utilization. Further studies are needed to investigate methods to reduce post-CTO PCI hospitalizations in order to maximize the benefits from the procedure.

These results should be cautiously interpreted in the context of limitations for using administrative database to identify CTO PCI. First, we cannot ensure the success of the procedure which may affect the postprocedure readmission rates however this is likely a small number, and that does not explain the increase in the hospitalization rates post-CTO PCI. Second, we may have captured non-CTO PCI patients; however it is less likely since we limited our cohort to a single-vessel PCI, excluded patients with ACS event, and the current practice paradigm favors coronary artery bypass graft for patient with multivessel coronary artery disease.[4] Finally, this analysis is restricted to inpatient procedures only, and does not capture outpatient CTO PCI, which is a big portion of this patient population with a possible different patient risk profile between both groups.

Funding

Self-funded.

Disclosure

The authors have nothing to disclose, and no relationship with industry.

Ahmed Elkaryoni, MD[a]
Islam Y. Elgendy, MD[b]
Ivo Genev, MD[c]
Mahmoud Khalil, MD, MSc[d]
Amir Darki, MD, MSc[ac*]

[a] Division of Cardiovascular Disease, Loyola University Medical Center, Loyola Stritch School of Medicine, Maywood, Illinois
[b] Division of Cardiovascular disease, Weill Cornell Medicine-Qatar, Doha, Qatar
[c] Department of Internal Medicine, Loyola University Medical Center, Loyola Stritch School of Medicine, Maywood, Illinois
[d] Lincoln Medical Center, New York
30 November 2020

1. Brilakis ES, Mashayekhi K, Tsuchikane E, Abi Rafeh N, Alaswad K, Araya M, Avran A, Azzalini L, Babunashvili AM, Bayani B, Bhindi R, Boudou N, Boukhris M, NŽ Božinović, Bryniarski L, Bufe A, Buller CE, Burke MN, Büttner HJ, Cardoso P, Carlino M, Christiansen EH, Colombo A, Croce K, Damas de Los Santos F, De Martini T, Dens J, Di Mario C, Dou K, Egred M, ElGuindy AM, Escaned J, Furkalo S, Gagnor A, Galassi AR, Garbo R, Ge J, Goel PK, Goktekin O, Grancini L, Grantham JA, Hanratty C, Harb S, Harding SA, Henriques JPS, Hill JM, Jaffer FA, Jang Y, Jussila R, Kalnins A, Kalyanasundaram A, Kandzari DE, Kao HL, Karmpaliotis D, Kassem HH, Knaapen P, Kornowski R, Krestyaninov O, Kumar AVG, Laanmets P, Lamelas P, Lee SW, Lefevre T, Li Y, Lim ST, Lo S, Lombardi W, McEntegart M, Munawar M, Navarro Lecaro JA, Ngo HM, Nicholson W, Olivecrona GK, Padilla L, Postu M, Quadros A, Quesada FH, Prakasa Rao VS, Reifart N, Saghatelyan M, Santiago R, Sianos G, Smith E, C Spratt J, Stone GW, Strange JW, Tammam K, Ungi I, Vo M, Vu VH, Walsh S, Werner GS, Wollmuth JR, Wu EB, Wyman RM, Xu B, Yamane M, Ybarra LF, Yeh RW, Zhang Q, Rinfret S. Guiding principles for chronic total occlusion percutaneous coronary intervention. *Circulation* 2019;140:420–433.
2. Sapontis J, Salisbury AC, Yeh RW, Cohen DJ, Hirai T, Lombardi W, McCabe JM, Karmpaliotis D, Moses J, Nicholson WJ, Pershad A, Wyman RM, Spaedy A, Cook S, Doshi P, Federici R, Thompson CR, Marso SP, Nugent K, Gosch K, Spertus JA, Grantham JA. Early procedural and health status outcomes after chronic total occlusion angioplasty: a report from the OPEN-CTO registry (outcomes, patient health status, and efficiency in chronic total occlusion hybrid procedures). *JACC Cardiovasc Interv* 2017;10:1523–1534.
3. Overview of the Nationwide Readmissions Database (NRD). Healthcare Cost and Utilization Project (HCUP). https://www.hcupus.ahrq.gov/nrdoverview.jsp.
4. Doshi R, Patel N, Kalra R, Arora H, Bajaj NS, Arora G, Arora P. Incidence and in-hospital outcomes of single-vessel coronary chronic total occlusion treated with percutaneous coronary intervention. *Int J Cardiol* 2018;269:61–66.
5. Elkaryoni A, Chhatriwalla AK, Kennedy KF, Saxon JT, Cohen DJ, Arnold SV. Change in hospitalization rates following transcatheter mitral valve repair: a nationwide cohort sample. *Circ Cardiovasc Interv* 2019;12:e008342.

https://doi.org/10.1016/j.amjcard.2020.12.011

The Chronic Kidney Disease Phenotype of HFpEF: Unique Cardiac Characteristics

Heart failure (HF) is highly prevalent in patients with chronic kidney disease (CKD), with HF with preserved ejection fraction (HFpEF) accounting for half of these cases.[1] CKD is independently associated with worse outcomes and higher mortality rates in patients with HFpEF.[2] With no proven therapies available to improve outcome in HFpEF patients, critical questions remain unsolved across the spectrum of HFpEF. One key question towards providing improved care for HFpEF is to discern whether subpopulations of HFpEF should be treated according to their pathophysiological phenotype. By assessing cardiac, exercise capacity, and body composition parameters and biomarkers, we aimed to characterize the phenotype of patients with HFpEF and CKD in order to identify pathophysiological mechanisms that are unique to this group.

Seventeen HFpEF patients with normal renal function (NRF) (Male/Female: 5/12; median [IQR] Age: 54 [50 to 60] years); N-terminal pro-brain natriuretic peptide (NTproBNP) 110 [48 to 255] pg/ml; estimated glomerular filtration rate (eGFR, by CKD EPI formula) 88 [75 to 96] ml/kg/1.73m^2) and 10 patients with HFpEF and CKD (Male/Female: 5/5; Age: 53 [47 to 67] years; NTProBNP 135.5 [33.0 to 333.3] pg/ml; eGFR 50 [42 to 57] ml/kg/1.73m^2) were studied. The investigation conformed with the principles outlined by the Declaration of Helsinki. Ethical approval was provided by the Virginia Commonwealth University Institutional Review Board and all participants provided written informed consent. A conservative ramping, maximal effort cardiopulmonary exercise test was performed on a treadmill as previously described.[3] Breath-by-breath gas analysis averaged over 10 seconds intervals was acquired with an automated gas analyzer to measure peak oxygen consumption (VO_{2peak}). Echocardiographic Doppler measures of systolic and diastolic function were performed at rest and at immediately postexercise. Measures included left ventricular ejection fraction, end-systolic volume index (LVESVI), end-diastolic volume index, mitral inflow velocities (E wave; A wave; E/A ratio; E wave deceleration time [DT]), early diastolic mitral annular velocity (e'), and e' indexed to DT (e'$_{DT}$). Diastolic function reserve index was calculated as e'$_{rest}$ x Δ e'$_{exercise}$. Body composition was estimated by single-frequency bioelectrical impedance analysis. Self-reported functional status

This work was supported by National Institutes of Health [R34HL118348; UL1TR000058] and the American Heart Association [19CDA34740002 to DK; 19CDA34660318 to SC].

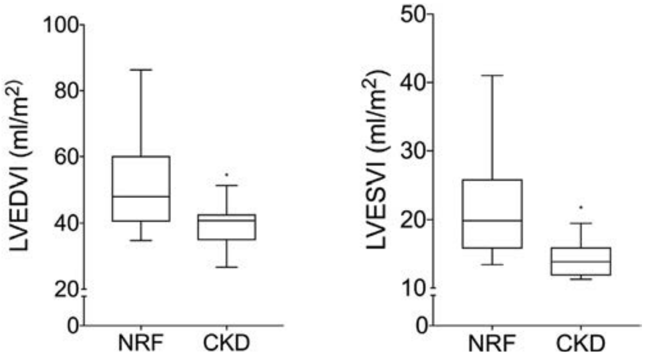

Figure 1. Smaller left ventricle volumes were evident in HFpEF patients with CKD compared to those with normal renal function. CKD, chronic kidney disease; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end -systolic volume index; NRF, normal renal function *, p<0.05.

and quality of life were obtained with the Duke Activity Status Index score and the Minnesota Living with Heart Failure Questionnaire respectively. Variables were compared between CKD and NRF with Mann-Whitney U tests. Correlations were assessed with Spearman's rho.

There were no differences in gender, age, race, and body composition between NRF and CKD patients. Compared with NRF, CKD patients had significantly lower end-diastolic volume index (CKD *vs* NRF: 40.78 [34.85 to 42.66] *vs* 48.06 [40.44 to 60.16] ml/1.73m^2, p = 0.03) and LVESVI (13.86 [11.84 to 15.94] *vs*19.86 [15.77 to 25.82] ml/1.73m^2, p = 0.03). These smaller LV volumes are indicative of disadvantageous LV geometry such as concentric remodeling or hypertrophy. Systolic function, reported as left ventricular ejection fraction, was greater in CKD patients (63 [62 to 66] *vs* 58[53 to 60]%, p = 0.04). However, CKD patients had worse diastolic function (E/A ratio: 0.87 [0.84 to 1.02] *vs* 1.10 [0.99 to 1.50], p = 0.02; DT: 204 [157 − 240] *vs* 265 [224 to 294] ms, p = 0.03; E'$_{DT}$: 0.27 [0.20 to 0.42] *vs* 0.47 [0.32 to 0.66], p = 0.01) compared with NRF. The differences in cardiac function between groups had no effect on exercise capacity (VO$_{2peak}$: 14.5 [11.3 to 19.0] *vs* 13.7 [12.4 to 16.2] ml/kg/min, p = 0.9) or self-reported functional status (16 [14 to 27] *vs* 25 [16 to 38], p = 0.2) or quality of life (65 [45 to 74] *vs* 48 [22 to 80], p = 0.6). Serum galectin-3 levels were significantly higher in CKD (24.2 [20.3 to 33.0] ng/ml) compared with NRF (17.5 [12.6 to 20.1] ng/ml, p = 0.002). In all patients, reduced kidney function (eGFR) was associated with increased galectin−3 levels (r = -0.71, p = 0.01). Additionally, increased galectin−3 levels were associated with impaired diastolic function (Δ e'$_{exercise}$: r = −0.7, p = 0.001; Diastolic function reserve index: r = −0.7, p < 0.003), reduced LVESVI (r = −0.5, p = 0.02) and lower VO$_{2peak}$ (r = −0.5, p = 0.02). In the CKD group, increased levels of galectin-3 was strongly associated with a higher fat mass index (FMI) (r = 0.89, p < 0.001) and a lower VO$_{2peak}$ (r = −0.8, p = 0.02). Furthermore, in this cohort an increased FMI was associated with a lower VO$_{2peak}$ (r = −0.78, p < 0.001). These associations were not evident in the NRF group.

The results of this study propose Galectin-3 as a biomarker and possible mediator, of altered LV geometry and impaired cardiorespiratory fitness in patients with HFpEF associated with CKD. Preclinical models of acute kidney injury have shown that kidney injury and dysfunction directly increased the expression of Galectin-3 that initiates downstream cardiac inflammatory and fibrotic processes, culminating in HF.[4] Our findings show that the CKD phenotype of HFpEF has small-volume LV geometry with normal systolic function but reduced diastolic reserve. Although we can only speculate about the mechanisms behind this pathology, it would be consistent with a galectin-mediated fibrotic process. In addition, Galectin-3 has been linked with adipose tissue inflammation, fibrosis, and adipocyte differentiation, independent of fat mass quantity.[5] We propose that in HFpEF patients with CKD, kidney injury and dysfunction upregulate galectin-3 levels exerting adverse effects on both cardiac function and fat mass ultimately impairing exercise capacity. The galectin-3 pathway may be a potential therapeutic target for exercise intolerance in HFpEF that is unique to patients with CKD. This hypothesis requires further exploration with larger samples that allow more complex statistical modelling in addition to translational clinical research studies.

Danielle L Kirkman, PhD*
Salvatore Carbone, PhD
Justin M. Canada, PhD
Cory Trankle, MD
Dinesh Kadariya, MD
Leo Buckley, PharmD
Hailey Billingsley, MS
Jason M Kidd, MD
Benjamin W Van Tassell, PharmD
Antonio Abbate, MD
Virginia Commonwealth University,
Richmond, Virginia

1. Saran R, Robinson B, Abbott KC, Agodoa LYC, Bragg-Gresham J, Balkrishnan R, Bhave N, Dietrich X, Ding Z, Eggers PW, Gaipov A, Gillen D, Gipson D, Gu H, Guro P, Haggerty D, Han Y, He K, Herman W, Heung M, Hirth

RA, Hsiung JT, Hutton D, Inoue A, Jacobsen SJ, Jin Y, Kalantar-Zadeh K, Kapke A, Kleine CE, Kovesdy CP, Krueter W, Kurtz V, Li Y, Liu S, Marroquin MV, McCullough K, Molnar MZ, Modi Z, Montez-Rath M, Moradi H, Morgenstern H, Mukhopadhyay P, Nallamothu B, Nguyen DV, Norris KC, O'Hare AM, Obi Y, Park C, Pearson J, Pisoni R, Potukuchi PK, Repeck K, Rhee CM, Schaubel DE, Schrager J, Selewski DT, Shamraj R, Shaw SF, Shi JM, Shieu M, Sim JJ, Soohoo M, Steffick D, Streja E, Sumida K, Kurella Tamura M, Tilea A, Turf M, Wang D, Weng W, Woodside KJ, Wyncott A, Xiang J, Xin X, Yin M, You AS, Zhang X, Zhou H, Shahinian V. US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2019;73:A7–A8.

2. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Cornel JH, de Zeeuw D, Pocock S, van Veldhuisen DJ. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006;113:671–678.
3. Van Tassell BW, Trankle CR, Canada JM, Carbone S, Buckley L, Kadariya D, Del Buono MG, Billingsley H, Wohlford G, Viscusi M, Oddi-Erdle C, Abouzaki NA, Dixon D, Biondi-Zoccai G, Arena R, Abbate A. IL-1 blockade in patients with heart failure with preserved ejection fraction. *Circ Heart Fail* 2018;11:e005036.
4. Prud'homme M, Coutrot M, Michel T, Boutin L, Genest M, Poirier F, Launay JM, Kane B, Kinugasa S, Prakoura N, Vandermeersch S, Cohen-Solal A, Delcayre C, Samuel JL, Mehta R, Gayat E, Mebazaa A, Chadjichristos CE, Legrand M. Acute kidney injury induces remote cardiac damage and dysfunction through the galectin-3 pathway. *JACC Basic Transl Sci* 2019;4:717–732.
5. Martinez-Martinez E, Calvier L, Rossignol P, Rousseau E, Fernandez-Celis A, Jurado-Lopez R, Laville M, Cachofeiro V, Lopez-Andres N. Galectin-3 inhibition prevents adipose tissue remodelling in obesity. *Int J Obes (Lond)* 2016;40:1034–1038.

https://doi.org/10.1016/j.amjcard.2020.12.012

State-Level Temporal Trends in Smokeless Tobacco and Cigarette Use Among U.S. Adults

Smokeless tobacco (SLT) is a term used to describe noncombustible forms of tobacco products, and includes loose leaf, plug, twist, snus, or snuff. SLT use has been linked with an increased risk for cancers and cardiovascular and cerebrovascular diseases. Recent estimates have shown that SLT use has been on the rise. Data from the Centre for Disease Control has shown that between 2000 and 2015, the consumption of combustible forms of tobacco decreased by 38.7%, whereas that of SLT increased by 23.1% in the United States.[1] However, the regional variations in the use of cigarettes and SLT, which may be affected by state-specific policies as well as regional differences in perceptions of these products is not well studied. We therefore evaluated the state-level temporal trends from 2016 to 2018 in the prevalence of SLT and cigarette use using data from the nationally administered and self-reported Behavioral Risk Factor Surveillance System survey. SLT use was defined as use of chewing tobacco, snus, or snuff every day or on some days. Current cigarette use was defined as use on some days or every day. We first ascertained current cigarette use and current SLT use for respondents from each US state in 2016 and in 2018. Relative change in SLT or cigarette use was then calculated as: (prevalence in 2018 - prevalence in 2016)/prevalence in 2016, and plotted using heat maps. We also classified states based on SLT use as low prevalence (below median prevalence in 2016) and high prevalence (above median prevalence in 2016) and reported their relative change in 2018.

There were 909,754 survey respondents in total. The overall prevalence of current SLT use was 3.62% in 2016 and 3.58% in 2018 whereas that of current cigarette use was 16.33% in 2016 and 15.53% in 2018. Overall, a relative decrease was observed for cigarette use, median (interquartile range) −4.5% (−9.1%, −0.7%), and SLT, −1.5% (−9.6%, 14.7%) between 2016 and 2018. Twenty-five states (47.2%) reported concomitant decrease in SLT and cigarette use, whereas, 19 states (35.8%) showed a relative increase in SLT use despite a decrease in cigarette use. Five states (9.4%) reported a concomitant increase in SLT and cigarette use while 4 states (7.5%) demonstrated a relative increase in cigarette use despite a decrease in SLT use (Figure 1).

Further, 52% (14/27) states with low prevalence of SLT use in 2016 (i.e., below median prevalence of 4.0%) showed a relative increase in SLT use in 2018, whereas 38% (10/26) states with high prevalence of SLT use in 2016 showed a relative increase in SLT use in 2018.

There has been a steady decline in the overall prevalence of cigarette smoking in the United States in the last two decades, mostly owing to the widespread implementation of public health campaigns and legal measures.[1] At the same time, the use of SLT has shown a heterogeneous trend, with an increase in use in certain demographics and a decrease in others, with limited data available for recent years. Our study highlights that while the trends for SLT use may not be too impressive when viewed on a national level, there exists significant geographical variation in terms of its public health burden. The prevalence and increase of SLT use, while seemingly small actually translates to millions of U.S. adults who use SLT. The aggressive marketing of SLT products as a safer alternative and as a means to quit smoking, its affordability, ease of use of SLT in smoke-free zones, and rising cigarette bans are other avenues that are often stressed upon by SLT advertisements, and that has driven a number of seasoned smokers to switch to SLT or in some cases become dual users.

These trends provide actionable information to public health professionals in these states and pave the way for federal and the state-level policy making to regulate the marketing and the use of SLT.

Disclosures

The authors have no conflicts of interest to declare.

Submitted from: Cleveland, Ohio, United States.
Date: 11/26/2020