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Cerebral Blood Flow in Chronic Kidney Disease

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Abstract

The prevalence of mild cognitive impairment increases with age and is further exacerbated by chronic kidney disease (CKD). CKD is associated with (1) mild cognitive impairment, (2) impaired endothelial function, (3) impaired blood-brain barrier, (4) increased cerebral microhemorrhage burden, (5) increased cerebral blood flow (CBF), (6) impaired cerebral autoregulation, (7) impaired cerebrovascular reactivity, and (8) increased arterial stiffness. We report preliminary findings from our group that demonstrate altered cerebrovascular reactivity in a mouse model of CKD-associated vascular calcification. The CBF of CKD mice increased more quickly in response to hypercapnia ($p < 0.05$) but then decreased prematurely during hypercapnia challenge ($p < 0.05$). Together, these results indicate that altered kidney function can lead to alterations in the cerebral microvasculature, and hence brain health.

Keywords

Chronic kidney disease; Laser speckle contrast imaging; Cerebral blood flow; Vascular dysfunction; Vasomotor reactivity; Speckle contrast

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Introduction

Mild cognitive impairment affects 6.7–25.2% of individuals over the age range of 60 to 84 years old.[1] The prevalence of mild cognitive impairment increases with age and is further exacerbated by chronic kidney disease (CKD).[2–4] A study of over one million subjects revealed that there is an eightfold increase in the incidence rate of dementia in patients with end-stage kidney disease.[5]

A current overarching hypothesis is that abnormal cerebral blood flow (CBF) is a precursor to cognitive impairment.[6] A study of 1730 adults revealed that low CBF velocity in the middle cerebral artery, measured with transcranial Doppler, was a risk factor for cognitive decline and atrophy in the hippocampus and amygdala.[7] In the Rotterdam Study which excluded end-stage kidney disease patients, analysis of over 2500 participants demonstrated that lower kidney function was independently associated with lower cerebral blood flow measured by MRI[8] Interestingly, a *higher* CBF has been observed in patients with end-stage kidney disease.[9,10] This elevated CBF is associated with a lower hemoglobin content. In pediatric patients, regions of increased CBF have been observed, but the bulk regional CBF is not significantly different.[11]

Here, we discuss recent journal articles that describe associations between CKD and the cerebral microvasculature. We then report on preliminary findings that demonstrate that cerebrovascular reactivity is altered in a mouse model of CKD. Together, these results indicate that altered kidney function can lead to alterations in the cerebral microvasculature, and hence brain health.

Associations betweeen CKD and cerebral microvasculature

With CKD, the clearance of uremic toxins is reduced, which in turn can lead to global vascular dysfunction.[4] Multiple serum biomarkers of endothelial dysfunction, including sVCAM–1 and thrombomodulin, are elevated in patients with stage 5 CKD.[12] Also, CKD is associated with increased blood-brain barrier (BBB) permeability.

Using IgG as a marker of increased BBB permeability,[13] Lau et al.[14] observed a tenfold increase in IgG immunostaining in mice with CKD. They also observed an increased cerebral microhemorrhage burden with CKD. Specifically, they observed a twofold increase in CMH burden and a fourfold increase in the area of each CMH in mice with CKD.

Increased BBB permeability may be a consequence of impaired cerebral autoregulation associated with CKD. Castro et al.[15] performed transcranial Doppler measurements of blood flow in the middle cerebral artery of 46 subjects with ischemic stroke. Frequency and coherence analysis of the Doppler waveforms enable assessment of cerebral autoregulation. Their analyses indicate an increased degree of impaired cerebral autoregulation with increased CKD severity. Impaired autoregulation can lead to an increased pressure across the capillary bed, which can result in capillary damage and increased BBB permeability.[16]

Pilot preclinical study on CBF in CKD model

Cerebrovascular reactivity is altered in people with a history of stroke or individual suffering from dementia.[17–21] Individuals in early stages of Alzheimer's disease have impaired cerebrovascular reactivity compared to those with normal cognitive function.[22] Using laser speckle imaging (LSI) measurements of CBF, Shin et al.[23] demonstrated that hyperemia associated with hypercapnia was attenuated in aged wild-type mice, and further attenuated in Tg2576 mice with cerebral amyloid angiopathy. Using two-photon excited fluorescence microscopy, Han et al.[24] demonstrated decreased cerebrovascular reactivity in Tg2576 mice with considerable vascular amyloid deposition, and this decreased reactivity was associated with a hypercontractile vascular state. Also using LSI, Saito et al.[25] measured a decrease in cerebrovascular reactivity in Tg-SwDI mice, and demonstrated near-complete restoration of reactivity in Tg-SwDI mice treated with taxifolin.

To investigate the effects of CKD on cerebral blood flow, we utilized the DBA/2J mouse strain, which is well-known to develop bone/mineral abnormalities including elevated parathyroid hormone, arterial calcification and high-turnover bone disease when subjected to CKD and high-phosphate feeding.[26,27] Female DBA/2J mice were fed a diet containing 0.2% adenine for 18 days to incur tubulointerstitial nephritis, followed by high-phosphate diet for 4 weeks to induce arterial calcification. Mice were exposed to a second period of adenine diet for one week in the middle of the 4-week high-phosphate course, to maintain CKD.[27,28] In accordance with a protocol approved by the Animal Use Committee at University of California, Irvine, each mouse was anesthetized with isoflurane (1.5–2.0%, balance room air) and placed in a stereotactic frame. A midline incision in the scalp was made to enable visualization of brain regions between lambda and bregma. The exposed skull was hydrated with saline and a glass cover slip placed on top to maintain skull hydration and hence transparency. We used a custombuilt LSI device to measure blood flow dynamics in response to a hypercapnia protocol we previously used in a preclinical study of Alzheimer's disease.[29] We collected images during (1) normoxia for three min, (2) hypercapnia (mixture of 5% CO2 and 95% room air) for five min, and (3) normoxia for five min.

We used standard LSI processing techniques[30] to convert each raw speckle image to a speckle flow index (SFI) of blood flow, using a simplified speckle imaging equation.[31] For each subject, a ROI was identified and analyzed from each image in the acquired sequence. We then calculated the mean SFI of the ROI from each image and extracted the following key parameters: (1) peak increase in CBF during hypercapnia (ΔBF_{max}), (2) time required for CBF to increase from baseline to 50% of ΔBF_{max} (t_{rise}), and (3) time required for CBF to decrease from ΔBF_{max} back to 50% of ΔBFmax (t_{fall}).

No difference in the maximum increase in CBF was found [Fig. 1A,B (left)]. In contrast, the characteristic time t_{rise} required for the CBF to increase was shorter for the CKD mice [Fig. 1B (middle)]. Moreover, the characteristic time t_{fall} was shorter for the CKD mice [Fig. 1B (right)]. Together, these results suggest that cerebrovascular dysfunction is triggered by kidney damage induced by uremic vascular calcification.

Arterial medial calcification is associated with CKD, resulting in part from calcium and phosphorous release from bone, elastin degradation, and loss of endogenous inhibitors of calcification including klotho and fetuin-A.[32,33] Transcranial Doppler measurements have revealed an inverse association between degree of cerebral artery stenosis and stiffness, and CKD.[34,35] Our data demonstrated abnormal cerebrovascular reactivity that is suggestive of increased cerebrovascular stenosis and/or stiffness. Taken together, there is growing evidence that CKD cerebrovascular disease alters CBF and vascular function, and may contribute to cognitive impairment.

In summary, results from the literature, combined with our preliminary findings, collectively indicate that CKD leads to impaired cerebrovascular structure and function. In particular, we document that CKD is associated with (1) mild cognitive impairment, (2) impaired endothelial function, (3) impaired blood-brain barrier, (4) increased CMH burden, (5) increased CBF, (6) impaired cerebral autoregulation, and (7) impaired cerebrovascular reactivity that may be due to increased arterial stenosis and/or stiffness. Additional research is required to study the effects of CKD on structure and function of the neurovascular unit and on cognition.

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References

1. Petersen RC, Lopez O, Armstrong MJ, et al.Practice guideline update summary: mild cognitive impairment: report of the guideline development, dissemination, and implementation subcommittee of the american academy of neurology. Neurology2018;90(3):126–135. 10.1212/WNL.0000000000004826. [PubMed: 29282327]
2. Brodski J, Rossell SL, Castle DJ, Tan EJ. A systematic review of cognitive impairments associated with kidney failure in adults before natural age-related changes. J Int Neuropsychol Soc2019;25(1):101–114. 10.1017/S1355617718000917. [PubMed: 30463631]
3. Kurella M, Chertow GM, Fried LF, et al.Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. J Am Soc Nephrol2005;16(7):2127–2133. 10.1681/ASN.2005010005. [PubMed: 15888561]
4. Viggiano D, Wagner CA, Martino G, et al.Mechanisms of cognitive dysfunction in CKD. Nat Rev Nephrol2020;16 (8):452–469. 10.1038/s41581-020-0266-9. [PubMed: 32235904]
5. Kuo YT, Li CY, Sung JM, et al.Risk of dementia in patients with end-stage renal disease under maintenance dialysis-a nationwide population-based study with consideration of competing risk of mortality. Alzheimers Res Ther2019;11(1):31. 10.1186/s13195-019-0486-z.Published 2019 Apr 9. [PubMed: 30967155]

6. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol2018;14(3):133–150. 10.1038/nrneurol.2017.188. [PubMed: 29377008]
7. Ruitenberg A, den Heijer T, Bakker SL, et al.Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. Ann Neurol2005;57(6):789–794. 10.1002/ana.20493. [PubMed: 15929050]
8. Sedaghat S, Vernooij MW, Loehrer E, et al.Kidney function and cerebral blood flow: the Rotterdam Study. J Am Soc Nephrol2016;27(3):715–721. 10.1681/ASN.2014111118. [PubMed: 26251352]
9. Jiang XL, Wen JQ, Zhang LJ, et al.Cerebral blood flow changes in hemodialysis and peritoneal dialysis patients: an arterial-spin labeling MR imaging. Metab Brain Dis2016;31 (4):929–936. 10.1007/s11011-016-9829-7. [PubMed: 27167984]
10. Cheng BC, Chen PC, Chen PC, et al.Decreased cerebral blood flow and improved cognitive function in patients with end-stage renal disease after peritoneal dialysis: an arterial spin-labelling study. Eur Radiol2019;29(3):1415–1424. 10.1007/s00330-018-5675-9. [PubMed: 30105409]
11. Liu HS, Hartung EA, Jawad AF, et al.Regional cerebral blood flow in children and young adults with chronic kidney disease. Radiology2018;288(3):849–858. 10.1148/radiol.2018171339. [PubMed: 29893643]
12. Gennip ACEV, Broers NJH, Meulen KJT, et al.Endothelial dysfunction and low-grade inflammation in the transition to renal replacement therapy. PLOS One2019;14 (9):0222547. 10.1371/journal.pone.0222547. Published 2019 Sep 13.
13. Seitz RJ, Heininger K, Schwendemann G, Toyka KV, Wechsler W. The mouse blood-brain barrier and blood-nerve barrier for IgG: a tracer study by use of the avidinbiotin system. Acta Neuropathol1985;68(1):15–21. 10.1007/BF00688950. [PubMed: 3901654]
14. Lau WL, Nunes ACF, Vasilevko V, et al.Chronic kidney disease increases cerebral microbleeds in mouse and man. Transl Stroke Res2020;11(1):122–134. 10.1007/s12975-019-00698-8. [PubMed: 31055735]
15. Castro P, Azevedo E, Rocha I, Sorond F, Serrador JM. Chronic kidney disease and poor outcomes in ischemic stroke: is impaired cerebral autoregulation the missing link?BMC Neurol2018;18(1):21. 10.1186/s12883-018-1025-4.Published 2018 Mar 2 [PubMed: 29499637]
16. Panerai RB. Assessment of cerebral pressure autoregulation in humans-a review of measurement methods. Physiol Meas1998;19(3):305–338. 10.1088/0967-3334/19/3/001. [PubMed: 9735883]
17. Iadecola CThe pathobiology of vascular dementia. Neuron2013;80(4):844–866. 10.1016/j.neuron.2013.10.008. [PubMed: 24267647]
18. Silvestrini M, Pasqualetti P, Baruffaldi R, et al.Cerebrovascular reactivity and cognitive decline in patients with Alzheimer disease. Stroke2006;37(4):1010–1015. 10.1161/01.STR.0000206439.62025.97. [PubMed: 16497984]
19. Glodzik L, Randall C, Rusinek H, de Leon MJ. Cerebrovascular reactivity to carbon dioxide in Alzheimer's disease. J Alzheimers Dis2013;35(3):427–440. 10.3233/JAD-122011. [PubMed: 23478306]
20. Vicenzini E, Ricciardi MC, Altieri M, et al.Cerebrovascular reactivity in degenerative and vascular dementia: a transcranial Doppler study. Eur Neurol2007;58(2):84–89. 10.1159/000103642. [PubMed: 17565221]
21. Miller KB, Howery AJ, Harvey RE, Eldridge MW, Barnes JN. Cerebrovascular reactivity and central arterial stiffness in habitually exercising healthy adults. Front Physiol2018;9:1096. 10.3389/fphys.2018.01096.Published 2018 Aug 17. [PubMed: 30174609]
22. Den Abeelen AS, Lagro J, Van Beek AH, Claassen JA. Impaired cerebral autoregulation and vasomotor reactivity in sporadic Alzheimer's disease. Curr Alzheimer Res2014;11(1):11–17. 10.2174/1567205010666131119234845. [PubMed: 24251392]
23. Shin HK, Jones PB, Garcia-Alloza M, et al.Age-dependent cerebrovascular dysfunction in a transgenic mouse model of cerebral amyloid angiopathy. Brain2007;130(Pt 9):2310–2319. 10.1093/brain/awm156. [PubMed: 17638859]
24. Han BH, Zhou ML, Johnson AW, et al.Contribution of reactive oxygen species to cerebral amyloid angiopathy, vasomotor dysfunction, and microhemorrhage in aged Tg2576 mice. Proc Natl Acad Sci USA2015;112(8):E881–E890. 10.1073/pnas.1414930112. [PubMed: 25675483]

25. Saito S, Yamamoto Y, Maki T, et al.Taxifolin inhibits amyloid-β oligomer formation and fully restores vascular integrity and memory in cerebral amyloid angiopathy. Acta Neuropathol Commun2017;5(1):26. 10.1186/s40478-017-0429-5.Published 2017 Apr 4. [PubMed: 28376923]
26. Lau WL, Leaf EM, Hu MC, et al.Vitamin D receptor agonists increase klotho and osteopontin while decreasing aortic calcification in mice with chronic kidney disease fed a high phosphate diet. Kidney Int2012;82(12):1261–1270. 10.1038/ki.2012.322. [PubMed: 22932118]
27. Lau WL, Linnes M, Chu EY, et al.High phosphate feeding promotes mineral and bone abnormalities in mice with chronic kidney disease. Nephrol Dial Transplant2013;28(1):62–69. 10.1093/ndt/gfs333. [PubMed: 23045434]
28. Lau WL, Liu S, Vaziri ND. Chronic kidney disease results in deficiency of ABCC6, the novel inhibitor of vascular calcification. Am J Nephrol2014;40(1):51–55. 10.1159/000365014. [PubMed: 24994603]
29. Lin AJ, Liu G, Castello NA, et al.Optical imaging in an Alzheimer's mouse model reveals amyloid-β-dependent vascular impairment. Neurophotonics2014;1(1):011005. 10.1117/1.NPh.1.1.011005. [PubMed: 25133200]
30. Choi B, Tan W, Jia W, et al.The role of laser speckle imaging in port-wine stain research: recent advances and opportunities. IEEE J Sel Top Quantum Electron2016;2016 (3):6800812. 10.1109/JSTQE.2015.2493961. [PubMed: 27013846]
31. Ramirez-San-Juan JC, Ramos-García R, Guizar-Iturbide I, Martínez-Niconoff G, Choi B. Impact of velocity distribution assumption on simplified laser speckle imaging equation. Opt Express2008;16(5):3197–3203. 10.1364/oe.16.003197. [PubMed: 18542407]
32. Reiss AB, Miyawaki N, Moon J, et al.CKD, arterial calcification, atherosclerosis and bone health: Inter-relationships and controversies. Atherosclerosis2018;278:49–59. 10.1016/j.atherosclerosis.2018.08.046. [PubMed: 30253289]
33. Lau WL, Ix JH. Clinical detection, risk factors, and cardiovascular consequences of medial arterial calcification: a pattern of vascular injury associated with aberrant mineral metabolism. Semin Nephrol2013;33(2):93–105. 10.1016/j.semnephrol.2012.12.011. [PubMed: 23465497]
34. Song X, Li J, Hua Y, et al.Chronic kidney disease is associated with intracranial artery stenosis distribution in the middle-aged and elderly population. J Atheroscler Thromb2020;27(3):245–254. 10.5551/jat.49569. [PubMed: 31462617]
35. Kim ED, Tanaka H, Ballew SH, et al.Associations between kidney disease measures and regional pulse wave velocity in a large community-based cohort: the atherosclerosis risk in communities (ARIC) study. Am J Kidney Dis2018;72(5):682–690. 10.1053/j.ajkd.2018.04.018. [PubMed: 30007506]

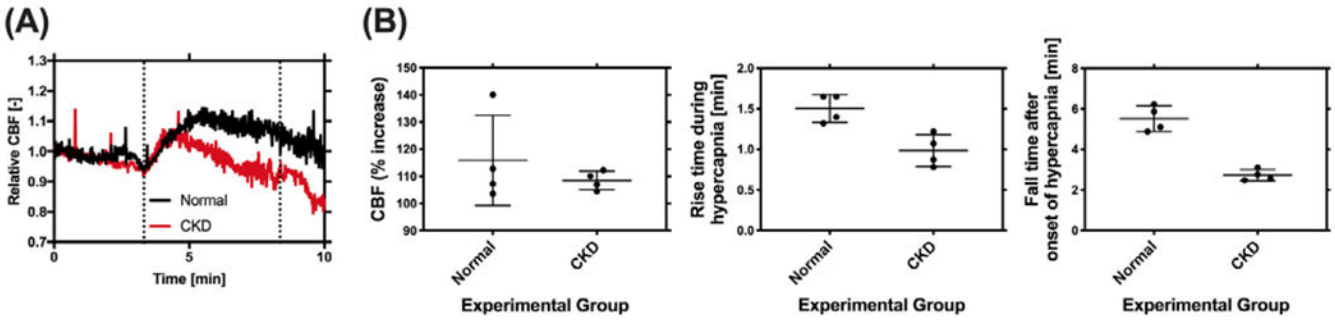

Fig. 1.

Differences in cerebral vascular reactivity between wild-type ("Normal") and mice with uremic vascular calcification ("CKD", chronic kidney disease). (A) Representative time traces of CBF changes in normal and CKD mice. (B) Although the maximum increase in CBF was similar for normal and CKD mice (left graph, Mann-Whitney test, $p = 0.69$*), the CBF of CKD mice increased more quickly in response to hypercapnia (middle graph,* $p < 0.05$*) but then decreased prematurely during hypercapnia challenge (right graph,* $p < 0.05$*). Dashed lines indicate period of hypercapnia.*