

The Effect of a Smartphone and Wearable-based Stress Management Application on Cardiac Symptoms in Women with Coronary Artery Spasms: a Multicenter, Single-Arm, One-way Crossover Study

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Abstract

Background: Mental stress is a well-known trigger of cardiac symptoms in patients with coronary artery spasms. Hence, stress management is recommended beyond medical therapy. However, specific programs for patients with coronary spasms are lacking. We collaborated with patients to develop a smartphone-based application as a tailored solution. The application provides biofeedback based on HRV-driven stress level estimations.

Objective: Our study aimed to evaluate the effect of a biofeedback-driven smartphone stress management application on cardiac symptoms in women with coronary vasospasms.

Methods: We enrolled 117 women aged 18-70 diagnosed with coronary vasospasms, as confirmed by a gold standard coronary function test. A multicenter single sequence 2-period cross-over study was performed, consisting of a four-week control period followed by four weeks using the Wavy intervention app. The intervention comprised suggested breathing-based exercises if measured stress levels were too high. The primary outcome was the Seattle Angina Questionnaire summary score; secondary outcomes included quality of life using the SF-36, stress by means of the PSS-10. Additionally, the user experience and the impact of the breathing exercise on HRV were evaluated.

Results: Within the 102 patients that finished the study, no significant improvements were observed in the SAQ-SS scores following the intervention period, with control group values at 50.4 ± 15.4 SD and intervention group values at 50.9 ± 15.0 SD. Similarly, no differences were found in the quality-of-life and perceived stress in hebben tezamen met patiënten en een ergotherapeut nieuwe functionaliteiten etrics. However, the 1,236 breathing relaxation exercises performed during the study led to a significant improvement in heart rate variability (HRV), as indicated by a median (IQR) RMSSD increase from 18.59 ms (8.38–36.58) before the exercises to 34.93 ms (24.19–50.64) after the exercises ($Z = -13.72$, $p < 0.001$). Furthermore, two-thirds of participants indicated they would use a more refined version in the future.

Conclusions: A four-week intervention using the Wavy application did not significantly alleviate anginal symptoms in female patients with coronary vasospasms. However, the breathing exercises demonstrated a notable improvement in HRV values,

suggesting a reduction in stress levels. Patient feedback indicated broad support for the application and its wearable-based functionality, emphasizing the need for substantial refinements. Future development should incorporate patient perspectives to optimize the application as a comprehensive lifestyle management tool. Clinical Trial: ClinicalTrials.gov Identifier: NCT06171893. Assessing the Effect of the 'Wavy' Application, on Stress and Burden of Disease in Women With INOCA, available at <https://classic.clinicaltrials.gov/ct2/show/NCT06171893>.

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Original Manuscript

Original Paper

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Conclusions: A four-week intervention using the Wavy application did not significantly alleviate anginal symptoms in female patients with coronary vasospasms. However, the breathing exercises demonstrated a notable improvement in HRV values, suggesting a reduction in stress levels. Patient

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Trial Registration: ClinicalTrials.gov Identifier: NCT06171893. Assessing the Effect of the 'Wavy' Application, on Stress and Burden of Disease in Women With INOCA, available at <https://classic.clinicaltrials.gov/ct2/show/NCT06171893>.

Keywords: Coronary Vasospasms, e-Health, heart rate variability, mental stress, social-psychological factors



Introduction

The global burden of patients experiencing chronic angina pectoris is high, with an ever-increasing estimated prevalence of 112 million patients in 2015 (1). Nearly two-thirds of women with angina referred for coronary angiography exhibit no obstruction of the coronary arteries (2). As much as 60 to 90% of these patients appear to have underlying coronary vascular dysfunction (CVDys), comprising coronary epicardial vasospasm and coronary microvascular dysfunction, which can be diagnosed by a coronary function test (CFT) (3-5). CVDys generally affects middle-aged women and typically results in chronic and severe angina, sometimes accompanied by exertional dyspnea, significantly impairing quality of life (6). Moreover, patients with CVDys face an elevated risk of major cardiovascular events (7). This condition results in work limitations as well as increased healthcare utilization and associated costs (8).

Emotional stress is a well-known trigger for coronary artery spasms and subsequent angina in this specific patient group (9, 10). Hence, stress reduction is one of the cornerstones in managing CVDys, as indicated in the European Association of Percutaneous Cardiovascular Interventions (EACPI) consensus document on CVDys (11). However, specific stress reduction programs tailored to CVDys patients are still lacking.

To address this gap and provide a patient-centered stress management solution, the Wavy Assistant (Wavy) smartphone application was developed. The prototype application integrates breathing-based exercises triggered by elevated stress levels, as detected through a real-time biofeedback system connected to the Garmin Vivosmart 4 (12, 13). This system uses heart rate variability (HRV) as a proxy measure for stress. This study selected HRV as a measure of stress due to its well-established role as an indicator of parasympathetic activity and its inverse relationship with mental stress. Both acute and chronic stress have been consistently associated with decreased HRV, reflecting a shift in autonomic balance toward sympathetic dominance. In contrast, higher HRV reflects greater parasympathetic (vagal) activity and greater adaptability to stress. Numerous studies have demonstrated that HRV reliably decreases under stressful conditions, underscoring its validity as a physiological proxy for stress (14). Moreover, higher HRV values have been linked to a reduced risk of cardiovascular disease (15).

Aiming for a proof of concept, this study evaluated the impact of the prototype Wavy application on cardiac symptoms, quality of life, and stress levels, aiming to determine its potential as an effective stress management tool.

Methods

Patient population

Patients with proven coronary artery spasms were screened for enrollment in six Dutch hospitals: Radboud University Medical Center Nijmegen, Maastricht University Medical Center, Zuyderland Hospital Heerlen, St. Elisabeth Hospital Tilburg, Catharina Hospital Eindhoven, VieCuri Hospital Venlo, and Maastad Hospital Rotterdam.

Adult women were eligible when diagnosed with CVDys, entailing coronary epicardial vasospasms or microvascular dysfunction as determined by CFT with Acetylcholine according to the definition by the Coronary Vasomotor Disorders International Study Group (COVADIS) definitions (5, 16).

The upper age limit for inclusion was 70 years to enhance digital literacy. Further exclusion criteria included obstructive CAD, defined as $\geq 70\%$ coronary artery stenosis or fractional flow reserve (FFR) < 0.80 or both, and practical inability to participate in the study, e.g., due to a language barrier.

Study Design

The study was designed as a single sequence 2-period cross-over study, allowing for a within-patient comparison between control and intervention. After signing informed consent, participants had one habituation week to get used to the Garmin Vivosmart 4 wearable.

During this week, the researchers had a one-on-one digital or in-person meeting with the patient, setting up the connection and addressing potential questions and issues. The patients were instructed to wear the wearable during the daytime; nighttime usage was optional. The four-weeks control period was initiated when Bluetooth successfully connected the wearable.

After the control period, the consecutive four-weeks intervention period commenced, in which the Wavy application was updated to the full access version. The researchers guided patients in installing the Wavy app, and patients were personally informed on the available features mentioned below. Considering that the study utilized a prototype version of the application, technical support was a priority, and was readily accessible throughout the study period. Incoming data were closely monitored to promptly identify and address any technical issues. If no data were received for two consecutive days, researchers proactively initiated technical support. This support was provided through one-on-one virtual meetings, which included assisted screen sharing to resolve issues efficiently.

Wavy Assistant App

The Wavy application was designed in three iterative phases, in which developers updated the application version according to patient-based feedback. The feedback was derived from three small four-week pilot rounds involving 10-20 patients each, and in total 48 patients participated in these pilot rounds. These patients were also eligible for the study described in this paper.

The result was a prototype application version [Figure 1] that integrates data from a wearable device to continuously monitor stress levels and provide real-time biofeedback, leading to the suggestion of breathing exercises if elevated stress levels were detected. Future features of different relaxation exercises and data-sharing was not yet included. The prototype utilizes a machine-learning algorithm based on wearable data, specifically the heart rate (HR) and HRV, from the Garmin Vivosmart 4. This smartwatch uses photoplethysmography to measure beat-to-beat intervals (BBI) and supplies the data to Wavy in real-time via Bluetooth. The wearable is also used by Carreuri et al., for stress-related research (17). Apart from supporting HRV measurements, the wearable is small and

has a seven-day battery life, making it suitable for the current research phase. Upcoming Wavy iterations aim to be device-agnostic.

The HRV metric served as the proxy for stress and was calculated as the Root Mean Square of Successive Differences (RMSSD) in milliseconds (ms) (14, 18). This metric was computed from beat-to-beat-interval (BBI), as measured in the background with ultrashort frames of 30 seconds every 15 minutes and continuously during the breathing exercise. These ultrashort timeframes capture the HRV RMSSD values well, as concluded by the validation study of Munoz et al. (19). Based on the RMSSD values, Wavy displayed a color-coded overview of their stress patterns per hour for the past week [Figure 2-3].

If the application estimated stress levels higher than 1.5 times the patient's standard deviation (SD), a notification was sent that offered a brief stress-reducing exercise. The exercise entailed a visually guided box breathing exercise with four seconds in, hold, out, and hold stages (20). Patients were told that shorter intervals were acceptable if they had shortness of breath.

Blank Control App

To evaluate the effect of the Wavy app, Wavy needed to be compared to a control version. The "Blank" application solely displayed the connection status of the wearable device without providing any additional feedback or intervention. Like the Wavy app, the Blank version allowed symptom registration for this trial.

Statistical Analysis

Outcome measures

The main objective was to assess the effect of Wavy on anginal burden. To this end, the primary outcome was the difference in the average Seattle angina questionnaire summary score (SAQ-SS) (21), measured after four weeks of intervention with the Wavy application versus the control version. For reference, a score of 0 to 24 indicates poor, 25 to 49 fair, 50 to 74 good, and 75 to 100 excellent health status. As secondary outcomes, we looked into differences in quality of life by the short-form 36 health survey (SF-36) (22) and the perceived stress score (PSS-10) (23), which were sent at baseline, directly after the four-week control and four-week intervention period. The applied questionnaires were validated to assess experiences over the past month, making them suitable to indicate a difference between the control and intervention periods of one month.

Furthermore, we looked into the effect of the breathing exercises on estimated stress levels as measured with HRV, expecting stress reducing results. Thus, HRV values before, during, and after exercises were analyzed.

Given that the application was still under development, we monitored application stability based on incoming user data as well as participants feedback or support requests. This study also assessed the participants' experience, measured by user experience questions, which can be found in the supplementary material.

Sample Size Calculation

A two-sided sample size calculation was performed with β of 0.8 and α of 0.05. The calculation was based on the primary outcome of the SAQ-SS; an alteration of 5 points is generally regarded as clinically relevant. The reference standard deviation was estimated on fifteen based on patients with stable CAD, derived from Chan et al. (21, 25, 26). This calculation indicated a required sample size of 97 patients. To account for potential technological challenges, we added 20% to correct for the potential dropout rate; thus, 117 patients were to be included.

Questionnaires

Descriptive statistics were reported as mean $\pm$ SD or median with interquartile range (IQR), depending on the normality of the data distribution. Questionnaire-based outcomes were analyzed with a paired t-test between the control and intervention months.

Statistical analysis of questionnaire-based data was performed using SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Wearable Data Analysis

In analyzing this semi-continuous HRV data, we focused on the relaxation exercises in the intervention month. To this end, the last available HRV measurements were taken before the exercise, during the exercise itself, and the first post-exercise measurement. Exercises with a duration shorter than one minute were filtered out. Considering the measurement interval was 15 minutes, the before and after measurements are between 0 and 15 minutes apart from each exercise. The effect of the exercise on stress was indicated by a Wilcoxon test of the HRV measurements prior to the exercise, as well as during and after.

A skewed distribution was expected as RMSSD has a lower limit of zero. Thus, results are displayed as the median and the IQR.

According to the hypothesis the HRV should increase during the exercise, suggesting decreased stress, and continue to be elevated to, albeit a lesser extent, in the first post-exercise measurement.

HRV analysis was performed using Python 3.1 with the Pandas software library (Python Software Foundation).

Data Management

All data were pseudo-anonymized, and the encryption table with the key was kept on the secured hard drive of Radboudumc. Questionnaire data were collected through the Castor Electronic Data Capture System and are stored at the Radboudumc secured hard drive for 15 years.

Regarding HRV data, the coordinating researcher provided pseudo-anonymized login codes for patients to log into the app. The pseudo-anonymized code was used in the data collection to ensure that Wavy did not gain access to personal information. The HRV data were stored at the European OVH-cloud, which is certified for storing medical data.

Ethical approval

All participants provided informed written consent before participation; the study procedures comply with the ethical standards of the Declaration of Helsinki (2013). Moreover, the CMO region Arnhem-Nijmegen reported no objections to conducting the study, and local ethical approval was acquired for each center. Patients received no financial compensation for participation.

Results

Patient Inclusion

In total, we screened 241 women with CVDys as diagnosed by the CFT with Acetylcholine. Of those, 137 provided informed consent. Forty-eight patients participated in the smaller pilot iteration rounds aiming to develop and improve the Wavy application further, of which twenty-eight continued to the study at hand. The resulting 117 patients were included in the main trial described in this paper. Technological barriers and other issues with the application prohibited proper application usage for fifteen patients, leaving 102 patients to finish the trial [Figure 4]. The trial enrollment was split into three periods, with group A starting in August, B in September, and C in November 2022.

Evaluation Outcomes

Baseline characteristics are described in [Table 1]. The mean age was 58 years $\pm$ 7.3 SD, 69.2% exhibited microvascular dysfunction and 45.0% had epicardial spasms as their endotype of CVDys. The mean study duration was 59 days $\pm$ 9.2 days. The average number of days with a successful HRV measurement was 49 $\pm$ 10.6 SD; the remaining days, no measurement was registered. Per day with HRV registration, 61% of the maximum measurements during the day were successfully recorded. In total, 1236 breathing exercises were performed with an average duration of 1 minute and 43 seconds, $\pm$ 43 seconds SD.

Table 1: Baseline characteristics

Study population	N= 102
Age (Years $\pm$ SD)	58 ($\pm$ 7.32)
Sex (female, %)	102 (100%)
Etiology	
Epicardial (n, %)	46 (45,0%)
Microvascular (n, %)	71 (69,6%)
Baseline Questionnaires	
SF-36 Summary score (mean $\pm$ SD)	52,9 $\pm$ 14.0
SF-36 Mental component (mean $\pm$ SD)	55,6 $\pm$ 15,5
SF-36 Physical component (mean $\pm$ SD)	51,7 $\pm$ 15,4
SAQ Summary score (mean $\pm$ SD)	49,6 $\pm$ 16,8
PSS-10 (mean $\pm$ SD)	19,7 $\pm$ 6,9

The primary outcome average SAQ-SS following the control and intervention phases was 50.4 $\pm$ 15.4 SD and 50.9 $\pm$ 15.0 SD, respectively. These values indicated a fair to good quality of life in both groups and comparison exhibited no statistically significant difference ($p=0.593$) [Figure 5]. The mean SF-36 summary scores and individual components did not differ significantly ($p=0.92$) [Figure 6]. Furthermore, the mean perceived stress score also showed no statistical difference [Figure 7].

However, HRV analysis showed a significant increase of RMSSD, indicating a relaxing effect

during and after breathing exercises, compared to the 15-minute prior measurement, with a median (IQR) RMSSD of 18.59 (8.38 to 36.58) ms before and 34.93 (24.19 to 50.64) ms during the relaxation exercise, $Z = -13.72$ ($p < 0.001$). Compared to the before measurement, this effect is attenuated at 15 minutes after the exercise with a normalized median (IQR) of 30.72 (18.97 to 47.76) ms, $Z = -11.75$ ($p < 0.001$). A visual overview is displayed in [Figure 8].

Regarding the user experience, the Wavy app, which was still in development, suffered from technical instability. With measurements each 15 minutes in total 96 timepoints could be gathered each day, and 61% of possible data points from were retrieved in total. Technical issues were prevalent, with the majority of patients reporting technical issues, including difficulties logging in, connecting the wearable to the phone, and crashing. These problems resulted in intensified technical support by the researchers. Nevertheless, 67% of patients reported that they would use such an application in the future, provided it would be a stable version.

Discussion

Principal Results

The study was conducted to assess the impact and potential of the prototype Wavy application that strives to aid in lifestyle management for patients with CVDys. The primary outcome, the SAQ-SS, and secondary measures (SF-36, PSS-10,) did not exhibit significant improvements after a four-weeks intervention period. However, the study was hampered by technical difficulties faced due to the application being in development.

Notably, the results of the HRV analysis indicated increased HRV levels during the breathing exercise, with normalized values after the breathing exercise. Thus, showing a significant positive effect of breathing exercises on stress levels.

Comparable Studies

In reviewing the literature, no comparable studies of HRV-biofeedback based stress management on cardiac symptoms and quality of life were found for this specific patient group. However, various studies investigated the effect of HRV-biofeedback based stress management on mental stress and anxiety levels. Goessl et al. conducted a meta-analysis comprising 24 studies investigating the stress-reducing effects of HRV biofeedback aiming to regulate HRV, in clinical (n=10) and community setting (=14), based mainly in the USA and EU (n=18) (27-29). In total, thirteen studies that were mentioned in Goessl et al. included a comparison group, constituting standard care, sham, or other means of stress reduction. In some studies, the HRVB training could be performed at home with a device, while others included a personal trainer; the frequency of HRVB sessions varied between one to fifty. When comparing the HRV based stress management to the comparison condition, the biofeedback resulted in an effective reduction of anxiety and stress (27). While Wavy did not achieve the desired effectiveness in improving perceived stress scores, we found a significant HRV improvement, indicating stress reduction.

In contrast to our intervention, which involves providing breathing exercises upon the detection of increased stress to enhance HRV and subsequently reduce stress, Held., et al. explored the reduction in HRV induced by exposure to a stressful working condition in 26 clinically anxious and 14 control participants. Notably, the magnitude of HRV changes observed in both groups closely resembled the inverse HRV results presented in our paper. The decline in HRV during a cognitive stressful task in both healthy and anxious individuals align with the HRV increase observed during the breathing exercises for these patients (30). Taking the study of Held. et al., for reference, the magnitude identified in our HRV analysis indicates a relevant stress reduction.

In comparison to other remote HRV-biofeedback studies, compliance was decent with 1236 performed breathing exercises, ~3 per week per patient, whilst a comparable study of Hirten et al., failed feasibility of remote monitoring due to compliance (33). Remote, wearable-based studies face significant challenges in acquiring a representative sample of available data points. For instance, Galarnyk et al. reported that only 5.6% of all recorded R-R interval data were usable, with 43% of participants never activating their device. In the current study, despite similar technical challenges, 61% of the total achievable data points—each representing approximately 30 seconds of recording every 15 minutes—were successfully collected (34). This outcome underscores the importance of active data monitoring and proactive technical support in maximizing data retention. Additionally, it highlights the role of an initiative-taking patient population, which likely contributed to the relatively high data capture rate observed in this study.

Strengths and Limitations

Strengths and limitations

Although stress management is part of the current guidelines in the management of coronary vasospasms, our study is the first to evaluate a stress reduction program in women with proven coronary artery spasms. The fact that 67% of patients expressed willingness to engage in further application usage after stabilization underscores the willingness of the patients to apply a home-based, digital form of stress management.

As the application was still in the development phase, we encountered more technical issues than anticipated. While nearly all challenges were addressed through active data monitoring and personalized support, including screen-sharing sessions, these recurring efforts placed an additional burden on participants and likely impacted their overall user experience. Consequently, it is difficult to draw definitive conclusions about the program's effectiveness in alleviating symptoms.

Despite these technical challenges, HRV analysis demonstrated a positive effect of the breathing exercises on stress reduction. Additionally, unlike many stress management interventions reported in the literature—which often span longer durations—our study employed a relatively short intervention period. Considering evidence suggesting that extended intervention durations may yield greater improvements in self-reported stress and anxiety, the limited timeframe of this study may have been a key limitation (27).

Regarding the primary outcome of the SAQ, there is some debate on its applicability when it comes to non-obstructive coronary disease. As was primarily developed for obstructive coronary artery disease, this may have been a limitation (31). However, other studies support this psychometric for a more widespread population, including non-obstructive CAD (26) (32). A more sensitive outcome measure may yield more insightful results in future research.

Conclusions

In conclusion, the current digital stress reduction prototype Wavy application did not affect perceived anginal burden in female patients with coronary vasospasms as measured by various questionnaires. However, considering the hampering technical issues of the device being under development, it is too early to state that such an application providing biofeedback could not complement current treatment strategies. The significant improvement in HRV during and after the breathing exercise, indicating the potential stress-reducing effect of the stress management app, is encouraging.

Future research is warranted with a technically stable device and longer follow-up duration to establish the true effect of stress reduction with breathing exercises on stress symptoms in the growing CVDys population.

Acknowledgements

PDF, AM, and SE designed the study, PDF coordinated the study. PDF, AV, JM, AVH, PW, JW, and VP aided in the inclusion and contributed to the acquirement of data. PDF, EV, and GS contributed to the analysis. All authors reviewed the paper before publication.

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

BBI:				beat-to			beat-interval
CFT:			coronary		function		test
COVADIS:	Coronary	Vasomotor	Disorders	International	Study	Group	
CVDys:		coronary		vascular		dysfunction	
EACPI:	European	Association	of	Percutaneous	Cardiovascular	Interventions	
FFR:		fractional		flow		reserve	
HR:			heart			rate	
HRV:		heart		rate		variability	
IQR:	interquartile range						
JMIR:	Journal of Medical Internet Research						
Ms:	milliseconds						
PSS-10:	perceived stress score						
RMSSD:	root mean square of successive differences						
SAQ:	Seattle angina questionnaire						
SAQ-SS:	Seattle angina questionnaire summary score						
SD:	standard deviation						
SF-36:	Short-Form 36 Health Survey						

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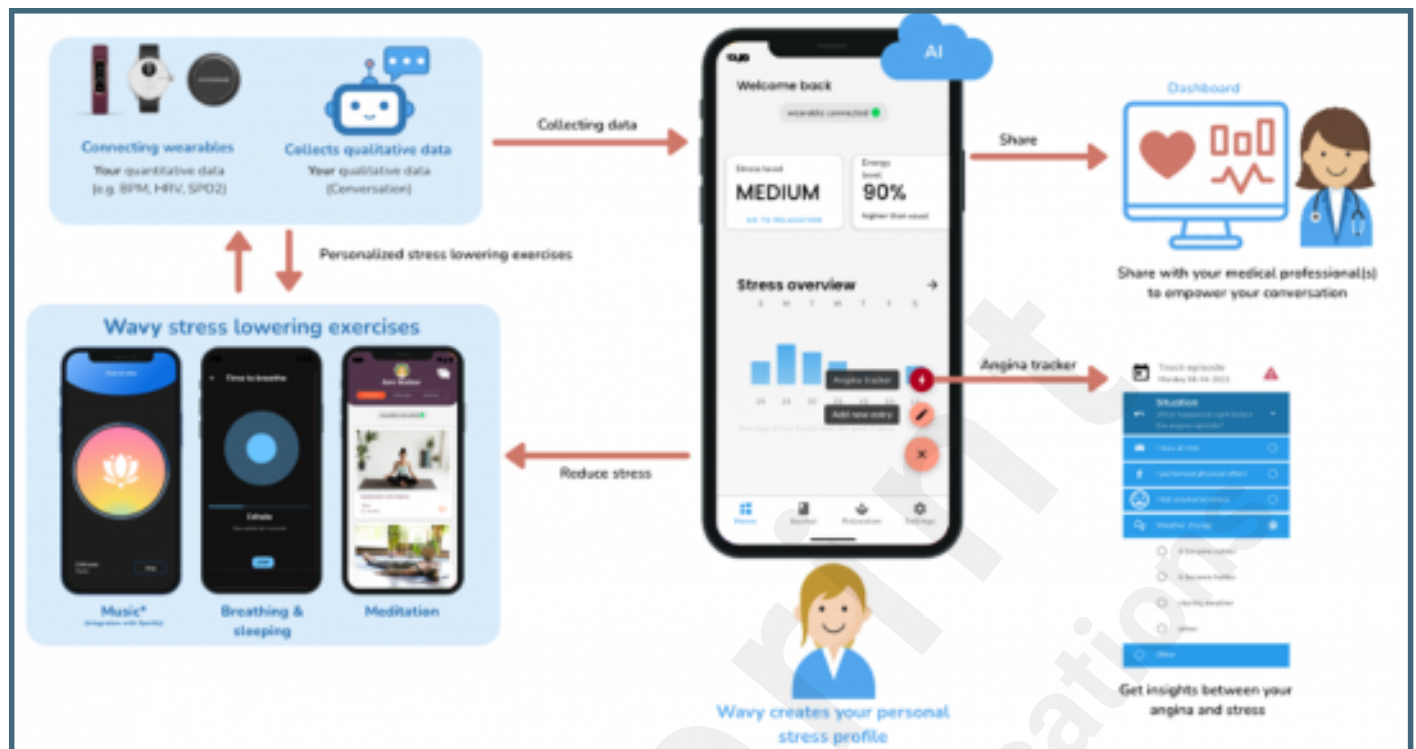
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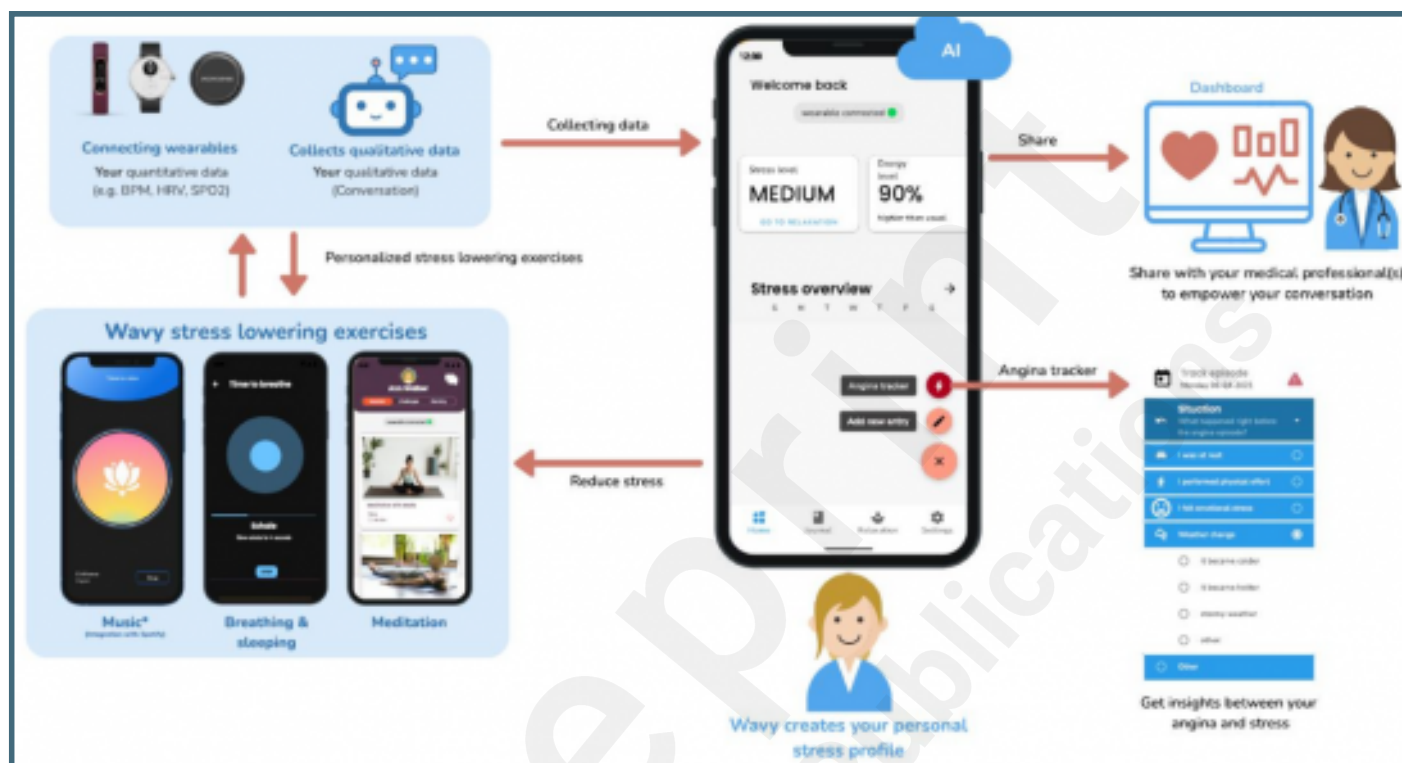
Supplementary Files

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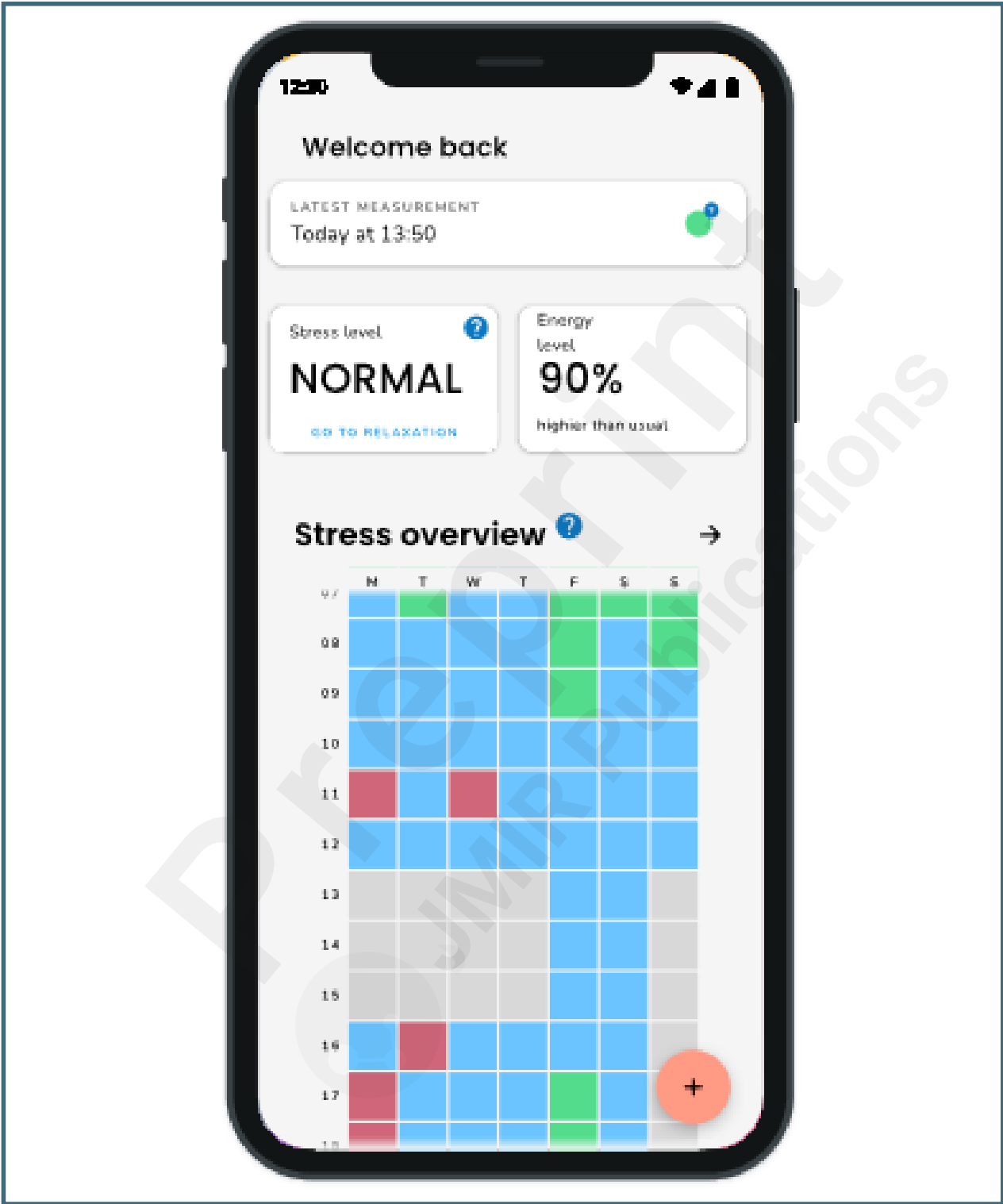


Figures

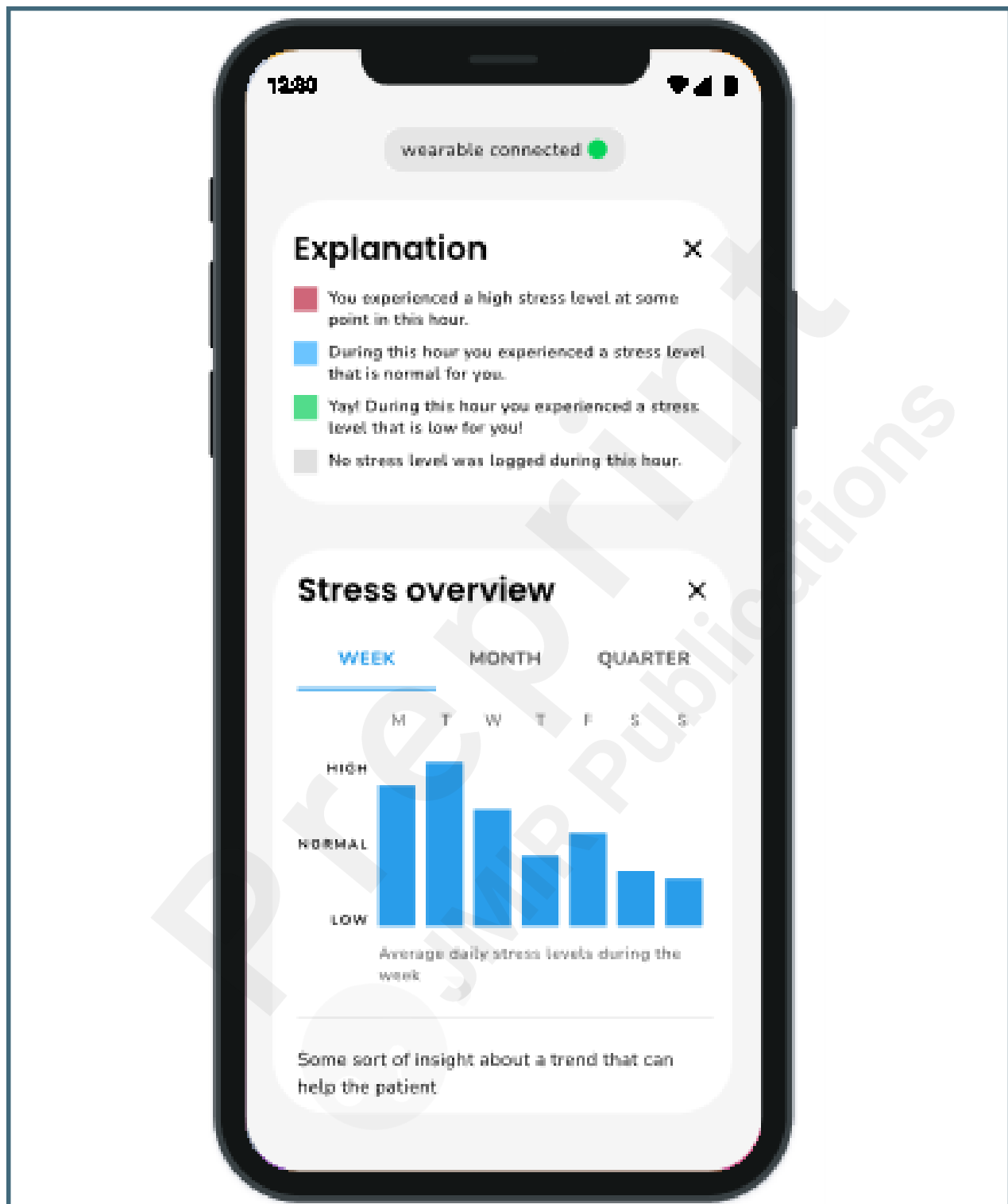
Visualizing Wavy: The application is installed on a smartphone (With either an Android or Apple operating system), this application retrieves data from the by Bluetooth connected wearable (in this case the Garmin Vivosmart 4). Based on the raw BBI data from the wearable, stress related features are computed (in particular RMMSD). After a one-week baseline, personalized thresholds for stress are determined which updates continuously based on a rolling average. In case of exceeding the thresholds, a notification is send, recommending a box breathing exercise. Furthermore, the application can track angina, and hereby in the future assist with Doctor appointments.



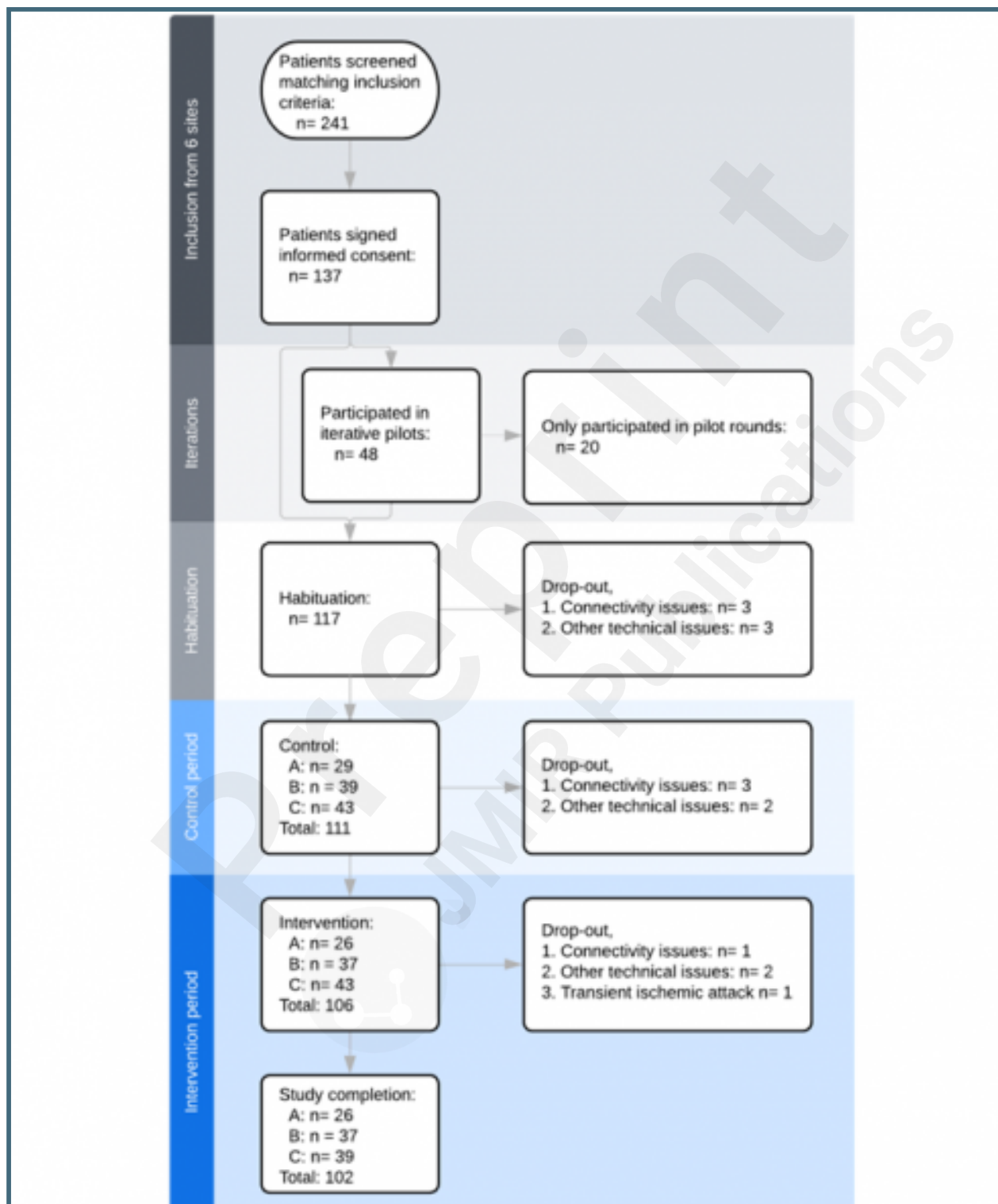
Stress overview: The home page is displayed, containing the connection status; latest stress level and an hour-by-hour stress overview of the past week.



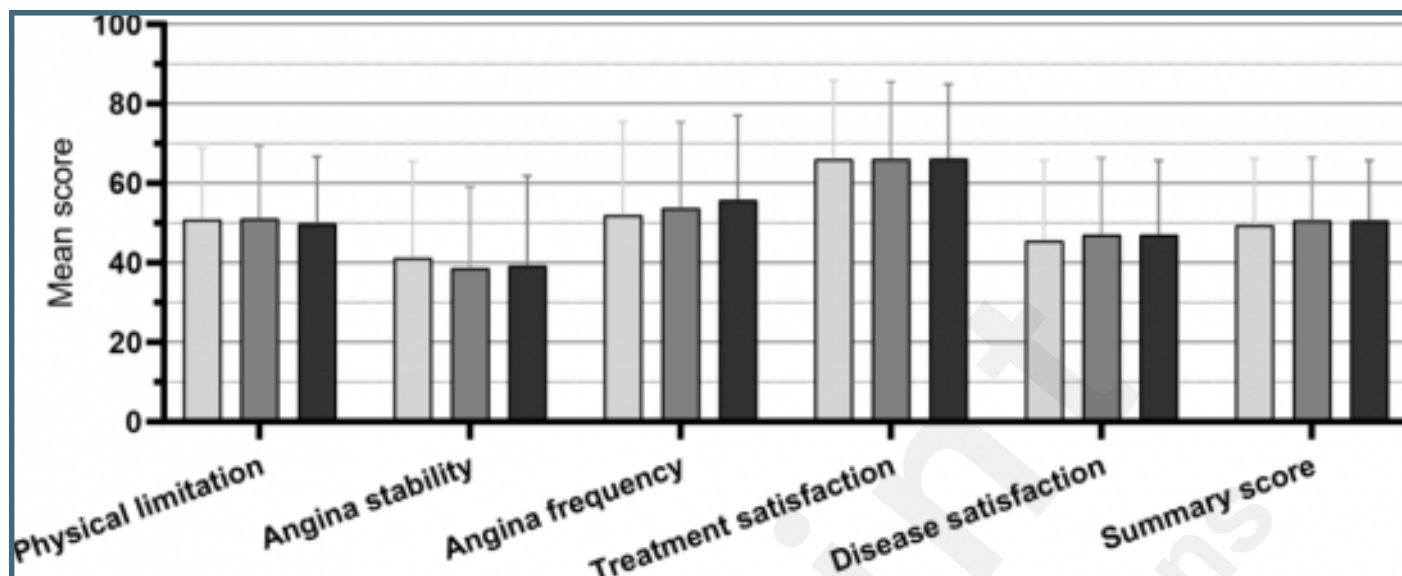
Shows the provided explanation of the overview, as well as a longer period stress overview.



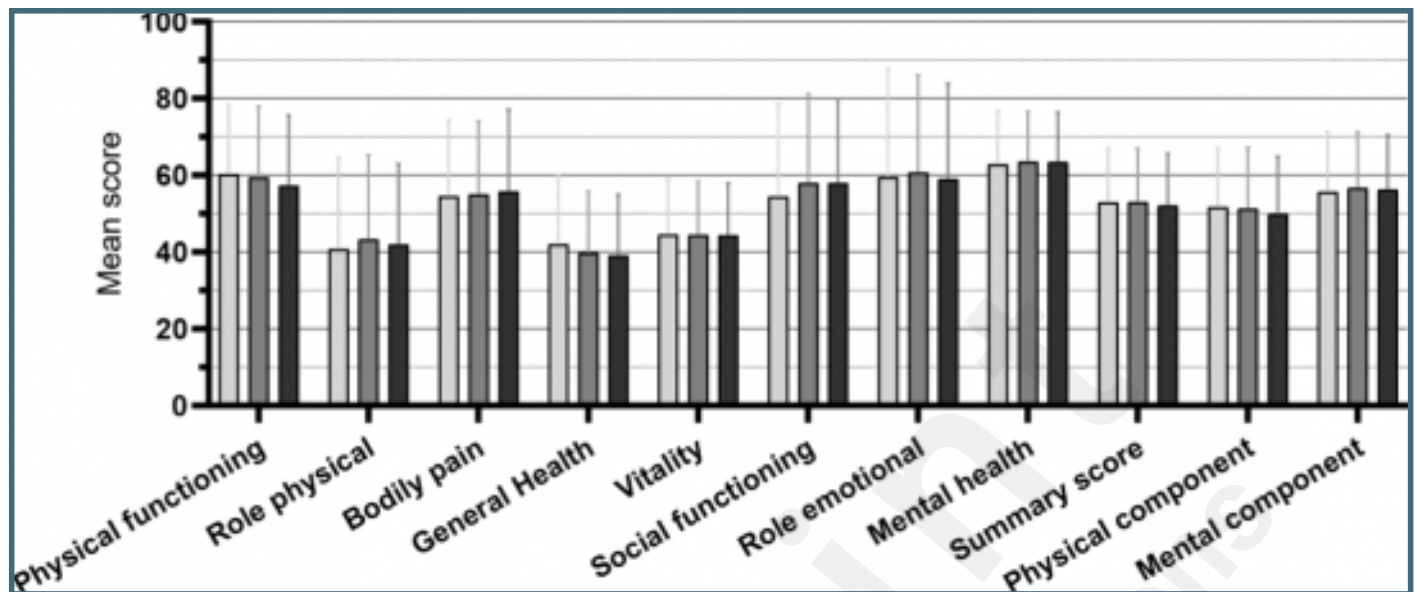
Study flowchart: In total 241 patients were screened, of which 137 provided written informed consent. In total 48 patients participated in pilot trials, of which 28 continued to the final trial. Consequently, 117 patients started the study, unfortunately, 15 dropped out due to technical issues. The rest was split into different starting waves (A-C) and completed the trial.



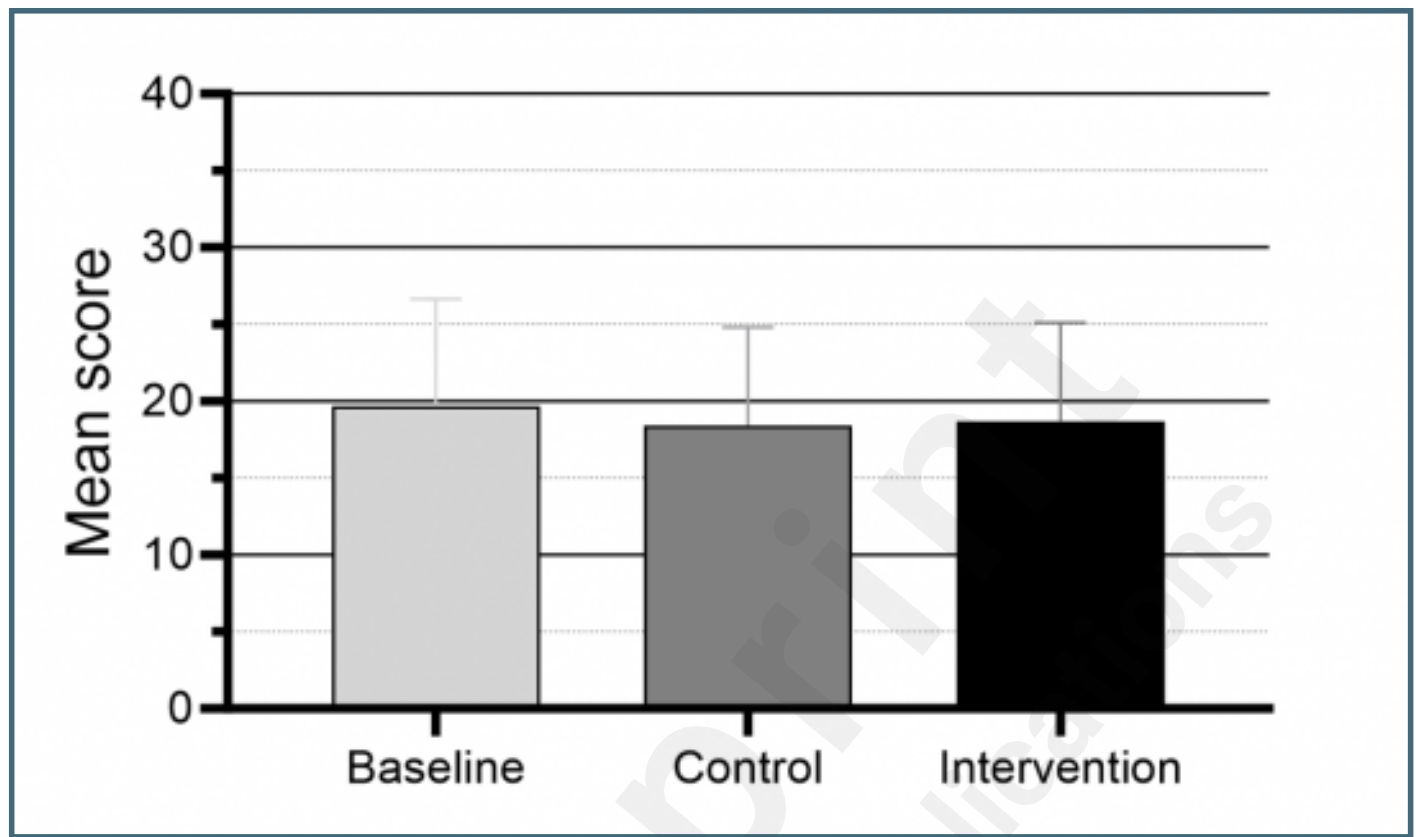
Seattle Angina Questionnaire, components and summary scores.



Short-form 36 health survey: Components and summary score.



Perceived stress score.



Breathing exercises on Heart Rate Variability: This displays the relative timepoints to the breathing exercises.

