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Ambulatory and Challenge-Associated Heart Rate Variability Measures Predict Cardiac Responses to “Real-World” Acute Emotional Stress

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Abstract

Background—Heart rate variability (HRV) measures homeostatic regulation of the autonomic nervous system in response to perturbation, and has been previously shown to quantify risk for cardiac events. In spite of known interactions between stress vulnerability, psychiatric illness, and cardiac health, however, to our knowledge this is the first study to directly compare the value of laboratory HRV in predicting autonomic modulation of “real-world” emotional stress.

Methods—We recorded ECG on 56 subjects: first, within the laboratory, and then during an acute emotional stressor: a first-time skydive. Laboratory sessions included two five-minute ECG recordings separated by one ambulatory 24-hour recording. To test the efficacy of introducing a mild emotional challenge, during each of the five-minute laboratory recordings subjects viewed either aversive or benign images. Following the laboratory session, subjects participated in the acute stressor wearing a holter ECG. Artifact-free ECGs (N=33) were analyzed for HRV, then statistically compared across laboratory and acute stress sessions.

Results—There were robust correlations ($r=0.7-0.8$) between the laboratory and acute stress HRV, indicating that the two most useful paradigms (long-term wake, followed by short-term challenge) also were most sensitive to distinct components of the acute stressor: the former correlated with the fine-tuned regulatory modulation occurring immediately prior and following the acute stressor, while the latter correlated with gross amplitude and recovery.

Conclusions—Our results confirmed the efficacy of laboratory-acquired HRV in predicting autonomic response to acute emotional stress, and suggest that ambulatory and challenge protocols enhance predictive value.

Keywords

heart rate variability; stress; emotion; fear; anxiety; autonomic; schizophrenia; depression

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Introduction

The autonomic nervous system functions as a negative feedback loop, in which excitatory and inhibitory components are modulated by the sympathetic and parasympathetic nervous systems, respectively. The dynamic interplay between autonomic components enables efficient cardiovascular responses to both endogenous and exogenous influences, and can be quantified using heart rate variability analysis (HRV), which describes changes in the instantaneous heart rate over different time-scales. The most widely used method for HRV analysis is power spectrum density analysis, which measures heart rate changes in the frequency domain. Studies isolating the sympathetic and parasympathetic components using pharmacological blockers have established that the high frequency bandwidth (HF; 0.15-0.5 Hz) is predominantly associated with parasympathetic nervous system while the low frequency bandwidth (LF; 0.04-0.15 Hz) includes contributions from both the parasympathetic and sympathetic nervous systems(1-3). Since LF is not solely influenced by sympathetic activity, the LF/HF ratio is typically used as a measure of the sympathovagal balance(4). Clinical research has shown that HRV shows potential applications as a diagnostic instrument, predicting risk for sudden cardiac death(5) and hypertension(6).

Though less widely studied than physical stress reactivity, in recent years cardiology has displayed a renewed interest in the relationship between cardiovascular disease and emotional stress reactivity. Emotional arousal(7,8), as well as psychiatric illnesses associated with dysregulation of emotional arousal, such as trait (9,10) and pathological (11,12) anxiety and depression, panic disorder(13,14), and paranoid schizophrenia(15), are known to be associated with lowered HRV. This association has direct implications for cardiovascular health; for example, emotional stress reactivity has been linked to risk of angina(16), myocardial ischemia in patients with and without coronary artery disease (17-19), and left ventricular dysfunction (20). Yet despite the presumed ubiquity and deleterious effects of emotional stress in modern life, to our knowledge this is the first study that directly measures the degree to which HRV calculated from ECG signals obtained in a clinician's office can actually predict autonomic reactivity to emotional stress.

This may be a consequence of the fact that emotional stress is significantly more difficult to experimentally induce than its physical counterpart, exercise. Emotion studies in non-patient populations typically rely upon three different types of paradigms: personality measures such as trait anxiety, anger, depression, or perceived stress; naturalistic studies that monitor individuals already undergoing a "real-world" stressor such as a natural disaster; or experimentally inducing emotional stress under laboratory conditions, such as with timed computer tasks. Each of these is far from ideal from both scientific and clinical perspectives. Personality measures depend upon a patient's self-report, "real-world" stressors are by their very nature uncontrolled and therefore differences in the stressor severity can bias interpretation of individual variability, and laboratory stressors—while affording strong experimental control—normally have no genuine life consequences and therefore may not be a realistic proxy for even mild psychological trauma. Our general experimental aim was therefore to test the degree to which laboratory-obtained HRV correlates with "real-world" emotional stress reactivity, using a paradigm that reliably induced a powerful emotional response without sacrificing experimental control. Within this framework, we also sought to establish more specifically which types of acquisition parameters were most predictive.

Researchers have used both "short-term" (five to 30 minute) and "long-term" (24 to 48 hour) measurements to assess the diagnostic accuracy of HRV. Yet studies have shown conflicting results with respect to which of these is the more valuable in analyzing HRV as a diagnostic tool. Clinically, this is a question with direct practical importance, since short-term measurements can be easily obtained within an office visit, while long-term measurements

require either use of an ambulatory holter-monitor or overnight hospitalization, both of which can incur significant expense and potential patient discomfort. Frequency domains of a spectral analysis yielded similar results in long and short-term HRV for patients with hypertrophic cardiomyopathy(21) and different study, testing HRV in heart-transplanted children, found that short term spectral HRV recordings were as reliable as a 24-hour ECG(22). On the other hand, other studies have reported that while long term and short term HRV values often correlate, 24-hour HRV is significantly more accurate in assessing cardiac risk(23,24). A study on exercise and HRV revealed that short-term HRV recovery depended on the type of exercise, unlike long-term HRV, which was dependent on the total work of the body and uniquely revealed abnormalities up to 48 hours from the event(25). Some studies therefore argue that the two methods are equivalent, while other studies point to enhanced sensitivity and accuracy in using long-term HRV. A reasonable theoretical justification for greater accuracy with 24-hour HRV is that longer-term ambulatory measurement provides increased diversity of inputs, challenging the system sufficiently to obtain a more complete assessment of homeostatic regulation. But, if so, it also suggests the possibility that short-term HRV enhanced with perturbations (i.e., an emotional “stress test”) might deliver many of the same benefits as long-term HRV without the latter’s inconvenience.

Methods and Materials

Study Design

The purpose of this study was to determine, using a within-subjects design, the degree to which laboratory HRV measurements correlate with autonomic response to a real-world acute emotional stressor in healthy adults. In order to compare whether long and short-term HRV measurements capture the same information with the same sensitivity, the laboratory HRV measurement included both seated five-minute and ambulatory 24-hour data. In order to compare whether short-term HRV measurements could be made more sensitive by introducing a challenge condition, the five-minute HRV component was performed twice for each subject. These were performed on consecutive days counter-balanced for order between subjects: once during a emotionally neutral condition in which subjects were passively presented benign images, and once undergoing a mildly stressful condition in which the same subjects watched aversive images. The “real-world” acute emotional stressor, to which the subjects’ laboratory measures were compared, was a first-time tandem skydive. Subjects achieved altitude in 15 minutes, jumped at 4km (13,000 ft), and were in free-fall for one full minute, at which point the parachute opened and subjects landed four minutes later. Our previous studies confirmed this protocol’s efficacy in providing a reliably powerful, temporally-uniform, and well-controlled stressor, inducing marked increases of both cortisol and self-reported state anxiety (26,27). Unlike a solo skydive, which can be physically demanding, in a tandem skydive the tandem-master assumes full responsibility for all stabilization and steering. Therefore for our subjects, who were attached to the tandem-master, the skydive produced a predominantly emotional, rather than physical, stressor. As illustrated by Figure 1, ECG for each subject was thus recorded during four conditions: two five-minute laboratory measurements (neutral and challenge), one 24-hour laboratory measurement, and throughout subjects’ participation in a real-world acute emotional stressor (first-time tandem skydive, with ECG recorded from two hours pre-jump until one hour post-jump, by which time heart rate had achieved full recovery). In order to maintain as much control as possible over the subjects’ physical and emotional environments, the first three components of the study occurred while subjects were continuously hospitalized at the Stony Brook University Hospital’s General Clinical Research Center for 48 hours. Wake/sleep times as well as ECG data recording times for all four components were standardized across subjects to minimize individual variance due to diurnal variability.

Subjects

Subjects were recruited from a sample of individuals who had contacted an areas skydiving school in order to schedule their first-time tandem skydives. All subjects were consented as per procedures formally approved by the State University of New York at Stony Brook. We tested 56 healthy adult subjects with no history of cardiac or mental illness, as determined by physical exam, medical history, and screening using the screening portion of the Structured Clinical Interview for DSM-IV(28). Of these, 33 data sets met our quality control criteria of being at least 95% artifact-free for all four study components, including the skydive (30% female; Age: 18-48, $\mu=24$, s.d.=7.82, $n=33$; Body Mass Index: 18-34, $\mu=24$, s.d.=3.69, $n=33$). Of note, although our subjects self-selected to participate in a recreational tandem skydive, as a whole they actually were *more* anxious than the general population, with mean trait anxiety scores in the 76th percentile (Spielberger Trait Anxiety Scale(29): 27-55, $\mu=41.63$, s.d.=10.62, $n=33$). This had the advantage of providing a sufficiently diverse sample with which to test emotional stress reactivity. There were no differences between the included and excluded subjects with respect to gender ($F=2.26$, $df=1$, $p=0.14$), age ($F=0.15$, $df=1$, $p=0.70$), or trait anxiety ($F=0.71$, $df=1$, $p=0.41$).

Short-Term HRV

To control for diurnal variability, each subject participated in this portion of the protocol during two sessions at identical times (10:30—10:35am) on consecutive days. On each day, subjects viewed 48 images (six seconds each(30)) obtained from the International Affective Picture Scale(31), a well-validated research-based inventory of images designed for inducing emotional responses. Subjects sat two meters from a 1.23m (48") plasma screen in an otherwise completely dark sound-proof chamber. On one day, subjects viewed pictures whose content was rated "neutral" (pictures with median ratings for pleasure and dominance and lowest ratings for arousal). On the other day, subjects viewed pictures whose content was rated "negatively arousing" (pictures with lowest ratings for pleasure and dominance and highest ratings for arousal). To control for order effects, the order of condition presentation was counter-balanced for order between subjects (of the $n=33$ with > 95% artifact-free ECGs for all four components of the study, 56% performed the study as described by Figure 1a and 44% performed the study as described by Figure 1b). ECG was acquired using the Biopac Systems MP-150 unit with ECG100-C amplifiers and Acknowledge software (Goleta, CA) with a 200 Hz sampling rate.

Long-Term HRV

Subjects' ECG was monitored continuously for 24 hour immediately following the first day's laboratory testing using the Aria holter monitor (Del Mar Reynolds Medical, Irvine, CA) with a sampling rate of 128 samples per second. Participants were hospitalized during the experiment, and asked to maintain wake-times of 7:30am and sleep-times of 11:30pm. In addition, both participants and nurses kept logs of sleep and wake times, which were confirmed using group mean changes in heart rate.

Acute Stressor

An ECG holter (Vivometrics, Ventura CA) was attached upon arrival to the airfield. The timing (9:00am plane takeoff, 9:15am jump time) as well as skydive durations (five minutes, of which one minute was in freefall and four minute were under the parachute) were equivalent across all subjects. Subjects' skydive ECGs were divided into six different portions: 120-30 minutes pre-jump, 30-15 minutes pre-jump, 15-0 minutes pre-jump, 0-5 minutes post-jump, 5-30 minutes post-jump, and 30-60 minutes post-jump.

Heart Rate Variability Analyses

Records were reviewed and edited using the Impresario Holter Analysis system (Del Mar Reynolds Medical, Irvine, CA). The ECG was manually reviewed to check for any misclassifications or errors. Identified erroneous R-R intervals were replaced with values obtained by cubic spline. The R-R intervals were further filtered using an adaptive filtering technique(32) in order to remove artifacts and misclassifications that were not identified during the manual scan. The R-R intervals were converted to instantaneous heart rate with a sampling rate of 4 Hz using previously validated(33) methods; they were low-pass filtered at 0.5 Hz, down-sampled to 1 Hz and zero-measured. Power spectrum density was estimated using 256 point FFT, with a Hanning window the same size. The HR data were divided into consecutive five-minute segments (one segment for the short-term HRV conditions, which only lasted five minutes). For the long-term HRV and acute stress HRV study components we then estimated the average power spectrum density for each of the relevant time-segments: sleep and wake durations for long-term HRV and six sampling periods during the acute stress HRV. For each, the power spectrum density was calculated within two frequency bands: LF band (0.04 – 0.15 Hz) and HF band (0.15-0.5 Hz). The sympathovagal balance was estimated by taking the ratio LF/HF.

Statistical Analyses

To permit comparison between acquisition parameters' sensitivities in capturing subjects' global reactivity to the emotional stressor, we performed a Repeated Measures ANOVA (six time-segments as within-subjects factor) with four laboratory measures (short-term neutral and challenge, long-term wake and sleep) as covariates. To investigate whether different laboratory measures predicted distinct anticipatory, peak, and recovery components of the stressor, we additionally performed bivariate Pearson correlations between LF/HF for each of the laboratory conditions as compared to the real world acute stressor. Because of the problem of Type I error inflation due to multiple comparisons, we confined our correlational analyses to 24 tests: six HRV measurements during the acute stressor and the four laboratory measures. After Bonferroni or Sidak correction, this yielded an adjusted threshold for statistical significance from $p \leq 0.05$ to $p \leq 0.002$.

Results

Global comparison of acquisition parameters

Of the four laboratory conditions, long-term wake LF/HF provided the strongest covariation ($F=11.46$, $df=1$, $n=33$, $p=0.005$) with the emotional stress response over all time-points, followed by short-term challenge ($F=9.01$, $df=1$, $n=33$, $p=0.01$), long-term sleep ($F=8.52$, $df=1$, $n=33$, $p=0.01$), and short-term neutral ($F=6.41$, $df=1$, $n=33$, $p=0.03$) conditions.

Correlations between short-term HRV and real-world acute emotional stressor

LF/HF during the neutral laboratory period correlated with LF/HF during the jump portion of the skydive ($r=0.66$, $n=33$, $p=0.006$), a relationship that was enhanced for the challenge condition, ($r=0.69$, $n=33$, $p=0.001$). There was no significant correlation between either of the short-term LF/HF conditions and the first 30 minutes of the recovery period. However, LF/HF during both the neutral and challenge laboratory periods correlated strongly with the second 30 minutes of the recovery period (respectively, $r=0.73$, $n=33$, $p=0.002$ and $r=0.76$, $n=33$, $p=0.000$).

Correlations between long-term HRV and real-world acute emotional stressor

LF/HF during the wake portions of the 24 hour HRV correlated strongly with the sympathetic dominance during the 15 minutes prior to the jump ($r=0.78$, $n=33$, $p=0.000$) and also with both

of the recovery periods post-landing, with the first 30 minutes' recovery being more strongly correlated ($r=0.84$, $n=33$, $p=0.000$) than the second ($r=0.65$, $n=33$, $p=0.005$). Sleep HRV correlated only with the second 30 minutes' recovery ($r=0.60$, $n=33$, $p=0.01$).

Results for all correlations that passed statistical thresholds for Bonferroni correction are provided in Figure 2. Neither variation in elapsed time between laboratory and skydive measurements nor menstrual cycle phase (for females) were found to be significant covariates for any results.

Discussion

Heart-rate variability is a technique with demonstrated clinical utility; however, one of the critical assumptions underlying its use is that measurements taken in the laboratory provide an accurate snapshot of the autonomic regulation that occurs as a part of everyday stressors, both physical and emotional. This study focused on a specific type of stressor (emotional rather than physical, acute rather than chronic) in order to address several clinically relevant questions. Do laboratory measurements provide reasonable predictive accuracy for emotional stressors that occur within “real-world” environments? If so, does the more clinically and analytically-taxing 24-hour HRV increase that accuracy as compared to short-term laboratory HRV? Finally, does the introduction of a challenge condition for short-term laboratory HRV improve its sensitivity?

Our analyses made clear that the broad choice between five-minute versus 24-hour HRV may not be the most appropriate way to analyze the question of predictive power. While long-term HRV provided a more robust association with the acute emotional stress, this was true only for wake values; after correction for multiple comparisons, long-term sleep HRV was not predictive for any component of the response. Likewise, while short-term neutral HRV—the version that would typically administered in a clinician's office—showed a 44% decrease in effect-size for covariance with the acute stressor as compared to long-term wake HRV (and, like long-term sleep HRV, did not pass thresholds for statistical significance after multiple comparisons correction), its effect size increased by nearly 30% with the introduction of a mild challenge. Our results additionally suggest that the two most useful paradigms also seem to be most sensitive to distinct components of the stressor, with short-term challenge HRV correlating most strongly with the gross amplitude and recovery of the stressor's autonomic response, and long-term wake HRV correlating most strongly with the more fine-tuned regulatory modulation occurring immediately prior and following the stressor.

Our results therefore suggest three conclusions for using HRV to predict autonomic response to acute emotional stress. First, laboratory HRV does appear to be able to provide a marker for future reactivity to a “real-world” acute emotional stressor: we found a number of robust correlations between the two, with coefficients in ranges ($r=0.7-0.8$) large enough to be considered strongly predictive. Second, for non-challenge conditions, long-term wake measurements provide additional information as compared to short-term wake measurements; however, at least in our sample, wearing a holter ECG during sleep delivered no additional benefits. Third, for clinical environments where only short-term ECG is feasible, introduction of an “emotional stress test,” conceptually analogous to the “physical stress test” commonly used diagnostically, may be a relatively straightforward way to perturb homeostatic regulation sufficiently to gain some of the benefits associated with longer-term ambulatory data collection. Finally, challenge versus rest conditions may provide distinct types of information with respect to the dynamics of stress resilience, and therefore a comprehensive protocol may benefit from including both.

The ability for laboratory-based HRV to predict both reactivity to and recovery from real-world stressors has important implications for the study of psychopathology. Interactions between emotional stress and underlying vulnerability to it have been suggested as critical mediators of signs and symptoms in various psychiatric disorders, including schizophrenia (34-36) as well as anxiety disorders and depression (37-45). The neural pathways that link emotional arousal and HRV are the limbic outputs to the autonomic nervous system; indeed, limbic and autonomic dysregulation have been shown to be coupled in trait anxiety (9,10). As such, HRV has the potential to provide an inexpensive and noninvasive, if relatively coarse-grained, instrument for inferring limbic regulation in response to acute stress for patients with mental illness. The ability to fine-tune our interpretation of laboratory-based HRV measures, by increasing their sensitivity as well being able to optimize for either the amplitude of the stress response or its modulation, may increase detection power for individual components of the stress response that differ in ways that are disorder-specific. Just as importantly, it may inform cognitive-behavioral therapeutic strategies tailored toward addressing distinct types of stress vulnerabilities.

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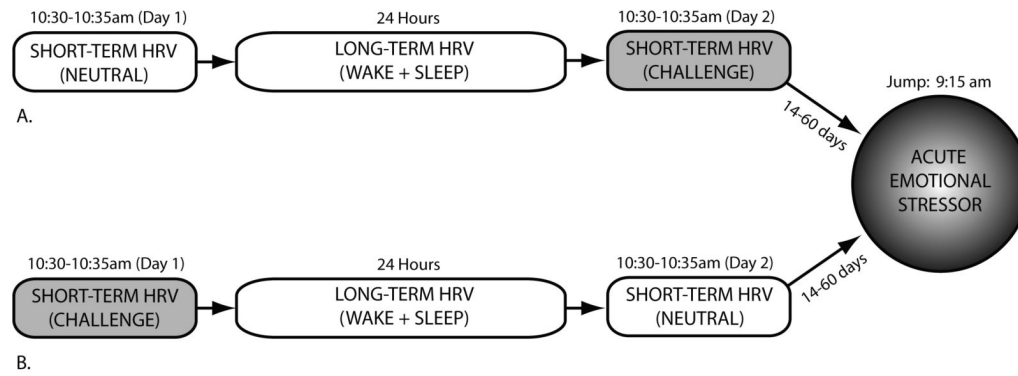


Figure 1. Schematic of Experiment

Each subject ($N=33$ artifact-free data) participated in four laboratory sessions during which we recorded ECG and subsequently calculated heart rate variability, a measure of sympathetic dominance. These included two five-minute sessions (neutral and emotional challenge) separated by 24-hour ambulatory recording. Session order (*a* versus *b*) was counterbalanced between subjects. Following laboratory sessions, subjects participated in a first-time tandem skydive, to determine the degree to which laboratory ECG predicted autonomic response to an acute emotional stressor.

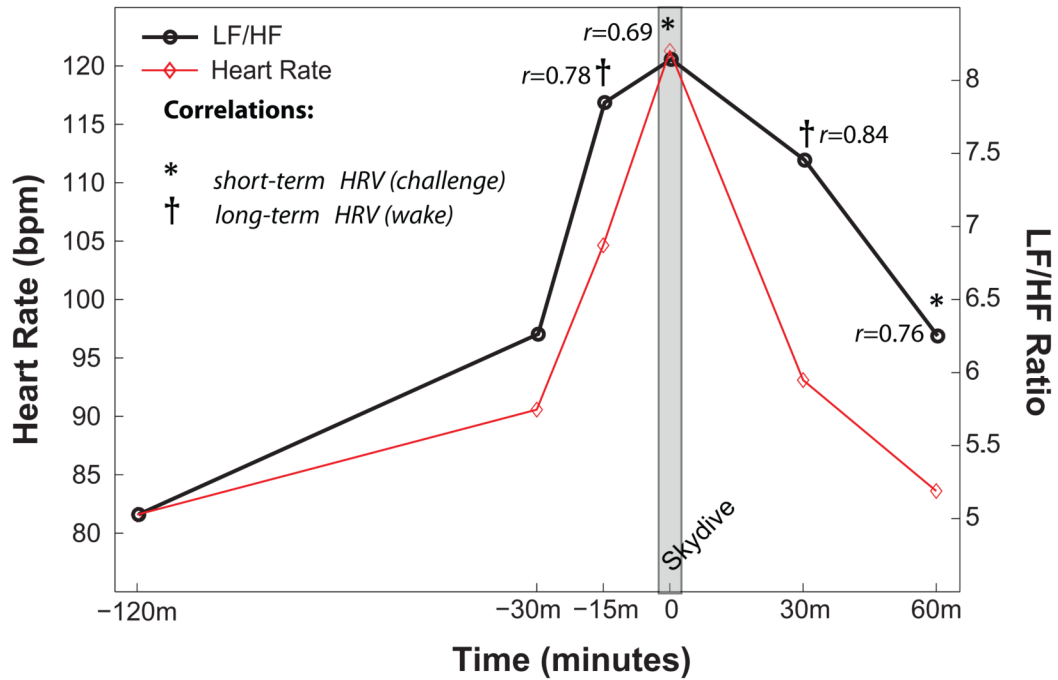


Figure 2. Correlations of Laboratory Heart Rate Variability with Heart Rate Variability During Acute Emotional Stressor

Short-term emotional challenge and long-term wake measurements both strongly predicted heart rate variability during the first-time tandem skydive but were sensitive to distinct components of the anticipatory, peak, and recovery response. Short-term neutral and long-term sleep measurements did not meet thresholds for statistical significance after Bonferroni correction, and therefore results are not presented here.

Table 1

Mean Heart-Rate Variability Values for All Laboratory and Acute Stress Conditions

	Cardiac Variables (N=33)					
	LF μ / s.d.	HF μ / s.d.	norm LF μ / s.d.	norm HF μ / s.d.	LF/HF μ / s.d.	LF/HF μ / s.d.
Laboratory Conditions						
short-term HRV (neutral)	3.933/3.288	5.280/8.786	0.538/0.224	0.462/0.224	2.062/2.433	2.062/2.433
short-term HRV (challenge)	3.570/3.472	4.654/4.766	0.483/0.218	0.507/0.218	1.549/1.701	1.549/1.701
long-term HRV (wake)	5.864/2.920	1.787/1.066	0.764/0.088	0.236/0.088	4.383/2.196	4.383/2.196
long-term HRV (sleep)	2.891/1.734	1.872/1.643	0.633/0.121	0.368/0.119	1.997/1.181	1.997/1.181
Acute Stressor						
-120 minutes	7.189/4.530	1.875/1.273	0.793/0.091	0.207/0.091	5.028/2.737	5.028/2.737
-30 minutes	8.031/3.487	1.856/1.453	0.822/0.082	0.178/0.024	6.263/3.690	6.263/3.690
-15 minutes	6.074/3.921	1.283/1.732	0.846/0.077	0.154/0.077	7.848/4.837	7.848/4.837
Skydrive	12.863/9.932	2.716/3.152	0.850/0.093	0.151/0.093	8.145/4.808	8.145/4.808
30 minutes	6.512/3.036	1.475/1.178	0.823/0.091	0.177/0.091	7.456/5.120	7.456/5.120
60 minutes	7.736/4.302	1.667/1.128	0.808/0.102	0.192/0.102	6.251/4.321	6.251/4.321