Relation of Alcohol Consumption to Left Ventricular Fibrosis Using Cardiac Magnetic Resonance Imaging

Aleksandr Voskoboinik, MBBS[a,c,d], Benedict T Costello, MBBS[c,d], Andre La Gerche, MBBS, PhD[c], Sandeep Prabhu, MBBS[a,c,d], Geoff Wong, MBBS[a,d], Michael D Flannery, MBBS[c], Chrishan Nalliah, MBBS[a], Hariharan Sugumar, MBBS[a,c,d], Fabian Springer, MBBS[c,e], Jonathan M. Kalman, MBBS, PhD[a,b], Andrew J. Taylor, MBBS, PhD[c,d], and Peter M. Kistler, MBBS, PhD[b,c,d,*]

Light-to-moderate regular alcohol consumption has been associated with reduced mortality, heart failure, and sudden death, with a well described "U-shaped" relationship. We sought to determine whether markers of diffuse ventricular fibrosis as assessed by cardiac magnetic resonance imaging (CMR) T_1 mapping differ between nondrinkers and regular drinkers. We prospectively recruited 165 participants to undergo 3T CMR ventricular T1 mapping which included 120 regular light-to-moderate drinkers (7 to 28 standard drinks per week for >12 months) and 45 age and gender-matched nondrinking controls (1 standard drink ~12 g alcohol). Diffuse ventricular fibrosis was assessed using ShMOLLI T1 mapping sequences performed in mid-short axis. Native T1, postcontrast T1 times and extracellular volume were compared in the left ventricle between regular drinkers and lifelong nondrinkers. In total 165 participants (mean age 59 ± 12 years, 70% male, 36% hypertension, mean LVEF 58 ± 11%) underwent CMR. Moderate alcohol intake (mean alcohol intake 16 ± 6 SDs/week) was associated with lower markers of diffuse ventricular fibrosis: native T1 time 1140 ± 47 vs 1173 ± 39 ms, $p < 0.001$; postcontrast T1 time 470 ± 47 vs 445 ± 43 ms, $p = 0.01$; extracellular volume 25.0 ± 2.7% vs 27.0 ± 2.8%, $p = 0.003$ despite similar LV size ($p = 0.55$) and mass compared with nondrinkers ($p = 0.78$). Quantity of alcohol intake and beverage type did not predict lower native T1 times. In conclusion, light-to-moderate or "social" alcohol consumption is associated with T1 changes on CMR suggestive of a reduction in diffuse ventricular fibrosis. These preliminary findings may provide some insights into the association between modest alcohol intake and reduction in sudden death and heart failure. **(Am J Cardiol 2019;123:460−465)**

A U-shaped relationship is well described between alcohol consumption and cardiovascular mortality. Population studies suggest increased survival in light-to-moderate regular drinkers[1,2] compared with abstainers and heavy drinkers.[3] Proposed mechanisms include antioxidant and anti-inflammatory effects,[4] which may explain observed reductions in heart failure[5,6] independent of coronary artery disease.[7] Ventricular T1 mapping using cardiac magnetic resonance imaging (CMR) has emerged as a validated noninvasive tool for quantifying fibrosis from collagen accumulation within the interstitium, and is also useful for characterization of infiltrative pathologies and acute myocardial injury.[8] In particular, the native T1 time is particularly sensitive to myocardial edema and fibrosis.[9] We hypothesized that light-to-moderate alcohol consumption may have favorable effects on the ventricular myocardium, and sought to examine the relation between alcohol consumption and markers of diffuse ventricular fibrosis on CMR.

Methods

This is a single center observational study performed at Baker Heart and Diabetes Institute, Melbourne, Australia between August 2015 and May 2018. We aimed to prospectively recruit 165 participants to undergo 3T CMR with ventricular T1 mapping. Participants were healthy volunteers whom underwent CMR solely for the purpose of research. An alcohol intake history was taken to estimate average alcohol consumption in standard drinks per week (SDs/week) over the preceding 12 months, where 1 SD ~ 12 g alcohol which is equivalent to 100 ml glass of 13% red wine, 375 ml can of mid-strength (3.5%) beer, and 30 ml of 40% spirits. Consumption over the preceding month was

[a]Department of Cardiology, Royal Melbourne Hospital, Melbourne, Australia; [b]Department of Medicine, University of Melbourne, Melbourne, Australia; [c]Baker Heart & Diabetes Institute, Melbourne, Australia; [d]Heart Centre, The Alfred Hospital, Melbourne, Australia; and [e]Department of Diagnostic and Interventional Radiology, University Hospital Tübingen, Tübingen, Germany. Manuscript received September 6, 2018; revised manuscript received and accepted October 29, 2018.

Funding Sources/conflicts of interest: Dr. Voskoboinik is supported by cofunded NHMRC/NHF postgraduate scholarships and Baker IDI Bright Sparks scholarships (APP1114940). Prof. Kalman is supported by a NHMRC practitioner fellowship (APP1059039). A/Prof La Gerche is supported by an NHMRC/NHF Future Leader Fellowship (APP1089039). This research is supported in part by the Career Development Fellowship. Relationship(s) with industry: Nil.

*Corresponding author. Tel: 03 85321427; fax: 03 85321111.

E-mail address: peter.kistler@baker.edu.au (P.M. Kistler).

0002-9149/
https://doi.org/10.1016/j.amjcard.2018.10.026

assessed to exclude recent binge drinkers and the potential impact of acute inflammation.

Regular light-to-moderate drinkers (7 to 28 SDs/week for >12 months) and lifelong nondrinkers as controls were recruited consecutively, with a frequency-matching study design used to match for age and gender. Exclusion criteria included: (1) infrequent alcohol intake defined as 1 to 6 SDs/week; (2) heavy alcohol intake >28 SDs/week; (3) frequent (>monthly) or recent (last 1 month) binge drinking, as defined as >5 SDs over a 2 hour period; (4) alcoholic liver cirrhosis; (5) significant renal impairment (eGFR < 30 ml/min); (6) significant known structural heart disease (LVEF < 40% or previous myocardial infarction with regional wall motion abnormality).

Our CMR scanning and analysis protocol has been described previously.[10] CMR examinations were performed on a 3T scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany). Postprocessing of images was performed using a dedicated CMR analysis workflow of the Syngo.via software package (Siemens Healthineers, Erlangen, Germany). After acquisition of scout images, cine sequences were acquired in the 4-chamber, 2-chamber, 3-chamber, and short-axis views extending from the mitral valve annulus to the LV apex (8-mm slice thickness, no gap) using an ECG-gated balanced steady-state free precession sequence in expiration. LV mass and LV volumetric analysis (summation of disk method) were analyzed on commercially available postprocessing software and indexed to body surface area. Papillary muscles were considered part of the ventricular cavity. Myocardial T1 times were derived using the ShMOLLI sequence (Siemens Healthineers, Erlangen, Germany) which automatically generated pixel maps of T1 times. These were used during postprocessing with a motion correction algorithm applied to the raw images, as shown in Figure 1. Postcontrast sequences were analyzed 10 minutes following intravenous bolus injection of gadolinium-diethylene triamine penta-acetic acid (0.2 mmol/kg BW, Magnevist, Schering, Germany).

Each sequence was acquired within an end-expiration breath-hold using an ECG-triggered single-shot acquisition with a balanced steady-state free precession readout in a single mid-LV short-axis slice. Native T1 (precontrast) and postcontrast T1 times were measured in the myocardium and left ventricular blood pool using a region of interest on the T1 pixel map, T1 measurements were taken at the mid SAX level, both by including the entire myocardium (excluding artifact) and by taking a region within the septum. The myocardial extracellular volume (ECV) was calculated from the dynamic steady state concentration of extracellular contrast in the myocardium relative to the blood pool, incorporating the participant's hematocrit, as previously described.[11] CMR measurements and T1 mapping were performed by 2 experienced CMR cardiologists (CMR fellowship trained, >1000 cases experience) in accordance with recommendations stipulated by the Society for Cardiovascular Magnetic Resonance position statement.[8] Both cardiologists were blinded to the drinking status of each patient.

The primary outcome measure was a comparison of T1 mapping parameters (native ventricular T1 time, postcontrast T1 time, and ECV) between regular drinkers and lifelong nondrinkers. We estimated we would need to enroll 96 patients to detect a 5% absolute difference in the native T1 time between the 2 groups to provide a power of 0.8 at an alpha value of 0.05. The Shapiro-Wilk test was performed to confirm normal data distribution and a student *t* test then performed. Continuous data are summarized as mean ± standard deviation or median, as appropriate. Between-group comparisons were performed using a Chi-square or Fisher exact test. Complete-case analysis was performed using Statistical Package for the Social Sciences for

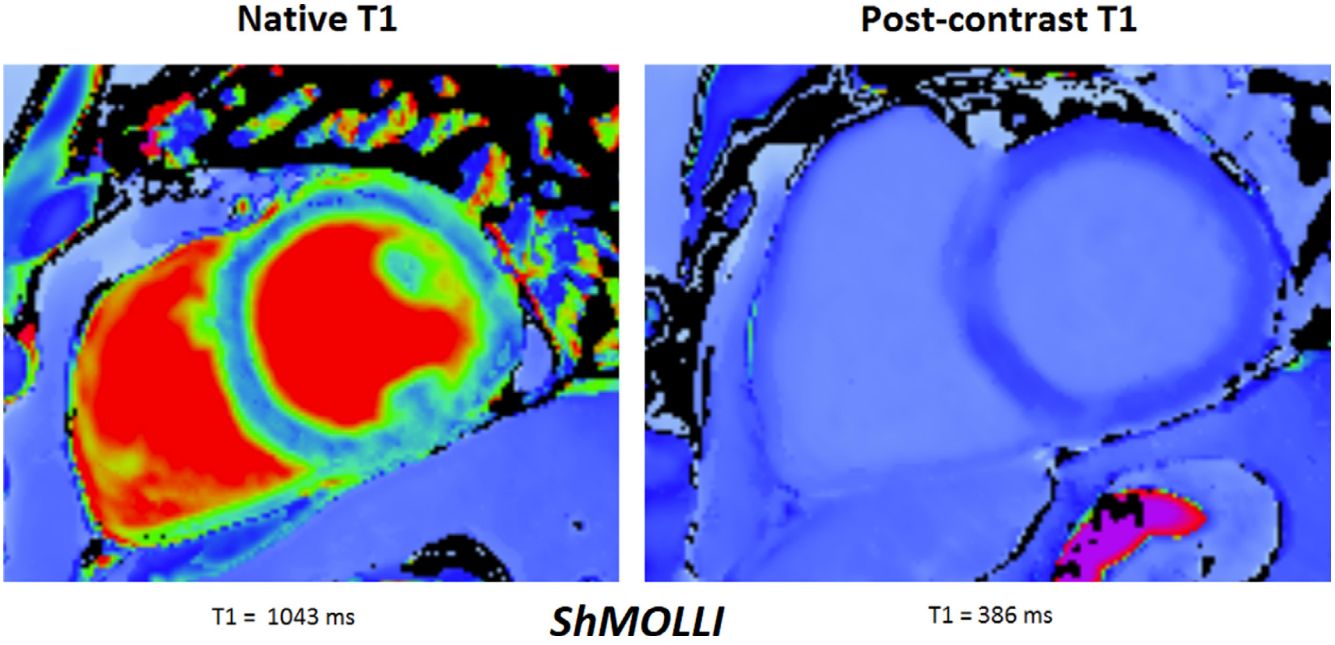

Figure 1. Pixel map images using ShMOLLI technique for native T1 and postcontrast T1 mapping.

Table 1
Baseline clinical characteristics

Parameter	Alcohol drinkers		p value
	No (n = 45)	Yes (n = 120)	
Age (years)	58 ± 14	60 ± 11	0.22
Men	67%	72%	0.56
Hypertension	36%	34%	0.89
Diabetes mellitus	7%	9%	0.63
Dyslipidemia	20%	17%	0.61
Smoker	8%	12%	0.49
Anglo-Saxon	84%	87%	0.60
Body mass index (kg/m^2)	27 ± 5	27 ± 5	0.93
Weight (kg)	83 ± 15	86 ± 17	0.44
Medications			
ACE inhibitors / ARBs	13%	16%	0.71
Beta Blockers	25%	27%	0.88
Statins	16%	13%	0.73

Definition(s): dyslipidemia: LDL ≥130 mg/dl, HDL <40 mg/dl, total cholesterol ≥200 mg/dl, or triglycerides ≥150 mg/dl.

Windows (SPSS version 23, IBM). p values <0.05 were considered statistically significant. The study was approved by Alfred Health Human Research Ethics Committee.

Results

In total 165 participants were recruited between August 2015 and June 2018, comprising 120 regular light-to-moderate drinkers (7 to 28 standard drinks per week for >12 months) and 45 age-matched nondrinkers. Baseline clinical characteristics did not differ significantly between the groups as shown in Table 1. Patients in both groups were mostly male (69.5%), "middle-aged" (mean age 59 ± 12 years), and Anglo-Saxon (86%), with a relatively low prevalence of medical comorbidities (35% hypertension, 7% diabetes mellitus).

Alcohol consumption patterns are summarized in Table 2. The majority of patients consumed approximately 1 to 3 standard drinks per day (mean intake 16.3 SDs/week) for a large portion of their adult life (26.1 ± 10.5 years duration). Wine was the most common (55%) alcoholic beverage consumed followed by beer (35%). Cardiac MRI characteristics are shown in Table 3. Regular alcohol consumption (mean alcohol intake 16 ± 6 SDs/week) was associated with lower markers of diffuse ventricular fibrosis with respect to all 3 T1 mapping parameters (as shown in Figure 2):

Table 2
Alcohol intake details (n = 120)

Parameter	Value
Alcohol intake (SDs/wk)	16.3 ± 6.4
Duration of regular alcohol intake (yrs)	26.1 ± 10.5
Beverage consumed	
Beer	34.5%
Wine	55.1%
Spirits	10.9%

*Values are provided as mean ± standard deviation.
Definition(s): SDs/wk − standard drinks per week, where 1 SD ~ 12 g alcohol.

Table 3
Cardiac MRI parameters

Parameter	Non-drinkers (n = 45)	Drinkers (n = 120)	p value
Stroke volume (ml)	100 ± 23	102 ± 27	0.77
Left ventricular ejection fraction (%)	60 ± 12	58 ± 10	0.35
Left ventricular end diastolic volume (ml)	163 ± 36	176 ± 42	0.15
Right ventricular end diastolic volume (ml)	160 ± 36	166 ± 39	0.75
Left ventricular mass (g)	122 ± 39	135 ± 42	0.16
Left ventricular end diastolic volume indexed (ml/BSA)	79 ± 13	81 ± 16	0.55
Left ventricular mass indexed (g/BSA)	63 ± 15	64 ± 18	0.78
Native T1 time (ms)	1173 ± 39	1140 ± 47	**<0.001**
Postcontrast T1 time (ms)	445 ± 43	470 ± 47	**0.01**
Extracellular volume	27.0 ± 2.8%	25.0 ± 2.7%	**0.003**

- Native T1 time 1140 ± 47 vs 1173 ± 39 ms in non-drinkers; p < 0.001,
- Postcontrast T1 time 470 ± 47 vs 445 ± 43 ms in non-drinkers; p = 0.01, and
- ECV 25.0 ± 2.7% vs 27.0 ± 2.8% in non-drinkers; p = 0.003.

As shown in Table 3, regular drinkers had similar indexed LV size, LV systolic function, and LV mass compared with nondrinkers. Delayed Gadolinium Enhancement (DGE) was infrequently observed and minor when present, occurring in 3 (6.7%) nondrinkers (2 subtle linear midwall, 1 subendocardial DGE) and 5 (2.4%) of regular drinkers (4 subtle linear midwall, 1 subendocardial DGE). All 3 T1 mapping parameters were compared with respect to quantity of alcohol intake and type of beverage consumed (beer, wine, and spirits), as summarized in Table 4. There were no dose-related or beverage-specific effects observed with respect to any of the T1 parameters (p > 0.05). Nevertheless, all drinking groups had less ventricular fibrosis than lifelong nondrinkers.

Multiple linear regression was performed looking at the impact of patient factors (i.e., gender, age, cardiovascular risk, and factors) and imaging variables (LV systolic function, LV mass) on native T1 time (dependent variable) in our cohort (Table 5). Regular moderate alcohol consumption was identified as a significant independent predictor of shorter native T1 time (Standardized Beta coefficient = −0.255; p = 0.008). There was no statistical interaction of the gender (p = 0.51) and age (p = 0.09) with alcohol consumption and fibrosis.

Discussion

Mild to moderate levels of alcohol consumption are associated with reductions in heart failure, all-cause mortality, and sudden death in observational studies. The present study is hypothesis-generating and provides some preliminary insights into a possible mechanism for the observed

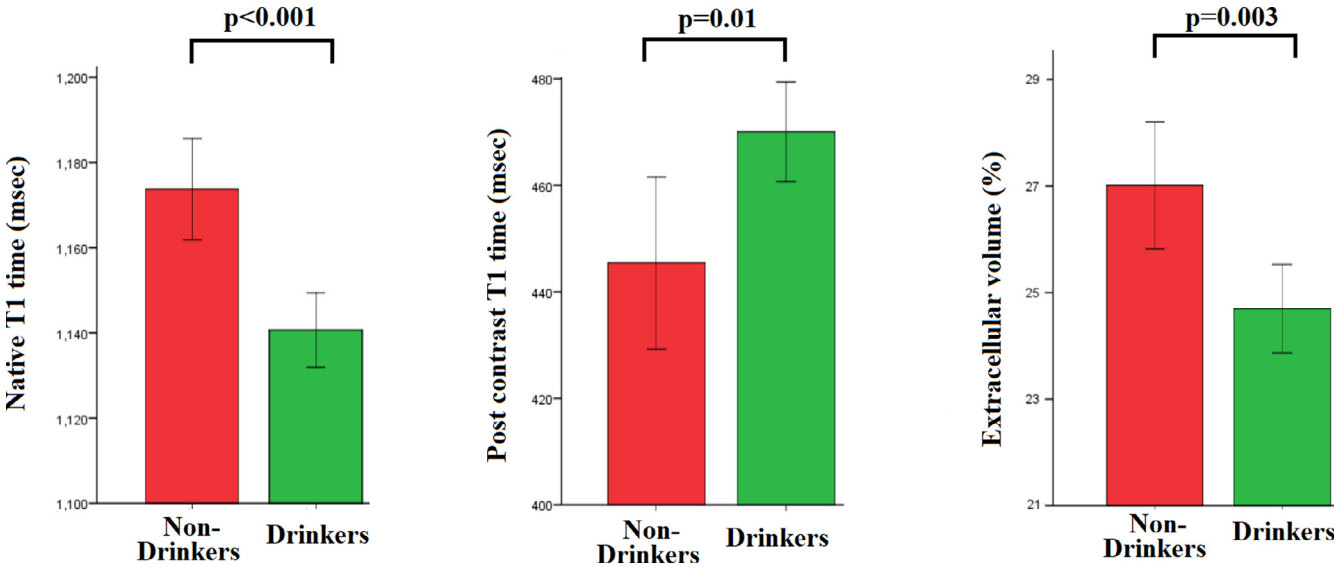

Figure 2. Comparison between mild-moderate regular drinkers and lifelong non-drinkers with respect to T1 mapping parameters.

Table 4
T1 mapping parameters by quantity of alcohol intake and beverage

Drinking category	Native T1 time (ms)	Postcontrast T1 time (ms)	ECV (%)
Non-drinkers	1173 ± 39	445 ± 43	27.0 ± 2.8%
7 − 14 SDs/week	1139 ± 48	480 ± 46	25.0 ± 2.6%
14.1 − 21 SDs/week	1143 ± 50	457 ± 53	25.5 ± 2.8%
21.1 − 28 SDs/week	1138 ± 42	472 ± 35	24.4 ± 2.6%
Beer	1144 ± 50	480 ± 46	25.2 ± 2.7%
Wine	1137 ± 47	468 ± 45	25.0 ± 2.8%
Spirits	1136 ± 53	460 ± 38	24.5 ± 3.0%

U-shaped relation, namely reduction in diffuse ventricular fibrosis. Heavy drinkers are at higher risk of sudden cardiac death (>42 drinks per week)[12,13] and may develop alcoholic cardiomyopathy (>50 drinks per week for >10 years).[14] Histological changes include myocytolysis, cytoplasmic lipid droplet formation, myofibrillatory disarray, interstitial fibrosis, and myocyte apoptosis.[15]

T1 mapping has been validated in human studies as a reliable noninvasive measure of interstitial fibrosis. Bull et al demonstrated a strong correlation between collagen volume fraction (CVF) and native T1 time in 19 patients with aortic stenosis.[16] In 44 patients who underwent cardiac biopsy, CVF correlated more closely with native T1 time, followed by ECV. Iles et al demonstrated a strong correlation between postcontrast myocardial T1 times and histological diffuse myocardial fibrosis.[17] A further study in 19 heart failure and hypertrophic cardiomyopathy patients found that degree of myocardial interstitial fibrosis measured at explant/myectomy correlated significantly with postcontrast T1 times.[18] In a study of 117 diastolic heart failure patients, CMR ECV correlated with histological ECV on myocardial biopsy, brain natriuretic peptide levels, exercise capacity, and hospitalizations.[19]

Table 5
Multivariate analysis of predictors of shorter native T1 time in our cohort

Independent variable	Standardized beta coefficient	Significance
Age	0.092	0.365
Alcohol consumption	−0.255	0.008
Gender	−0.114	0.277
Hypertension	0.115	0.271
Diabetes mellitus	−0.022	0.813
LV ejection fraction	−0.086	0.354
LV mass	0.173	0.116

The myocardial extracellular collagen network, comprising type I and III fibrillary collagen, functions to preserve tissue architecture, tensile strength, and maintain chamber geometry in all individuals. Collagen turnover is dynamic and influenced by numerous homeostatic mechanisms,[20] and collagen concentrations and intermolecular cross-linking increase with age.[21] Beneficial anti-inflammatory and antioxidant effects of mild-moderate alcohol consumption have been well-described, and may prevent excessive accumulation of collagen resulting in a reduction in CVF.

Light to moderate regular alcohol consumption is associated with reductions in inflammatory markers. In a population-based study of 840 women, Oliveira et al found a U-shaped relation between hs-CRP and alcohol intake, with those consuming up to 30 g/day having lower levels than nondrinkers.[22] Imhof et al demonstrated a U-shaped relation for both alpha1-globulins ($p = 0.0006$) and CRP ($p = 0.048$) and an inverse U-shaped relation between negative acute-phase reactants albumin ($p = 0.006$) and alcohol consumption in 781 males.[23] In 6,793 healthy adults, intake of either beer or wine (up to 40 g/day) was associated with lower CRP, fibrinogen and white cell count compared with heavy and nondrinkers. A crossover study of healthy men found significant reductions in hs-CRP, intercellular adhesion molecule-1, interleukin-6, and monocyte chemoattractant protein-1 after 30 g/day wine intake for 1 month.[24] In a randomized study, moderate beer consumption (4 glasses/day in men, 3 glasses/day in women) for just 3 weeks was associated with a reduction in CRP and

fibrinogen compared with nonalcoholic placebo.[25] Collagen turnover is subject to the effects of various inflammatory mediators.[26] In the present study mild-moderate alcohol consumption over many years is associated with a reduction in diffuse ventricular fibrosis.

A reduction in ventricular fibrosis may in part explain a reported reduction in heart failure in a large dose-response meta-analysis involving 202,378 patients and 6,211 incident cases of heart failure.[27] Di Castelnuovo et al recently demonstrated that consumption of 7 to 28 SDs/week (as in our cohort) reduced the risk of new-onset HF by 22% over 8 years compared with never drinkers.[28] In 6,797 patients with severe systolic dysfunction, light-to-moderate drinking up to 14 SDs/week reduced all-cause mortality (7.2 vs 9.4 deaths/100 person years).[29] These findings were consistent in ischemic and dilated cardiomyopathy.

This hypothesis-generating observational study posits a mechanistic explanation linking the observed beneficial effects of mild-moderate alcohol consumption on ventricular fibrosis and heart failure, mortality, and sudden death outcomes. It adds to the growing body of evidence that suggests that mild-moderate amounts of alcohol are not detrimental to the ventricle, and on the contrary, may reduce the markers of ventricular fibrosis. These preliminary findings may have potential clinical implications as many physicians continue to counsel patients with cardiomyopathy to abstain from alcohol entirely.[30]

This study has several limitations. While T1 mapping has been widely validated histologically, it remains a relatively novel technique and the clinical significance of small but statistically significant differences are unclear. Lack of histological and biochemical validation are potential limitations. The benefits of alcohol observed may be related to unknown confounders, such as associated diet or socioeconomic status. Thus the negative association between alcohol and ventricular fibrosis does not imply "causation." Alcohol intake was self-reported and hence may be inaccurate, potentially explaining the absence of a dose-response relation. While reduction in native T1 time observed in the drinking group can relate to fat deposition, the findings of the postcontrast and ECV do not support this. It should also be noted that ECV has correlates significantly ($p < 0.05$) with native T1 and postcontrast T1 ($r = 0.31$ and $r = -0.57$ respectively), hence the findings in all 3 T1 mapping parameters are not entirely independent.

In conclusion, regular light-to-moderate or "social" alcohol consumption is associated with a reduction in the markers of diffuse ventricular fibrosis as determined by CMR. These preliminary findings may potentially explain the association between modest alcohol intake and reduction in sudden death and heart failure.

1. Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. Relationship of alcohol consumption to all-cause, cardiovascular, and cancer-related mortality in U.S. adults. *J Am Coll Cardiol* 2017;70:913–922.
2. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med* 2006;166:2437–2445.
3. Whitman IR, Agarwal V, Nah G, Dukes JW, Vittinghoff E, Dewland TA, Marcus GM. Alcohol abuse and cardiac disease. *J Am Coll Cardiol* 2017;69:13–24.
4. Albert MA, Glynn RJ, Ridker PM. Alcohol consumption and plasma concentration of C-reactive protein. *Circulation* 2003;107:443.
5. Walsh CR, Larson MG, Evans JC, Djousse L, Ellison RC, Vasan RS, Levy D. Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med* 2002;136:181–191.
6. Abramson JL, Williams SA, Krumholz HM, Vaccarino V. Moderate alcohol consumption and risk of heart failure among older persons. *JAMA* 2001;285:1971–1977.
7. Bryson CL, Mukamal KJ, Mittleman MA, Fried LP, Hirsch CH, Kitzman DW, Siscovick DS. The association of alcohol consumption and incident heart failure: the Cardiovascular Health Study. *J Am Coll Cardiol* 2006;48:305–311.
8. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB. Friedrich MGClinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson* 2017 Oct 9;19:75.
9. Taylor AJ, Salerno M, Dharmakumar R, Jerosch-Herold M. T1 mapping: basic techniques and clinical applications. *JACC Cardiovasc Imaging* 2016;9:67–81.
10. Costello BT, Springer F, Hare JL, Gerche A, Iles L, Ellims AH, Schmitt B, Taylor AJ. SASHA versus ShMOLLI: a comparison of T1 mapping methods in health and dilated cardiomyopathy at 3T. *Int J Cardiovasc Imaging* 2017;33:1551–1560.
11. Kellman P, Wilson JR, Xue H, Ugander M, Arai AE. Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. *J Cardiovasc Magn Reson* 2012;14:63.
12. Wannamethee G, Shaper AG. Alcohol and sudden cardiac death. *Br Heart J* 1992;68:443–448.
13. Dyer AR, Stamler J, Paul O, Berkson DM, Lepper MH, McKean H, Shekelle RB, Lindberg HA, Garside D. Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiologic studies. *Circulation* 1977;56:1067–1074.
14. Fernández-Solà J. Cardiovascular risks and benefits of moderate and heavy alcohol consumption. *Nat Rev Cardiol* 2015;12:576–587.
15. Urbano-Márquez A, Fernández-Solà J. Effects of alcohol on skeletal and cardiac muscle. *Muscle Nerve* 2004;30:689–707.
16. Bull S, White SK, Piechnik SK, Flett AS, Ferreira VM, Loudon M, Francis JM, Karamitsos TD, Prendergast BD, Robson MD, Neubauer S, Moon JC, Myerson SG. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. *Heart* 2013;99:932–937.
17. Iles L, Pfluger H, Phrommintikul A, Cherayath J, Aksit P, Gupta SN, Kaye DM, Taylor AJ. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol* 2008;52:1574–1580.
18. Iles LM, Ellims AH, Llewellyn H, Hare JL, Kaye DM, McLean CA, Taylor AJ. Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. *Eur Heart J Cardiovasc Imaging* 2015;16:14–22.
19. Duca F, Kammerlander AA, Zotter-Tufaro C, Aschauer S, Schwaiger ML, Marzluf BA, Bonderman D, Mascherbauer J. Interstitial fibrosis, functional status, and outcomes in heart failure with preserved ejection fraction: insights from a prospective cardiac magnetic resonance imaging study. *Circ Cardiovasc Imaging* 2016;9. pii: e005277.
20. Weber KT, Sun Y, Tyagi SC, Cleutjens JP. Collagen network of the myocardium: function, structural remodeling and regulatory mechanisms. *J Mol Cell Cardiol* 1994;26:279–292.
21. De Souza RR. Aging of myocardial collagen. *Biogerontology* 2002;3:325–335.
22. Oliveira A, Rodríguez-Artalejo F, Lopes C. Alcohol intake and systemic markers of inflammation—shape of the association according to sex and body mass index. *Alcohol Alcohol* 2010;45:119–125.
23. Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. Effect of alcohol consumption on systemic markers of inflammation. *Lancet* 2001;357:763–767.
24. Vázquez-Agell M, Sacanella E, Tobias E, Monagas M, Antúnez E, Zamora-Ros R, Andres-Lacueva C, Lamuela-Raventos RM, Fernandez-Sola J, Nicolas JM, Estruch R. Inflammatory markers of atherosclerosis are decreased after moderate consumption of cava (sparkling wine) in men with low cardiovascular risk. *J Nutr* 2007;137:2279–2284.

25. Sierksma A, van der Gaag MS, Kluft C, Hendriks HF. Moderate alcohol consumption reduces plasma C-reactive protein and fibrinogen levels: a randomized, diet-controlled intervention study. *Eur J Clin Nutr* 2002;56:1130–1136.
26. Rodriguez-Feo JA, Sluijter JP, de Kleijn DP, Pasterkamp G. Modulation of collagen turnover in cardiovascular disease. *Curr Pharm Des* 2005;11:2501–2514.
27. Larsson SC, Orsini N, Wolk A. Alcohol consumption and risk of heart failure: a dose-response meta-analysis of prospective studies. *Eur J Heart Fail* 2015;17:367–373.
28. Di Castelnuovo A, Costanzo S, Bonaccio M, Rago L, De Curtis A, Persichillo M, Bracone F, Olivieri M, Cerletti C, Donati MB, de Gaetano G, Iacoviello L. Moli-sani Investigators. Moderate alcohol consumption is associated with lower risk for heart failure but not atrial fibrillation. *JACC Heart Fail* 2017;5:837–844.
29. Cooper HA, Exner DV, Domanski MJ. Light-to-moderate alcohol consumption and prognosis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000;35:1753–1759.
30. Maisch B. Alcoholic cardiomyopathy: the result of dosage and individual predisposition. *Herz* 2016;41:484–493.