Unexpectedly, Cluster Headache Does Not Appear to Involve a Cardiac Autonomic Problem, as Reflected by Continuous Wavelet Transform

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Abstract

Cluster headache is a severe form of the primary headache syndromes, yet the basic pathology is unknown. We examined cardiac autonomic function in 14 subjects with Cluster Headache (CH) during headache period and 11 subjects in "quiescent" period (QP) versus a control group (C ,n=9). Subjects rested supine for 30 min before performing: Isometric Handgrip (HG) and Active Change in Posture (CP). Time frequency analysis of respiration, heart rate (HR) and continuous blood pressure (BP) was performed using a modified Continuous Wavelet Transform (CWT). There were no differences in HR or spectral content of HR at any time. LF fluctuations in BP in response to CP were significantly greater in C compared with CH or QP. During HG, QP had significantly greater increases in BP than CH or C, despite similar LF of BP. We conclude that cardiac autonomic control is normal in CH, but less LF fluctuations in BP are required to increase BP.

1. Introduction

Cluster headache is the most severe and disabling form of headache of the primary headache syndromes, yet the basic pathology is unknown. This type of headache appears in particular in young males and is characterized by severe unilateral pain localized around the eye, accompanied by ipsilateral autonomic phenomena such as conjunctival injection, tearing, rhinorrea or nasal stuffiness, meiosis and ptosis [1]. Lacrimation and nasal secretion are probably due to massive trigeminal-paraysmpathetic discharge [2].

On average, the cluster period lasts about 8 weeks. Cluster attacks may last from 20 min to 3 hrs (average around 90 min), and patients may have 1-8 attacks in a 24 hour period with characteristic appearance at night [1]. Cluster headache has a strong biological rhythm with a seasonal propensity of bout onset. Cluster headache is frequently misdiagnosed, and as a result, sufferers undergo unnecessary imaging studies and surgery, and are denied effective treatment by third-party payers and physicians [3]. The average time from onset of cluster to correct diagnosis is 6.6 years.

Examination of circadian and sleep time autonomic function based on 24 hr Holter recordings in a subgroup of our patients showed that VLF, LF and HF were significantly higher in patients (CH) than in normal controls when the entire recorded day (vs. sleep time) was considered [4]. We speculated that vasomotor changes accompany CH attacks, as suggested by a higher VLF in CH when compared to normal control subjects.

An earlier study examined autonomic control in patients suffering from: migraine, tension headache or normal controls [5]. Migraine patients displayed markedly enhanced low frequency fluctuations of HR (LF_{HR}), while tension headache patients and controls displayed no enhancement in their LF_{HR}

Our goal in the current study was to examine autonomic control in cluster patients both during their active headache (CH) and quiescent periods (QP), to gain a better understanding of the pathophysiological basis of cluster headache. A second goal was to find clinically useful HRV parameters to distinguish cluster headache patients and improve diagnostic speed and accuracy.

2. Experimental procedures

The study was approved by the Helsinki committee of Ichilov hospital and all subjects signed an informed consent form before participating. All patients were diagnosed with cluster headache by a senior Neurologist, based on the International Headache Society classification criteria [1]. Patients contacted the Neurologist at the onset of a cluster headache period and were subsequently referred to our laboratory as soon as possible after diagnosis. Patients were tested before the administration of medications for their cluster headache. Subjects were connected to the data acquisition devices and after an initial trial run of experimental procedures, were instructed to rest quietly without falling asleep in a thermo neutral room for 30 minutes. Following the rest

period, subjects were instructed to perform the following autonomic provocations: Isometric Handgrip at 30 percent of individually measured maximal strength held till fatigue (30% MVC), and active Change in Posture from supine to stand followed by 5 min quiet standing (CP).

Each provocation was followed by a rest period to allow HR and BP to return to baseline levels. While standing, subjects were instructed not to lean on the bed. Because the duration of the handgrip was different for each subject, peak isometric exercise (fatigue) was labeled as 100% of exercise. The handgrip time was then divided into quarters so data could be compared at 25, 50, 75 and 100% of peak effort.

3. Subjects

Patients were tested during the active headache period (CH, n=14), and/or during the quiescent period (QP, n=11) and compared to control subjects (C, n=9) with similar smoking habits (average of 15-20 cigs/day). Subject characters are displayed in **Table 1**.

Parameters	Cluster Headache n=14	Quiescent period n=11	Controls n=9	Statistics One-way ANOVA
Age (years)	41.1 ± 10.6	39.6 ± 7.9	42.4 ± 8.8	p= 0.82
Height (cm)	179 ± 7	180 ± 6	176 ± 9	p = 0.59
Weight (kg)	87.7 ± 11.5	90.9 ± 8.9	82.8 ± 14	p =0.34
Male (%)	100	100	100	
% Body fat	21.7 ± 4	23.7 ± 3.1	25 ± 4.9	p = 0.21
W/H ratio	0.90 ± 0.06	0.93 ± 0.06	0.91 ± 0.07	p = 0.61
% Smokers	72	73	89	
Cigarettes/day	15.7 ± 12.8	14.5 ± 13.4	19.3 ± 6.2	p = 0.67
Rest SBP (mm Hg)	128 ± 14	125 ± 11	117 ± 6	p =0.12
Rest DBP (mm Hg)	77 ± 8	78 ± 9	74 ± 4	p =0.44
Rest HR	67 ±10	66 ± 10	59 ± 8	p = 0.17
Stand SBP (mm Hg)	129 ± 22	131 ± 15	116 ± 8	p = 0.18
Stand DBP (mm Hg)	82 ± 7	87 ± 8	75 ± 4	***p* =0.006**
Stand HR	77 ± 14	78 ± 8	71 ± 9	p =0.42
Supine-stand change in SBP(mmHg)	1.5 ± 13	7.5 ± 7	-0.5 ± 7	p = 0.25
Supine-stand change in DBP	5.6 ± 8	9.4 ± 6	1 ± 6	**p =0.056**

Table 1 - Subject Characteristics

4. Methods

The following signals were sampled simultaneously, on-line, resulting in synchronized signals, at a sampling rate of 500 Hz using a Biopac multi-channel device (MP100-BIOPAC).

- ECG
- Respiration (Respitrace pneumo-plethysmograph)
- Continuous non-invasive Blood Pressure (Portapres^{TM})
- Blood Pressure measurements with standard cuff – once at rest and once at end of 5 min stand.

Respiration signal was low-pass filtered (cut off frequency 4 Hz) and decimated to 10 Hz. The BP signal of the Portapres device, which includes Physiocal intervals (calibration signals), was interpolated according to a previously published algorithm [6]. R waves from the recorded ECG were detected automatically using in-house software and detection was verified manually. Resulting RR intervals were interpolated to an equally spaced HR time series [7;8] and sampled at an effective sampling rate of 10 Hz. For spectral analysis, HR was filtered through a median high-pass filter to avoid the masking effect of non-stationarities on the spectrum.

5. Time-frequency analysis

Time-frequency decomposition of the signals was performed by Continuous Wavelet Transform (CWT) as we have previously described [9]. This wavelet transform contains many aspects of the Selective Discrete Fourier Transform Algorithm (SDA) developed in our laboratory [10]. The CWT reflects the power of each spectral component at each point in time by applying a time window, the duration of which is inversely proportional to the analyzed frequency. Varying the window duration allows an improved time resolution for higher frequencies and improved frequency resolution for lower ones. CTW was calculated for HR over the entire recording period.

We focused on two main regions of power: a high frequency peak (in HR only) located around the respiratory frequency (HF from 0.18-0.4 Hz), reflecting primarily vagal activity, and a low frequency peak (LF within 0.02-0.18 Hz) centered around 0.1 Hz. The LF content of HR fluctuations is an estimate of combined vagal and β- sympathetic activity, while the LF content of BP fluctuations is an estimate of α–sympathetic activity. Time-dependent Power Integrals in the specific frequency bands were calculated and compared between groups.

6. Statistics

Time-frequency power was calculated every second during the recording. Due to a skewed distribution, all integral values were log transformed prior to statistical analysis. For statistical analysis, power integrals were averaged every 5-seconds throughout the testing protocol.

Comparisons between groups were made by repeated-measures ANOVA and resting values were compared by one-way ANOVA. $p < 0.05$ was considered significant. Data are shown as means ± SE.

7. Results

Respiration: Respiratory spectrum was calculated from the rib signal and examined to ensure that respiratory frequency was within the defined HF range. There were no differences in the respiratory spectrum between groups.

HR during CP: There were no significant differences in resting HR, peak HR with CP or standing HR, between the groups. There was a reduction in high frequency fluctuations in HR (HF_{HR}) upon transition to stand which returned to resting levels after approximately 30 seconds of standing. These changes in HF_{HR} were similar between groups. Resting values of Low Frequency fluctuations of HR (LF_{HR}) were similar between groups. LF_{HR} increased during CP and remained elevated above resting levels throughout the stand. There were no differences between the groups in LF_{HR}. The ratio between LF_{HR} and HF_{HR} was also similar between all groups at rest and changed similarly during CP.

BP during CP: BP recordings for one QP patient and one C patient were of poor quality and their BP data could not be used. Resting blood pressure was not different between groups nor were there differences in BP during the 60 sec after CP although C had a tendency toward lower BP during rest and CP (not significant). At the end of the 5 min stand, controls had significantly lower cuff DBP than did CH or QP.

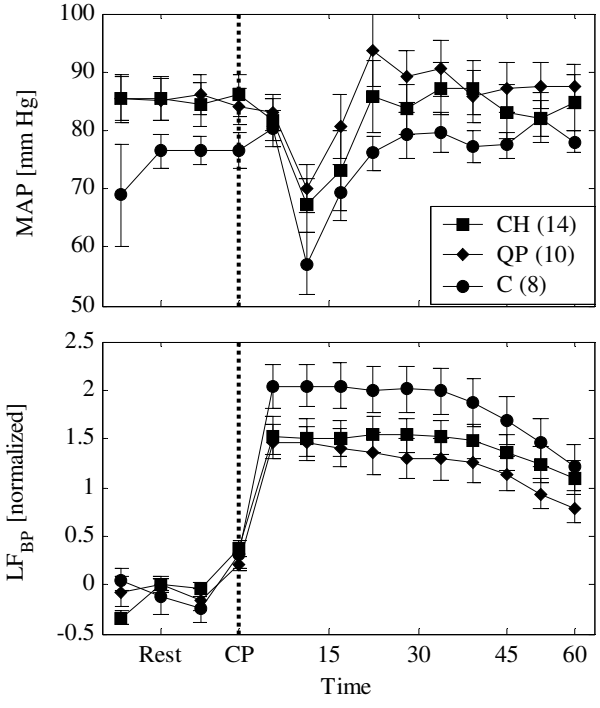

Figure 1 – Resting values represent average of 10 min prior to stand. CP indicates transition to stand. Time following CP is in seconds. Upper panel: BP changes during CP. Lower panel: changes in LF_{BP} during CP. Note that Controls had a significantly greater increase in LF_{BP} than either of the cluster groups.

Examination of the first minute after CP showed that LF fluctuations in BP (LF_{BP}) were different between groups ($p<0.006$). CH and QP had similar levels of LF_{BP} at rest and during CP. The increase in LF_{BP} after CP (compared to baseline levels) was significantly higher in Controls than in either group of patients (**Figure 1**). The SBP and DBP values and their LF fluctuations showed the same pattern as MAP, therefore they are not discussed separately.

HR during Handgrip: No differences were observed between groups in resting HR or HR response to isometric handgrip, nor in any of the frequency parameters of HR.

BP during Handgrip: BP response to 30% MVC handgrip was different between groups. When normalized to their baseline values, the BP of C and CH groups changed identically. The QP group had significantly greater increases in BP than either of the other groups ($p<0.052$). Despite significant differences in BP increase with Handgrip, there were no differences in the LF_{BP} between groups see **Figure 2**. SBP and DBP and their LF fluctuations changed in parallel with BP.

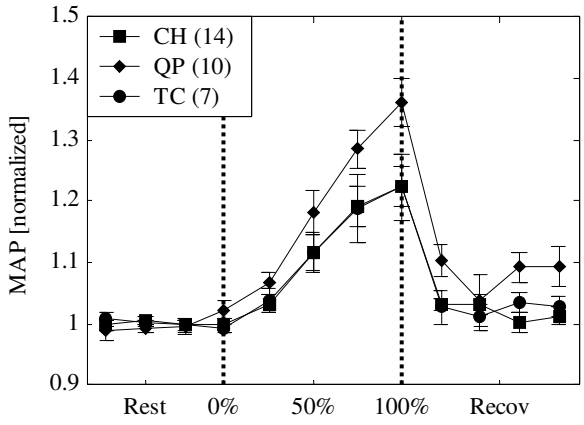

Figure 2 Changes in BP during 30% MVC isometric Handgrip. Rest and Recovery periods represents an average of 5 min. Patients in Quiescent period had significantly greater increases in BP with HG than did patients during active headache period or controls.

8. Discussion and conclusions

Cardiac autonomic control was similar across the board between all three groups. HR and its frequency parameters were similar both during CP and during the

isometric Handgrip leading us to conclude that cardiac autonomic control is not affected in the subjects suffering from cluster headache, whether during the active headache or during the quiescent period.

Isometric Handgrip, known as a sympathetic autonomic manoeuvre caused greater increases in BP levels in patients during their quiescent period than in patients during the active headache period or controls. BP fluctuations associated with this increase in BP were similar across all groups.

It appears that minimal LF fluctuations in BP cause a greater BP response during the quiescent period than during active headache period, or in controls. This leads us to believe that perhaps patients suffering from cluster headache are not "normal" during their quiescent period. There appears to be a hypersensitivity to alpha sympathetic activity in patients with cluster headache which is more pronounced during the quiescent than during the active headache period.

HRV changes in response to autonomic provocations such as CP and HG may provide a simple and inexpensive diagnostic criterion to distinguish between Cluster and Migraine headache, thus greatly reducing the time to accurate diagnosis and effective treatment. Cluster patients do not display any elevation in LF_{HR} at rest in comparison with controls, while Migraine patients have twofold higher resting levels of LF_{HR} fluctuations than do normal individuals. Additionally we have shown that cluster patients – both during the active and quiescent periods – have similar increases in HR in response HG as controls, while Pogacnik et al [11] demonstrated that HR increase during HG was significantly reduced in migraineurs compared to controls. We conclude that cluster headache is not characterized by cardiac autonomic dysfunction, but rather by peripheral hypersensitivity to fluctuations in BP.

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