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Review

Heart rate variability in alcohol use: A review

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ABSTRACT

Background: Prior studies have shown that resting heart rate variability (HRV) is reduced in those with alcohol use disorders (AUD). However, HRV following an acute stressful stimulus (reactive HRV), and the relationship between resting or reactive HRV and drinking, craving and relapse in AUD have received less attention.
Methods: Studies using HRV in relationship to acute or chronic alcohol consumption were included in this review. Manuscripts that related to alcohol in the context of cardiovascular disease were excluded.
Results: Thirty-three articles were included and findings are presented in healthy social drinkers, moderate/heavy drinkers without AUD and individuals with AUD. Results on resting and reactive HRV were presented separately. Acute alcohol reduced *resting* HRV in healthy subjects but healthy controls had higher resting HRV then AUD subjects and moderate/heavy drinkers (in some studies). Resting HRV improved in AUD subjects only after at least 4 months of abstinence. AUD subjects had higher *reactive* HRV scores when compared to controls. In AUD subjects increased reactivity was related to more craving, faster relapse and more negative mood. Reactive HRV showed slower improvement with abstinence in AUD subjects.
Conclusions: Chronic, heavy alcohol has a negative effect on the autonomic nervous system and may be a sensitive biomarker of craving and relapse.

1. Introduction

Converging evidence in the last two decades has led to models linking stress to the development and maintenance of AUD (alcohol use disorder) (Koob, 2014). Most models of stress and AUD focus on the hypothalamic-pituitary-adrenal (HPA) axis although both HPA and autonomic systems synergistically modulate alcohol use. Stress activates the HPA axis, causing the release of pituitary adrenocorticotropin (ACTH) which in turn stimulates the adrenal glands to release cortisol. Cortisol facilitates metabolic responses to stress and feeds back to turn off a wide range of physiological and behavioral responses to stress. Acute alcohol consumption acutely activates the HPA axis but social drinking of 1–2 drinks maintains HPA axis tone and stress response equilibrium (Koob, 2003). In contrast, increased alcohol intake, binge drinking, and alcohol withdrawal reduce the HPA axis response to stress which is thought to result in reduced inhibitory feedback control of stress responses (Sinha and Tuit, 2012). In addition, reduced HPA axis responses in AUD have been associated with increased anxiety, craving, and relapse (Ralevski et al., 2016; Sinha et al., 2009; Fox et al., 2007). *Significantly less work has evaluated the impact of alcohol use on autonomic responses to stress and if changes in autonomic regulation are associated with alcohol use, craving or relapse. In this review, we focus on studies investigating the relationship of alcohol use and alcohol use disorders on heart rate variability (HRV), with a focus on high frequency HRV, a marker of parasympathetic nervous system activity.*

HRV is the variation in beat-to-beat intervals in heart rate and is considered important in cardiac health. The autonomic nervous system regulates heart rate and heart rate variability through the sympathetic (SNS) and parasympathetic (PNS) branches that usually work antagonistically. Changes to either branch of the system alter the dynamics of heart rate response to meet internal and external demands. Increased activity in the SNS and decreased activity in the PNS reflect impairment of the system's ability to cope with varied environmental challenges (Xhyheri et al., 2012) and have been linked to a wide range of health problems including diabetes, coronary artery disease, heart failure, syncope, mitral valve disease, and sleep apnea.

Multiple methods have been used to quantify HRV from continuous ECG recordings and they can be divided into two broad categories: frequency domain methods and time domain methods (Bilchick and Berger, 2006). The frequency domain methods are the most common and use time series analyses to evaluate HRV within different spectral components, most typically a high-frequency component (HF-HRV) that ranges from 0.15–0.40 Hz and a low-frequency component (LF-HRV) that ranges from 0.04–0.15 Hz. LF-HRV is determined by both SNS and

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PNS inputs to the heart, while HF-HRV is a more specific measure of cardiac PNS activity (Xhyheri et al., 2012; Akselrod et al., 1981; Chiu et al., 2003; Appel et al., 1989). The time domain methods evaluate variability without consideration of frequency. These statistical methods include standard deviation of all interbeat intervals (SDNN), and square root of the mean squared difference of successive interbeat intervals (rMSSD), which correlate well with the high-frequency component of HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Lower resting HF-HRV has also been linked to problematic behavioral traits and behavioral disorders. The neurovisceral integration model (Thayer and Lane, 2000) and the polyvagal theory (Porges, 1995) propose that HF-HRV is a good marker of ability to regulate cognitive, behavioral, and emotional responses to stress (Thayer and Lane, 2000; Thayer et al., 2009; Thayer and Brosschot, 2005; Appelhans and Luecken, 2006). These models suggest that parasympathetic influence on HRV reflects a similar regulatory activity acting within behavioral components of the central nervous system. Low resting HF-HRV has been linked to a range of mental health pathology (Beauchaine and Thayer, 2015) including bipolar disorder (Faurholt-Jepsen et al., 2017), depression (Kemp et al., 2010), anxiety disorders (Ray et al., 2017), impulsivity, and alcohol use disorder (Karpyak et al., 2014).

Relatively less is known about the behavioral correlates of HRV reactivity (reactive HRV) to physical, cognitive, and emotional challenges (Butler et al., 2006; Berna et al., 2014; Park et al., 2014). Typically, in healthy social drinkers, emotional pictures and alcohol cues cause a transient increase in HF-HRV, which is understood as a marker of attention or emotional engagement. A decrease in HF-HRV is produced by physical stressors or more intense emotional stressors (Thayer et al., 2012; Laborde et al., 2018) that require activation of metabolic resources.

Two reviews, written by the same group, summarized the findings on the effects of alcohol use on HRV (Karpyak et al., 2014; Romanowicz et al., 2011). Both reviews focused on comparing findings using different HRV measurement methods and assessing the relationship between resting HRV measures and other physiological indices including respiration, heart rate, and blood pressure. Their review of acute alcohol effects indicated that many, but not all, studies showed a decrease in HF-HRV that was dose dependent. This finding tended to be consistent among healthy social drinkers, polysubstance users, heavy drinkers and individuals with coronary artery disease. Results with LF-HRV were less consistent with some studies finding that acute alcohol increased while others decreased LF-HRV (Romanowicz et al., 2011). The second review (Karpyak et al., 2014) focused on examining resting HRV in chronic drinkers with and without alcohol dependence, and in patients undergoing alcohol withdrawal. They reported that people who regularly consumed low doses of alcohol (1–2 drinks) had higher resting HRV. However, individuals who were drinking > 1–2 drinks daily had lower resting HF-HRV. Low resting HF-HRV in heavy drinkers improved with alcohol abstinence in some but not all studies. Findings with LF-HRV in individuals in alcohol withdrawal were much more inconsistent. No review to date has focused on reactive HRV and its relationship to AUD clinical outcomes. The objectives of the current review were: 1. update findings on resting HRV and report findings on reactive HRV in across the spectrum of alcohol use; and 2. review the studies of associations between HRV and psychological aspects of alcohol use including mood, subjective intoxication, craving, and drinking behavior.

2. Method

The method for this narrative review and the inclusion/exclusion criteria for study selection were determined before the start of the review. Peer–reviewed clinical trials and experimental studies in humans that examined effects of alcohol use on HRV, written in English, were included. No demographic restrictions were applied. Two databases (Medline and Google Scholar) were searched using various alcohol and HRV terms.

Thirty-three articles were selected for this review. Basic information for all selected studies is presented in 3 Tables: one focused on healthy social drinkers, one summarizing studies in regular moderate to heavy drinkers without AUD diagnosis, and the final table listing studies conducted in individuals with AUD. Tables include basic details on study design, subject characteristics, HRV measurements (indicating resting or reactive HRV), other main outcome measures and results. For the sake of consistency and for easier comparison among studies HF-HRV and LF-HRV are presented as the main outcome measures even when other HRV measures were reported. When HF-HRV was not available other HRV outcomes were included. Alcohol measures varied widely (grams; g/kg; breath alcohol level (BrAC) mg/dl). For comparative purposes, conversions were made (when possible) to estimates of standard drinks. We estimated that 1 standard drink was ~15 g and estimated to be approximately equal to BrAC of ~20 mg/dl. For example, 30 g of alcohol was estimated to be equal to BrAC ~40 mg/dl or about 2 drinks, and 75 g of alcohol to be equal to BrAC ~100 mg/dl or about 5 drinks.

3. Results

3.1. Effects of acute and prolonged alcohol exposure on HRV in healthy social drinkers

3.1.1. Effect of acute alcohol on resting HRV

Nine studies measured resting HRV following acute oral alcohol consumption in the lab (Nishimura et al., 2002; Murata et al., 1994; Newlin et al., 1990; Weise et al., 1986; Spaak et al., 2010; Vaschillo et al., 2008; Sehested et al., 1998; Koskinen et al., 1994; Gonzalez Gonzalez et al., 1992) (see Table 1). Acute administration of a low dose of alcohol (about 2 standard drinks) suppressed HF-HRV in 4 studies (Nishimura et al., 2002; Newlin et al., 1990; Spaak et al., 2010; Gonzalez Gonzalez et al., 1992). A moderate dose of alcohol (about 3–4 standard drinks) suppressed HF-HRV in one study (Weise et al., 1986) but had no effect in another (Murata et al., 1994). In addition, a high dose of alcohol (about 4.5 to 5 standard drinks) suppressed HF-HRV in all four studies (Spaak et al., 2010; Vaschillo et al., 2008; Sehested et al., 1998; Koskinen et al., 1994). The effect of acute alcohol ingestion on LF-HRV, evaluated in 6 studies, was much less consistent (Nishimura et al., 2002; Murata et al., 1994; Spaak et al., 2010; Sehested et al., 1998; Koskinen et al., 1994; Gonzalez Gonzalez et al., 1992), with some reporting an increase in LF-HRV following both low and high doses of alcohol (Spaak et al., 2010; Gonzalez Gonzalez et al., 1992), 2 studies reporting a decrease following a high dose of alcohol (Sehested et al., 1998; Koskinen et al., 1994), and 2 studies reporting no change following administration of low and moderate doses of alcohol (Nishimura et al., 2002; Murata et al., 1994).

3.1.2. Effects of prolonged (1 week) alcohol exposure on resting HRV

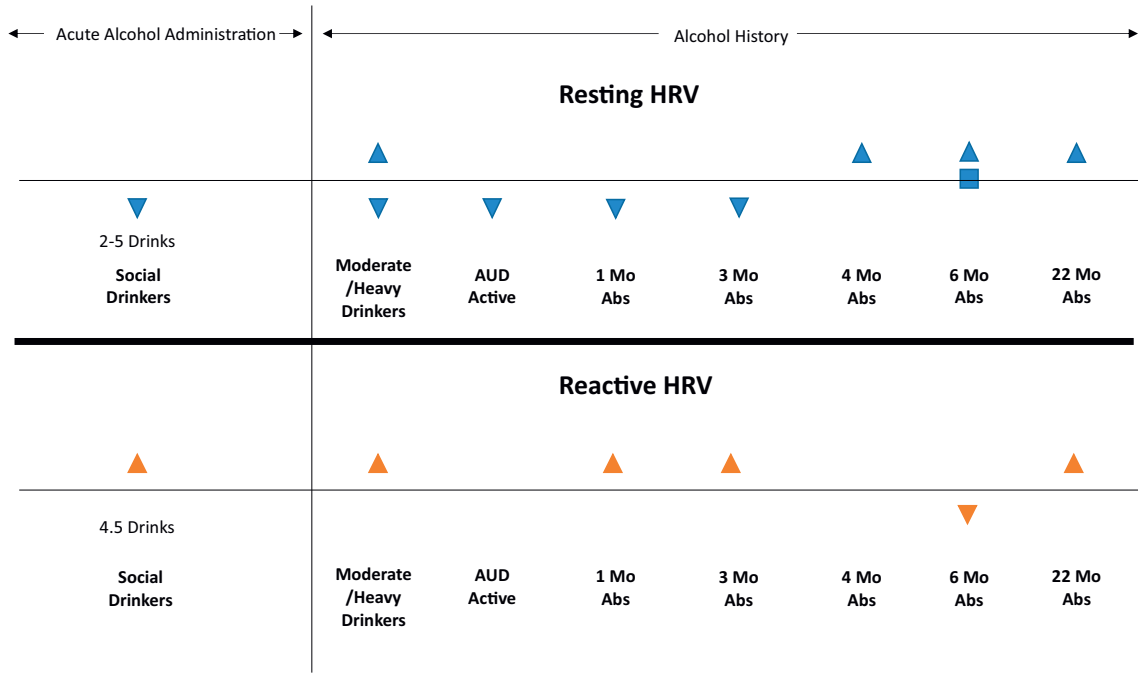
In contrast to the above findings, prolonged alcohol exposure (1 week) of low doses of alcohol (about 2 standard drinks) when compared to abstinence (1 week), resulted in a resting HF-HRV increase and LF-HRV decrease when measured 12 h following the last ingestion of alcohol (Flanagan et al., 1986).

3.1.3. Reactive HRV

One study (Vaschillo et al., 2008) examined reactive HRV following a randomized presentation of negative, positive, and neutral pictures after ingestion of alcohol, placebo (ethanol float), or a control (orange juice). The 0.1 Hz HRV (a measure designed to be more sensitive to challenge cues) was increased after alcohol ingestion, particularly in response to negative pictures. Pictures were presented at a 0.1 Hz frequency and only HRV calculated in a narrower 0.1 Hz frequency band was able to detect an HRV response to pictures, not the wider frequency

Table 1
Alcohol effects on HRV in healthy social drinkers.

Study	Subject character	Groups	HRV/ECG recording	Measures	Study type	Design	Results
Spaak et al. 2010	N = 12, M, F, age = 35	Single group, three conditions: condition A = Red wine 1 drink (BrAC = 40 mg/dl or ~2 drinks) followed by a second drink (BrAC = 90 mg/dl or ~4.5 drinks); Condition B = ethanol 1 drink (BrAC = 40 mg/dl or ~2 drinks) followed by a second drink (BrAC = 90 mg/dl or ~4.5 drinks); condition C = water	ECG data sampled at 1000 Hz, recorded continuously	Resting HF-HRV and LF-HRV	Laboratory, 3 test days, 2 weeks apart	Randomized, within subjects comparison of Conditions A, B, and C	No differences in resting HRV between test days. One glass of red wine suppressed HF-HRV more than water but not when compared to baseline; two glasses of either wine or ethanol suppressed HF-HRV, and increased LF-HRV more than water; no differences between alcohol conditions
Vaschillo et al. 2008	N = 36, M, F, age = 21.8	Three groups: alcohol group (n = 12, 3 separate drinks to reach BrAC = 90 mg/dl (~4.5 drinks)); placebo group (n = 12, 100 µl ethanol float per cup), and control group (n = 12, orange juice)	ECG data resulted in FH-HRV and 0.1-Hz HRV	Resting and reactive 0.1-Hz HRV and HF HRV; Presentation of positive, negative and neutral pictures	Laboratory, 1 test day	Randomized, between subjects comparison of alcohol to placebo and control; within subjects comparison of HRV before/after ingestion of drinks, and randomized presentation of positive, negative and neutral pictures	HF-HRV suppressed by alcohol when compared to placebo or control conditions; no differences in HF-HRV based on picture condition; negative pictures resulted in greater increase of 0.1-Hz HRV when compared to positive and neutral pictures
Nishimura et al. 2002	N = 36, M, F, mostly Japanese (n = 34), ~22 years old	Two groups each receiving alcohol (beer, 0.4 ml/kg ~2 drinks) over 20 min: aldehyde dehydrogenase deficient (ND, n = 14) and non-deficient (NN, n = 22)	ECG recording, HF-HRV, LF-HRV	Resting HF-HRV, LF-HRV and measures of drunkenness, drowsiness and pleasantness	Laboratory, 1 test day	Between subjects comparison based on genotype (ND, NN); within subjects comparison of HRV measures before/after alcohol consumption and other self-report measures	HF-HRV suppressed by alcohol in ND but not NN subjects; ND subjects reported feeling more drunk but no differences in drowsiness and pleasantness between the two groups; no effects on LF-HRV
Flanagan et al., 2002	N = 21, M, F, age range = 21–41	Two conditions: condition A = daily alcohol for 1 week (3 units of alcohol (1 unit = 8 g ethanol, ~2 drinks/day); condition B = abstain from alcohol for 1 week	ECG recording for 5 min	Resting HF-HRV and LF-HRV	Laboratory, 2 test days, 4 weeks apart	Randomized, cross over design	HF-HRV increased and LF-HRV decreased with regular alcohol use
Sehested et al. 1998	N = 9, M, (no age provided)	Two conditions: condition A = alcohol mixed with juice (500 ml drink containing 1 g/kg alcohol (~85 mg/dl or ~4 drinks); condition B = alcohol mixed with juice (same as A) + 750 ml mineral water	ECG recording converted to LF and HF HRV	Resting and reactive LF-HRV and HF-HRV	Laboratory, 2 test days, 1 week apart	Randomized, cross over design	Both LF and HF-HRV was suppressed by alcohol in both group A (7 out of 9 subjects) and group B.
Murata et al. 1994	N = 11, M, Japanese, age = 22	Single group, two conditions: alcohol condition (0.54–0.66 g/kg or ~3 drinks of Japanese spirit) followed by control condition (200 ml orange juice)	ECG recording HF-HRV, LF-HRV	Resting LF-HRV and HF-HRV	Laboratory, 2 test days (not specified how many days apart)	Within subjects design	Alcohol did not significantly alter HRV
Koskinen et al., 1994	N = 12, M, age = 23.8	Single group, two conditions: alcohol condition (1 g/kg or ~5 drinks) + juice over 30 min; control = same volume of juice as alcohol condition	Computerized ECG recording	Resting HRV; LF, medium (MF) and high HF-HVR	Laboratory, 2 test days, 7 days apart	Randomized, crossover design	Alcohol significantly suppressed HRV when compared to juice; difference was most pronounced using the HF-HRV measure
Gonzalez Gonzalez et al. 1992	N = 18, M, age = 28.5	Single group, two conditions: alcohol condition (0.3 g/kg ~2 drinks over 5 min); control condition = same volume of juice as alcohol condition	ECG recording	Resting HRV; LF, MF, and HF-HRV	Laboratory, 2 test days, 30 days apart	Within subjects design	Alcohol suppressed HF and medium frequency, but increased LF HRV
Newlin et al. 1990	N = 15, M, > 21 old	Two groups: group 1 = mixer of 0.5 g ethanol/kg 100 proof mixed (~2.5 drinks) with juice on sessions 1 and 2 and juice on session 3; group 2 = pure juice on all three sessions	ECG recording	Vagal tone index	Laboratory, 3 sessions	Between, within subject design	Alcohol suppressed HRV
Weise et al. 1986	N = 8, M, F, age = 24.3	Single group, one condition: alcohol (0.7 g/kg or ~3.5 drinks) + juice over 10 min	ECG recording	Resting HRV (mean momentary arrhythmia [MMA])	Laboratory, 1 test day	Experimental	Alcohol suppressed HRV



Abs= Abstainers; AUD= Alcohol Use Disorder; Mo= Month

Fig. 1. Overview of results for all thirty-three studies used in this review. Arrows indicate either an increase or a decrease in HRV reported in specific studies (square indicates no change). The middle line does not indicate normative HRV (it is just a dividing line) since no such values have been established. The placement of the arrows does not indicate the magnitude of either increase or decrease in HRV since calculations reflecting magnitude of change were beyond the scope of this review.

band typically used to calculate HF-HRV.

3.1.4. Resting HRV and other outcomes

Nishimura et al. (2002) evaluated the role of genetic deficiency in aldehyde dehydrogenase in Japanese men in relationship to HRV and subjective alcohol effects (feeling drunk, drowsy, or liking the pleasant effects of alcohol). HF-HRV suppression after a dose of alcohol was associated with feeling more drunk suggesting that HRV suppression may be an objective biomarker of intoxication.

3.1.5. Summary

Data consistently (except for one study) show that acute alcohol administration suppresses resting HF-HRV or time-domain HRV following low, moderate and high doses of alcohol in healthy social drinkers (see Fig. 1). The interesting finding in one study that resting HRV suppression was related to feeling drunk needs replication. Data on LF-HRV is much less consistent, suggesting that alcohol has relatively greater effects on the parasympathetic system which has a more exclusive impact on determining HF-HRV. One study in prolonged (~2 standard drinks) alcohol exposure reported an increased resting HRV, a finding consistent with some but not all studies showing reduced cardiac illness with daily consumption of low doses of alcohol (reviewed in Karpyak et al. (2014)). It is important to note that all studies were in younger individuals (age < 36) therefore the findings cannot be generalized to a population of older healthy social drinking men and women. The consistency in findings is more impressive when considering that the number of individuals in most studies was relatively small (in 7 studies $N < 22$), HRV calculation methods varied, and the studies spanned over 24 years.

Fig. 1 provides a visual outline of results from all studies in this review. Results on resting HRV are summarized separately from those on reactive HRV.

3.2. HRV in moderate and heavy drinkers without AUD

3.2.1. Resting HRV

Five studies measured resting HRV in moderate and heavy drinkers (Quintana et al., 2013; Thayer et al., 2006; Ryan and Howes, 2002; Kupari et al., 1993; Minami et al., 2002) (see Table 2). In three studies, moderate and heavy drinkers had higher HF-HRV or RMSSD (Quintana et al., 2013; Thayer et al., 2006; Ryan and Howes, 2002), but two studies reported opposite results (Kupari et al., 1993; Minami et al., 2002). The results from Kupari et al. (1993) study with wide range of drinking habits found that greater alcohol consumption was associated with lower HF-HRV, particularly in women. Another study using a cross-over design found that for moderate drinkers (~3.5 drinks per day) HF-HRV increased when individuals reduced their drinking by at least half (Minami et al., 2002). Only 2 studies reported findings using LF-HRV with one showing increase of LF-HRV with drinking (Ryan and Howes, 2002) while the other showing a decrease (Minami et al., 2002).

3.2.2. Resting HRV and psychological outcomes

One study (Quintana et al., 2013) examined differences in anxiety, depression, stressful events and physical activity between regular (habitual) drinkers (AUDIT score 2–5) and controls (nonhabitual drinkers, AUDIT score 0–1). Regular drinkers had increased HRV (more specifically in men) and were not different on any psychological measures from controls.

3.2.3. Reactive HRV in high-risk drinkers

Among high-risk drinkers, those with higher risk alcohol behaviors (greater inability to regulate alcohol use) had greater 0.1 Hz HRV responses to emotional picture presentations and alcohol and drug cues (Mun et al., 2008).

3.2.4. Summary

Studies evaluating HF-HRV in non-AUD moderate and heavy

Table 2
Alcohol effects on HRV in moderate and heavy drinkers.

Study	Subject characteristics	Groups	HRV/ECG recording	Measures	Study type	Design	Results
Quintana et al. 2013	N = 47, M, F, age = 20.51, moderate drinkers and light drinkers	Two groups: habitual drinkers n = 25 (AUDIT score 2–5 equivalent to drinking 5 days a week); non-habitual drinkers n = 22 (AUDIT score < 1 equivalent to drinking < 2 drinks one time in past month)	Chest strap, ambulatory Polar monitor measuring 1000 Hz rate	Resting HF-HRV; anxiety, depression, stress, physical activity	Laboratory, 1 test day	Between subjects comparison	Increased HF-HRV in habitual drinkers (more specific to males) when compared to controls; no differences between groups on anxiety, depression, stress, or physical activity
Mun et al. 2008	n = 16, M, F, age = 21–24 years old, light to at risk drinkers	Two groups: high alcohol risk and normative drinkers	ECG recording	Resting and reactive HF-HRV	Laboratory study, 1 test day	Between groups before and after presentation of positive and negative pictures	The high-risk group had higher HF-HRV after both positive and negative pictures while the normative group had a higher HF-HRV only after negative pictures
Thayer et al. 2006	N = 542, M, F, age = 42.2, moderate drinkers	Two groups: high alcohol use group n = 196 (> 20 g per day ~1.5 drinks); low alcohol use group n = 346 (< 20 g per day)	ECG recording, ambulatory, at a rate of 400 Hz connected for about 15 h	Resting HRV expressed as the root mean square of successive differences (RMSSD)	Laboratory, 1 test day	Between subjects comparison	Increased HRV for the high alcohol use group when compared to the control group
Ryan and Howes 2002	N = 28, M, age = 50, heavy drinkers	Single group: heavy drinkers (~5 standard drinks/day)	ECG recording, ambulatory (Rozinn Holter) for about 24 h	Resting HF-HRV, LF-HRV; amount of alcohol consumed	Laboratory, 1 test day	Within subjects; evaluating HRV over 24 h	HRV positively linked to alcohol intake
Minami et al. 2002	N = 33, M, Japanese, age = 36.9, habitual moderate drinkers	Single group: moderate drinkers consuming ~3.5 drinks every day	BP recording, ambulatory, 26 h	Resting HF-HRV, LF-HRV; daily alcohol intake	Laboratory, 2 test days, not specified now many days apart	Cross over design with 3 weeks on usual drinking intake and 3 weeks on reduced daily intake (at least half of daily intake)	HF-HRV and LF-HRV higher during reduced alcohol intake phase when compared to regular alcohol use phase
Kupari et al. 1993	N = 88, M, F, ~39 years old, wide range of drinking habits	Randomly selected individuals living in Helsinki born in 1954. Alcohol consumption ranged	ECG recording (12-lead), 200 Hz for 5–10 min	Resting HF-HRV, LF-HRV; lifestyle diary for average of 64 days that included alcohol consumption (range 0–84 g or 0 to ~5.6 drinks)	Laboratory, 1 test day	Correlational study	Alcohol use not related to HRV measures in men; women had a greater HRV decrease with increased alcohol use

drinkers were not consistent (see Fig. 1). Some laboratory studies found increased resting HF-HRV or time domain HRV (Thayer et al., 2006) compared to a control group and some found decreased HRV associated with higher alcohol intake. There could be a number of reasons for discrepant findings. First, drinking habits varied considerably among individuals, and in most instances, it was not clear how long the participants maintained the same level of drinking. Second, most studies were cross sectional. The only study that evaluated changes in HRV over time during moderate to heavy drinking in comparison to during reduced drinking found that HRV increased when drinking was reduced. Third, all studies did not use comparable HRV measures. Finally, there was a large age range (mean age 20–50) that could have contributed to those differences since HRV is known to decrease with age.

3.3. HRV in individuals with AUD

3.3.1. Resting HRV in outpatients with active AUD

Only three studies evaluated resting HRV in active drinkers with AUD (Murata et al., 1994; Depetrillo et al., 1999; Irwin et al., 2006) and all compared them to controls (Murata et al., 1994; Depetrillo et al., 1999; Irwin et al., 2006). In comparison to controls, individuals with AUD exhibited lower resting HF-HRV (Murata et al., 1994; Irwin et al., 2006) or lower time-series HRV (Depetrillo et al., 1999) (Table 3).

3.3.2. Resting HRV in abstainers

Twelve of the studies in AUD patients recruited abstainers and studied the effects of abstinence on resting HRV. Abstinence duration varied from a few days to almost 2 years. Recently detoxified inpatients (7–8 days abstinence) (Agelink et al., 1998), abstainers for 3 weeks (Rechlin et al., 1996), 1–10 days (Weise et al., 1985), or 1–9 weeks (Malpas et al., 1991; Karimullah et al., 2001) all had significantly lower HF-HRV or time-domain HRV than controls. Two studies evaluating abstainers over time (before and after treatment) found no improvement in resting HF-HRV after 6 weeks of biofeedback (Penzlin et al., 2015) or in time domain HRV after 10 weeks of mindfulness treatment (Garland et al., 2010). Resting HF-HRV and time-domain HRV did improve after 4 and 6 months of abstinence in most patients in two studies (Weise et al., 1986; de Zambotti et al., 2015). However, another study (Claisse et al., 2017) found no overall differences in resting HF-HRV between short term and long term (> 6 months) abstainers.

3.3.3. Reactive HRV in abstainers

Short-term abstinence (~3 months) was associated with an increase in reactive HRV to an alcohol script and other alcohol cues when compared to controls (Ingjaldsson et al., 2003), an expected outcome because alcohol cues are likely to be more salient to individuals in short-term abstinence than to control individuals. Garland et al. (2010) conducted a randomized trial of mindfulness therapy for individuals who had been abstinent up to 22 months. They found a greater HRV response and more rapid recovery following alcohol cues in the group treated with mindfulness therapy. This was interpreted as a greater engagement of emotion regulation resources in the mindfulness group. Claisse et al. (2017) reported a reduction in reactive HRV in response to emotional picture cues in 6 months abstainers when compared to short-term abstainers. This was consistent with the increased response to emotional picture cues found in active high-risk drinkers (Mun et al., 2008) and short-term abstiners (Ingjaldsson et al., 2003).

3.3.4. HRV in relationship to psychological outcomes

Four studies evaluated the relationship between HRV and craving or relapse (Quintana et al., 2013; Claisse et al., 2017; Ingjaldsson et al., 2003; Garland et al., 2012). One study found that resting HF-HRV was negatively related to craving (Quintana et al., 2013) even after controlling for drinking, anxiety and age suggesting greater vulnerability to relapse in those with reduced HF-HRV. In contrast, there was a positive relationship between reactive HRV to picture cues and craving (Claisse et al., 2017). Interestingly, the positive relationship between reactive HRV and craving persisted regardless of abstinence duration (Claisse et al., 2017). In addition, increased reactive HF-HRV to alcohol cues in short-term abstainers (~3 months) was associated with increased risk of relapse (Garland et al., 2012). Similarly, increased reactive time-domain HRV to an alcohol script after 3 months of abstinence was related to more negative mood and less ability to resist alcohol (Ingjaldsson et al., 2003). Those studies suggest that reactive HRV has a potential for being a biomarker of craving in AUD.

3.3.5. Summary

Results from studies with AUD individuals are highly consistent (see Fig. 1). Resting HF-HRV was lower in chronic drinkers with significant but slow improvement (although not in all studies) only after at least 4 months of abstinence. Studies assessing reactive HF-HRV to alcohol cues and emotional pictures showed that reactive HRV was increased in AUD individuals even after long-term abstinence (> 6 months) suggesting that reactive HRV takes longer to normalize following alcohol abstinence. Craving and relapse vulnerability were associated with reduced resting HRV and increased reactive HF-HRV and time domain HRV.

4. Discussion

There is a growing body of literature showing that acute and chronic alcohol use impacts HF-HRV and time-domain HRV. In addition, HF-HRV seems to have potential as a marker of craving and risk for relapse. A total of thirty-three studies were included in this narrative review leading to converging observation regarding alcohol effects on resting HRV and HRV response to challenges: 1. The studies in healthy social drinkers showed that *acute* oral alcohol consumption *lowered* resting HF-HRV. 2. Resting HRV was also *decreased* in those with AUD and was inversely related to drinking severity in moderate and heavy drinkers. Resting HRV increased with abstinence in several studies but only after at least 4 months of abstinence. 3. Studies evaluating HF-HRV reactivity to emotional pictures and alcohol cues were more limited but relatively consistent. Reactive HRV to emotional pictures was increased after an acute dose of alcohol in social drinkers. Reactive HRV was also higher following presentations of negative pictures, alcohol cues, or alcohol-related scripts in short term abstainers. This increase in HRV reactivity in abstainers was attenuated with longer abstinence (> 6 months) in some but not all studies. 4. AUD abstainers who showed stronger reactivity to negative stimuli were more likely to report negative mood, crave alcohol more and relapse faster than the comparison group. 5. Both resting and reactive HRV were able to detect differences between abstainers and controls but only reactive HRV detected differences between the groups of abstainers suggesting that reactive HRV may be a more sensitive measure of autonomic dysregulation in those with AUD.

The findings in acute alcohol consumption (low, moderate or high dose of alcohol) in healthy social drinkers and findings after chronic heavy alcohol consumption were more consistent in HF-HRV than LF-HRV suggesting that alcohol has more predictable effects on the parasympathetic branch of the autonomic nervous system. Some have suggested that acute and long-term effects of alcohol use on HF-HRV are due to toxic damage to the vagus nerve (Weise et al., 1986; Ziegler et al., 1992). Vagal nerve neuropathy has been documented in individuals with chronic alcohol dependence (Guo et al., 1987; Villalta et al., 1989). Alternatively, changes in HF-HRV with chronic, heavy alcohol use may result from impaired central inhibitory feedback control of the parasympathetic branch of the autonomic system that requires long-term abstinence before regaining the ability to effectively regulate the PNS (Rechlin et al., 1996; Jochum et al., 2010).

In short-term abstinence, greater HF-HRV responsiveness was related to more negative mood, greater inability to resist alcohol, and faster relapse suggesting that HRV may be a promising marker of craving and relapse. Longer abstinence decreased reactive HF-HRV

Table 3
Alcohol effects on HRV in alcohol use disorders.

Study	Subject character	Groups	HRV/ECG recording	Measures	Study type	Design	Results
Claisse et al. 2017	N = 90, M, F, age = 18–60, outpatients, alcohol abstainers and controls	Three groups: short-term abstinence (STA, n = 31, abstinent < 1 month); long-term abstinence (LTA, n = 28, abstinent > 6 months); controls (C, n = 31)	BIOPAC amplifier and ECG; signal digitized at a 24-bit resolution and 1000-Hz sample rate	Resting HF-HRV, (baseline and recovery) and reactive (after cue presentation), mood, cognition, drinking, craving	Laboratory, 1 test day	Randomized, between groups comparison before and after presentation of pictures with positive, negative and neutral valence	No differences between groups in resting HRV; reactive HF-HRV higher in STA group when compared to LTA and controls; positive relationship between craving and increased HF-HRV following negative cues in both STA and LTA subjects
Penzlin et al. 2015	N = 48, M, F, age = 42, inpatients with alcohol dependence	Two groups: group A = 6 sessions (over 2 weeks) HRV biofeedback + standard rehabilitation (n = 24); group B = standard rehabilitation only (n = 24)	ECG recording, 10 min at a rate of 400 Hz per second	Resting HF-HRV, LF-HRV, craving, anxiety, before and after treatment	Treatment trial with 3 and 6 weeks follow ups	Randomized, between groups comparison, and within subjects comparison before and after treatment	More improvement in craving, anxiety (only at follow up), and a trend towards an increase in HRV in group A when compared to group B
Penzlin et al., 2017	N = 27, M, F, age = 42.9, inpatients with alcohol dependence	Two groups: HRV biofeedback + standard rehabilitation (n = 15); standard rehabilitation only (n = 12)	No recording	1 year follow up of patients in Penzlin et al., 2015 study	Survey study of treatment trial follow up	Survey sent by mail 1 year after discharge to determine rates of abstinence	Rates of abstinence were higher (but not statistically significant) in the HRV biofeedback group
de Zambotti et al. 2015	N = 28, M, age ~44, outpatients in residential treatment who were abstinent for 1 month, controls	Two groups: abstainers (n = 15) and controls (n = 13)	ECG recording	Resting HF-HRV, LF-HRV	Laboratory study with follow-up up to 4 months	Between group comparison of HRV from baseline and month 2 and month 4	Abstainers showed recovery in HF-HRV after 4 months follow up
Quintana et al. 2013	N = 26, M, F, age = 39.42, outpatients with alcohol dependence	Single group: alcohol dependent	Chest strap Polar monitor measuring 1000 Hz rate	Log transformed resting HF-HRV, OCDS, AUDIT-C, alcohol consumption	Laboratory, 1 test day	Completed questionnaires and resting HRV measures were collected	HRV significantly and negatively related to craving (even after controlling for drinking, anxiety, and age)
Garland et al. 2010	N = 36 for whom HRV data was available post treatment, (total N = 53), M, F, age = 40.3, patients with AUD living in a residential program (~22 months)	Two groups: group A = 10 mindfulness sessions (n = 27); group B = support therapy (n = 26)	ECG data sampled at 500 Hz recorded continuously	Resting and reactive HRV (RMSSD), stress-primed alcohol cues	Treatment study and Laboratory study 1 test day after 10 weeks of treatment	Randomized treatment study, between group comparisons, before and after treatment and following presentations of stress induced alcohol cues	No HRV differences between groups before treatment; mindfulness group had increased HRV following stress and alcohol cues; greater HRV recovery in the mindfulness group
Garland et al. 2012	N = 47 who completed treatment described in Garland et al. (2010), M, F, age ~40.3	Same groups as Garland et al. (2010)	ECG data sampled at 500 Hz recorded continuously	Reactive HF-HRV during and after stress-primed cues and rates of relapse 6 months after treatment	Laboratory, 1 test day and 6 month follow up study	Between groups comparisons following presentations of stress induced alcohol cues	Those with higher HF-HRV cue-reactivity more likely to relapse and sooner than those with lower HF-HRV cue-reactivity
Irwin et al. 2006	N = 28, M, age ~38, outpatients with alcohol dependence and age matched controls	Two groups: alcohol dependent (abstinent 2 weeks) (n = 14); age-matched controls (n = 14)	ECG data converted to LF and HF-HRV	Resting HF-HRV over time (sleep and awake)	Laboratory study with overnight stay	Between group comparison of HRV	Those with alcohol dependence had lower HF-HRV than controls
Ingjaldsson et al. 2003	N = 94, M, F, alcohol dependent patients (age = 45.5) recruited from inpatient unit (abstinent = 81.5 days) and controls (age = 42)	Two groups: alcohol dependent (n = 49); controls (n = 45)	PSYLAB software and hardware	Resting and reactive HRV (mean of successive R-R interval differences), OCDS, craving, mood, ability to resist alcohol	Laboratory, 1 test day	Between group comparison, within subjects comparison on all main outcome measures; alcoholic and non-alcoholic content picture were presented and participants were to press a button to identify them. At the end participants heard an imaginary alcohol script and were asked to imagine situation related to drinking.	Resting HRV lower in alcohol dependent patients when compared to controls; HRV increased during exposure for the alcohol dependent group but not the controls; negative correlation between HRV and ability to resist alcohol, negative mood, compulsive scores (OCDS), in the alcohol dependent group; positive correlation between HRV and positive mood in both groups
Karimullah et al. 2001	N = 20, M, F, age = 41.4, inpatient alcoholics	Single group, Additional comparisons were made to a sample of outpatient	ECG recording, 5 min	Resting HF-HRV, LF-HRV	Laboratory study on inpatient unit over 4 weeks	Within subject design measuring HRV at various times over 4 weeks	HRV lower in both inpatients and outpatients when compared to controls

(*continued on next page*)

Table 3 (*continued*)

Study	Subject character	Groups	HRV/ECG recording	Measures	Study type	Design	Results
		alcoholics and controls from De Petrillo et al. 1999 study					
DePetrillo et al. 1999	N = 61, M, F, age = 40, individuals with alcohol dependence and healthy controls	Two groups: alcohol dependent (n = 13); controls (n = 45)	ECG recording, 7 min	Hurst exponent (H) a direct measure of dynamics of interbeat intervals (IBI)	Laboratory study, 1 test day	Between group comparison	Alcohol dependent subjects (specifically males) had higher H values suggesting decreased cardiac signal complexity compared to controls
Agelink et al. 1998	N = 115, M, F, age = 41, alcohol dependent inpatients and age, sex, body weight and cigarette consumption matched controls	Two groups: detoxified alcohol dependent (n = 35); controls (n = 80)	ECG recording, 5 min	Resting HRV; LF-, MF-, and HF-HRV	Laboratory study, 1 test day 7–8 days after detoxification	Between group comparison	HF-HRV significantly lower in a subgroup of alcohol dependent patients (n = 22 or 62.8%) with polyneuropathy
Rechlin et al. 1996	N = 120, M, F, age = 40, inpatients with alcohol dependence and matched controls	Two groups: alcohol dependent inpatients (abstinent 3 weeks) (n = 60); controls (n = 60)	ECG recording, 5 min	Resting HRV; Low, medium and high frequency HRV were calculated	Laboratory study, 1 test day	Between group comparison	HF-HRV significantly lower in alcohol dependent subjects when compared to matched controls; no significant differences between groups on LF-HRV or medium frequency
Murata et al. 1994	N = 46, age = 50, outpatients with alcohol dependence and age-matched controls.	Two groups: alcohol dependent (n = 23); controls (n = 23)	ECG recording converted to LF and HF HRV	Resting LF-HRV and HF-HRV	Laboratory study 1 test day (not clearly outlined)	Between group comparison but design not clearly outlined	HF-HRV significantly lower in alcohol dependent subjects when compared to matched controls
Malpas et al. 1991	N = 34, M, age = 54 (alcohol dependent outpatients), age = 34–68 (controls)	Two groups: alcohol dependent (abstinent 1–9 weeks) (n = 23); controls (n = 11)	Holter monitor, 24-hours	Resting HRV(standard deviation of the successive differences between RR intervals [SDSD])	Laboratory study, 24-hour test day	Between groups comparison	HRV lower in alcohol dependent subjects over the entire 24 h when compared to controls
Weise et al. 1986	N = 18, M, F, age = 40.5 with alcohol addiction, healthy controls	Two groups: Individuals with alcohol addiction (abstinent up to 22 months) (n = 11); controls (n = 7)	ECG recording, 10 min	Resting HRV mean difference between successive instantaneous heart rate scores called mean momentary arrhythmia (MMA)	Laboratory study of subjects in follow up	Between group comparison and within subjects evaluation at 5, 12, 24 weeks, and for a subset of subjects 19 and 22 months.	HRV increased with abstinence of at least 6 months; 4 patients (36.4%) showed little improvement probably due to long drinking history
Weise et al. 1985	N = 62, M, F age = 35.9 (with alcohol addiction), age = 31.7 (controls)	Four groups: Alcohol group was divided into group I n = 15 (abstinent 1–5 days), group II n = 9 (abstinent 6–10 days), and group III n = 7 (abstinent > 10 days). Controls n = 31	ECG recording, 10 min	Reactive HRV (MMA)	Laboratory study, 2 test days 5 weeks apart	Between groups comparison (active [3 groups] vs controls) and within subjects evaluation at baseline and 5 weeks	HRV was lower in those with alcohol addiction when compared to controls

suggesting an improvement in cardiac regulatory control but interestingly, there was still a positive relationship between increased reactive HRV and craving regardless of length of abstinence suggesting that even after long-term abstinence HF-HRV may be a marker of vulnerability to relapse. Those findings and conclusions need to be interpreted with caution since the results are based on a small number of studies. More studies evaluating HF-HRV in relationship to craving and relapse are needed to understand better the potential validity of reactive HF-HRV as a biomarker and the mechanisms involved.

To our knowledge, this is the first review to summarize findings on the association of HRV with psychological aspects of alcohol use, including mood, subjective intoxication (Nishimura et al., 2002), craving, and drinking behavior.

The current review also raises some recurrent methodological issues that could have influenced the findings. Detailed information on age, cardiovascular fitness (Perini and Veicsteinas, 2003), socioeconomic class and education (Lampert et al., 2005), smoking (Yun et al., 2005), and other health conditions that can affect HRV were not always provided and this may have limited the ability to detect effects of alcohol, especially in cross-sectional studies. The effect size of the differences between active participants and controls was beyond the scope of this study but larger meta-analysis evaluating the magnitude of the difference may shed a better light on the current results. This is very important since no clear boundaries or cutoffs between normal and abnormal HRV have been established. HRV is influenced by many factors including physical conditioning, heart disease, age and diabetes, so the utility of any HRV value in clinical practice of alcohol treatment is limited. HRV is likely to be more useful as a marker of recovery and risk of relapse over time. How HRV measures are collected has evolved over the last few decades and although using different methods to collect HRV may allow for generalizability it may also confound the results. Developing consensus on which specific HRV measure best captures differences between clinical samples and/or controls is sorely needed. Many studies had small samples, increasing the likelihood of a chance finding. Methodologically, there was a large variance in the studies. Although most used laboratory design, posture during measurement and activity before the pre-rest period were not always indicated and this could have influenced results. For the sake of consistency and clarity we limited HRV outcome measures but including all the HRV measures utilized in each study could have given a greater insight into participants' cardiac health. In studies using moderate and heavy drinkers, and those with AUD severity and duration of alcohol use, use of medications, and use of other substances creates heterogeneity in population and this could increase the likelihood of spurious findings. Studies evaluating reactive HRV were small with only two studies in non-AUD individuals thus limiting conclusions. Finally, although we performed an exhaustive search, due to time constraints, resources and limited literature we did not complete a systematic review that may have been less susceptible to biases due to selection and publication.

In conclusion, the autonomic nervous system clearly adapts in response to chronic alcohol use and plays a role in craving and relapse. HF-HRV appears to be a sensitive marker of these changes and may be a useful biomarker in studies of the pathophysiology of AUD and studies of treatment of AUD. In addition, treatments targeting the autonomic nervous system may be of benefit in treatment of AUD.

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Conflict of interest

Drs. Ralevski and Altemus have no conflict of interest to declare. Dr. Petrakis has served as a consultant for Alkermis.

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