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**Sinusoidal changes in transcutaneous oxygen pressure, suggesting Cheyne-Stokes
respiration, are frequent and of poor prognosis, among patients with suspected critical limb
ischemia**

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1 ABSTRACT

2 **Background and aims:** Transcutaneous oxygen pressure (T_{cp}O₂) is used in patients with
3 suspected critical limb ischemia (CLI). Sinusoidal changes (SC~) in T_{cp}O₂ are found in patients
4 with Cheyne-Stokes respiration (CSR). We aimed to determine the characteristics of T_{cp}O₂-
5 changes at rest in patients with suspected CLI, define the objective criteria for SC~ T_{cp}O₂
6 patterns (SC+), and estimate the prevalence of SC+ in our population and its impact on the
7 outcome.

8 **Methods:** We retrospectively analyzed 300 chest T_{cp}O₂ recordings performed in a 16-month
9 period. We determined the presence / absence of SC~ T_{cp}O₂ by visual analysis. We determined
10 the acceptable error in the regularity of peaks of the cross-correlation with ROC curve analysis,
11 among patients with typical SC~ T_{cp}O₂ and non-sinusoidal patterns. Then, we defined SC+ as a
12 minimum of five peaks, a standard deviation of T_{cp}O₂ >1.25 mmHg, an error in regularity of
13 peaks of the cross-correlation < 10%, and a cycle length between 30 and 100 s. In patients
14 included until October 2019, we compared the outcome as a function of SC+ or SC- with Cox
15 models.

16 **Results:** Mathematical detection of SC+ found that 43 patients (14.3%) fulfilled all four defined
17 criteria at the chest level, but only 23 did so at the limb level. In the follow-up of 207 patients, the
18 presence of Sc~T_{cp}O₂ at the chest significantly increased the risk of mortality: hazard ratio: 2.69
19 [95%CI: 1.37-5.30]; $p < 0.005$.

20 **Conclusions:** SC~T_{cp}O₂ is frequent, and is associated with a poor outcome in patients with
21 suspected CLI.

1 **Introduction:**

2 Cheyne-Stokes respiration (CSR) is considered to be rare in the general population and is
3 characterized by regular cycles of crescendo and decrescendo changes in breathing amplitude,
4 followed by periods of transient apnea. The prevalence of CSR is high in patients with heart
5 failure, and its presence increases the mortality of affected patients.[1, 2] To the best of our
6 knowledge, little is known about the prevalence of CSR in patients with lower extremity arterial
7 disease. Patients with critical limb ischemia,[3] or "chronic limb-threatening ischemia"[4](CLI),
8 have a high risk of morbidity and mortality,[5, 6] independently of the possibility of
9 vascularization of the affected limb,[7, 8] or of the type of revascularization.[9] Transcutaneous
10 oxygen pressure (TcPO₂) is largely used as a diagnostic tool for CLI, to classify the risk of
11 amputation in CLI patients, or to estimate the probability of healing of lower limb ulcers
12 suspected to be of vascular origin.[10-15] TcPO₂ has also been used for the evaluation of
13 treatment of CSR in heart failure patients.[16] In these patients, CSR resulted in the presence of
14 sinusoidal changes (SC~) in the TcPO₂ values.[16] Amazingly, despite the worldwide use of
15 TcPO₂ in patients referred for TcPO₂ measurements for suspected CLI, the prevalence of
16 SC~TcPO₂, assumed to result from CSR in such patients, has never been reported.

17
18 We hypothesized that in patients with suspected CLI, the computer recording of TcPO₂ could
19 allow an estimation of the SC~TcPO₂ prevalence. First, we analyzed the characteristics of TcPO₂
20 changes at rest in patients with suspected CLI and verified whether or not SC~TcPO₂ patterns
21 were observed at both limb and chest levels. Second, we proposed objective criteria for the
22 presence (SC+) or absence (SC-) of SC patterns in TcPO₂ recordings. Third, we estimated the
23 prevalence of SC+ (assumed to result from CSR) in our population, using these objective criteria.
24 Finally, we compared the incidence of mortality in patients with SC+ *versus* SC-.

Materials and methods

Population

The referral population was all the patients referred to the Vascular Medicine service of the University Hospital in Angers for TcpO₂ investigations at rest because of suspicion of CLI (resting pain, or wound). Almost all patients were Caucasian; race and ethnicity were not recorded. During their medical visit, we systematically recorded the indication of the test, age, height, body weight, sex, systolic and diastolic pressure, history of diabetes mellitus, cardiac or respiratory insufficiency. For patients of the “New Oxymetry Variability Indices in Critical limb ischEmia (NOVICE)” protocol, patient files were re-analyzed to record the information available at the date of the TcpO₂ visit focusing on the presence/absence of lower extremity arterial disease (LEAD), and ongoing treatments. Ongoing treatment was simplified as categories focusing on: beta-blockers, antiplatelet or anticoagulant drugs, sartan or renine-angiotensine inhibitors or diuretic, cholesterol lowering drugs, psychotropic drugs, and pain killers. The presence of LEAD was based on the presence of either: an abnormal ultrasound imaging (occlusion or significant stenosis at rest of an arterial trunk? or a history for revascularization), an ankle brachial index \leq 0.90 (non-measurable or non-compressible ankle pressures were considered not contributive for the presence of stenosis or occlusions of distal arteries), or a toe brachial index \leq 0.70.

Ethical considerations

The ethics committee has approved the “Critical Ischemia and TRAnscutaneous oximetry (CITRA)” study for the retrospective analysis of patients with suspected CLI referred for TcpO₂ recordings, searching for sinusoidal changes in the recordings, under reference 2019-44. It was registered in Clinicaltrial.gov: NCT04369781. At admission, patients were aware that their medical file could be used for research purposes, and of their right to deny the use of the medical

1 file at any time. As an analysis of our routine practice, according to the French Law, individual
2 written consent was not required from the patients. If patients deny the use of their files for
3 research purposes, this decision was recorded in the patient's administrative file. Exclusion
4 criteria for "CITRA" were missing or corrupted chest or limb TcpO₂ recording, TcpO₂ recordings
5 < 5 min. The NOVICE follow-up study aimed at determining the outcome of patients referred for
6 suspected CLI (Clinicaltrial.gov: NCT04209998). This required second specific information to
7 patients of CITRA. The exclusion criterion for NOVICE was a rebuttal of follow-up since the
8 visit to our laboratory. Both studies conformed to the ethical guidelines of the 1975 Declaration
9 of Helsinki. The corresponding author has full access to all the data in the study and takes
10 responsibility for its integrity and data analysis. Data is accessible upon reasonable request from
11 the author or promoter.

13 **Transcutaneous oximetry**

14 As it has been performed per routine and for decades in our department, TcpO₂ (TINA TCM400,
15 Radiometer, Copenhagen, Denmark) was measured on the limb and at chest level while the
16 patients rested in an air-conditioned room at a temperature of 21±2°C. Calibration was performed
17 twice before each session, as recommended by the manufacturer. Each electrode temperature was
18 set to 44.5 °C to heat the underlying tissue and maximize local vasodilation and gas diffusion
19 through the skin.[17] The electrodes were screwed in fixation rings below the right clavicular
20 prominence and at the dorsal aspect of the foot, or as distal as possible in case of amputation. In
21 patients with known right subclavian artery occlusion or a history of right thoracotomy, the chest
22 probe was placed on the left side. The probe at the chest accounts for systemic pO₂ changes
23 during eventual provocative maneuvers.[18] A minimal pretest heating period of 15 min was
24 required to allow local heating of the skin. On our routine, patients were resting alone in the

room, and a timer was used to recall the nurse in charge of the test to retrieve the values appearing on the screen of the TCM400 apparatus after this pretest heating period, while the patient was in the recumbent position. Whether or not all patients remained awakened was not determined. Sensitization maneuvers (such as leg elevation or leg lowering), pending on values observed at rest, were performed. All recordings were stopped after a minimum of 5 min after the end of the sensitization procedures with the patient returned to the resting recumbent position.

Recording of TcpO₂

Since mid-November 2018, a custom-made program has become available to allow real-time recording of TcpO₂ tests performed in our service.[19] Since then, the TCM400 was connected to a computer that allowed recording data on a 1 Hz basis. The program was to be used on a routine basis to allow post-procedure quality control by the physician in charge of test interpretation. For most patients, the recording was started at the beginning of the test and was stopped once all procedures were completed. After the investigation, anonymized data were saved as text file spreadsheets for offline analysis.

Calculation of number of subjects

Based on the prevalence of CSR in patients with cardiovascular (cardiac) diseases [1], we estimated that the prevalence of CSR (and then of SC+) in our population could be as high as 15%. The minimum number of observations to have a confidence level of 95% and that the real value was within $\pm 5\%$ of the expected value was 196. Based on the laboratory's past activity and progressive use of the program by our nurses, we calculated that a period of 16 months was required to reach the required number of tests. We then analyzed the TcpO₂ recordings performed

in our laboratory between 15 November, 2018 and 15 March, 2020. For patients referred multiple times, only the first recording was kept for analysis.

Data collection and visual analysis

For all included patients, we retrieved medical files and TcpO₂ recordings performed. Then, TcpO₂ recordings were analyzed on an Excel spreadsheet, and graphs of chest and limb recording against time were visually analyzed. The visual analysis of the chest recording was classified as “typically sinusoidal,” “possible”, or “non-sinusoidal” patterns. The “possible” classification was based mainly on the observation of transient sinusoidal pattern, while the rest of the recording showed no apparent sinusoidal pattern, sinusoidal patterns of moderate amplitude, or relatively unstable rhythmicity of the changes. Then, observers selected a period of interest focusing on the suspected area of a minimum of 5 min to be analyzed mathematically. Note that this period could be different at the chest and limb levels to optimize the detection at each probe position.

Analysis of data

Variables in chart reviews, results of TcpO₂ analyses, and follow-up search results were anonymized and assembled in a database using an Excel spreadsheet.

From the TcpO₂ recordings:

- 1- We counted the number of consecutive peaks in the selected period.
- 2- We estimated the standard deviation of the TcpO₂ values over the period of interest.
- 3- We estimated the length of each cycle from the autocorrelation analysis of the data.
- 4- We analyzed the regularity of the peaks of the autocorrelation analysis, as a way of confirming that the initial signal was sinusoidal. Indeed, in case of SC changes, the ratio of time for the occurrence of the second (T2nd) and third (T3rd) peaks to the time of occurrence of the first peak

(T1st) on the cross-correlation analysis should be 2 and 3, respectively, confirming that the second and third peaks are harmonics of the first peak.[20] Then, we determined the time for the peaks for the first, second, and third peaks, and calculated the (T2nd/T1st) and (T3rd/T1st) time of peak ratios. Last, we calculated the absolute relative errors of these ratios from their theoretical values using the following formulas: $\%D2/1 = ((T2^{nd}/T1^{st}) - 2)/2 \cdot 100$ and $\%D3/1 = ((T3^{rd}/T1^{st}) - 3)/3 \cdot 100$. When both $\%D2/1$ and $\%D3/1$ were available, we used the higher of the two ratios (H%D) to determine the optimal H%D to be used to determine the presence of a sinusoidal pattern. Using the H%D, we aimed to determine the acceptable H%D to discriminate non-sinusoidal from sinusoidal results. We then excluded “possible” results and used the ROC analyses. In ROC analysis, the optimal cutoff point was to minimize the distance of the curve to the 100/100% sensitivity/specificity angle. Figure 1 illustrates the different steps of the recordings and analyses.

Determination of the prevalence of SC+

To determine the presence (SC+) or absence (SC-) of SC~TcpO₂ on objective criteria, we applied the following criteria to our results on chest (Chest-SC) and limb (Limb-SC):

- 1- Number of consecutive peaks in the selected period ≥ 5 .
- 2- A minimal SD value ≥ 1.25 mmHg. This arbitrary value corresponds to a minimum amplitude of sinusoids of 3.5 mmHg while excluding random changes of less than 8 mmHg approximately.
- 3- A cycle of autocorrelation between >30 s and <100 s.
- 4- H%D inferior to the cutoff point determined from the ROC analysis.

Determination of outcome

Follow-up time for patients included in “CITRA” until October 2019 (n=211), and not denying the “NOVICE” study, was considered as the interval between the date of TcpO₂ recording until the occurrence of death or until the subject was censored (lost to follow-up after a minimum period of 3 months monitoring and a maximum of one year or until March of 2020 without death). This last point aimed to avoid the integration of the COVID-19 epidemic period that occurred in April in the Loire valley. For the follow-up, the outcome was determined on office follow-up and from the hospital patient file. If office follow-up visits were not available, alternate data sources included medical records from other hospital departments, the local electronic medical database, and telephone interviews of the referring physician.

Statistical analysis

Statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and “R” (R-foundations for statistical computing, Vienna, Austria). Considering the normality of the continuous variable, either t-test or the Wilcoxon signed ranks test were performed, and results were expressed as mean +/- SD or median with 25/75° centiles. Proportions are reported with 95% confidence intervals when appropriate. Categorical variables expressed as percentages were compared using the Fisher exact test. Survival analysis was represented using Kaplan–Meier method. Univariate analysis models were performed with a log-rank test to detect differences in overall survival. Thereafter, multivariate analysis were performed to account for potential confounders of the CSR to mortality relationship eventually found in the univariate models taking into account: Age < 75 or ≥ 75 years old, the presence or absence of cardiac insufficiency, respiratory insufficiency, LEAD, diabetes mellitus, ongoing treatments with the previously defined drug categories. Models validity were evaluated by analysis of the Schoenfeld’s residuals. Two models were performed: one for chest-SC, and one for limb-SC. Last,

1 comparison of these two models was performed using the partial likelihood ratio test for mis-
2 specified nonnested semi-parametric Cox model. [21] For both the univariate and multivariate
3 models, hazard ratios are reported with 95% confidence intervals [95%CI]. For all statistical
4 tests, a two-tailed probability level of $p < 0.05$ was used to indicate statistical significance. Non-
5 significant results are reported as N.S.

6

RESULTS

As shown in figure 2, throughout the “CITRA” study period of analysis, 426 patients were referred to our laboratory. Note that most of the 84 tests that were not recorded on a computer in the first three months of program availability were due to the progressive learning of program used by nurses and computer issues. Since May 2019, an average of 92% of the TcpO₂ performed have been electronically recorded. We finally had 300 recordings from different patients (197 males/103 females), aged 76.0 ± 12.1 years, BMI 27.5 ± 6.4 kg/m². The absolute chest TcpO₂ was on the average 55.9 ± 13.9 mmHg, and limb TcpO₂ was 28.3 ± 19.9 mmHg.

On the visual analysis of each recording, 31(10.3%; 95CI: 7.1-14.3%) of the chest recordings were encoded “typically sinusoidal,” and 36 (12.0%; 95CI: 8.3-15.7%) recordings were encoded “possible.” The remaining 245 recordings were encoded as non-sinusoidal. Examples of “typical” and “possible” sinusoidal chest patterns and their simultaneous limb recordings are presented in Figure 3.

Figure 4 illustrates the selection of the area of interest in a patient with a typical sinusoidal pattern of the chest recording. Note that in patients who were visually classified as having a non-sinusoidal pattern, we tried to focus on an area of eventual TcpO₂ instability. On the selected 5-min areas of interest, at the chest level, in 92 patients, no transient TcpO₂ peaks were found in the recording. For the other 208 observations, the visual analysis identified one to 25 peaks with a median number of 5 [3 -8]. The variability of absolute chest TcpO₂ recordings found in the 300 recordings was 1.93 (1.28 - 2.95) mmHg. At the limb level, in 134 patients, no transient peaks were found in the recording. For the other 166 observations, the visual analysis identified from

one to 25 peaks with a median number of four [2 -6]. The variability of limb absolute limb TcpO₂ recordings found in the 300 recordings was 1.85 (1.18 - 2.91) mmHg.

From the cross-correlation analysis, the presence of a first, second, and third peak was found in only 254, 226, and 188 recordings, respectively, at the chest level, and in 215, 173, and 132 recordings, respectively, at the limb level. When present, the delay for the occurrence of the first peak of the cross-correlation analysis (phase of the sinusoid in case of the sinusoidal pattern) was 110 (62- 211) s (n=254) at the chest and 158 (84-253) s (n=216) at the limb levels, respectively. When both %T1 and %T2 were available in the cross-correlation analysis, %HD (highest of the %D₂/1 and %D₃/1 ratios) was ≤ 5% in 43 cases, ≤ 10% in 52 cases, and ≤ 15% in 69 of the 188 chest results. At the limb level, results were ≤ 5% in 23 cases, ≤ 10% in 42 cases, and ≤ 15% in 54 of the 132 limb results. After exclusion of “possible” visual results, the ROC curve analysis determined that %HD ≤ 10% provided the best cutoff point to discriminate sinusoidal patterns from non-sinusoidal patterns at both the chest and limb levels. This cutoff had a sensitivity of 90.3% and a specificity of 76.2% at the chest level and a sensitivity of 73.9% and specificity of 80.2% at the limb level and with areas of 0.904±0.028 (*p* <0.001) and of 0.817±0.053 (*p* <0.001) for chest and limb ROC surfaces, respectively. Then, we applied H%D<10% as the last criterion for the objective determination of SC~TcpO₂ prevalence in the CITRA, and analysis of mortality in the NOVICE studies.

Using the four predefined criteria (including H%D<10%) on the areas of interest, we found 43 patients who fulfilled all four criteria at chest level, this resulted in a prevalence of 14.3% (95%CI: 10.4% – 18.3%) of SC+ in our population. When considering the limb results, only 23 patients fulfilled all four criteria, which resulted in an apparent prevalence of only 7.7 % (95%CI:

4.7% – 10.7%), based on limb results. Table 1 reports the characteristics of patients with (SC+) or without SC~TcpO₂ (SC-) based on chest TcpO₂ mathematical analysis.

Characteristics of the sub-group of 207 patients that accepted the NOVICE follow-up are reported in Table 1. Note that the difference in systolic pressure observed for the CITRA population was not found in the CITRA subgroup. During the follow-up period, 43 (20.8%) patients died, with the shortest delay being 6 days after TcpO₂ recording. The presence of SC+, based on objective criteria applied to limb results, found no significant difference in mortality between limb-SC+ and limb-SC- patients: hazard ratio : 1.35 [95%CI: 0.46-3.99] ; $p=0.559$. As shown in Figure 5, the presence of SC~TcpO₂ based on objective criteria applied to chest recordings (Chest-SC+) was associated with a significant increase in mortality over the follow-up period: Hazard ratio : 2.69 [95%CI: 1.37-5.30] ; $p=0.004$.

Results for the multivariate analysis are reported in table 2 and confirm that chest-SC is still significantly associated with mortality after adjustment for possible confounders. Of interest is to note that the hazard ratio for chest SC~TcpO₂ observed after adjustment for age is almost similar to the one resulting from the univariate analysis. Also of interest is to note that if limb-TcpO₂ is used, age ≥ 75 years is the only factor associated with mortality. Last, comparison of Cox models for chest-SC and limb-SC confirms that chest-TcpO₂ is preferable to limb-TcpO₂ analysis, with a significant difference between these two measurements in their association with mortality: $p=0.0258$.

1 DISCUSSION

2
3 Our study is the first to report sinusoidal oscillatory patterns of TcpO₂ recordings in patients with
4 suspected CLI and their relationship to mortality.

5
6 TcpO₂ is a cornerstone for the investigation of patients with suspected CLI. TcpO₂ requires local
7 heating of the skin to allow stable maximal local vasodilation, which decreases the tissue to
8 surface transcutaneous gradient. Microvascular studies have shown that stable maximal
9 vasodilation is attained after 10 or 15 min of local heating.[22, 23] Therefore, in clinical routine
10 and in addition to the duration of the calibration process, time is required after probe positioning
11 before measurements can be recorded, making TcpO₂ a time-consuming approach. Arsenault et
12 al. studied the association between the risk of lower limb amputation healing failure leading to
13 amputation revision and a TcpO₂ level below cutoffs of 10 to 40 mmHg. The relative risk of
14 lower limb amputation healing failure for patients with a TcpO₂ value below a cutoff appears to
15 decrease with increasing cutoff values, while no single cutoff appeared optimal.[24] This is not
16 surprising due to the unpredictable transcutaneous gradient. Indeed, a moderately low absolute
17 limb TcpO₂ value can either result from a low tissue pO₂ associated with a low transcutaneous
18 gradient, or from a normal tissue pO₂, but is associated with a high transcutaneous gradient.
19 Despite this uncertainty in absolute values, relative changes in chest TcpO₂ have repeatedly
20 shown a good correlation with changes in tissue or arterial pO₂. [25, 26]

21
22 TcpO₂ has been previously used to study the changes in CSR cycles under treatment.[16] In heart
23 failure patients, the measurement site to detect oxygen saturation changes in CSR does not seem
24 to matter.[27] In our patients, SC~TcpO₂ observed at the chest level may not be visible at the

limb level (specifically in case of low limb absolute value), underlying the interest of the use of a chest probe in CLI-suspected patients. It is important to note that the oscillations that we searched have a reasonably low temporal frequency. Clark-type electrodes are reported to provide a 90% response to an abrupt change in the value to be recorded, ranging from 20 to 25 s.[28] TcpO₂ changes are comparable with photoelectric probes but seem to be slower with paramagnetic probes.[29, 30] Therefore, it is uncertain whether the present results with Clark-type electrodes could be observed with all TcpO₂ technologies.

Cheyne-Stokes respiration (CSR), sometimes referred to as Hunter-Cheyne-Stokes breathing, is a type of breathing disorder characterized by cyclical episodes of apnea, followed by increasing then decreasing ventilation amplitude, resulting in sinusoidal changes in arterial pO₂. Although visual analysis can detect the SC~TcpO₂ changes, we used the autocorrelation to confirm with objective criteria that the second and third peaks were harmonic values of the first peak, which characterizes a sinusoidal pattern. Beyond CSR, there are multiple types of abnormal respirations that potentially lead to permanent or transient hypoxemia at rest, including sleep obstructive apnea syndrome, chronic hypoventilation, Kussmaul respiration, sighing respiration, Biot respiration, apneustic breathing, and central neurogenic hypoventilation.[31] CSR is different from most abnormal respirations, and also from obstructive sleep apnea syndrome. The ventilation cycle length in patients with CSR is typically 40 s or more (generally 40 to 90 s) in CSR; thus, the interval 35 to 100 s was used in our study. Of note, patients can show CSR either during wakefulness or sleep or both.[32] In practice, while attention is generally paid to temperature conditions of the measurement room when performing TcpO₂ recordings, it might be that a calm and quiet room is needed to allow patients with suspected CLI to fall asleep during the recording to unmask CSR not only during wakefulness, but also during sleep. Further, we likely underestimated the true prevalence of SC~TcpO₂ because the room where we performed

our measurements is very active and rather noisy, and we probably missed sinusoidal changes only occurring while patients were sleeping.

The American Academy of Sleep Medicine (AASM) requires the presence of five or more central apneas or central hypopneas per hour associated with the crescendo/decrecendo breathing pattern recorded over a minimum of two hours of monitoring to define CSR. Our short-term recording (far less than 2 hours) with most patients remaining awakened, may miss some patients with SC+ and do not allow us to fulfill the definition of CSR, but we observed in all cases more than five consecutive cycles of ascending and descending sinusoidal pO_2 changes (one of our 4 criteria for a positive test). The use of standard deviation (SD) of the $TcpO_2$ signal as a fourth criterion is based on the fact that for strictly sinusoidal signals, the ratio of the peak-to-peak amplitude of changes to SD is $2\sqrt{2}$ (~ 2.83), while this ratio ranges from 6 to 8 in the case of random, square, or other non-sinusoidal changes.[20] As a consequence, defining a minimal SD value is important to confirm that reasonably ample $TcpO_2$ oscillations occurred while simultaneously excluding random changes of mild to moderate amplitudes.

CSR has received considerable attention in the last decade due to its association with cardiovascular diseases. The prevalence of CSR in the general population is rare but could be as high as 20% in patients with stroke or heart failure, two major causes of mortality and morbidity.[1] Amazingly, CSR prevalence in patients with lower limb arterial disease and specifically CLI was unknown. However, $TcpO_2$ is largely used in patients with severe lower limb peripheral artery disease and was previously proposed as a technique that can be used to diagnose CSR.[16] The present results suggest that CSR, assumed to induce SC~ $TcpO_2$ changes, could be an underestimated frequent condition in CLI. We recorded the values with a custom-made program to try to attain an objective definition of SC~ $TcpO_2$ changes (rather than account

for the sole visual analysis of changes). Nevertheless, the SC~ pattern in TcpO₂ can be easily observed in everyone's routine provided that: 1) a chest probe is used, 2) screen selection used on the TcpO₂ device is the one showing the temporal recording with adapted graphical scale and not the sole instantaneous numerical values. Nevertheless, the objective determination might help select the patients on objective criteria to determine whether SC~TcpO₂ is a risk factor for mortality in patients with suspected CLI.

Peripheral artery disease, even asymptomatic, carries a high risk of mortality, and this risk increases with the clinical severity of the disease. For example, in a 10-month follow-up of 2,173 symptomatic patients, the all-cause death rates per 100 person-years were 3.5 and 26.2 for claudication and CLI, respectively.[33] In CLI, some studies in small groups of patients (n=113) with favorable healing after revascularization report a 1-year death rate as low as 14%,[34] but most of the larger studies reported rates of 29 to 49%, independent of whether revascularization was performed.[7, 8]

Within a group of patients with CLI, determining the risk of short-term and mid-term mortality is of paramount importance. Various risk factors recordable at admission are predictive risk factors of a post-hospital midterm or long-term mortality in CLI. Biological markers such as low albumin or anemia,[35, 36] clinical factors such as diabetes mellitus,[37] renal failure requiring dialysis,[38, 39] sex,[40] underweight,[41] age >75 years,[34] non-ambulatory status,[34, 35] or sarcopenia (HR, 3.22)[39] have been proposed. All these factors showing hazard ratios ranging from 2.46 to 4.30.[34, 39] are reported for heart and pulmonary diseases. While ejection fraction <50 % was found as a risk factor of the two-year mortality after revascularization in patients with critical limb ischemia: (HR, 3.14; $p = 0.02$),[35] the five-year mortality was indeed lower in the no-heart-failure group than in heart failure patients but did not differ on the basis of ejection fraction in heart failure patients.[42-44] Last, the chronic obstructive pulmonary disease is an

independent predictor of 30 days, and 2 years of death,[45] or 30 days major adverse cardiovascular events,[37] in patients with CLI.

Limitations include the fact that we included patients with suspected rather than proven CLI. We believe that this is closer to the real world where patients referred for TcpO₂ have suspected, rather than already confirmed, CLI. Further, and as recently underlined, the definition of CLI remains largely debated, which would induce a possible bias if we aimed to select only confirmed CLI cases. Second, we do not have evidence on cardiac function in most of our patients, although patients were required to self-report the presence of cardiac disease. Whether the oscillations observed in our patients did rely on underlying cardiac dysfunctions is unknown but warrant future investigations. Third, we previously discussed the importance of comorbid conditions (e.g., sarcopenia, renal failure, and anemia) as risk factors for mortality in patients with CLI. We do not have these data for most of our patients. Comparison to other markers of mortality remains to be determined, with the advantage of SC~TcpO₂ being readily available. Fourth, oscillations in respiration in CSR are associated with oscillations in sympathetic nerve activation.[46] Although local heating abolishes local sympathetic tone, SC~TcpO₂ observed resulted from cutaneous vasoconstriction-vasodilation episodes rather than from arterial pO₂ changes. We advocate that whether or not TcpO₂ changes reflect local vasomotor changes or changes in systemic arterial pO₂ is not an issue because both mechanisms are assumed to rely on the same underlying disease (i.e., CSR). Overall, although we assume that the observed TcpO₂ oscillations likely resulted from CSR, in the present retrospective analysis, no patient was referred for pulmonary polysomnographic investigations to confirm our hypothesis and validate whether patients with SC~TcpO₂ fulfilled all of the AASM criteria for CSR. Similarly, only in very few cases the observation of abnormal breathing during the test was available in the notes of the most expert

nurses. In patients with suspected CLI, teaching nurses or technicians about CSR, and training them to detect and report abnormal respiration (among which CSR) is required.

In conclusion, the observation of abnormal breathing by a nurse performing TcpO₂ tests of patients with suspected CLI should be reported, but even if unreported, objective determination of SC~TcpO₂ is readily available to the physician supervising TcpO₂ results, provided that continuous recordings (and not only screen reading of instantaneous TcpO₂ values) are performed. Optimally, SC~TcpO₂ can be determined objectively based on mathematical criteria. The observation of these TcpO₂ oscillations at the chest level (assumed to rely on CSR) is associated with an increased mortality rate in patients referred for suspected CLI. Limb-TcpO₂ alone is insufficient to detect CSR, likely due to absolute low values. Whether the presence of SC~TcpO₂ should modify the decisions for treating patients is a challenging question for the future. These specific TcpO₂ changes convey original information and support the use of TcpO₂ in CLI-suspected patients.

Clinical trial registration number

<https://clinicaltrials.gov> NCT04209998 & NCT04369781

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

PA SH conceived and designed the study. PR JP, JH PA SH participated to the recruitment, WT FG JH participated to the data analysis and interpretation. PA and SH prepared the manuscript draft, PR, WT, FG, JP, JH critically revised the manuscript. All authors approved the final version of the manuscript

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FIGURE LEGENDS:

Figure 1: Schematic representation of the CITRA protocol.

Figure 2: Flowchart of the study

Figure 3: Four typical examples (patients A to D) of sinusoidal patterns with various amplitude and various cycle lengths.

In patient B, limb elevation results in $TcpO_2$ being almost zero and with no visible sinusoids, whereas the sinusoidal pattern persisted during limb elevation in patient D. Note that the time scale is similar for all recordings and that the range of all $TcpO_2$ scales is 40 mmHg to facilitate the comparison of the different amplitudes of sinusoids.

Figure 4: Two examples of recordings with (left panel) or without (right panel) sinusoidal changes.

After selection of an area of interest, lower panels are the respective results for each of the studied criteria and cross-correlation analyses.

Figure 5: Survival rate of patients included in the NOVICE study: SC+ and SC- refer to patients who fulfill or do not fulfill the criteria for the presence of sinusoidal changes in the chest transcutaneous oxygen pressure values.

Table 1: Characteristics of the patients fulfilling (SC+) or not fulfilling (SC-) mathematical analysis of the recordings.

	CITRA group			NOVICE sub-group		
	Chest SC+ (n=43)	Chest SC- (n=257)	<i>p</i> value	Chest SC+ (n=27)	Chest SC- (n=180)	<i>p</i> value
Characteristics						
Age (years)	79.5±12.7	75.4±12.0	0.053	80.3±12.1	75.6±12.0	0.060
Male sex	30 (69.8%)	167 (65.0%)	0.541	20 (74.1%)	117 (65.0%)	0.392
Height (cm)	167±10	167±10	0.652	170±12	168±17	0.508
Weight (kg)	79.4±26.3	77.4±20.3	0.641	79.6±27.1	76.4±20.2	0.489
BMI (kg/m ²)	27.8±7.4	27.6±6.3	0.855	27.2±7.8	26.9±6.8	0.844
Ongoing treatments						
Beta blockers	15 (34.9%)	80 (31.1%)	0.624	9 (33.3%)	60 (33.3%)	1.000
Antiplatelet or anticoagulant	26 (60.5%)	183 (71.2%)	0.156	16 (59.3%)	135 (75.0%)	0.086
RAA inhibitors or diuretics	24 (55.8%)	155 (60.3%)	0.578	16 (59.3%)	111 (61.7%)	0.811
Cholesterol lowering drugs	16 (37.2%)	119 (46.3%)	0.268	10 (37.0%)	90 (50.0%)	0.209
Psychotropic agents	12 (27.9%)	81 (31.5%)	0.635	10 (37.0%)	63 (35.0%)	0.836
Pain killers	20 (46.5%)	108 (42.0%)	0.582	12 (44.4%)	83 (46.1%)	0.871
Arm arterial blood pressure						
Systolic pressure (mmHg)	123±20	135±23	0.001	129±20	134±23	0.326
Diastolic pressure (mmHg)	72±17	74±15	0.309	76±18	76±15	0.833
Positive tests for lower extremity artery disease						
Positive ultrasound	38 (88.4%)	241 (93.8%)	0.199	23 (85.2%)	177 (98.3%)	0.001
Ankle / brachial index ≤ 0.90	21 (48.8 %)	111 (43.2%)	0.490	14 (51.9%)	76 (42.2%)	0.347
Toe / brachial index ≤ 0.70	13 (30.2%)	71 (27.6%)	0.725	7 (25.9%)	48 (26.7%)	0.768
Any of the three above	40 (93.0%)	246 (95.7%)	0.438	27 (100%)	177 (98.3%)	-
Symptoms at referral						
Rest pain without wound	5 (11.6%)	42 (16.3%)	0.431	2 (7.4%)	23 (12.8%)	0.425
Wounds	38 (88.4%)	215 (83.7%)	0.431	25 (92.6%)	157 (87.2%)	0.425
History of						
Diabetes mellitus	15 (34.8%)	125 (48.6%)	0.094	9 (33.3%)	90 (50.0%)	0.147
Respiratory insufficiency	7 (16.3%)	29 (11.3%)	0.351	4 (14.9%)	21(11.7%)	0.750
Cardiac insufficiency	15 (34.8%)	76 (29.6%)	0.482	8 (29.6%)	62 (34.4%)	0.670
Transcutaneous oxygen pressure at:						
Chest level(mmHg)	56.1±10.3	55.9±14.4	0.929	56.2±10.4	56.4±14.2	0.939
Limb level (mmHg)	24.1±21.1	29.0±19.6	0.159	23.6±19.4	27.9±19.7	0.292

Results are mean± standard deviation or number of observations and proportions within the group. BMI is defined as the body mass index. AP is for arm pressure; RAA is for renin-angiotensin-aldosterone system. Positive ultrasound is occlusion or significant stenosis at rest of an arterial trunk, or a history of revascularization.

Table 2: Results of the multivariate analysis of chest (upper panel) and limb (lower panel) recordings for the detection of sinusoidal changes in transcutaneous oxygen pressure (SC~TcpO₂) adjusted for possible confounders.

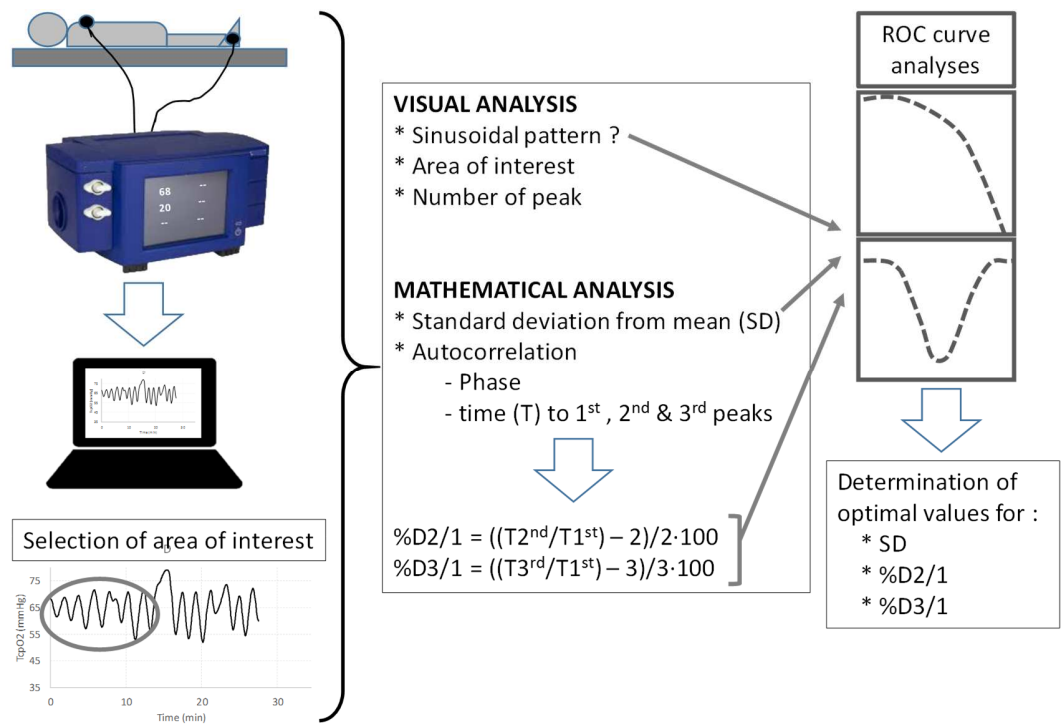
	Hazard ratio	Lower limit of 95% CI	Upper limit of 95% CI	<i>p</i>
Chest SC- TcpO ₂	2.40	1.19	4.83	0.014
Age ≥ 75 years old	2.45	1.13	5.31	0.023
Use of beta-blockers	1.75	0.93	3.28	0.083
Respiratory insufficiency	1.61	0.85	3.02	0.142
Lower extremity artery disease	1.34	0.14	12.79	0.800
Pain killers	1.22	0.63	2.35	0.559
Diabetes mellitus	1.21	0.59	2.46	0.605
Cardiac insufficiency	1.19	0.61	2.30	0.615
Use of diuretics or RAA inhibitors	1.04	0.52	2.10	0.906
Use of cholesterol lowering drugs	1.01	0.50	2.07	0.969
Psychotropic drugs	0.98	0.50	1.91	0.959
Use of anti-platelet or anticoagulant drugs	0.68	0.37	1.27	0.231

	Hazard Ratio	Lower limit of 95% CI.	Upper limit of 95% CI.	<i>p</i>
Limb SC- TcpO ₂	1.20	0.35	4.12	0.777
Age ≥ 75 years old	2.49	1.19	5.19	0.015
Use of beta-blockers	1.78	0.94	3.37	0.078
Respiratory insufficiency	1.76	0.90	3.41	0.097
Diabetes mellitus	1.15	0.60	2.20	0.677
Pain killers	1.15	0.62	2.17	0.655
Lower extremity artery disease	1.11	0.15	8.43	0.918
Use of diuretics or RAA inhibitors	1.08	0.56	2.11	0.813
Cardiac insufficiency	1.08	0.56	2.09	0.825
Psychotropic drugs	1.02	0.53	1.96	0.946
Use of cholesterol lowering drugs	0.91	0.47	1.75	0.777
Use of anti-platelet or anticoagulant drugs	0.65	0.34	1.24	0.186

RAA stands for renine-angiotensin-aldosterone system. 95% CI is the 95% confidence interval in the determination of the hazard ratio.

1 **FIGURES**

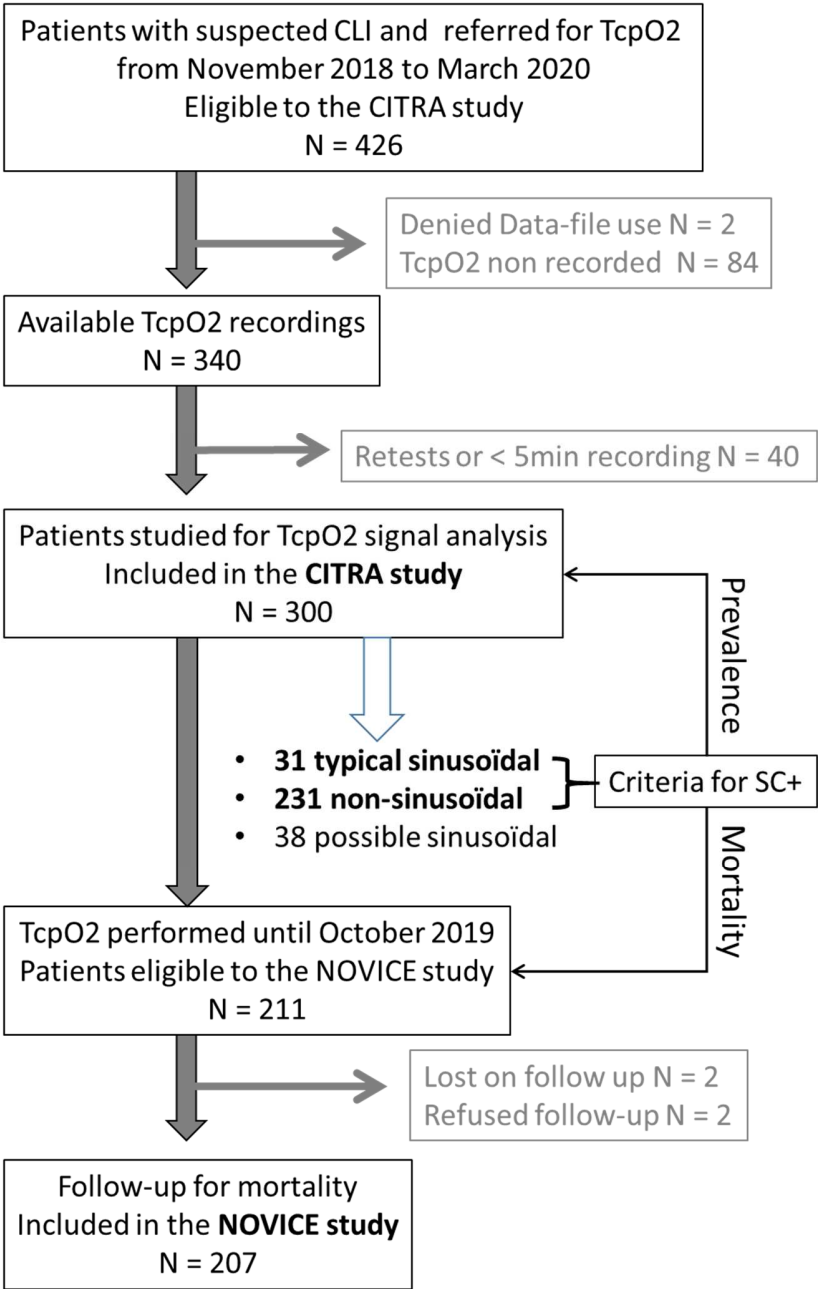
2 Figure 1:



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1 Figure 2.

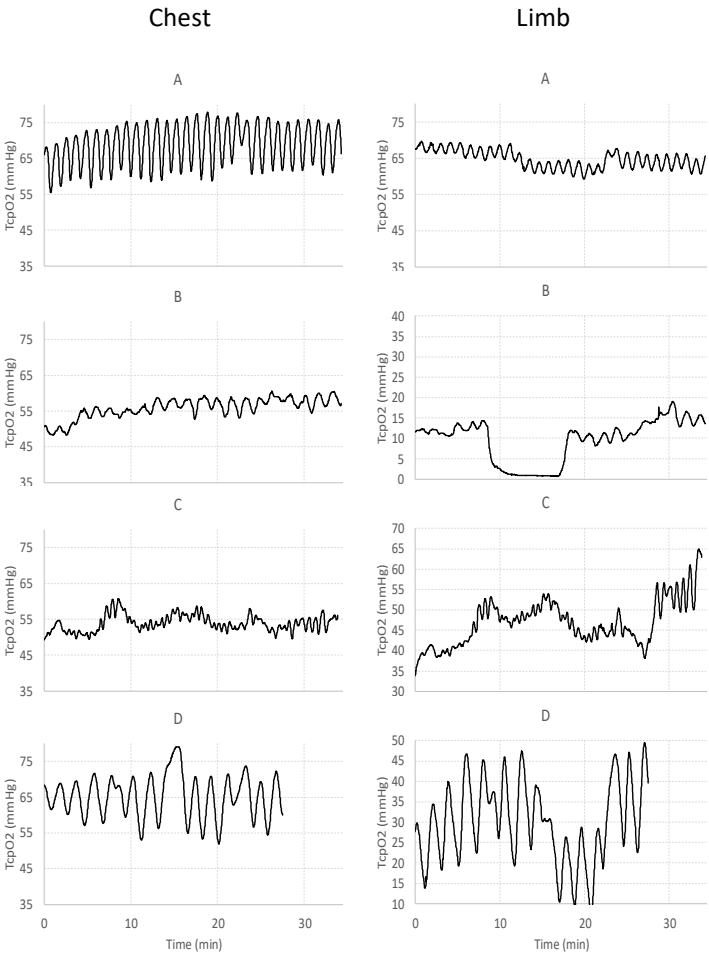


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1 Figure 3



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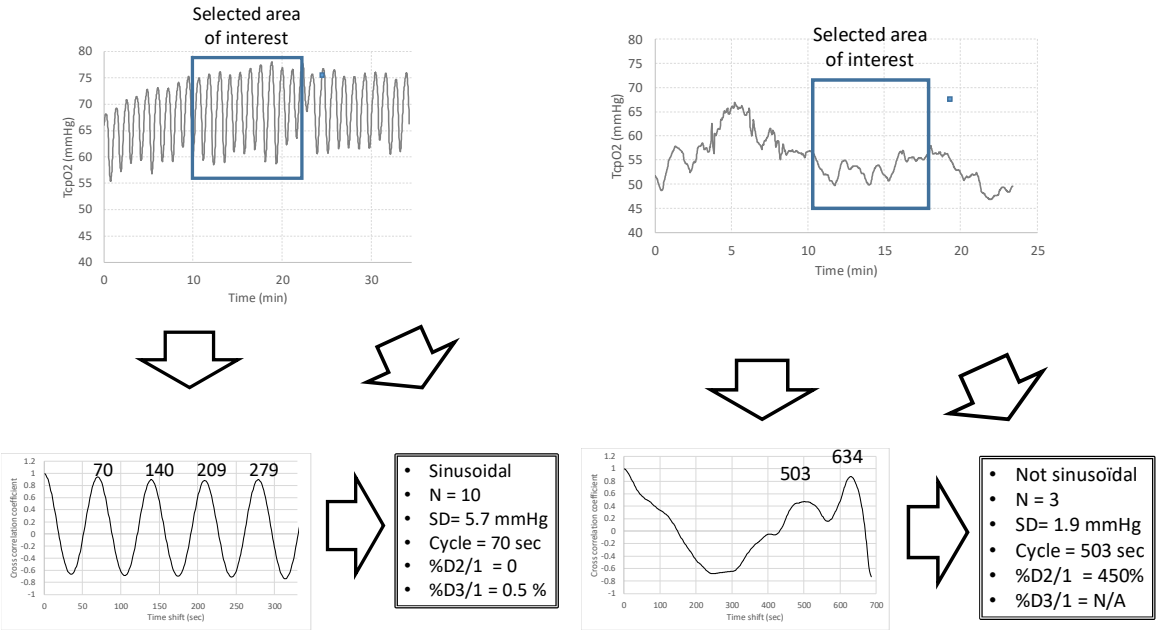
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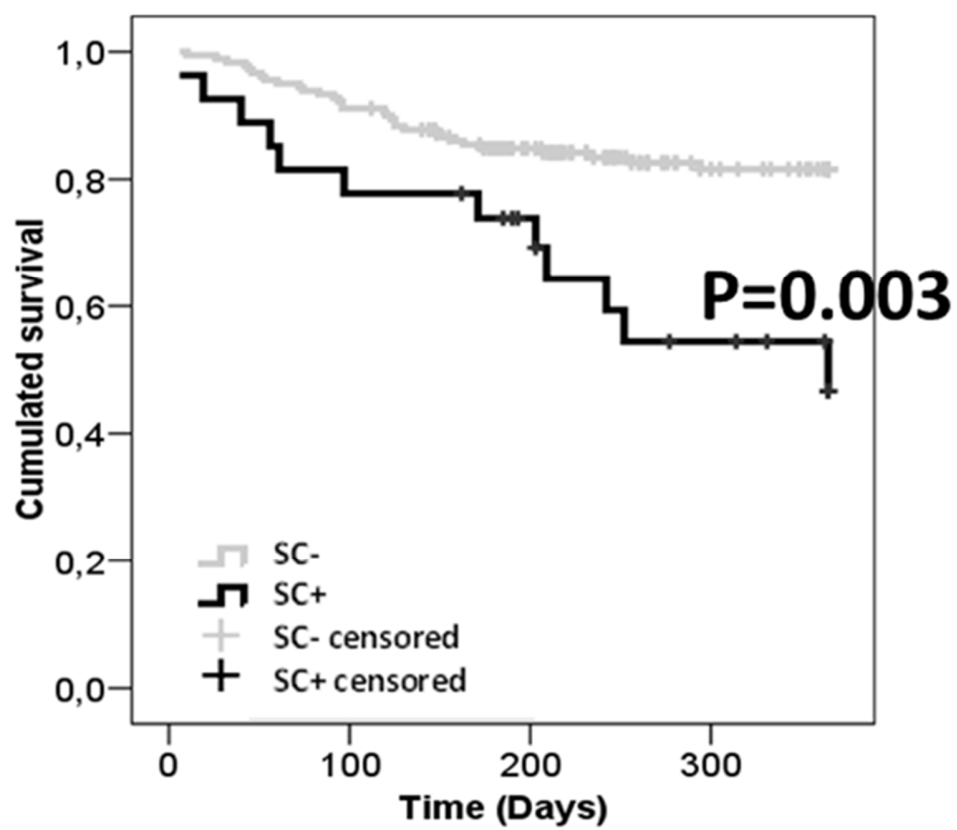


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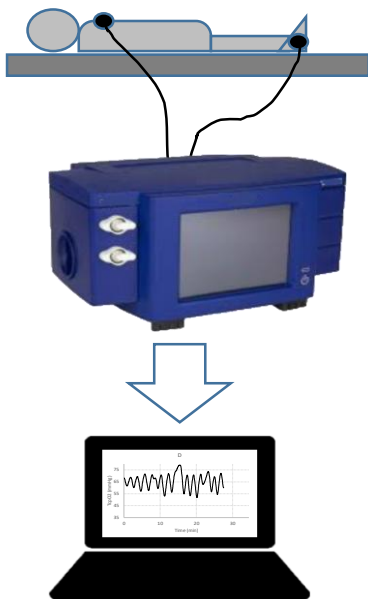
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2 Figure 5:



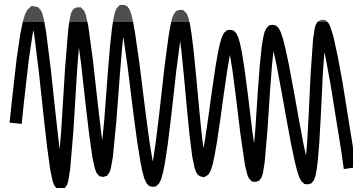
3

Prevalence and impact on mortality of sinusoidal changes in transcutaneous oxygen pressure in suspected critical limb ischemia



Detection of
sinusoids (SC+)

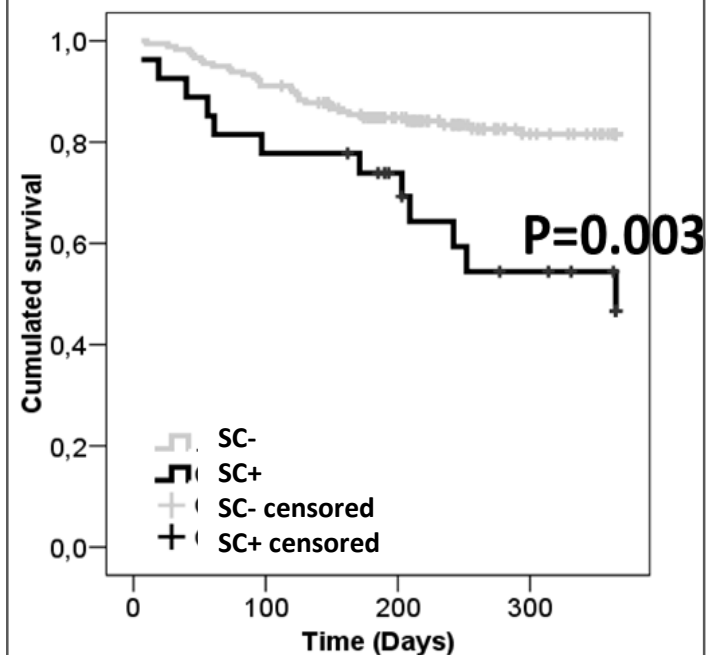
SC⁺ = 14.3 %



SC⁻ = 85.7 %



Prevalence of
sinusoids



Mortality in
SC+ versus SC-