Intensive care unit-acquired weakness: early diagnosis, symptomatology and prognosis
Wieske, L.

Citation for published version (APA):
CHAPTER 6

EXAMINATION OF CARDIOVASCULAR AND PERIPHERAL AUTONOMIC FUNCTION IN THE ICU: A PILOT STUDY

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ABSTRACT

Critical illness may affect the autonomic nervous system. Decreased cardiovascular autonomic function measured by heart rate variability (HRV) has been reported in critically ill patients but limited information exists about other autonomic functions. The cold face test (CFT) and skin wrinkle test (SWT) have never been investigated in critically ill patients. Feasibility and safety of the CFT and SWT were investigated in critically ill patients. Exclusion criteria: polyneuropathy, autonomic neuropathy, admission after stroke, spinal cord injury or cardiac arrest. For the CFT, a cold pack was applied to the forehead to measure the maximal increase in RR interval. The simulated SWT was used and wrinkling was assessed on a five-point scale. HRV was investigated using power spectral analysis of continuous 5-min ECG recordings. Twelve critically ill patients were included (mean age 54). No adverse effects for the CFT and SWT were noted. The CFT could be performed in 10 patients and showed an abnormal response in 9. The SWT could be performed in 11 patients; results were abnormal in 6. HRV analysis showed decreased HRV in all patients. CFT and HRV responses were correlated with each other, no correlation was found between SWT and CFT or HRV results. The CFT and SWT are feasible and safe in critically ill patients. Cardiovascular dysfunction may be more prevalent in critical illness than peripheral sympathetic dysfunction. Influence of confounders and further validation of these tests needs to be investigated.
INTRODUCTION

Critical illness can lead to a spectrum of neurological disorders encompassing both the central and peripheral nervous system.  It is less well known that the autonomic nervous system (ANS) may also be affected. The ANS together with effector organs gives rise to various autonomic functions. Autonomic dysfunction is thought to play a role in the development and/or progression of the multiple-organ dysfunction syndrome (MODS). Moreover, autonomic dysfunction is independently associated with mortality and severity of illness.

The most frequently investigated autonomic function in critically ill patients is cardiovascular autonomic function by means of heart rate variability (HRV). HRV is mediated through different mechanisms including the sympathetic and parasympathetic nervous system. Interpretation is difficult, and the exact underlying ANS correlates have been questioned. Data on HRV results are available for specific intensive care unit (ICU) populations, like patients with sepsis or patients with MODS, but data for general ICU patients is lacking.

Other autonomic functions in critically ill patients have not been examined extensively. A thorough examination of autonomic function using conventional methods, like tilt-table testing or the Valsalva maneuver, is problematic in critically ill patients. Easy and safe tests which are feasible in the ICU setting are needed to provide further insight into the role of different autonomic functions in MODS.

Two relatively easy measures of autonomic function, the cold face test (CFT) and the skin wrinkle test (SWT), have never been investigated in the ICU. The CFT is a measure of cardiovascular autonomic function and based on the diving reflex. A cold pack is applied to the forehead, causing a decrease in heart rate mediated by the vagal nerve. The SWT is a measure for peripheral sympathetic nerve fiber function by assessing wrinkle formation of the fingertips. The aim of this pilot study was to investigate the feasibility of the CFT and SWT in critically ill patients and to compare the different autonomic functions as measured by CFT, SWT and the HRV in critically ill patients.

METHODS

In this pilot cohort study, critically ill patients admitted between February and July 2011 were included. The study was performed in a 30-bed, mixed medical/surgical tertiary ICU. Patients who were mechanically ventilated for at least 3 days were included. Exclusion criteria: ICU admission for neuromuscular disorders, stroke (ischemic, hemorrhagic or subarachnoid) or spinal cord injury, documented polyneuropathy or autonomic neuropathy in medical history. The study was approved by the Medical Ethical Committee of the Academic Medical Center (NL34849.018.10; METC 10/313) and was in accordance with Declaration of Helsinki (2008). All study participants and/or relatives of the participants gave informed consent prior to inclusion in the study.

Autonomic function tests

The cold face test was measured using a 4 °C cool pack applied to the forehead for a period of 40 s. If patients were awake during testing, they were instructed not to change their breathing pattern, and if patients were mechanically ventilated no changes in ventilatory settings were
made. As a drop in heart rate can occur during the CFT, this test was only performed when a sinus rhythm with a frequency >70 beats/min was present to avoid bradycardia with hemodynamic consequences during testing. Heart rate was recorded beat to beat by measuring RR intervals starting 1 min before the cold stimulus until 1 min after. Skin temperature of the forehead was measured before and after cold pack application using an infrared thermometer (Medisana AG, Hilden, Germany). Adverse effects (new onset of arrhythmias, hemodynamic instability, heart rate decrease >20 % compared to baseline and patient discomfort) were scored during and after the CFT. The cold face test response was assessed by calculating the maximal change in heart rate after cold pack application.\textsuperscript{11} The maximal change was defined as the longest RR interval occurring in the period after cold pack application until 1 min later, and was depicted as a percentage relative to the baseline RR interval (defined as the mean RR interval in the minute before cold pack application). An abnormal response was defined as a maximal change <6.4 % (10\textsuperscript{th} percentile of the control population in this study).

The simulated SWT was performed by applying approximately 0.5 g of EMLA cream (2.5 % lidocaine and 2.5 % prilocaine, AstraZeneca, The Netherlands) on the fingertip of the fourth finger.\textsuperscript{13} The finger was covered with a plaster for 30 min. Adverse effects (allergic reaction and impaired perfusion of the fingertip) were scored during and after the SWT. Wrinkle formation was assessed and recorded at bedside on a five-point scale ranging from 0 (no wrinkling), 1 (slight wrinkling and fingertip is not smooth), 2 (two or fewer lines of wrinkling on each side of the fingertip), 3 (three or more lines of wrinkling on each side of the fingertip) to 4 (complete distortion of the finger pulp by wrinkling).\textsuperscript{13} An abnormal response was defined as a wrinkle score <3.\textsuperscript{13}

HRV was measured using a continuous ECG recording from a bedside monitor for a period of 5 min when sinus rhythm was present. From the ECG signal RR intervals were extracted, stored digitally using custom-made software (based on National Instruments LabVIEW, Austin, Texas, United States; sampling frequency: 250 Hz, highpass filter: 100 Hz) and analysed offline. Heart rate variability analysis was done using Kubios HRV software.\textsuperscript{14} Before analysis the recording was checked for artefacts caused by interference or ectopic heartbeats. Artefacts were corrected by deleting the RR interval. If a recording consisted of more than 30 s of irregularities, it was not analyzed. Spectral domain analysis calculated with a fast Fourier transformation based on Welch’s periodogram was used to assess variability. Frequency band ranges were: 0.04–0.15 Hz (low frequency; LF) and 0.15–0.4 Hz (high frequency; HF) and are displayed in absolute (ms\textsuperscript{2}) and relative power (normalized units; n.u.).\textsuperscript{15} LF and HF power was summated to calculate total power. An abnormal response was defined as when both LF and HF were below the 2.5\textsuperscript{th} percentile of the corresponding age group reported by Ziegler et al.\textsuperscript{16}

CFT, SWT and HRV recording were all done within a 1-h period. The CFT and SWT were repeated twice weekly and the HRV was performed daily until ICU discharge. All procedures were performed in a supine position with the head elevated to 30\textdegree. To validate study procedures and to obtain local reference values for the CFT all autonomic function tests were also performed in healthy control subjects recruited from hospital staff.
Clinical data collection
From the patient file, clinical characteristics were collected including age, gender, admission type, presence of sepsis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and daily Sequential Organ Failure Assessment (SOFA) scores.

Data analyses and statistics
Autonomic function tests obtained from a single day, i.e., the first day that most of the autonomic function tests could be analyzed, were used for comparison to reference values from the control groups. For correlations between autonomic functions and severity of illness all longitudinal measurements were analyzed. Normality was assumed when W-statistic >0.90 (Shapiro–Wilk test). HRV variables were logarithmically transformed to obtain normality. Differences in temperature decline during the CFT were assessed with the Student’s t test. Differences in relative contributions of LF and HF to total power were analyzed with the paired t test. Correlations between normally distributed variables were calculated using Pearson’s r (presented with r and p value) while correlations between non-normally distributed variables were calculated using Spearman’s rho (presented with rho and p value). Mean values are presented with standard deviation (± SD) and median values with interquartile range (IQR). Statistical significance is defined as p<0.05. Analyses were done using IBM SPSS Statistics 19 (IBM, Armonk, New York, USA).

RESULTS
For this pilot study we included 12 critically ill patients (58 % males, mean age: 54 ± 15). Table 1 depicts clinical characteristics and different autonomic functions.

Validation of test procedures
Twenty healthy controls (35 % males, mean age 36 ± 12) were investigated. The median response for CFT was 17.2 % (IQR 11.3–30.7) and the median skin wrinkling score was 4 (IQR: 4–4). The median total power of HRV was 2330 ms2 (IQR: 1302–4583) with median LF and HF power of 1006 ms 2 (IQR: 658-1256) and 1355 ms 2 (IQR: 500-2768), respectively. Relative contribution of LF and HF to total power was similar (mean LF 48.8 ± 20.6 n.u. and HF 50.3 ± 21.7 n.u.; p:0.87).

Cold face test
A total of 44 CFTs were performed in 10 patients, and 36 tests (82 %) could be completed successfully. CFT could not be performed in two patients due to persistent arrhythmias (patient 8) and a wound on the forehead (patient 9). No CFT measures were prevented because of heart rates <70/min. CFT testing was temporarily hampered by ECG irregularities (5 times, in 4 patients) and delirium (3 times, in 2 patients). No adverse effects during or after CFT were noted. Skin temperature of the forehead was lowered in a similar degree in patients and controls by cold pack application (-6.6 ± 3.1 and -7.0 ± 2.6 °C; p:0.75). An abnormal response was seen in 9 of 10 patients. The median response was 3.85 % (IQR: 2.3–4.7). Figure 1 shows two typical examples of a response in a critically ill patient (panel A) and control (panel B). Reversibility to a normal response was observed in three patients during the study period.
Table 1. Patient characteristics and autonomic function

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Admission type</th>
<th>APACHE II score</th>
<th>Sepsis</th>
<th>CFT abnormal response</th>
<th>HRV abnormal response (LF / HF 2.5th percentile)</th>
<th>SWT abnormal score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>medical</td>
<td>13</td>
<td>n</td>
<td>+</td>
<td>4.7% / 26 ms²</td>
<td>374 / 52 ms²</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>M</td>
<td>medical</td>
<td>12</td>
<td>y</td>
<td>+</td>
<td>1.7% / 4 ms²</td>
<td>1670 / 269 ms²</td>
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<tr>
<td>3</td>
<td>59</td>
<td>F</td>
<td>medical</td>
<td>16</td>
<td>y</td>
<td>+</td>
<td>2.2% / 13 ms²</td>
<td>442 / 62 ms²</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>F</td>
<td>medical</td>
<td>6</td>
<td>y</td>
<td>+</td>
<td>3.1% / 21 ms²</td>
<td>374 / 52 ms²</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>F</td>
<td>medical</td>
<td>13</td>
<td>y</td>
<td>+</td>
<td>4.6% / 26 ms²</td>
<td>442 / 62 ms²</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>M</td>
<td>surgical</td>
<td>9</td>
<td>n</td>
<td>+</td>
<td>4.9% / 11 ms²</td>
<td>859 / 129 ms²</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>surgical</td>
<td>15</td>
<td>y</td>
<td>+</td>
<td>4.7% / 21 ms²</td>
<td>521 / 74 ms²</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>M</td>
<td>surgical</td>
<td>19</td>
<td>n</td>
<td>nd</td>
<td>nd</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>M</td>
<td>medical</td>
<td>15</td>
<td>y</td>
<td>nd</td>
<td>+</td>
<td>10 / 11 ms²</td>
</tr>
<tr>
<td>10</td>
<td>31</td>
<td>M</td>
<td>medical</td>
<td>13</td>
<td>y</td>
<td>-</td>
<td>24.9% / 199 ms²</td>
<td>1197 / 186 ms²</td>
</tr>
<tr>
<td>11</td>
<td>56</td>
<td>F</td>
<td>medical</td>
<td>25</td>
<td>y</td>
<td>+</td>
<td>2.3% / 3 ms²</td>
<td>521 / 74 ms²</td>
</tr>
<tr>
<td>12</td>
<td>63</td>
<td>F</td>
<td>medical</td>
<td>20</td>
<td>y</td>
<td>+</td>
<td>2.6% / 6 ms²</td>
<td>374 / 52 ms²</td>
</tr>
</tbody>
</table>

APACHE II: Acute Physiology and Chronic Health Evaluation II; CFT: cold face test (abnormal = <6.4% increase); HRV: heart rate variability (abnormal = both LF and HF below 2.5th percentile of age matched reference values from 9); SWT: skin wrinkle test (abnormal = <3); nd = not done, because the test was not feasible in this patient, see text for explanation; M = male, F = female; y = yes, n = no. Single test results performed on the same time point are reported.
Skin wrinkle test

A total of 38 SWTs were performed in 11 patients, and 35 tests (92%) could be completed successfully. SWT could not be tested in one patient on all occasions due to severe peripheral vasoconstriction. The reason for temporarily unsuccessful SWT testing was delirium (3 times, 2 patients). No impaired perfusion of the fingertip or allergic reactions were noted. Abnormal wrinkling was seen in 6 of 11 critically ill patients. The median score was 2 (IQR: 0-4). Figure 2 displays typical examples of a SWT in a critically ill patient (A) and control (B). Reversibility to normal wrinkling was observed in two patients during the study period.

Figure 1. Cold face test: example of a patient (A) and control (B)
CFT cold face test

Figure 2. Skin wrinkle test: example of a patient (A; patient 6) and control (B)
Heart rate variability
A total of 102 HRV measurements were successfully performed in 11 patients. One patient could not be tested due to persistent arrhythmias. All patients showed abnormal HRV. Median total power was 21.3 ms² (IQR: 6.3–59.2) with median absolute LF and HF power of 11.1 ms² (IQR: 3.9–25.7) and 10.5 ms² (IQR: 1.8–26.3), respectively. Relative contribution of the LF frequency band to total power was higher compared to the HF frequency band (LF 66.7 ± 14.1 n.u. and HF 34.9 ± 15.7 n.u.; p<0.01). Figure 3 displays two representative power spectra of a critically ill patient (A) and control (B). Reversibility to normal was observed in two patients during the study period.

![Figure 3. Heart rate variability power spectra: example of a patient (A) and control (B)](image)
PSD: power spectral density, LF: low frequency band (0.04–0.15 Hz); HF: high frequency (0.15–0.4 Hz); range of y axes not equal to allow visualization of both spectra

Correlation of autonomic function tests with severity of illness
No correlations were found between the SOFA score and CFT or SWT performed on the same day (rho: -0.32; p:0.07 and rho: -0.18; p:0.37). HRV showed an inverse correlation with SOFA score at the day of measurement (total power; r: -0.27; p:0.01).

Correlation between autonomic function tests
Concurrently performed cardiovascular autonomic function tests were positively correlated in patients and in controls (CFT response and HRV (total power): in patients rho: 0.72; p<0.01 and in controls rho: 0.76; p<0.01). Both in patients and in controls the SWT was neither correlated with the CFT response nor with the HRV (data not shown).

DISCUSSION
In this pilot study, we found that in critically ill patients both the CFT and SWT are feasible, easy and safe to perform. The most prevalent reason for failure of successful CFT testing was cardiac arrhythmias. Skin wrinkle testing was prevented in one patient due to severe vasoconstriction. Delirium can hamper CFT and SWT testing. Cardiovascular autonomic dysfunction, as measured by the HRV and the CFT, was present in almost all patients. Peripheral sympathetic autonomic dysfunction, as measured by the SWT, was present in half of the patients. Comparing our
Cold face test is a multisynaptic reflex. Application of a cold stimulus triggers afferent fibers of the trigeminal nerve which relay the signal to the brainstem, where vagal cardiac motor neurons are activated, causing a decrease in heart rate. Failure to induce a reflex bradycardia can in theory be explained by dysfunction on each of these levels. Abnormal CFT results have been attributed to efferent and/or afferent dysfunction (e.g., in patients with familial dysautonomia or pure autonomic failure). The causes of the diminished responses seen in this study remain to be elucidated.

In this study the simulated SWT was used. This is more practical compared to the original SWT using water immersion and has comparable performance. Scores seen in controls in this study resemble those reported in an earlier study using healthy controls. Wrinkling in the SWT is thought to occur due to EMLA-induced triggering of the small peripheral sympathetic C fibers. Decreased wrinkling can therefore be interpreted as a sign of peripheral sympathetic dysfunction. Low wrinkling scores have a high predictive value for low intra-epidermal nerve fiber density. The reversibility of decreased wrinkling seen in some of our patients suggests that temporary dysfunction of C fibers might be a more likely explanation. Skin biopsies can be used to investigate this further.

Decreased HRV was found in all our patients, and results are comparable to other series of specific ICU patient groups. Median control values in our study were comparable to values reported by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Powerspectral analysis of HRV is known to be influenced by artefacts introduced by ectopic beats or interference. In this study, this was limited because we used measurements during sinus rhythm and deleted RR intervals caused by artefacts. Deletion or interpolation of erroneous RR intervals are possible solutions for artefacts, but there is no consensus which method is best. The ability of HRV to localize dysfunction in the ANS has been questioned. There is debate about which ANS division is responsible for variability seen in the different frequency bands. The underlying physiological mechanism of the very low frequency (VLF) band is unclear, and was therefore not used in this study. Parasympathetic activity has been identified as being solely responsible for modulation in the HF band, but constituents of the LF band are unclear. Sympathetic cardiac modulation is thought to be the dominant contributor to LF modulations, but parasympathetic modulation can also operate in and around this frequency range. The LF band is therefore a representation of both sympathetic and parasympathetic modulation. Localizing the factors underlying the decreased HRV seen in this study cannot be done confidently. Combination of abnormal HRV and CFT results seen in almost all patients in this study suggests that at least parasympathetic central and efferent dysfunction are present.

Several limitations of this study exist. We have included a limited number of patients in this pilot study, so the true prevalence of the various types of autonomic dysfunction may be different. Furthermore, group size was too small to assess confounders for SWT and CFT or the clinical implication of autonomic dysfunction detected by these tests. Autonomic function tests
Cardiovascular and peripheral autonomic function in the ICU

are susceptible for various confounders, many of which are present in the ICU patient. So far, other studies investigating confounders for HRV testing have found that sedation, mechanical ventilation or catecholamines did not influence HRV sufficiently to bias results in critically ill patients. To investigate correlations between autonomic function tests, we used correlation coefficients which are not corrected for repeated measures. A last limitation of our study is the use of reference values obtained from healthy controls. HRV is age-dependent, and therefore age-matched cut-off value were used. For the CFT and SWT unmatched cut-off values were used.

Autonomic function is the result of the combined function of afferent visceral nerves, central modulation, efferent autonomic nerves and the effector organ. Autonomic dysfunction in critically ill patients could be localized anywhere in this pathway. Furthermore, functionally distinct autonomic divisions can probably not only operate independently but can also be affected differently during critical illness. This is illustrated by the lack of correlation between the SWT and the HRV or CFT seen in our study and has also been suggested by others. Possible localizations for autonomic dysfunction have been investigated. Bolton et al. showed abnormal sympathetic skin responses in ICU patients which may indicate sympathetic afferent, central or efferent fibre dysfunction. Axonal degeneration in the sympathetic chain and vagal nerve was found on autopsy in patients with critical illness polyneuropathy. Selective apoptosis of autonomic nuclei in the brainstem has been found in patients who died of septic shock. Changes at the level of effector organ may also play a role in autonomic dysfunction. Inflammation changes characteristics of cardiac pacemaker cells and this may contribute to decreased HRV. Downregulation or decreased responsiveness of β-receptors due to inflammation has also been reported.

Future studies investigating autonomic function in critical illness should use a combination of tests so that information on different parts (i.e., the efferent, central, afferent ANS and effector organs) and different divisions (e.g., parasympathetic cardiovascular or peripheral sympathetic vasoconstrictor) can be collected. The SWT and CFT used in combination with other tests may serve this purpose. Ultimately, better understanding of autonomic dysfunction in critically ill patients can lead to better understanding of the pathophysiology of MODS.

CONCLUSION

The CFT and SWT are feasible and safe to perform in critically ill patients and can be used to investigate the cardiovascular and peripheral autonomic function. Our pilot results may indicate that cardiovascular autonomic dysfunction is more prevalent than peripheral sympathetic dysfunction influence of confounders present in the ICU and further validation by using a gold standard and assessing prognostic implications needs to be investigated.

ACKNOWLEDGMENTS

The authors thank G. Sussenbach for his work on development of the HRV recording equipment and software. This research was performed within the framework of CTMM, the Center for Translational Molecular Medicine (http://www.ctmm.nl), project MARS (grant 04I-201). Dr. L. Wieske is supported by a personal grant from the Netherlands Organization for Health Research and Development (ZonMw–AGIKO grant [project number 40-00703-98-11636]).
CONFLICTS OF INTEREST
The authors declare that they have no conflict of interest.

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