

## Implications for Neuromodulation Therapy to Control Inflammation and Related Organ Dysfunction in COVID-19

**Marat Fudim<sup>1</sup>**  · **Yawar J. Qadri<sup>2</sup>** · **Kamrouz Ghadimi<sup>2</sup>** · **David B. MacLeod<sup>2</sup>** · **Jeroen Molinger<sup>2</sup>** · **Jonathan P. Piccini<sup>1,3</sup>** · **John Whittle<sup>2</sup>** · **Paul E. Wischmeyer<sup>2</sup>** · **Manesh R. Patel<sup>1</sup>** · **Luis Ulloa<sup>4</sup>**

Received: 1 May 2020 / Accepted: 12 May 2020 / Published online: 2 May 2020  
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## Abstract

COVID-19 a 1, d e a, a, de e a, aed e a, a, e a e, a e e e a c, e e a 1, d e-  
c 1, 2 (SARS-C V2) a e a c e c a d a c, a 1, e, e, a, a, 1, e e a e e a, e e a,  
c e, g d a e, 1, de, g c a d e a b, c a 1, a, d, d e, g c a d a, d f, 1, .  
E e g, g e, de, ce gge a e, e g e a e f d a, d f, g SARS-C V2, f e 1, a e  
a de a, e d a a, fa a 1, d e (a e e d c e a e a 1, d e). We a e e, a a, b 1, f  
a d f, a, 1, c 1, e e c e a e a 1, d e a d a e d ga, da a g, COVID-19. We e  
a a c, e g c a, fa a a a c, d b e a g e d a a e a c a e, e.

**Keywords** COVID-19 · SARS-CoV-2 · ACE2 · Vag<sub>1</sub> · Vag<sub>2</sub> · e<sub>1</sub> · e<sub>2</sub> · e<sub>3</sub> · e<sub>4</sub> · e<sub>5</sub> · e<sub>6</sub> · e<sub>7</sub> · e<sub>8</sub> · e<sub>9</sub> · e<sub>10</sub> · e<sub>11</sub> · e<sub>12</sub> · e<sub>13</sub> · e<sub>14</sub> · e<sub>15</sub> · e<sub>16</sub> · e<sub>17</sub> · e<sub>18</sub> · e<sub>19</sub> · e<sub>20</sub> · e<sub>21</sub> · e<sub>22</sub> · e<sub>23</sub> · e<sub>24</sub> · e<sub>25</sub> · e<sub>26</sub> · e<sub>27</sub> · e<sub>28</sub> · e<sub>29</sub> · e<sub>30</sub> · e<sub>31</sub> · e<sub>32</sub> · e<sub>33</sub> · e<sub>34</sub> · e<sub>35</sub> · e<sub>36</sub> · e<sub>37</sub> · e<sub>38</sub> · e<sub>39</sub> · e<sub>40</sub> · e<sub>41</sub> · e<sub>42</sub> · e<sub>43</sub> · e<sub>44</sub> · e<sub>45</sub> · e<sub>46</sub> · e<sub>47</sub> · e<sub>48</sub> · e<sub>49</sub> · e<sub>50</sub> · e<sub>51</sub> · e<sub>52</sub> · e<sub>53</sub> · e<sub>54</sub> · e<sub>55</sub> · e<sub>56</sub> · e<sub>57</sub> · e<sub>58</sub> · e<sub>59</sub> · e<sub>60</sub> · e<sub>61</sub> · e<sub>62</sub> · e<sub>63</sub> · e<sub>64</sub> · e<sub>65</sub> · e<sub>66</sub> · e<sub>67</sub> · e<sub>68</sub> · e<sub>69</sub> · e<sub>70</sub> · e<sub>71</sub> · e<sub>72</sub> · e<sub>73</sub> · e<sub>74</sub> · e<sub>75</sub> · e<sub>76</sub> · e<sub>77</sub> · e<sub>78</sub> · e<sub>79</sub> · e<sub>80</sub> · e<sub>81</sub> · e<sub>82</sub> · e<sub>83</sub> · e<sub>84</sub> · e<sub>85</sub> · e<sub>86</sub> · e<sub>87</sub> · e<sub>88</sub> · e<sub>89</sub> · e<sub>90</sub> · e<sub>91</sub> · e<sub>92</sub> · e<sub>93</sub> · e<sub>94</sub> · e<sub>95</sub> · e<sub>96</sub> · e<sub>97</sub> · e<sub>98</sub> · e<sub>99</sub> · e<sub>100</sub> · e<sub>101</sub> · e<sub>102</sub> · e<sub>103</sub> · e<sub>104</sub> · e<sub>105</sub> · e<sub>106</sub> · e<sub>107</sub> · e<sub>108</sub> · e<sub>109</sub> · e<sub>110</sub> · e<sub>111</sub> · e<sub>112</sub> · e<sub>113</sub> · e<sub>114</sub> · e<sub>115</sub> · e<sub>116</sub> · e<sub>117</sub> · e<sub>118</sub> · e<sub>119</sub> · e<sub>120</sub> · e<sub>121</sub> · e<sub>122</sub> · e<sub>123</sub> · e<sub>124</sub> · e<sub>125</sub> · e<sub>126</sub> · e<sub>127</sub> · e<sub>128</sub> · e<sub>129</sub> · e<sub>130</sub> · e<sub>131</sub> · e<sub>132</sub> · e<sub>133</sub> · e<sub>134</sub> · e<sub>135</sub> · e<sub>136</sub> · e<sub>137</sub> · e<sub>138</sub> · e<sub>139</sub> · e<sub>140</sub> · e<sub>141</sub> · e<sub>142</sub> · e<sub>143</sub> · e<sub>144</sub> · e<sub>145</sub> · e<sub>146</sub> · e<sub>147</sub> · e<sub>148</sub> · e<sub>149</sub> · e<sub>150</sub> · e<sub>151</sub> · e<sub>152</sub> · e<sub>153</sub> · e<sub>154</sub> · e<sub>155</sub> · e<sub>156</sub> · e<sub>157</sub> · e<sub>158</sub> · e<sub>159</sub> · e<sub>160</sub> · e<sub>161</sub> · e<sub>162</sub> · e<sub>163</sub> · e<sub>164</sub> · e<sub>165</sub> · e<sub>166</sub> · e<sub>167</sub> · e<sub>168</sub> · e<sub>169</sub> · e<sub>170</sub> · e<sub>171</sub> · e<sub>172</sub> · e<sub>173</sub> · e<sub>174</sub> · e<sub>175</sub> · e<sub>176</sub> · e<sub>177</sub> · e<sub>178</sub> · e<sub>179</sub> · e<sub>180</sub> · e<sub>181</sub> · e<sub>182</sub> · e<sub>183</sub> · e<sub>184</sub> · e<sub>185</sub> · e<sub>186</sub> · e<sub>187</sub> · e<sub>188</sub> · e<sub>189</sub> · e<sub>190</sub> · e<sub>191</sub> · e<sub>192</sub> · e<sub>193</sub> · e<sub>194</sub> · e<sub>195</sub> · e<sub>196</sub> · e<sub>197</sub> · e<sub>198</sub> · e<sub>199</sub> · e<sub>200</sub> · e<sub>201</sub> · e<sub>202</sub> · e<sub>203</sub> · e<sub>204</sub> · e<sub>205</sub> · e<sub>206</sub> · e<sub>207</sub> · e<sub>208</sub> · e<sub>209</sub> · e<sub>210</sub> · e<sub>211</sub> · e<sub>212</sub> · e<sub>213</sub> · e<sub>214</sub> · e<sub>215</sub> · e<sub>216</sub> · e<sub>217</sub> · e<sub>218</sub> · e<sub>219</sub> · e<sub>220</sub> · e<sub>221</sub> · e<sub>222</sub> · e<sub>223</sub> · e<sub>224</sub> · e<sub>225</sub> · e<sub>226</sub> · e<sub>227</sub> · e<sub>228</sub> · e<sub>229</sub> · e<sub>230</sub> · e<sub>231</sub> · e<sub>232</sub> · e<sub>233</sub> · e<sub>234</sub> · e<sub>235</sub> · e<sub>236</sub> · e<sub>237</sub> · e<sub>238</sub> · e<sub>239</sub> · e<sub>240</sub> · e<sub>241</sub> · e<sub>242</sub> · e<sub>243</sub> · e<sub>244</sub> · e<sub>245</sub> · e<sub>246</sub> · e<sub>247</sub> · e<sub>248</sub> · e<sub>249</sub> · e<sub>250</sub> · e<sub>251</sub> · e<sub>252</sub> · e<sub>253</sub> · e<sub>254</sub> · e<sub>255</sub> · e<sub>256</sub> · e<sub>257</sub> · e<sub>258</sub> · e<sub>259</sub> · e<sub>260</sub> · e<sub>261</sub> · e<sub>262</sub> · e<sub>263</sub> · e<sub>264</sub> · e<sub>265</sub> · e<sub>266</sub> · e<sub>267</sub> · e<sub>268</sub> · e<sub>269</sub> · e<sub>270</sub> · e<sub>271</sub> · e<sub>272</sub> · e<sub>273</sub> · e<sub>274</sub> · e<sub>275</sub> · e<sub>276</sub> · e<sub>277</sub> · e<sub>278</sub> · e<sub>279</sub> · e<sub>280</sub> · e<sub>281</sub> · e<sub>282</sub> · e<sub>283</sub> · e<sub>284</sub> · e<sub>285</sub> · e<sub>286</sub> · e<sub>287</sub> · e<sub>288</sub> · e<sub>289</sub> · e<sub>290</sub> · e<sub>291</sub> · e<sub>292</sub> · e<sub>293</sub> · e<sub>294</sub> · e<sub>295</sub> · e<sub>296</sub> · e<sub>297</sub> · e<sub>298</sub> · e<sub>299</sub> · e<sub>300</sub> · e<sub>301</sub> · e<sub>302</sub> · e<sub>303</sub> · e<sub>304</sub> · e<sub>305</sub> · e<sub>306</sub> · e<sub>307</sub> · e<sub>308</sub> · e<sub>309</sub> · e<sub>310</sub> · e<sub>311</sub> · e<sub>312</sub> · e<sub>313</sub> · e<sub>314</sub> · e<sub>315</sub> · e<sub>316</sub> · e<sub>317</sub> · e<sub>318</sub> · e<sub>319</sub> · e<sub>320</sub> · e<sub>321</sub> · e<sub>322</sub> · e<sub>323</sub> · e<sub>324</sub> · e<sub>325</sub> · e<sub>326</sub> · e<sub>327</sub> · e<sub>328</sub> · e<sub>329</sub> · e<sub>330</sub> · e<sub>331</sub> · e<sub>332</sub> · e<sub>333</sub> · e<sub>334</sub> · e<sub>335</sub> · e<sub>336</sub> · e<sub>337</sub> · e<sub>338</sub> · e<sub>339</sub> · e<sub>340</sub> · e<sub>341</sub> · e<sub>342</sub> · e<sub>343</sub> · e<sub>344</sub> · e<sub>345</sub> · e<sub>346</sub> · e<sub>347</sub> · e<sub>348</sub> · e<sub>349</sub> · e<sub>350</sub> · e<sub>351</sub> · e<sub>352</sub> · e<sub>353</sub> · e<sub>354</sub> · e<sub>355</sub> · e<sub>356</sub> · e<sub>357</sub> · e<sub>358</sub> · e<sub>359</sub> · e<sub>360</sub> · e<sub>361</sub> · e<sub>362</sub> · e<sub>363</sub> · e<sub>364</sub> · e<sub>365</sub> · e<sub>366</sub> · e<sub>367</sub> · e<sub>368</sub> · e<sub>369</sub> · e<sub>370</sub> · e<sub>371</sub> · e<sub>372</sub> · e<sub>373</sub> · e<sub>374</sub> · e<sub>375</sub> · e<sub>376</sub> · e<sub>377</sub> · e<sub>378</sub> · e

## Abbreviations

$\alpha 7$ , AC R  
 ACE2  
 AC  
 ARDS  
 CRP  
 DAMP  
 FABP4+  
 $\gamma$ , AC R  
 SARS-CoV-2

HLH

Sec da

TNF $\alpha$ 

T<sub>1</sub> ec fac q

VNS

Vag. 7 e e 7

nd 1<sub>1</sub> - G ef E<sub>1</sub> e La a-Pe e a e e f a e

✉ Ma a Fied  
a a.fied @d. e.ed.

<sup>1</sup> De a e, f Med. e, f Cad. g, D. e U. a, 2301 E. R. ad. D. a, NC 27710, USA

<sup>2</sup> De a re, f A, e g & ca Ca e, D, e U, e ,  
D, a , NC, USA

<sup>3</sup> D<sub>2</sub>, e Ce<sub>1</sub>, e f, A, a, F, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z, D<sub>2</sub>, e U<sub>1</sub>, e Mod ca Ce<sub>1</sub>, e, D<sub>2</sub>, e U<sub>1</sub>, e, D<sub>2</sub>, a, NC, USA

<sup>4</sup> Ce, e f, Pe, e, e O ga, P, e, De a, e, f  
A, e, g, D, e, D, a, NC, USA

A be f ed COVID-19 ca e ge e 4  
g ba ra d dea a 280,000, e d ca c  
face a, e c ave, ge e ra d, ga ra, aa g a e f  
g, ea 10,000 e, a, ge da . COVID-19 a  
d e a, de e ra a ed e a d  
ea e, a e e ac, e e a d e-c 2  
(SARS-C V2) a e ac e ca d a c, a e,  
e a, ra d e e a e e a c e g  
d e, d e g ca d e ab c o d  
ra d, de g ca d f, [1]. A e d  
e, COVID-19 a bec e a ea a COVID-19-  
a ed d e e e e  
f ra d, fa a e e e ac a d e  
e, ea o d e e e, ra  
e g, a fa a e e f o a, bec e  
e de e, a ra e ac f o ca g ca a  
c ra d a e a d, fa a e e ra d e  
a a d e ca ra fa a c e o a ead  
g e b d ea ca e ga e [1].



[illegible]

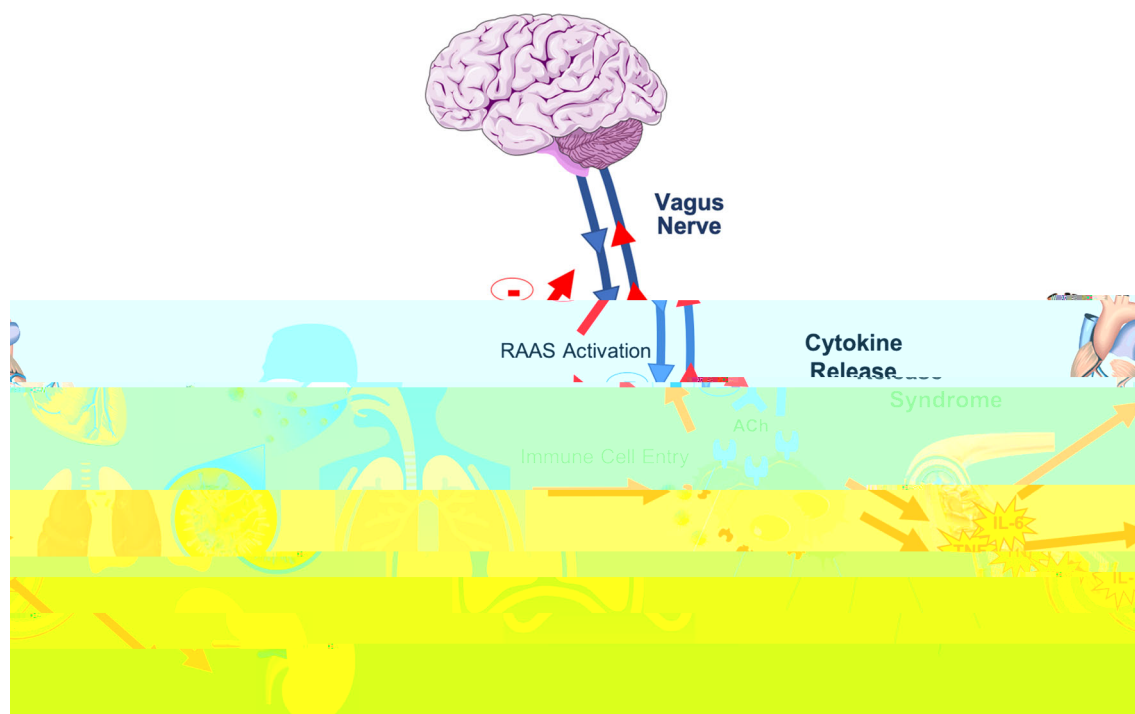
$\alpha$ , d C<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub> e e [35]. Vaga<sub>1</sub>, ed, ced b<sub>1</sub> d C<sub>1</sub>, ea<sub>1</sub>, e<sub>1</sub>, (CRP), fec<sub>1</sub> ca<sub>1</sub>, e<sub>1</sub>, a<sub>1</sub> d abd<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub> ed<sub>1</sub>, 5<sub>1</sub> f 7<sub>1</sub>, e<sub>1</sub>, C<sub>1</sub>, d ea e. Vaga<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub> ed<sub>1</sub>, ca<sub>1</sub>, f e<sub>1</sub>, a<sub>1</sub> d a<sub>1</sub>, d<sub>1</sub> g<sub>1</sub> f ca<sub>1</sub>, e<sub>1</sub> ed<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub> a<sub>1</sub> f<sub>1</sub>, fa<sub>1</sub> a<sub>1</sub> c<sub>1</sub>, e<sub>1</sub> c a TNF- $\alpha$ , d IL-18<sub>1</sub>, e<sub>1</sub>, afe 3<sub>1</sub>, f ea<sub>1</sub>, e<sub>1</sub>, [34].  $\alpha$ , a<sub>1</sub>, d ec<sub>1</sub>, a<sub>1</sub>, f aga f be<sub>1</sub> ed, ced<sub>1</sub>, fa<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub>, de<sub>1</sub>, g c<sub>1</sub>, a a e b<sub>1</sub>, a g af<sub>1</sub>, g<sub>1</sub>, gga<sub>1</sub>, g a VNS<sub>1</sub> a<sub>1</sub>, e<sub>1</sub>, a<sub>1</sub>, ef<sub>1</sub>, a<sub>1</sub> f de<sub>1</sub>, c e<sub>1</sub>, g<sub>1</sub>, e<sub>1</sub>, fa<sub>1</sub>, e<sub>1</sub>, [36]. A<sub>1</sub>, a<sub>1</sub>, ca<sub>1</sub>, a a e c<sub>1</sub>, e<sub>1</sub>, ge<sub>1</sub>, d<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub> (ca<sub>1</sub> a<sub>1</sub> g<sub>1</sub>, #NCT04053127), ea<sub>1</sub>, e<sub>1</sub>, ca<sub>1</sub> a<sub>1</sub> g<sub>1</sub>, #NCT03425422), a<sub>1</sub>, c b a<sub>1</sub>, ca<sub>1</sub> a<sub>1</sub> g<sub>1</sub>, #NCT02974959), a<sub>1</sub>, d a<sub>1</sub>, ca<sub>1</sub> a<sub>1</sub> g<sub>1</sub>, #NCT03533140). C<sub>1</sub>, ca<sub>1</sub>, VNS<sub>1</sub> a<sub>1</sub>, be a<sub>1</sub>, e<sub>1</sub> ed<sub>1</sub>, a<sub>1</sub> ac<sub>1</sub>, g ca<sub>1</sub>, a e<sub>1</sub>, ca<sub>1</sub>, a<sub>1</sub>, e c<sub>1</sub>, ca<sub>1</sub>, aga<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, e ea<sub>1</sub>, b a e c<sub>1</sub>, ac<sub>1</sub>, c<sub>1</sub>, e (Table 1). I<sub>1</sub>, a<sub>1</sub>, c<sub>1</sub>, AC R<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, e e<sub>1</sub>, e<sub>1</sub>, f ACE2 [13–15], c<sub>1</sub>, a b e<sub>1</sub>, d e f e d a<sub>1</sub>, e<sub>1</sub>, e a g e e c e f SARS-C V2 [37]. T<sub>1</sub>, a<sub>1</sub>, aga<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub>, SARS-C V2 a<sub>1</sub>, aga<sub>1</sub>, b<sub>1</sub>, g ACE2 e<sub>1</sub>, e<sub>1</sub>, g<sub>1</sub>, ce<sub>1</sub>, e<sub>1</sub>, aga f be<sub>1</sub> a<sub>1</sub>, e<sub>1</sub>, a e e ea<sub>1</sub>, e ag<sub>1</sub>, a<sub>1</sub>, d a<sub>1</sub>, c<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub>, e a e b e<sub>1</sub>, a g e d f<sub>1</sub>, e VNS. T e<sub>1</sub>, ca<sub>1</sub>, ed “ e a ” VNS a<sub>1</sub>, c<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, age<sub>1</sub>, b<sub>1</sub>, a<sub>1</sub>, ba<sub>1</sub>, a a c a ed<sub>1</sub>, g<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub>, c<sub>1</sub>, a<sub>1</sub>, da<sub>1</sub>, d<sub>1</sub>, e<sub>1</sub>. Rece<sub>1</sub>, a<sub>1</sub>, c<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub>, VNS<sub>1</sub> a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, ed<sub>1</sub>, a<sub>1</sub>, g<sub>1</sub>, ag<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, g<sub>1</sub> f ca<sub>1</sub>, dec ea e<sub>1</sub>, e<sub>1</sub>, fa<sub>1</sub>, a<sub>1</sub>, d a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, d<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, [38].  $\alpha$ , a<sub>1</sub>, a<sub>1</sub>, d<sub>1</sub>, ed<sub>1</sub>, a<sub>1</sub>, c<sub>1</sub>, g<sub>1</sub>, e a VNS<sub>1</sub> a<sub>1</sub>, g<sub>1</sub>, e<sub>1</sub>, e c a d ac<sub>1</sub>, g- ca<sub>1</sub>, e<sub>1</sub>, (f 72- d<sub>1</sub>), e d e a<sub>1</sub>, e<sub>1</sub>, f<sub>1</sub>, e<sub>1</sub>, e a a f f a<sub>1</sub>, a<sub>1</sub>, ed, ced b “ e a ” VNS [39]. S<sub>1</sub>, a<sub>1</sub>, f ca<sub>1</sub>, e<sub>1</sub>, TNF- $\alpha$ , d IL-6<sub>1</sub>, e a<sub>1</sub>, e b<sub>1</sub>, g f ca<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub>, e a VNS g<sub>1</sub>, a f<sub>1</sub>, S a - $\alpha$ , ed<sub>1</sub>, d<sub>1</sub>, a<sub>1</sub>, g e<sub>1</sub>, f VNS a<sub>1</sub>, d<sub>1</sub>, e f a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, a<sub>1</sub>, dec ea ed<sub>1</sub>, c<sub>1</sub>, e a<sub>1</sub>, f TNF- $\alpha$ , d CRP. Of<sub>1</sub>, e<sub>1</sub>, e a<sub>1</sub>, f e<sub>1</sub>, fa<sub>1</sub>, a<sub>1</sub>, b<sub>1</sub>, a<sub>1</sub>, e<sub>1</sub>, e<sub>1</sub>

## Targeting the Cholinergic Anti-inflammatory Pathway via Vagus Nerve Stimulation

E de ca f e ag e e a bee  
 ed a d a ca e FDA a a  
 ga ed f e ea e f ef ac e 1997 a d f  
 e ea e f c c de e 2005. T e e ea e  
 a e aga be afe a d g f  
 ca de effec VNS a a bee a ga ed f e e  
 fa a d de c a e a d a [34]

[illegible]

S a e g	Age <sub>1</sub> / e o <sub>1</sub> a <sub>1</sub> g
P a a c a g c a	-N <sub>1</sub> c <sub>1</sub> e -GTS <sub>21</sub> , a <sub>1</sub> AC R a g <sub>1</sub>
Ne <sub>1</sub> d <sub>1</sub> a <sub>1</sub> e <sub>1</sub> / e <sub>1</sub>	-I <sub>1</sub> v <sub>1</sub> a <sub>1</sub> b e c <sub>1</sub> f f b a e d VNS -T a <sub>1</sub> c <sub>1</sub> a <sub>1</sub> e <sub>1</sub> / e <sub>1</sub> e <sub>1</sub> e <sub>1</sub> VNS <sub>1</sub> a <sub>1</sub> e <sub>1</sub> e <sub>1</sub> e <sub>1</sub> -E e c <sub>1</sub> a c <sub>1</sub> c <sub>1</sub> e <sub>1</sub> -S v <sub>1</sub> e <sub>1</sub> e <sub>1</sub> e <sub>1</sub> e <sub>1</sub>



**Figure 1** Cytokine release, vagus nerve, ACE2, RAAS Activation, Cytokine Release, Immune Cell Entry, ACh release, Syndrome. ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

cardiac effect. A study [40] showed that VNS (Vagus Nerve Stimulation) can reduce the release of inflammatory cytokines and improve the immune response. The study [40] was a randomized controlled trial (RCT) with the following details: #NCT04341415. The study [40] was a randomized controlled trial (RCT) with the following details: #NCT04341415. The study [40] was a randomized controlled trial (RCT) with the following details: #NCT04341415.

A study [41] showed that VNS (Vagus Nerve Stimulation) can reduce the release of inflammatory cytokines and improve the immune response. The study [41] was a randomized controlled trial (RCT) with the following details: #NCT04171011. The study [41] was a randomized controlled trial (RCT) with the following details: #NCT04171011. The study [41] was a randomized controlled trial (RCT) with the following details: #NCT04171011.

## Conclusions

Efficiently, the study [41] showed that VNS (Vagus Nerve Stimulation) can reduce the release of inflammatory cytokines and improve the immune response. The study [41] was a randomized controlled trial (RCT) with the following details: #NCT04171011. The study [41] was a randomized controlled trial (RCT) with the following details: #NCT04171011.

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**Disclaimer** The authors declare that they have no conflict of interest. The authors declare that they have no conflict of interest. The authors declare that they have no conflict of interest.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest. The authors declare that they have no conflict of interest. The authors declare that they have no conflict of interest.

**Ethical Approval** The study was approved by the local ethics committee. The study was approved by the local ethics committee. The study was approved by the local ethics committee.

## References

1. Gao, K. J., Fed, J. A., Na, a, J., e a. (2020). C... 2019 (COVID-19) a d c a d a c a d e a e. *Circulation*.
2. Z..., F., Y., T., D., R., e a. (2020). ... COVID-19, W. a., O., a: a e ... *Lancet*.
3. R..., Q., Ya, g, K., Wa, g, W., a, g, L., & S..., J. (2020). ... COVID-19 ba ed ... *Intensive Care Med*.
4. H..., C., Wa, g, Y., X., e a. (2020). ... 2019 ... *Lancet*, 395, 497–506.
5. ..., M., ..., Y., Y., a, J. e a. (2020). T e v a d c a e f ... COVID-19 e e a d b ... *g-e* RNA e ... *g. ed*.
6. Me a, P., McA., e, D. F., B., ..., M., e a. (2020). COVID-19: c ... *Lancet*, 395, 1033–1034.
7. P..., E. K. (1982). A g ... *British Journal of Pharmacology*, 75, 9–11.
8. X., Z., ..., W., H., J., e a. (2017). A g ... *Scientific Reports*, 7, 44911.
9. M..., e, e, S., Ga., H., X., J., S., R., Z., b., A., & La ..., g. e, E. (2019). ACE2 a d ADAM17 I e ... *Hypertension*, 74, 1181–1191.
10. ..., H., Fe, g, Y., Ob., T. D., H., c., a., P. J., & La ..., g. e, E. (2009). A g ... *Hypertension*, 53, 210–216.
11. Haga, S., Ya a ..., N., Na ..., M. a ..., C., e a. (2008). M d ... *Proceedings of the National Academy of Sciences of the United States of America*, 105, 7809–7814.
12. K. ba, K., I ..., Y., Ra., S., e a. (2005). A c ... *Nature Medicine*, 11, 875–879.
13. Oa e, J. M., F. c., R. M., Ga d, e, J. D., La ..., g. e, E., & Y. e, X. (2018). ... *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 315, R895–R906.
14. Fe ..., M. F., Na ada, M. K., & F..., -C ..., D. R. (2008). ... WKY a d SHR ... *Journal of Molecular Neuroscience*, 35, 151–160.
15. Fe ..., M. F., Na ada, M. K., & F..., -C ..., D. R. (2007). ... *Journal of Molecular Neuroscience*, 33, 284–293.
16. U..., a, L. (2005). T e, a g, ..., e a d ... *Nature Reviews. Drug Discovery*, 4, 673–684.
17. L..., e, M. T., & T ace, K. J. (2005). H g - ... (HMGB1), ... *Nature Reviews. Immunology*, 5, 331–342.
18. T ace, K. J. (2002). T ..., fa a ..., e k e. *Nature*, 420, 853–859.
19. Ba ..., G. S., Ka, a ..., A., O., b a, N. C., Te ..., d, N., Ma ..., e, W., & U..., a, L. (2020). A, a ..., ca a d ... *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, 9, 943–950.
20. H., ..., J. M., O ..., M., R., a -B ..., a, M., e a. (2006). S ..., e ..., a e e c ..., fa a ..., a a d ..., g e a e d ... *The Journal of Experimental Medicine*, 203, 1623–1628.
21. ..., W., & O ..., B. (2011). I, fa a c ..., e a, ... *Heart Failure Reviews*, 16, 137–145.
22. Z a., Y. X., He, W., ..., g, X. H., e a. (2012). T a, c, a, e, ..., a c, a, a g, ..., e e ..., e c ..., e d ..., c a f, ..., acc ..., d, c e d ..., fa ..., *Evidence-based Complementary and Alternative Medicine*, 2012, 627023.
23. S..., g, X. M., ..., J. G., Wa, g, Y. L., e a. (2008). T e, ..., e effe ..., e c ..., e c ..., fa a ..., a a d ..., e c ..., a ..., *Shock*, 30, 468–472.
24. d ..., S..., C. C., S a., Y., A ..., A., S., ..., A. S., & Na ..., a, J. J. (2011). Ne ..., ..., e g ..., ..., f ..., a ..., d, c e d ..., g ..., *American Journal of Respiratory and Critical Care Medicine*, 183, 471–482.
25. Le ..., G., F ..., a., J. E., X., D. Z., e a. (2012). V a g, ..., e ..., d, a e g ..., ..., a d, ..., g e e ..., a, a - ..., e ..., c ..., *Journal of Trauma and Acute Care Surgery*, 73, 338–342.
26. ..., We e, D. J., G e b a e, I. A., M e e, J. C., e a. (2006). V a g, ..., e ..., ..., f c a g, ..., a, d f - ..., ..., g e d ..., a ..., *Journal of Thrombosis and Haemostasis*, 4, 1997–2002.
27. C ..., J. M., & Le ..., J. H. (2020). T ..., fa ..., a d ..., e c a g, ..., f COVID-19. *Journal of Thrombosis and Haemostasis*.
28. A c ..., G. L., W ..., e, J., T ..., e, A., e a. (2016). M ..., a e c ..., g a, ..., c d ..., a ..., e d c a d a c ..., ..., c a ..., e ..., *Critical Care Medicine*, 44, e614–e624.
29. H., ..., J. M., & T ace, K. J. (2011). T e, ..., e ..., fa ..., : e a ..., e c ..., e c ..., fa a ..., a a ..., ..., f ..., e a ..., *Journal of Internal Medicine*, 269, 45–53.
30. MMTFPM-PCPJH, da ...
31. Ma ..., a, K., K ..., T. W., F ed ..., & Ya a ..., Y. (2001). I, ..., e ..., c a c e c ..., e e c e - ..., f a c ..., a a ..., a d c ..., e e ..., f a, e a, a c ..., a g e, L o g ..., a a /, e, ..., f e b ..., e. *Journal of Immunology*, 167, 6518–6524.
32. Ma a a, Y., H ..., A., Ya a ..., Y., e a. (2005). W ..., e d, a e c ..., e d, ..., b C a ..., a /, e, ..., f e c e d ..., a ..., e a b ..., d c a, *International Immunopharmacology*, 5, 749–756.
33. E e e -Bae, M., C a c a e -N a ..., C., Ja -G a c a, J. D., e a. (2019). I, f ..., e f e a a e, a g e, a d g e d ..., e a a e, ..., a d, e e, ..., a d, ..., g a d, *Advances in Experimental Medicine and Biology*, 1133, 19–33.
34. K ..., a., F. A., C a ..., S. S., M ..., S., e a. (2016). V a g, ..., e ..., ..., c ..., e ..., d ..., a d a ..., a e d - e a e ..., e, ..., a d a ..., *Proceedings of the National Academy of Sciences of the United States of America*, 113, 8284–8289.
35. B ..., a, B., S ..., g e, V., H ff ..., D., e a. (2016). C ..., a g, ..., e, e ..., C ..., e a e: a 6- ..., f ..., ..., d ..., *Neurogastroenterology and Motility*, 28, 948–953.
36. R ..., P., R ..., A., De P ..., R., e a. (2012). I, c a d a g a, ..., a d e ..., ..., d e c e a e ..., ..., fa a ..., *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, 9, 943–950.



37. Huang I., M., Kuehl-Wedde, H., Scuderi, S., et al. (2020). SARS-CoV-2 causes direct ACE2 and TMPRSS2 activation leading to viral release. *Cell*, 181, 271–280 e8.
  38. Squitieri, S., Hillier, M.B., Scuderi, B.J., et al. (2015). Lipid metabolism, calcium signaling, and electrical coupling in cardiac myocytes. *Journal of the American College of Cardiology*, 65, 867–875.
  39. Squitieri, S., Hillier, M.B., Scuderi, B., et al. (2017). Lipid metabolism, calcium signaling, and electrical coupling in cardiac myocytes. *JACC: Clinical Electrophysiology*, 3, 929–938.
  40. Caffrey, M. (2020). A COVID-19 pandemic. *Cardiovascular Research*.
  41. Saad, P., Gnanapavan, G., Baig, J., Nabeeb, E., & Leck, R.M. (2020). Update on COVID-19 management. *Cardiovascular Research*.
  42. Vada, G., Pez, A.G., Dece, E.A., & Ure, L. (2011). A novel cardiac gene expression profile associated with heart failure. *Journal of Immunology*, 186, 4340–4346.
  43. Gupta, S.P.C., Laegle, J., Sa, A., Veledakis, M., Garg, A., N., Baric, P., et al. (2020). Novel cardiac biomarkers for COVID-19. *2019 ACR/ARP Abstracts Meeting 2019*.
  44. Zaccaro, D.P., Offord, S.J., Galarza, R.S., et al. (2019). Myocardial injury in COVID-19. *Nature Communications*, 10, 951.
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