# 運動如何降低新冠肺炎風險的生理機制

呂啓誠、方世華
國立臺灣體育運動大學競技運動學系

## 摘要

目前全球正面臨著詭譎多變、高發病率、高死亡率的新型冠狀病毒疾病 (COVID-19) 的嚴峻挑戰。新型冠狀病毒 SARS-CoV-2 藉由血管收縮素轉化酶 2 (Angiotensin converting enzyme 2, ACE2) 作為感染細胞的入口，後續造成細胞激素分泌及大量活性氧之生成，導致強烈發炎反應甚至死亡。適度的中高強度運動可增加 ACE2 表現量，進而活化抗發炎 (anti-inflammation)、抗纖維化 (anti-fibrogenesis) 及血管舒張 (vasodilation) 等訊號傳遞路徑，由於 ACE2 表現在許多組織器官，將有助於維持正常生理功能。此外，COVID-19 病患常發生肺部組織損傷與急性呼吸窘迫症候群，適度運動可以降低體內發炎細胞激素與壓力荷爾蒙含量，以減緩細胞激素風暴發生；另外，運動尚可活化免疫細胞趨化作用與吞噬能力，可能降低新冠病毒的入侵風險。目前 SARS-CoV-2 疫情環伺全球，未來對抗變異性病毒將是防疫的確定方向，適度且規律的運動以提升免疫力，可能將是長期對降低 SARS-CoV-2 感染的最佳策略之一。

**關鍵詞：新冠肺炎、血管收縮素轉化酶 2、運動生理、免疫系統**

通訊作者：方世華
E-mail：shfang@ntus.edu.tw
DOI：10.53106/2226535X2021061002001

# 壹、前言

2019 年底由中國武漢開始爆發的嚴重病毒型肺炎，其最主要的臨床症狀是造成急性呼吸窘迫症候群 (acute respiratory distress syndrome, ARDS)。世界衛生組織 (World Health Organization, WHO) 將此新型冠狀病毒所引起的疾病稱之為 COVID-19 (Coronavirus disease 2019)，國際病毒學分類學會將此致病病毒正式命名為嚴重急性呼吸道症候群冠狀病毒第二型 (Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) (Tsai et al., 2021; P. Zhou et al., 2020)。截至 2021 年 7 月中，根據世界衛生組織公布全球 COVID-19 確診人數達 1.88 億人及死亡人數超過 4 百萬人 (WHO, 2021)。

# 貳、新型冠狀病毒 SARS-CoV-2 簡介

SARS-CoV-2 是單股 RNA 病毒，主要的病毒結構蛋白包括：套膜 (envelope, E)、核酸外殼蛋白 (nucleocapsid, N)、膜蛋白 (membrane, M) 及上面的棘蛋白 (spike, S) (圖 1)。與過去造成嚴重急性呼吸道症候群 (Severe Acute Respiratory Syndrome, SARS) 所引起的冠狀病毒 SARS-CoV 相似，均是利用血管收縮素轉化酶 2 (Angiotensin converting enzyme 2, ACE2) 作為感染細胞的入口，棘蛋白經由跨膜蛋白酶絲胺酸 2 (Transmembrane protease serine 2, TMPRSS 2) 分解為棘醣蛋白 S1 (spike glycoprotein, S1) 與棘醣蛋白 S2 (spike glycoprotein, S2)，其中棘醣蛋白 S1 再與 ACE2 結合後侵入宿主細胞 (Li et al., 2003; Li, Geng, Peng, Meng, & Lu, 2020; Samavati & Uhal, 2020; Wu, 2020)。與其他冠狀病毒相比較，SARS-CoV-2 與 SARS-CoV 的棘蛋白最相近，有 76.5%相同 (Xu et al., 2020)，但發現 SARS-CoV-2 與 ACE2 結合位置存在較多的胺基酸變異，因此，可能是造成 SARS-CoV-2 對 ACE2 的結合力比過去的 SARS-CoV 較強的原因 (Wang et al., 2020; Yan et al., 2020)。SARS-CoV-2 引起的症狀主要為急性呼

吸窘迫症候群及肺纖維化 (pulmonary fibrosis)，同時升高血清中發炎細胞激素、減少淋巴細胞數目 (Torres Acosta & Singer, 2020)、促使大量活性氧物質 (reactive oxygen species, ROS) 的產生，過多發炎與氧化傷害誘發更強的細胞激素風暴 (cytokine storm) 及破壞肺臟的正常功能 (Delgado-Roche & Mesta, 2020)。

由於 SARS-CoV-2 經 ACE2 感染細胞的同時也會干擾 ACE2 原本參與的生理功能 (Samavati & Uhal, 2020)，這原因可能導致臨床上年長者、癌症患者、免疫不全者或是有心血管疾病、糖尿病、慢性腎病等代謝相關慢性疾病患者感染 SARS-CoV-2 後，易出現較為嚴重的症狀及較高的死亡率 (Guan et al., 2020; Zhou et al., 2020; Zhu et al., 2020)。目前可能對抗 SARS-CoV-2 感染的策略除嘗試過去已使用過的抗病毒藥物、抗 RNA 聚合酶藥物及免疫抑制藥物等之外 (Wang et al., 2020; Zhu et al., 2020)，還包括以棘蛋白為抗原目標的疫苗、抑制跨膜蛋白酶絲胺酸 2 的酵素活性、阻斷 ACE2 接受器及產生過量游離狀態 (soluble form) 的 ACE2，來降低新型冠狀病毒的感染能力 (Zhang, Penninger, Li, Zhong, & Slutsky, 2020)。

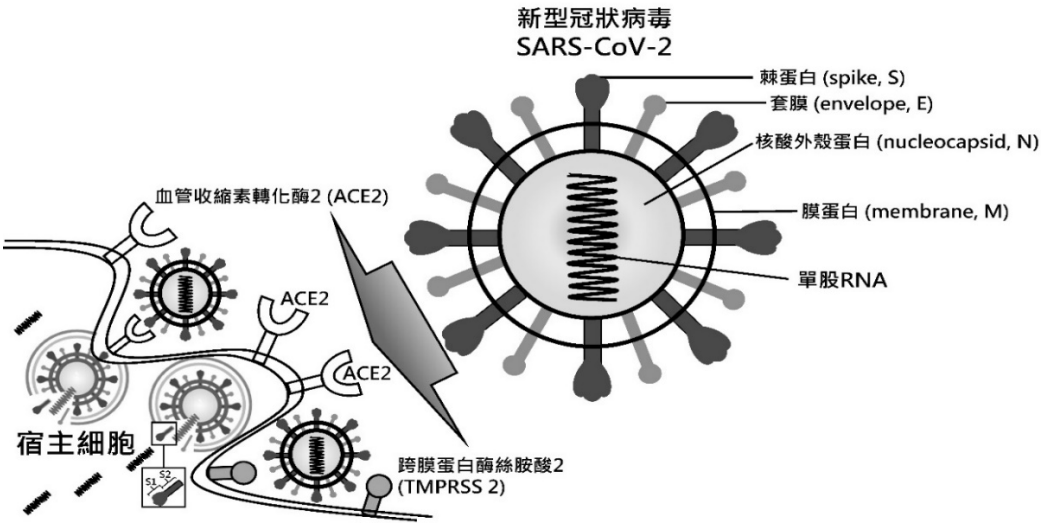


*圖 1.* 新型冠狀病毒 SARS-CoV-2 的結構，與進入宿主細胞時，血管收縮素轉化酶 2 (ACE2) 的角色

# 參、血管收縮素轉化酶 2 (ACE2) 的生理角色

ACE2 表現在肺泡上皮細胞 (alveolar epithelial cell) 及許多組織微血管內皮細胞 (capillary endothelial cell)，參與調控腎素-血管收縮素系統 (Renin-Angiotensin system, RAS)，這是體內調節電解質與血壓的重要機制路徑，因此與許多器官，如：肺、肝與腎的發炎生理反應有密切關係 (Tan, Liao, Zhou, Mei, & Wong, 2018; Uzunova et al., 2021) (圖 2)。由腎臟釋出的腎素可將血管收縮素原 (Angiotensinogen) 分解為血管收縮素 I ( Angiotensin I, Ang I)，ACE 中凝乳酶 (chymase) 可將 Ang I 分解為血管收縮素 II ( Angiotensin II, Ang II)，當 Ang II 結合到其第一型受體 (Angiotensin II type 1 receptor, AT1R)，將引起周邊交感神經的活化並增加兒茶酚胺 (catecholamine) 的分泌，導致血管收縮、肺纖維維母細胞 (fibroblast) 增生、活性氧物質的產生及發炎現象。如果 Ang II 結合到 AT2R，則將引起血管舒張、減少細胞增生與抗發炎的效果。ACE2 在生理上所扮演的角色是將血管收縮素 II 分解成血管收縮素 (1-7) [Angiotensin (1-7), Ang (1-7)]，這是 7 個胺基酸的胜肽，可結合到 MAS 接受器後，活化抗發炎 (anti-inflammation)、抗纖維化 (anti-fibrogenesis) 及血管舒張 (vasodilation) 的訊號傳遞路徑。過去對於肺部的相關疾病，採取藥物開發及治療的對策，除了以 ACE 抑制劑進行治療之外，抑制 Ang I/Ang II/AT1R 路徑或是活化 ACE2/Ang (1-7)/Mas 接受器路徑，與血管收縮素 II 的功用相互拮抗 (Tan et al., 2018)，可引起血管舒張、抗增生及抗發炎的效果 (Povlsen, Grimm, Wehland, Infanger, & Kruger, 2020; Wu, 2020)，進而減少白血球的移動、細胞激素的分泌及肺纖維化過程 (Simoes e Silva, Silveira, Ferreira, & Teixeira, 2013)、降低肺臟傷害及並保護心血管系統為目標 (Santos et al., 2003)。

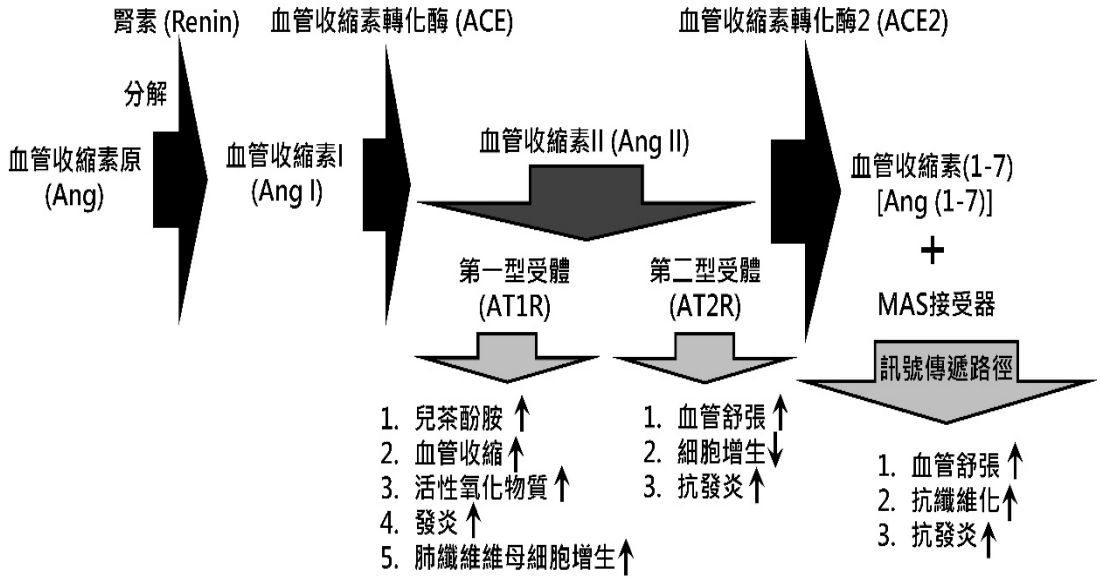


*圖 2.* 血管收縮素轉化酶 2 (ACE2) 與其相關分子參與之生理反應

由於 ACE2 是 SARS-CoV-2 進入到細胞的入口。因此，有學者們討論若是降低 ACE2 表現量是否有助於避免新型冠狀病毒的感染呢 (Pagliaro & Penna, 2020)？然而，ACE2 似乎扮演著雙重的角色，因 ACE2 表現在許多組織器官，如：肺、肝、心、腦、小腸及腎 (Li, Li, Zhang, & Wang, 2020) 等器官，臨床上的證據已顯示 ACE/ACE2 比例高時，會出現心臟功能不佳、高血壓、高血糖及蛋白尿等不好的反應 (Crackower et al., 2002; Mizuiri et al., 2008)。因此，感染 SARS-CoV-2 後 ACE/ACE2 比例變高，將加速病毒感染後各器官功能性惡化的結果。由於小孩的肺部表現較高量的 ACE2，可能受 SARS-CoV-2 感染後，各器官生理功能仍正常運作，結果症狀較不嚴重 (Chen et al., 2020)。另外，可能因為雌激素 (estrogen) 會活化 ACE2 促使 ACE2/Ang (1-7) 的產生 (Hilliard, Sampson, Brown, & Denton, 2013; Marquez et al., 2020)。在目前全球數據 COVID-19 依性別死亡公布中，大部分國家女性死亡比例約低於男性 1.0-3.5% (Dehingia & Raj, 2021)。目前

身體活動量增加已被發現可以增加 ACE2 表現量，進而降低 ACE/ACE2 比例 (Fernandes et al., 2011)，可能有助於改善感染新型冠狀病毒的嚴重性，也可作為預防 COVID-19 考量的方向。

## 肆、運動可能有助於降低 SARS-CoV-2 感染風險之細胞生物學證據

針對自發性高血壓的大鼠，介入 8 周高強度有氧運動可以增加 ACE2 的表現，藉由調控腎素-血管收縮素系統有效地降低血壓 (Almeida et al., 2020)。另外，在一個大鼠左心室肥大的疾病模式中，發現中高強度游泳運動的介入後，此有氧運動可以促進心臟上 AT2 接受器表現量並促進血管舒張，同時 ACE2 及血管收縮素 (1-7) 表現增加 (Gnoni, Longo, Gnoni, & Giudetti, 2020)；每周 6 天、每天 30 分鐘的跑步運動也會增加 ACE2 的表現量 (Kar, Gao, & Zucker, 2010)；另有每周 5 次、每次 1 小時最大負荷的 60%強度有氧運動，伴隨活化 ACE2 的藥物使用可顯著降低肺部纖維化的現象 (Prata et al., 2017)。運動能增加骨骼肌的 ACE2 濃度但不影響血清中 ACE2 的量，骨骼肌中的血管收縮素 (1-7) 量增加 (Echeverria-Rodriguez, Gallardo-Ortiz, Del Valle-Mondragon, & Villalobos-Molina, 2020; Kloting, Ristow, & Bluher, 2020) 及增進最大運動能力的表現 (Frantz et al., 2017; Gomes-Santos et al., 2014)，這些證據支持運動可增加 ACE2 表現量，將可能有助於維持正常生理功能，同時減少新型冠狀病毒感染後所造成的傷害 (圖3)。

在人體研究中，已發現 12 周的阻力運動可以明顯改善第一期高血壓的男性收縮壓 (Moraes et al., 2012)；當運動強度大於 50% 即可改善高血壓婦女的心血管反應 (de Freitas Brito et al., 2015)。顯示運動可有效協助腎素-血管收縮素系統調控血壓。針對 20-25 歲的男性所做的研究中，發現不

管是高強度間歇運動或是中強度長時間運動後立即採血，血漿中的 ACE2 濃度都比運動前顯著提高 (Magalhaes et al., 2020)。然而，高齡者經過運動介入後，有關 ACE2 表現及 SARS-CoV-2 感染後臨床症狀之改變尚不清楚，值得未來更多的研究進行分析。

# 伍、運動可能有助於降低 SARS-CoV-2 感染風險之免疫學證據

免疫反應除具抗原專一性外，還會因應感染病原體的特性而啟動適當的免疫攻擊，尤其是輔助型第一型 T 細胞 (helper type I T cell, TH1) 與輔助型第二型 T 細胞 (helper type II T cell, TH2) 反應的互相協調。細胞內的感染如病毒，則發動以細胞性免疫反應為主及體液性免疫反應為輔的免疫攻擊，以 TH1 為主 (Nieman, 2020)。過去許多研究已證實中高強度的規律運動會降低上呼吸道感染 (upper respiratory tract infection, URTI) 的機率及嚴重度 (Fernandes et al., 2011; Matthews et al., 2002; Simpson et al., 2020)，運動會提高施打流感疫苗後產生的免疫反應 (Bachi et al., 2013; Kohut, Cooper, Nickolaus, Russell, & Cunnick, 2002; Monteiro et al., 2020)。近期也有研究發現，針對約 21.2 萬南韓成年人研究統計發現，規律身體活動確實可以降低新冠肺炎病毒 SARS-CoV-2 染疫風險，即使感染其嚴重程度也會較輕微。免疫系統調控、減少過度發炎反應與抗體產生扮演重要角色 (Lee et al., 2021)。還有許多有關運動可能對降低 SARS-CoV-2 的證據及作用機轉 (圖 3) 如下：

## 一、減低病毒的入侵對運動表現的影響

中等強度運動後可觀察到血液中的周邊單核細胞 (peripheral blood mononuclear cell, PBMC) 所產生的干擾素-γ (interferon gamma, IFN-γ) 顯著增加 (Zamani, Salehi, & Alahgholi-Hajibehzad, 2017)。運動可以活化促分

裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 路徑，進而促進第一型與第二型干擾素基因表現 (Gonzalez et al., 2016; Platanias, 2005; Vijayaraghava & K, 2014)。若進行 40-60 分鐘的高強度運動，則會顯著造成周邊血液中自然殺手細胞與 CD8+毒殺型 T 細胞數目增加 (Campbell et al., 2009)，這些與抗病毒相關的免疫細胞，其趨化 (chemotaxis) 作用與吞噬 (phagocytosis) 的能力也在運動後增加 (Bigley et al., 2015; Simpson, Kunz, Agha, & Graff, 2015)。這些都可能有助於提升對抗 SARS-CoV-2 入侵的效果。

## 二、減緩免疫衰老

高齡者所面臨免疫衰老 (immunosenescence)，包括：具抗原呈現能力的吞噬細胞功能下降、輔助型第一型與第二型 T 細胞其細胞激素不平衡、T 細胞活化與增生減少、前發炎細胞激素產量較多等現象 (Salimi & Hamlyn, 2020; Shaw, Joshi, Greenwood, Panda, & Lord, 2010)。過去已有許多學者發現，規律運動會減緩免疫衰老及降低發炎程度 (de Souto Barreto, Vellas, & Rolland, 2021; Duggal, Niemiro, Harridge, Simpson, & Lord, 2019)，對於老年人很有幫助，可明顯地提升與抗病毒有關之免疫功能，如：促進樹突細胞 (dendritic cell) 的成熟、T 細胞活化及適當的平衡輔助型第一型與第二型 T 細胞反應等 (Chupel et al., 2017; Eustáquio et al., 2020; Furtado et al., 2020; Furtado et al., 2021)。觀察超過 6 個月運動，可降低免疫老化功能不佳及慢性發炎 (Cao Dinh et al., 2017)，這對於易受到 SARS-CoV-2 感染並有嚴重症狀的長者特別重要。

## 三、縮小細胞激素風暴

由於 COVID-19 病人肺部所聚集的吞噬細胞與嗜中性白血球，乃是產生許多發炎細胞激素及活性氧物質的來源，也是造成肺部組織損傷而出現急性呼吸窘迫症候群的主因 (Cao, 2020)。中強度與規律的運動會降低體內發炎細胞激素與壓力荷爾蒙含量，並降低類鐸受體 4 (Toll-like receptor 4,

TLR4) 及核轉錄因子 κB (Nuclear factor kappa B, NF-κB) 的表現，達到抗發炎的效果 (Zhu et al., 2016)。這可減輕因 SARS-CoV-2 所造成過大的細胞激素風暴，而降低對身體所造成嚴重的傷害。

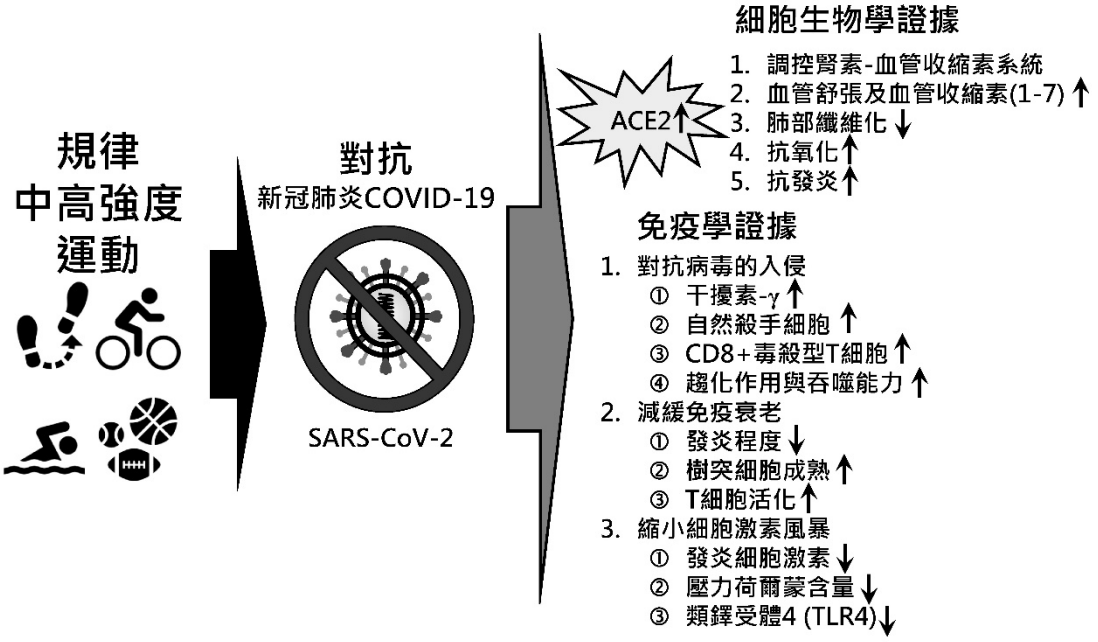


*圖 3.* 運動減緩新冠肺炎 COVID-19 風險的細胞生物學與免疫學證據

## 陸、結語

目前對於新型冠狀病毒 SARS-CoV-2 並無專一性有效的治療藥物，所幸已成功開發幾款疫苗可以刺激身體免疫系統產生抗體，一方面持續研究與優化現有疫苗對抗變種病毒的效果，也積極開發有效地治療藥物。由於每個人的免疫系統受到許多因素的影響，包括：基因、營養、睡眠、運動等，而這些也是影響接種疫苗後產生保護力多寡的因素。藉由過去研究顯示，運動會提升施打流感疫苗後，產生對抗流感病毒的免疫反應，雖尚未了解詳細的機轉。但針對降低 SARS-CoV-2 的感染率與致病力，同時提高

免疫力與疫苗的效果，由過去對於運動生理學的相關研究均顯示，適度且規律的運動可能是減低 SARS-CoV-2 感染的最佳策略。

# 參考文獻

Almeida, J. A., Motta-Santos, D., Petriz, B. A., Gomes, C., Nogueira, M. E., Pereira, R. W., . . . Franco, O. L. (2020). High-intensity aerobic training lowers blood pressure and modulates the renal renin-angiotensin system in spontaneously hypertensive rats. *Clinical and Experimental Hypertension, 42*(3), 233-238. doi:10.1080/10641963.2019.1619755

Bachi, A. L., Suguri, V. M., Ramos, L. R., Mariano, M., Vaisberg, M., & Lopes, J. D. (2013). Increased production of autoantibodies and specific antibodies in response to influenza virus vaccination in physically active older individuals. *Results in Immunology, 3*, 10-16. doi: 10.1016/j.rinim.2013.01.001

Bigley, A. B., Rezvani, K., Pistillo, M., Reed, J., Agha, N., Kunz, H., . . . Simpson, R. J. (2015). Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Part II: impact of latent cytomegalovirus infection and catecholamine sensitivity. *Brain, Behavior, and Immunity, 49*, 59-65. doi:10.1016/j.bbi.2014.12.027

Campbell, J. P., Riddell, N. E., Burns, V. E., Turner, M., van Zanten, J. J., Drayson, M. T., & Bosch, J. A. (2009). Acute exercise mobilises CD8+ T lymphocytes exhibiting an effector-memory phenotype. *Brain, Behavior, and Immunity, 23*(6), 767-775. doi:10.1016/j.bbi.2009.02.011

Cao Dinh, H., Beyer, I., Mets, T., Onyema, O. O., Njemini, R., Renmans, W., . . . Bautmans, I. (2017). Effects of Physical Exercise on Markers of Cellular Immunosenescence: A Systematic Review. *Calcified Tissue International, 100*(2), 193-215. doi:10.1007/s00223-016-0212-9

Cao, X. (2020). COVID-19: immunopathology and its implications for therapy. *Nature Reviews. Immunology, 20*(5), 269-270. doi:10.1038/s41577-020-0308-3

Chen, J., Jiang, Q., Xia, X., Liu, K., Yu, Z., Tao, W., . . . Han, J. D. J. (2020). Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. *Aging Cell, 19*(7), e13168. doi: 10.1111/acel.13168

Chupel, M. U., Direito, F., Furtado, G. E., Minuzzi, L. G., Pedrosa, F. M., Colado, J. C., . . . Teixeira, A. M. (2017). Strength training decreases inflammation and increases cognition and physical fitness in older women with cognitive impairment. *Frontiers in Physiology, 8*, 377. doi: 10.3389/fphys.2017.00377

Crackower, M. A., Sarao, R., Oudit, G. Y., Yagil, C., Kozieradzki, I., Scanga, S. E., . . . Penninger, J. M. (2002). Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature, 417*(6891), 822-828. doi:10.1038/nature00786

de Freitas Brito, A., Brasileiro-Santos Mdo, S., Coutinho de Oliveira, C. V., Sarmento da Nobrega, T. K., Lucia de Moraes Forjaz, C., & da Cruz Santos, A. (2015). High-Intensity Resistance Exercise Promotes Postexercise Hypotension Greater than Moderate Intensity and Affects Cardiac Autonomic Responses in Women Who Are Hypertensive. *Journal of Strength and Conditioning Research, 29*(12), 3486-3493. doi:10.1519/JSC.0000000000001009

de Souto Barreto, P., Vellas, B., & Rolland, Y. (2021). Physical activity and exercise in the context of SARS-Cov-2: A perspective from geroscience field. *Ageing Research Reviews, 66*, 101258. doi:10.1016/j.arr.2021.101258

Dehingia, N., & Raj, A. (2021). Sex differences in COVID-19 case fatality: do we know enough? *Lancet Global Health, 9*(1), e14-e15. doi:10.1016/S2214-109X(20)30464-2

Delgado-Roche, L., & Mesta, F. (2020). Oxidative Stress as Key Player in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection. *Archives of Medical Research, 51*(5), 384-387. doi:10.1016/j.arcmed.2020.04.019

Duggal, N. A., Niemiro, G., Harridge, S. D. R., Simpson, R. J., & Lord, J. M. (2019).

Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity? *Nature Reviews. Immunology, 19*(9), 563-572. doi:10.1038/s41577-019-0177-9

Echeverria-Rodriguez, O., Gallardo-Ortiz, I. A., Del Valle-Mondragon, L., & Villalobos-Molina, R. (2020). Angiotensin-(1-7) Participates in Enhanced Skeletal Muscle Insulin Sensitivity After a Bout of Exercise. *Journal of the Endocrine Society, 4*(2), bvaa007. doi:10.1210/jendso/bvaa007

Eustáquio, F. G., Uba, C. M., Guerra, M. L., Luis, R., Carlos, C. J., Eef, H., . . . Maria, T. A. (2020). The mediating effect of different exercise programs on the immune profile of frail older women with cognitive impairment. *Current Pharmaceutical Design, 26*(9), 906-915. doi: 10.2174/1381612826666200203123258.

Fernandes, T., Hashimoto, N. Y., Magalhaes, F. C., Fernandes, F. B., Casarini, D. E., Carmona, A. K., . . . Oliveira, E. M. (2011). Aerobic exercise training-induced left ventricular hypertrophy involves regulatory MicroRNAs, decreased angiotensin-converting enzyme-angiotensin ii, and synergistic regulation of angiotensin-converting enzyme 2-angiotensin (1-7). *Hypertension, 58*(2), 182-189. doi:10.1161/HYPERTENSIONAHA.110.168252

Frantz, E. D. C., Giori, I. G., Machado, M. V., Magliano, D. C., Freitas, F. M., Andrade, M. S. B., . . . Tibirica, E. (2017). High, but not low, exercise volume shifts the balance of renin-angiotensin system toward ACE2/Mas receptor axis in skeletal muscle in obese rats. *American Journal of Physiology. Endocrinology and Metabolism, 313*(4), E473-E482. doi:10.1152/ajpendo.00078.2017

Furtado, G. E., Carvalho, H. M., Loureiro, M., Patrício, M., Uba-Chupel, M., Colado, J. C., . . . Teixeira, A. M. (2020). Chair-based exercise programs in institutionalized older women: Salivary steroid hormones, disabilities and frailty changes. *Experimental Gerontology, 130*, 110790. doi: 10.1016/j.exger.2019.110790

Furtado, G. E., Letieri, R. V., Caldo, A., Sardão, V., Teixeira, A. M., de Barros, M. P., . . . Bachi, A. L. L. (2021). Sustaining efficient immune functions with regular physical exercise in the COVID-19 era and beyond. *European Journal of Clinical Investigation*, e13485. doi: 10.1111/eci.13485

Gnoni, A., Longo, S., Gnoni, G. V., & Giudetti, A. M. (2020). Carnitine in Human Muscle Bioenergetics: Can Carnitine Supplementation Improve Physical Exercise? *Molecules, 25*(1). doi:10.3390/molecules25010182

Gomes-Santos, I. L., Fernandes, T., Couto, G. K., Ferreira-Filho, J. C., Salemi, V. M., Fernandes, F. B., . . . Negrao, C. E. (2014). Effects of exercise training on circulating and skeletal muscle renin-angiotensin system in chronic heart failure rats. *PLoS One, 9*(5), e98012. doi:10.1371/journal.pone.0098012

Gonzalez, A. M., Hoffman, J. R., Townsend, J. R., Jajtner, A. R., Boone, C. H., Beyer, K. S., . . . Stout, J. R. (2016). Intramuscular MAPK signaling following high volume and high intensity resistance exercise protocols in trained men. *European Journal of Applied Physiology, 116*(9), 1663-1670. doi:10.1007/s00421-016-3417-8

Guan, W. J., Liang, W. H., Zhao, Y., Liang, H. R., Chen, Z. S., Li, Y. M., . . . China Medical Treatment Expert Group for COVID-19. (2020). Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *European Respiratory Journal, 55*(5). doi:10.1183/13993003.00547-2020

Hilliard, L. M., Sampson, A. K., Brown, R. D., & Denton, K. M. (2013). The "his and hers" of the renin-angiotensin system. *Current Hypertension Reports, 15*(1), 71-79. doi:10.1007/s11906-012-0319-y

Kar, S., Gao, L., & Zucker, I. H. (2010). Exercise training normalizes ACE and ACE2 in the brain of rabbits with pacing-induced heart failure. *Journal of Applied Physiology, 108*(4), 923-932. doi:10.1152/japplphysiol.00840.2009

Kloting, N., Ristow, M., & Bluher, M. (2020). Effects of Exercise on ACE2. *Obesity,*

*28*(12), 2266-2267. doi:10.1002/oby.23041

Kohut, M. L., Cooper, M. M., Nickolaus, M. S., Russell, D. R., & Cunnick, J. E. (2002). Exercise and psychosocial factors modulate immunity to influenza vaccine in elderly individuals. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 57*(9), M557-562. doi:10.1093/gerona/57.9.m557

Lee, S. W., Lee, J., Moon, S. Y., Jin, H. Y., Yang, J. M., Ogino, S., . . . Yon, D. K. (2021). Physical activity and the risk of SARS-CoV-2 infection, severe COVID-19 illness and COVID-19 related mortality in South Korea: a nationwide cohort study. *British Journal of Sports Medicine*. doi:10.1136/bjsports-2021-104203

Li, M. Y., Li, L., Zhang, Y., & Wang, X. S. (2020). Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infectious Diseases of Poverty, 9(1), 45. doi:10.1186/s40249-020-00662-x

Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., . . . Farzan, M. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature, 426*(6965), 450-454. doi:10.1038/nature02145

Li, X., Geng, M., Peng, Y., Meng, L., & Lu, S. (2020). Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of Pharmaceutical Analysis, 10*(2), 102-108. doi:10.1016/j.jpha.2020.03.001

Magalhaes, D. M., Nunes-Silva, A., Rocha, G. C., Vaz, L. N., de Faria, M. H. S., Vieira, E. L. M., . . . Simoes, E. S. A. C. (2020). Two protocols of aerobic exercise modulate the counter-regulatory axis of the renin-angiotensin system. *Heliyon, 6*(1), e03208. doi:10.1016/j.heliyon.2020.e03208

Marquez, E. J., Chung, C. H., Marches, R., Rossi, R. J., Nehar-Belaid, D., Eroglu, A., . . . Ucar, D. (2020). Sexual-dimorphism in human immune system aging. *Nature Communications, 11*(1), 751. doi:10.1038/s41467-020-14396-9

Matthews, C. E., Ockene, I. S., Freedson, P. S., Rosal, M. C., Merriam, P. A., & Hebert, J. R. (2002). Moderate to vigorous physical activity and risk of upper-respiratory

tract infection. *Medicine and Science in Sports and Exercise, 34*(8), 1242-1248. doi:10.1097/00005768-200208000-00003

Mizuiri, S., Hemmi, H., Arita, M., Ohashi, Y., Tanaka, Y., Miyagi, M., . . . Aikawa, A. (2008). Expression of ACE and ACE2 in individuals with diabetic kidney disease and healthy controls. *American Journal of Kidney Diseases, 51*(4), 613-623. doi:10.1053/j.ajkd.2007.11.022

Monteiro, F. R., Roseira, T., Amaral, J. B., Paixão, V., Almeida, E. B., Foster, R., . . . Apostólico, J. S. (2020). Combined Exercise Training and l-Glutamine Supplementation Enhances Both Humoral and Cellular Immune Responses after Influenza Virus Vaccination in Elderly Subjects. *Vaccines, 8*(4), 685.

Moraes, M. R., Bacurau, R. F., Casarini, D. E., Jara, Z. P., Ronchi, F. A., Almeida, S. S., . . . Araujo, R. C. (2012). Chronic conventional resistance exercise reduces blood pressure in stage 1 hypertensive men. *Journal of Strength and Conditioning Research, 26*(4), 1122-1129. doi:10.1519/JSC.0b013e31822dfc5e

Nieman, D. C. (2020). Coronavirus disease-2019: A tocsin to our aging, unfit, corpulent, and immunodeficient society. *Journal of Sport and Health Science, 9*(4), 293-301. doi:10.1016/j.jshs.2020.05.001

Pagliaro, P., & Penna, C. (2020). ACE/ACE2 Ratio: A Key Also in 20 19 Coronavirus Disease (Covid-19)? *Frontiers in Medicine., 7*, 335. doi:10.3389/fmed.2020.00335

Platanias, L. C. (2005). Mechanisms of type-I- and type-II-interferon-mediated signalling. *Nature Reviews. Immunology, 5*(5), 375-386. doi:10.1038/nri1604

Povlsen, A. L., Grimm, D., Wehland, M., Infanger, M., & Kruger, M. (2020). The Vasoactive Mas Receptor in Essential Hypertension. *Journal of Clinical Medicine, 9*(1). doi:10.3390/jcm9010267

Prata, L. O., Rodrigues, C. R., Martins, J. M., Vasconcelos, P. C., Oliveira, F. M., Ferreira, A. J., . . . Caliari, M. V. (2017). ACE2 activator associated with physical

exercise potentiates the reduction of pulmonary fibrosis. *Experimental Biology and Medicine, 242*(1), 8-21. doi:10.1177/1535370216665174

Salimi, S., & Hamlyn, J. M. (2020). COVID-19 and Crosstalk With the Hallmarks of Aging. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 75*(9), e34-e41. doi:10.1093/gerona/glaa149

Samavati, L., & Uhal, B. D. (2020). ACE2, Much More Than Just a Receptor for SARS-COV-2. *Microbiol Frontiers in Cellular and Infection Microbiology, 10*, 317. doi:10.3389/fcimb.2020.00317

Santos, R. A., Simoes e Silva, A. C., Maric, C., Silva, D. M., Machado, R. P., de Buhr, I., . . . Walther, T. (2003). Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. *Proceedings of the National Academy of Sciences of the United St ates of America, 100*(14), 8258-8263. doi:10.1073/pnas.1432869100

Shaw, A. C., Joshi, S., Greenwood, H., Panda, A., & Lord, J. M. (2010). Aging of the innate immune system. *Current Opinion in Immunology, 22*(4), 507-513. doi:10.1016/j.coi.2010.05.003

Simoes e Silva, A. C., Silveira, K. D., Ferreira, A. J., & Teixeira, M. M. (2013). ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *British Journal of Pharmacology, 169*(3), 477-492. doi:10.1111/bph.12159

Simpson, R. J., Campbell, J. P., Gleeson, M., Kruger, K., Nieman, D. C., Pyne, D. B., . . . Walsh, N. P. (2020). Can exercise affect immune function to increase susceptibility to infection? *Exercise Immunology Review, 26*, 8-22. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32139352

Simpson, R. J., Kunz, H., Agha, N., & Graff, R. (2015). Exercise and the Regulation of Immune Functions. *Progress in Molecular Biology and Translational Science, 135*, 355-380. doi:10.1016/bs.pmbts.2015.08.001

Tan, W. S. D., Liao, W., Zhou, S., Mei, D., & Wong, W. F. (2018). Targeting the

renin-angiotensin system as novel therapeutic strategy for pulmonary diseases. *Current Opinion in Pharmacology, 40*, 9-17. doi:10.1016/j.coph.2017.12.002

Torres Acosta, M. A., & Singer, B. D. (2020). Pathogenesis of COVID-19-induced ARDS: implications for an ageing population. *European Respiratory Journal, 56*(3), 2002049. doi:10.1183/13993003.02049-2020

Tsai, S. C., Lu, C. C., Bau, D. T., Chiu, Y. J., Yen, Y. T., Hsu, Y. M., . . . Yang, J. S. (2021). Approaches towards fighting the COVID19 pan demic (Review). *International Journal of Molecular Medicine, 47*(1), 3-22. doi:10.3892/ijmm.2020.4794

Uzunova, V. V., Todev, A., Zarkos, J., Addai, D., Ananiev, J., Rashev, P., . . . Tolekova, A. (2021). Strengthening CoViD-19 therapy via combinations of RAS modulators. *Medical Hypotheses, 150*, 110571. doi:10.1016/j.mehy.2021.110571

Vijayaraghava, A., & K, R. (2014). Alteration of Interferon Gamma (IFN-gamma) in Human Plasma with Graded Physical Activity. *Journal of Clinical and Diagnostic Research, 8*(6), BC05-07. doi:10.7860/JCDR/2014/9502.4440

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., . . . Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research, 30*(3), 269-271. doi:10.1038/s41422-020-0282-0

Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., . . . Qi, J. (2020). Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. *Cell, 181*(4), 894-904 e899. doi:10.1016/j.cell.2020.03.045

World Health Organization. (2021). *WHO Coronavirus (COVID-19) Dashboard*. Retrieved from https://covid19.who.int.

Wu, Y. (2020). Compensation of ACE2 Function for Possible Clinical Management of 2019-nCoV-Induced Acute Lung Injury. *Virologica Sinica, 35*(3), 256-258. doi:10.1007/s12250-020-00205-6

Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., . . . Hao, P. (2020). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China. Life Sciences, 63*(3), 457-460. doi:10.1007/s11427-020-1637-5

Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., & Zhou, Q. (2020). Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science, 367*(6485), 1444-1448. doi:10.1126/science.abb2762

Zamani, A., Salehi, I., & Alahgholi-Hajibehzad, M. (2017). Moderate Exercise Enhances the Production of Interferon-gamma and Interleukin-12 in Peripheral Blood Mononuclear Cells. *Immune Network, 17*(3), 186-191. doi:10.4110/in.2017.17.3.186

Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Medicine, 46*(4), 586-590. doi:10.1007/s00134-020-05985-9

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., . . . Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet, 395*(10229), 1054-1062. doi:10.1016/S0140-6736(20)30566-3

Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., . . . Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature, 579*(7798), 270-273. doi:10.1038/s41586-020-2012-7

Zhu, L., She, Z. G., Cheng, X., Qin, J. J., Zhang, X. J., Cai, J., . . . Li, H. (2020). Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metabolism, 31*(6), 1068-1077 e1063. doi:10.1016/j.cmet.2020.04.021

Zhu, L., Ye, T., Tang, Q., Wang, Y., Wu, X., Li, H., & Jiang, Y. (2016). Exercise

Preconditioning Regulates the Toll-Like Receptor 4/Nuclear Factor-kappaB Signaling Pathway and Reduces Cerebral Ischemia/Reperfusion Inflammatory Injury: A Study in Rats. *Journal of Stroke and Cerebrovascular Diseases, 25*(11), 2770-2779. doi:10.1016/j.jstrokecerebrovasdis.2016.07.033

# The Physiological Mechanism of Exercise to Reduce the Risk of COVID-19

Chi-Cheng Lu, Shih-Hua Fang

Department of Sport Performance, National Taiwan University of Sport

## *Abstract*

The whole world is now facing a very severe and treacherous challenge of a new coronavirus disease (COVID-19) with high morbidity and high mortality rate. The SARS-CoV-2 entered cells through angiotensin converting enzyme 2 (ACE2), which subsequently caused the secretion of cytokines and the production of a large number of reactive oxygen species (ROS), resulting in a strong inflammatory reaction that is harmful to life. Regularly moderate high-intensity exercise can increase ACE2 expression and help maintain normal physiological functions, and achieved anti-oxidation and anti-inflammatory effects. In addition, COVID-19 patients often suffer from lung tissue damage and acute respiratory distress syndrome. Moderate exercise can reduce inflammatory cytokines and stress hormones in the body to slow down the occurrence of cytokine storms. In addition, the activation of the chemotaxis and phagocytosis of immune cells moderate exercise may resist the invasion of SARS-CoV-2. Nowadays, the SARS-CoV-2 epidemic is threating the world, and fight against the mutant viruses will be the definite direction of epidemic prevention in the future. Through moderate and regular exercise to improve immunity may be one of the best strategies against SARS-CoV-2.

**Keywords: COVID-19, ACE2, Exercise physiology, Immune system**