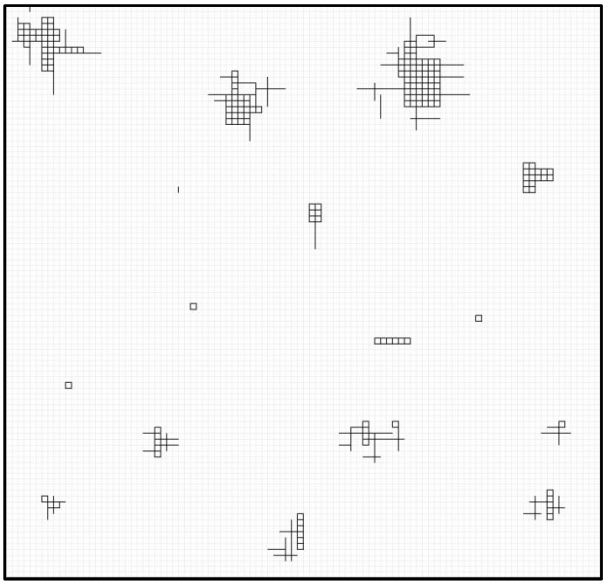

Figure.3. Infinite cluster structure of activated Channelsabove the percolation threshold: $P_{K\text{-}Ca}$ =0.17, P_K = 0.20, P_{Na} = 0.23, P_{Ca} =0.15, P_{ACE2} =0.07 andP_{NCX} = 0.18

3.2 Effect of ACE2 on the $[Ca^{2+}]_i$

To evaluate the link between the ACE2 and the NCX of a cardiac cellular electrical activity, we reduce the probability of the activated ACE2 near the percolation threshold. Fig.4showthe variation of the intracellular Ca^{2+} concentrations $[Ca^{2+}]_i$, as a function of the number of ACE2inhibited.

From Figure.4, it appears that from 5% inhibited ACE2, the intracellular $[Ca^{2+}]_i$ concentration does not reach its basal value during repolarization. The concentration increases more and more with the inhibition of the ACE2, until it reaches a stationary state when 15% of ACE2 are blocked. This behavior is identical to that presented in the study ofBeuckelmann, D.J et al.(1993)and Ozdemir,S. et al (2008), which reflects a marked reduction in the amplitude of the calcium transient and an increase in its total duration in the case of ventricular myocytes isolated from failed hearts of transplanted subjects, or following a block exchanger NCX by SEA-0400.

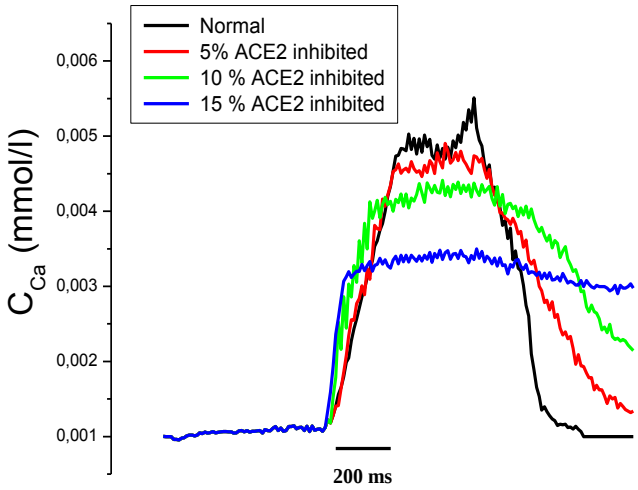

Figure.4. Oscillation of the intracellular calcium concentration $[Ca^{2+}]_i$ for different probability of ACE2 activity.

3.3 Effect of ACE2 on I_{NCX}

Figure. 5 show the I_{NCX} exchange current for a time scale of 200 ms as a function of the number of ACE2 inhibited. We notice from this figure that the inhibition of the ACE2 increases the duration and amplitude of the exchange current, probably resulting from the lengthening of the calcium transient. The exchanger under these conditions operates in inverse mode favoring the influx of Ca^{2+}. This figure is comparable to that ofWeber, R. et al. (2003)on the study of the I_{NCX} current of the ventricular cardiomyocyte. The Weber plots show for a non-failing heart a current entering during all the action potential except at the depolarization where an outgoing exchange current is reported, resulting from the increase of the intracellular concentration $[Ca^{2+}]i$. The notch of the incoming current is a consequence of repolarization. For a failing heart, the current is out for 400 ms, with an increase in the magnitude of the incoming current.

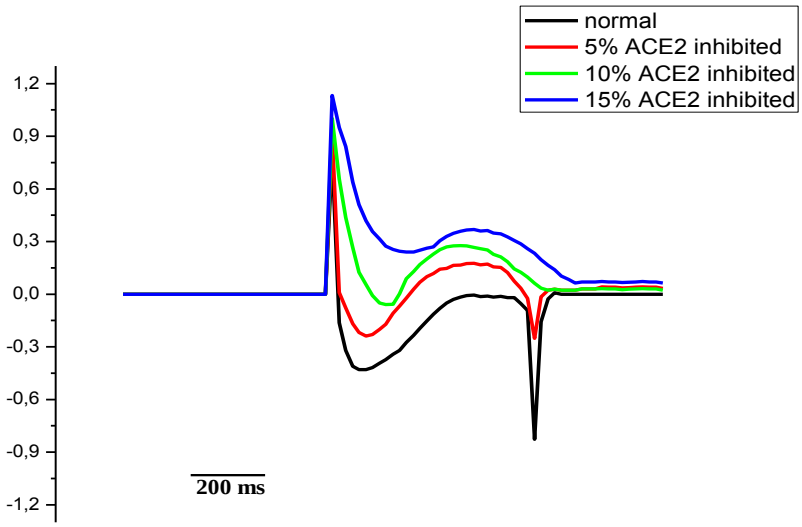

Figure.5. Variation of the current exchange I_{NCX} for a time scale of 200 ms as a function of the number of ACE2 inhibited.

3.4 Effect of ACE2 on the action potential AP

The most common anomaly in a cellular electrical activity of the cardiac hypertrophy is the prolongation of action potential, regardless of the species of mammal studied and whatever the origin of the hypertrophy (Egan, T.M. et al. 1989 &Fatkin, D. et al. 2014), this is what we observe in Figure. 6. A decrease in amplitude is announced when the ACE2 are inhibited, as a consequence of the increase in the I_{NCX} exchange current.

Note that experimentally, the extension of the action potential is associated with an increase in the amplitude of the plateau which can be very marked in species whose cardiac cell repolarization presents a biphasic course and a low terminal plateau (Bailly, P. et al. 1998).

Momtaz,A. et al. (1996) show the participation of the I_{NCX} exchange current in the development of the plateau, after inhibition of the outgoing transient potassium current by infusion of a Tyrode solution supplemented with 3 mM 4-aminopyridine.

The extension of the action potential is not limited to hypertrophy and is also manifested in the case of the human heart in terminal failure, whether it is hypertrophic cardiomyopathy or, more often, dilated cardiomyopathy.

Since ACE 2 is an ideal COVID-19 receptor, this will reduce its activity. Our results confirm that the decrease of the ACE2 is associated with enhanced cardiac hypertrophy and reduced pumping ability. It also shows a real connection between the activity expression of the ACE2 and the activity of the NCX exchanger.

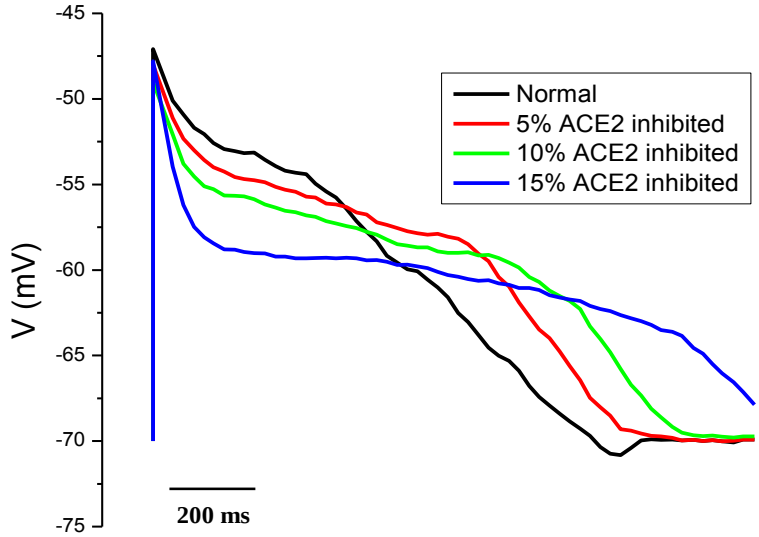

Figure.6. Variation of action potential AP for a time scale of 200 ms as a function of the number of ACE2 inhibited.

Conclusion

To our knowledge, there is not yet a pharmacological activator or inhibitor of ACE2 usable in humans. Some teams have proposed promoting the angiotensin / ACE2 / MasR pathway (Peiró, C. &Moncada, S. 2020), for example by administering soluble ACE2 as a treatment in patients infected with COVID-19 (Batlle, D. et al. 2020). The primary role of the study of the relationship between ACE2 and the NCX exchanger is to open an exploratory way for electrophysiologists and biochemists to find an efficient treatment and reduce the risk of mortality in patients suffering from high blood pressure and are tainted with COVID- 19.

We modeled for the first time the enzymatic activity by an electrical compound, switches, whose opening and closing according to the kinetics of ACE2 activity. The simple electric model of conductances and switches randomly distributed associated with complex mathematical concepts, percolation, the finite difference method and random walk, gave very interesting results identical to the experimental ones in the literature. It's important to emphasize that there is so much research to explore, and the deleterious role of ACE2 activation - potentially induced by SRA blockers - is only one hypothesis among others and should be studied.

Formatting of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Reference

Agata J, Ura N, Yoshida H, Shinshi Y, Sasaki H, Hyakkoku M, et al. Olmesartan (2006) is an angiotensin II receptor blocker with an inhibitory effect on angiotensin-converting enzyme. HypertensRes. ;29:865–74.

Andrew B Goulter, Martin J Goddard, Jennifer C Allen and Kenneth L Clark.(2004) ACE2 gene expression is up-regulated in the human failing heart ,*BMC Medicine* , 2:19

Bahlouli S, Makaddem A, Hamdache F, Riane H, Kameche M. (2015) Fractal behavior of the pancreatic β-cell near the percolation threshold: effect of the K_{ATP} channel on the electrical response. IEEE/ACM Trans ComputBiolBioinform 2015; 13:1;112-121. DOI:10.1109/TCBB.2415797

Bahlouli S, Hamdache F, Riane H. (2008)Modelisation of the contribution of the Na/Ca exchanger to cell membrane potential and intracellular ion concentrations. Gen PhysiolBiophys; 27:194–202

Batlle D, Wysocki J, Satchell K. (2020) Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? Clin Sci (Lond);134(5):543-5

Bailly P, Mouchoniere M, Benitah JP, Camilleri L, Vassort G, et al. (1998) Extracellular K+ dependence of inward rectification kinetics in human left ventricular cardiomyocytes. Circulation ;98:2753–2759

Beuckelmann D J, Nabauer M, Erdmann E. (1993) Alterations of K+ currents in isolated human ventricular myocytes from patients with terminal heart failure, Circ Res,;73, pp 379-385

Devaux C A, Rolain J-M, Raoult D. (2020) ACE2 receptor polymorphism: susceptibility to SARS-CoV-2, hypertension, multiorgan failure, and COVID-19 disease outcome. J MicrobiolImmunolInfec ; https://doi.org/10.1016/j.jmii.2020.04.015.

Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N et al. (2000) A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9. Circ Res; 87: E1–E9.

Egan T M, Cooper J D. **(**1989**)** Lung transplantation, CurrProblSurg;26;10, 681-751,https://doi.org/10.1016/0011-3840(89)90025-7

Eisenberg R S. (1990) Channels as Enzymes: "Oxymoron and Tautology". J Membr Biol;115 1-12.

El Wakil SA, Elhanbaly A, Zahran M A.(2001) Fractional (space-time) Fokker–Planck equation**..** Chaos solitons Fractals;12:6, 1035-1040

Esler M &Esler D. (2020) Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? Journal of Hypertension 2020, 38:000–000, DOI:10.1097/HJH.0000000000002450

Fang L, Karakiulakis G, Roth M. (2020) Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? The Lancet Respiratory Medicine.;8:30116. DOI: https://doi.org/10.1016/S2213-2600(20)30116-8, PMID: 32171062

Fatkin D, Seidman C E, Seidman J G. (2014) Genetics and Disease of Ventricular Muscle. Cold Spring HarbPerspect Med;4:a021063

Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. (2005) Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation ; 111:2605–2610.

Gallagher P E, Ferrario C M, Tallant E A. (2008) Regulation of ACE2 in cardiac myocytes and fibroblast. Am J Physiol Heart CircPhysiol*;* 295: H2373–H2379. doi:10.1152/ajpheart.00426.2008

Goldbeter A. (2013) Oscillatory enzyme reactions and Michaelis–Menten kinetics. FEBS Letters;587; 2778–2784, http://dx.doi.org/10.1016/j.febslet.2013.07.031

Hamming I, Cooper ME, Haagmans BL, Hooper NM, Osterhaus ADME et al.(2007)The emerging role of ACE2 in physiology and disease. J Pathol; 212: 1–11.

Hesama S, Nazemia A R, Haghbinb A. (2012) Analytical solution for the Fokker–Planck equation by differential transform method. Scientia Iranica B;19;4,1140–1145

Hille B. Ion Channels of Excitable Membranes.Sinauer Associates Inc. 3rd ed, US; 2001.

Hodgkin A L, Huxley A F. (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol (London);117:500-544.

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell.;181(2):271–80. https://doi.org/10.1016/j.cell.2020.02.052.

Huang C, Wang Y, Li X, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet ;395:497-506.

Huang Z, Cao J, Yao Y, Jin X, Luo Z, Xue Y et al. (2020)The effect of RAS blockers on the clinical characteristics of COVID-19 patients with hypertension, *Ann Transl Med* X;8(7):430http://dx.doi.org/10.21037/atm.2020.03.229

Hugtenburg RP, Yin Z.A (2001) Markov Chain Method for the Accurate Characterisation of a Therapeutic Linear Accelerator in Monte Carlo Based Dosimetry and Treatment Planning. APESM; 24: 225

Hunt A G. (2004) Percolative transport in fractal porous media. Chaos solitons Fractals;19 ;2, 309-325

Kai. H. &Kai. M. (2020) Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19, Hypertension Research https://doi.org/10.1038/s41440-020-0455-8

Kirkpatrick S. (1973) Percolation and Conduction. Rev Mod Phys;45:574-588.

Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B et al. (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nature Medicine; 11:875–879. DOI: https://doi.org/10.1038/nm1267, PMID: 16007097

Li B, Yang J, Zhao F, et al. (2020) Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China.Clin Res Cardiol.

Milescu L S, Akk G, Sachs F. (2005) Maximum likelihood estimation of ion channel kinetics from macroscopic currents.Biophys J;88:2494-2515

Momtaz A, Coulombe A, Richer P, Mercadier JJ, Coraboeuf E. (1996) Action Potential and Plateau Ionic Currents inModerately and Severely DOCA-salt Hypertrophied Rat Hearts. JMCC;28;12, P2511-2522,DOI:https://doi.org/10.1006/jmcc.1996.0243

Nakamura M. (1982) A method to improve the effective medium theory towards percolation problem.J Phys C: Solid State Phys;15: L749. doi: 10.1088/0022-3719/15/23/005.

Ozdemir S, Bito V, Holemans P, Vinet L et al. (2008) Pharmacological Inhibition of Na/Ca Exchange Results in Increased Cellular Ca^{2+} Load Attributable to the Predominance of Forward Mode Block. Circ Res;102;11:1398-405. doi: 10.1161/CIRCRESAHA.108.173922.

Peiró C, Moncada S. (2020) Substituting angiotensin-(1-7) to prevent lung damage in SARSCoV2 infection? Circulation;10.1161/CIRCULATIONAHA.120.047297. doi:10.1161/CIRCULATIONAHA.120.047297.

Pichler L, Masud A, L. A. Bergman L A. (2011) Numerical solution of the fokker-planck equation by finite difference and finite element methods – a Comparative study, COMPDYN 3rd ECCOMAS Thematic Conference on Computational Methods in Structural Dynamics and Earthquake Engineering. M. Papadrakakis, M. Fragiadakis, V. Plevris (eds.) Corfu, Greece, 25-28 May 2011.

Rice G I, Thomas D A, Grant P J, turner A J, Hooper N M. (2004) Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism.Biochem J; 383, 45–51

Rossi G P, Sanga V, Barton M, (2020) Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 Patients, eLife;9:e57278. DOI: https://doi.org/10.7554/eLife.57278

Sommerstein.R. &Gråni. C. (2020) Rapid response: preventing a Covid-19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid-19. BMJ.;368:m810https://doi.org/10.1136/bmj.m810.

Tarjan R. (1972) Depth-first search and linear graph algorithms.SIAM J Comput;1:146-160.

Tignanelli CJ, Ingraham NE, (2020) Sparks MA et al. Antihypertensive drugs and risk of COVID-19?Lancet RespirMed ;https://doi.org/10.1016/S2213-2600(20)30153-3

Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. (2020) Renin–angiotensin–aldosterone system Iinhibitors in patients with Covid-19. N Engl J Med. ;382:1653–9.https://doi.org/10.1056/NEJMsr2005760.

Venkataramanan L, Sigworth F J. (2002) Applying hidden Markov models to the analysis of single ion channel activity. Biophys J; 82:1930-1942

Wang D, Hu B, Hu C, et al. (2020) Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA.

Wang X, Ye Y, Gong H, Wu J, Yuan J, Wang S, et al. (2016) The effects of different angiotensin II type 1 receptor blockers on the regulation of the ACE-AngII-AT1 and ACE2-Ang(1-7)-Mas axes in pressure overload-induced cardiac remodeling in male mice. J Mol Cell Cardiol.;97:180–90.

Weber R. dos Santos, F. Dickstein F. (2003) On the Influence of a Volume Conductor on the Orientation of Currents in a Thin Cardiac issue. International Workshop onFunctional Imaging and Modeling of the Heart pp 111-121.