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Troponin and Nt-pro-BNP Fluctuation During Hemodialysis and Impact on Cardiovascular Prognosis

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Abstract

Introduction: Chronic elevation of high sensitivity troponin (hs-cTnT) and N-terminal brain-natriuretic peptide (Nt-pro-BNP) in end-stage renal disease is associated with worse cardiovascular outcomes. Little is known about how hemodialysis (HD) parameters acutely influence those biomarkers and prognosis.

Objective: To determine if the variation of those biomarkers on the short term is influenced by factors that are already associated with hemodialysis-induced cardiac injury and if it has a prognostic value.

Methods: Forty participants undergoing HD at our institution were enrolled. Factors known to influence hs-cTnT and Nt-pro-BNP levels were the principal exclusion criteria. Eight patients were excluded mainly for EF<40%. Six consecutive serum samples were analysed for hs-cTnT and Nt-pro-BNP before and after three HD sessions. Hs-cTnT and Nt-pro-BNP percentage variation after HD were analysed in respect with HD weight reduction percentage, ultrafiltration rate, Kt/V (HD adequacy parameter), presence of diastolic dysfunction, indexed left ventricular mass, peri-dialysis hypotension, blood filtration rate and with the other biomarker. Linear regression analysis was used in a fixed-effect model for multivariate assessment with variables already mentionned. Major adverse clinical events (hospitalization for heart failure, acute coronary syndrome and cardiovascular death) were recorded for a period of 21 months to analyze the sensitivity and specificity of biomarker fluctuation for predicting clinical events.

Results: Mean decrease after dialysis for hs-cTnT was 38.3% +- 3.9%, while it was 56% +- 3.5% for Nt-pro-BNP. There was a fair and significant association between variation in hs-cTnT and Nt-pro-BNP and the model's variables (Pearson coefficient of 0.646 ($p<0.001$) and 0. 0.53 ($p=0.001$), respectively). Variables having the most important influences on the biomarkers fluctuation were ultrafiltration rate (β = -0.558, $p=0.001$) and interdialytic weight decrease percentage (β = 0.399, $p=0.020$). Smaller troponin decrease (25th percentile) showed fair sensitivity (80%) for adverse clinical events. Hs-cTnT and Nt-pro-BNP levels are diminished after HD in a manner that is reproducible for the same patient and they change in a parallel manner.

Conclusion: Hs-cTnT and Nt-pro-BNP changes are highly reproducible for the same patient and vary parallelly. While seeming contradictory, but consistent with past literature, higher total fluid removal and slower ultrafiltration rates are associated with more important biomarker decreases. Since static levels of those biomarkers correlate with mortality, adopting a slower fluid removal during hemodialysis and prolonging sessions could improve mortality over the long run. This could be assessed in future dedicated studies.

Keywords: BNP • Troponin • Hemodialysis • Prognosis • Cardiovascular events

Introduction

In patients undergoing chronic hemodialysis, there is an elevation of high-sensitivity troponin (hs-cTnT) and brain-natriuretic peptide (Nt-pro-BNP). Baseline elevation of those biomarkers in that setting is directly associated with worse cardiovascular prognosis and higher mortality rates [1-4]. It is known that patients undergoing chronic hemodialysis experiment a phenomenon called "hemodialysis-induced cardiac injury", and cardiac biomarkers elevation might biochemically represent this phenomenon [5,6]. While some elaborate techniques using cardiovascular imaging during hemodialysis were attempted experimentally and successfully demonstrated cardiac injury, these methods are neither cost-efficient nor practical on a chronic basis [7]. Readily and financially accessible methods (such as hs-cTnT and Nt-pro-BNP levels fluctuation) may be useful to assist in the close follow-up of a patient's tolerance to hemodialysis and in the attempt to prevent hemodialysis-induced cardiac injury.

Earlier studies assessed hs-cTnT fluctuation over each dialysis session, but did not ascertain for associations with prognosis, hemodialysis parameters and the presence of diastolic dysfunction. It is known that a decrease of 10% in the level of hs-cTnT occurs after hemodialysis in about 75% of patients whereas 25% of hemodialysis patient have a level that is unchanged by hemodialysis [8].

Hemodialysis-induced cardiac injury is a phenomenon thought to be induced by chronic myocardial hypoperfusion during hemodialysis sessions

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due to rapid fluid shifts and hemodynamic stress. In human experimental setting, hypoperfusion causes transient regional myocardial dysfunction that may lead to permanent cardiac fibrosis and dysfunction [6]. These regional contractile anomalies have been identified as a significant and strong predictor of mortality in hemodialysis patients [6]. They are associated principally with ultrafiltration volume and hypotension during hemodialysis [6]. Since Hs-cTnT and Nt-pro-BNP are markers of myocardial injury and sheer stress respectively, they could be used in an experimental setting to assess this phenomenon. Hs-cTnT and Nt-pro-BNP are clinically more readily available and, less costly in time and resource. They could constitute valuable information to adjust hemodialysis parameters in the attempt to reduce hemodialysis-associated cardiac injury. The purpose of this study was to assess whether HS-cTnT and Nt-pro-BNP fluctuation is influenced by the same factors already stated to contribute to experimental hemodialysis induced cardiac injury. It was also prospectively evaluated if this biomarker fluctuation correlated with major cardiovascular events over time.

Materials and Methods

We conducted a prospective cohort study to quantify Hs-cTnT and Nt-pro-BNP fluctuations during hemodialysis sessions, to determine the factors influencing their fluctuations and whether the variation of those biomarkers correlates with prognosis. Treating nephrologists approached candidates to inform them of the research. Interested and eligible patients were referred to the research team for information about participation. Informed written consent was obtained for each participant. Then, the participant's medical records were reviewed in a standardized manner to ensure the inclusion and exclusion criteria were fully met.

Inclusion criteria were the following: Adult patients from 18-90 years old suffering from chronic Kidney Failure requiring hemodialysis by either central catheter or arterio-venous fistula. Hemodialysis had to be started more than one month prior to the beginning of the study and with long term need anticipated (until graft or deceased).

Exclusion criteria were the following: Left ventricular ejection fraction <40% and either one of the following events that occurred less than two weeks before recruitment: deep vein thrombosis or pulmonary embolism, myocardial infarction, decompensated heart failure, myocarditis, septic shock, stroke, heart surgery, percutaneous coronary intervention, severe aortic stenosis or hypertrophic obstructive cardiomyopathy.

The protocol was approved by our institution's research ethics committee (protocol no 2018-1615). Participant recruitment was accomplished during September 2017.

Blood samples were drawn over 3 consecutive hemodialysis sessions in K2-EDTA tubes. They were collected immediately before and immediately after each session and analysed for hs-cTnT and Nt-pro-BNP levels. Samples were analyzed during the months of October to November 2017.

The following hemodialysis parameters were noted for each hemodialysis session: blood flow rate, dialysis flow rate, ultrafiltration rate, presence of hemodialysis-associated hypotension (systolic blood pressure lower than 90 mmHg at least once during the course of the hemodialysis session), weight decrease percentage, type of filter and Kt/V (hemodialysis adequacy parameter, k = dialyzer clearance, t = dialysis time, V= volume of distribution of urea).

Medical records were reviewed for: demographics, medication, causes of renal failure and comorbidities. Recorded echocardiographic parameters (the most recent echocardiogram available ordered for an appropriate clinical indication by a treating physician) were: diastolic dysfunction (as defined by American Society of Echocardiography guidelines of 2016) [9], indexed left ventricular mass and left ventricular ejection fraction.

The following clinical events were recorded for a period of 21 months: Myocardial infarction, hospitalization for decompensated heart failure, all-cause mortality and a combined endpoint of all of those events.

Statistical Methods

Sample size calculations made to insure adequate statistical power for the study used an alpha error of 0.05 and a statistical power of 80%. Data that was used to calculate sample size were based on an earlier study of our group analyzing Hs-cTnT kinetic in patients with ESRD [8]. According to sample size calculation, a threshold of at least 15 participants per group was met to insure adequate statistical power.

Dichotomic demographic and baseline data were expressed as a number and a percentage of patients corresponding to each criteria. Continuous numerical data (eg. Age, indexed left ventricular mass) were expressed as a mean value with corresponding standard deviation. Biomarker levels before and after each hemodialysis session were expressed descriptively on a histogram. Clinical events were reported as a number of participants experiencing an event and a percentage of participants experiencing the event.

Hs-cTnT and Nt-pro-BNP fluctuations (Mean decrease percentage over the course of three hemodialysis sessions) were plotted against all of the hemodialysis parameters stated above, with diastolic dysfunction and indexed left ventricular mass using a multi-variable fixed model linear regression analysis (Pearson R correlation and linear regression test, IBM SPSS Statistics 25). Beta coefficients that were generated for each of the independent variable during this analysis had their statistical significance calculated using the t-test. P-value significance for this test was pre-set at 0.05.

Patients were then dichotomized between two categories: those having abnormal biomarker fluctuations and those having normal biomarker fluctuation during hemodialysis. The pre-specified cut-off between the two groups was the 25th percentile, meaning that a participant that would have a decrease that is less than the 25th percentile of the data obtained during this study for each biomarker would be classified has having an abnormal fluctuation. Sensitivity and specificity for composite clinical events described in the preceding section were calculated by using the following formula:

Sensitivity: True positive/(True positive + False negative)

Specificity: True negative/(True negative + False positive)

All the following analyzes were carried out using SPSS version 25. Wilson procedure with correction for continuity was utilized to determine confidence interval for sensitivity and specificity. For clinical events, they were expressed as a survival analysis using a Kaplan Meier curve for each type of biomarker fluctuation (''normal'' or ''abnormal'') and compared '*post-hoc*'' using the log-rank test.

Results

Study participants' recruitment and baseline characteristics

Fifty participants were screened initially. Of that number, 40 participants were included in the study after obtaining informed consent (Figure 1). Of the ten patients that did not enter the study, seven were excluded on the basis of the predefined exclusion criteria (five for dilated cardiomyopathy, one for hypertrophic cardiomyopathy and one for severe aortic stenosis); only one was lost to follow up due to moving away and two died before the beginning of the study, but after recruitment. They were censored in the subsequent analysis since no blood samples were collected. Over a maximum of four hundred and eighty biomarker analyses possible, twenty-two were unavailable due to clerical reasons (4.2%).

Participants had a mean age of 68 ± 14.1 years old, were all Caucasian and mostly male (60%), and on dialysis mainly for diabetic nephropathy (38%) and glomerulonephritis of varied causes (10%). All the participants had three hemodialysis sessions per week and they had either central dialysis catheter (53%) or peripheral arterio-venous fistulae (47%) as an access site. Forty-eight percent (48%) of the patients suffered from coronary heart disease as defined in the Appendix. Medication at the time of the study and comorbid conditions can be found in Table 1 in the appendix.

Participants had mostly normal ejection fraction (>75% of patients),

10% had borderline/normal ejection fraction and few patients had middle range ejection fraction (15%). A quarter (25%) of participants had diastolic dysfunction. Mean indexed left ventricular mass was in the normal range (88 ± 25 g/m^2).

Biomarkers fluctuations during hemodialysis and adverse clinical events

Mean decrease after dialysis sessions for hs-cTnT was of 38.3%±3.9%. Pearson's correlation coefficient was of 0.646 (p<0.001) between the decrease of Hs-cTnT and the multivariate model used. Smaller fluctuation of hs-cTnT (<25th percentile) for detecting future adverse clinical events over a 21 months period showed fair sensitivity of 80% (95% CI (49.02-94.33%)), however specificity was poor (31%; (95% CI (18.07- 45.43%)) (Table 2).

Nt-pro-BNP percentage fluctuated with a Pearson's correlation coefficient of 0.53 (p=0.001) (Figure 2) with the model used and standardised significant β coefficients were the following: troponin percentage decrease (0.570, p<0.001), ultrafiltration rate (-0.558, p=0.001), interdialytic weight decrease percentage (0.399, p=0.020) and presence of diastolic dysfunction (-0.159, p=0.035). Smaller Nt-pro-BNP decrease (<25th percentile) showed fair specificity (71% (95% CI 57.17-83.89%)) for adverse clinical events, but sensitivity was poor (0% 95 CI 0-11.1%). Adverse clinical events are shown in Table 3.

Post-hoc analysis of the biomarkers fluctuations are shown in Figure 3 (Hs-cTnT) and 4 (Nt-proBNP). There is a slight non statistically significant (p=0.363) tendency towards increased number of adverse clinical events in the "abnormal troponin fluctuation" group (Figure 3). The non-statistically significant difference is most important 12 months after the initial biomarker analysis. For Nt-Pro-BNP (Figure 4), there is a non-statistically significant tendency towards an increased occurrence of events in the "normal fluctuation group" (p=0.227).The peak maximal difference occurs also at 12 months (Supplementary data).

The parameter for haemodialysis adequacy, Kt/V, was not significantly associated with biomarkers fluctuation. Other study parameters (blood flow rate, hemodialysis-associated hypotension, indexed left ventricular mass and left ventricular ejection fraction) were not associated with biomarkers fluctuation during hemodialysis (Supplementary data).

Biomarkers fluctuated in a reproducible fashion over each dialysis session

Table 1. Demographic data.

Participant Cohort Characteristics	Number of Participants/% of Participants
Demographic Data	
Female sex	16/40
Caucasian race	40/100
Mean age (Years old)	68±14.1
Anemia (Hemoglobin <100 g/L)	25/10
Peripheral vascular disease	11/27.5
Hypertension	27/67.5
Coronary heart disease	19/48
Diabetes	15/37.5
Stroke/Transient ischemic attack	9/22.5
Chronic obstructive pulmonary disease	7/17.5
Smoking	11/27.5
Type of Vascular Access	
Central catheter	21/53
Arterio-venous fistulae	19/47.5
Medication	
Angiotensin conversion enzyme inhibitors	9/22.5
Beta-blockers	17/42.5
Alpha blocker	1/2.5
Calcium channel blockers	11/27.5
Diuretics	19/47.5
Nitrates	2/5
Low dose aspirin	18/45
Plavix	3/7.5
Ticagrelor	1/2.5
Coumadin	6/15
Amiodarone	4/10
Statin	16/40
Aranesp	20/50
Eprex	1/2.5
Iron	2/5
Oral hypoglycemic drugs	5/12.5
Insulin	13/32.5

Table 2. Clinical endpoints occurrence during the 21 months period.

Event	Number of patients (%)
Cardiovascular death	4/10
Acute coronary syndrome	3/7.5
Hospitalization for fluid overload	3/7.5
Total number of events	10

Table 3. Mean Nt-pro-BNP and hs-cTnT values for each dialysis session, average values/percentage decrease for all hemodialysis sessions deviation and mean individual standard deviation.

Variables	Mean Nt-pro-BNP (pg/ml)		Mean hs-cTnT (ng/ml)	
	Before HD	After HD	Before HD	After HD
1st session	12833.0	5047.0	72.5	43.4
2nd Session	15027.0	6352.0	71.9	45.7
3rd Session	9828.0	4188.0	64.6	39.7
Average for all session	11361.1	5241.0	69.6	42.9
Mean individual standard deviation	2104.7	923.3	11.1	6.7
Relative standard deviation (%)	18.5	17.6	15.9	15.7
Mean percentage decrease (%)*	56.1		38.3	
Mean individual percentage standard deviation*	3.5		3.9	
*Before and after dialysis				

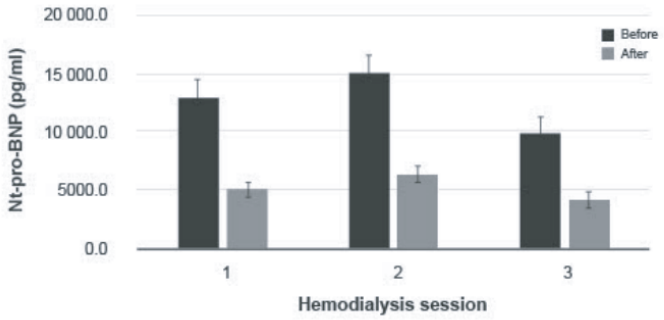

Figure 1. Fluctuation of Nt-pro-BNP before and after hemodialysis.

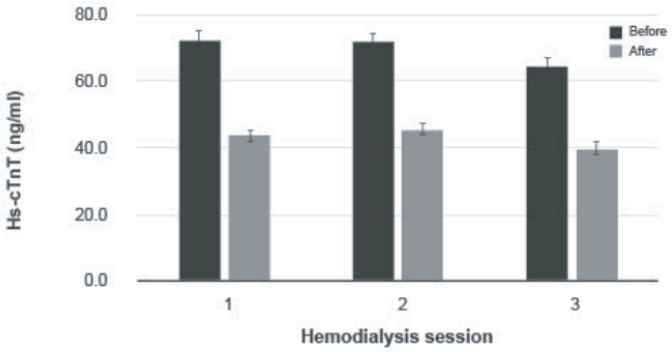

Figure 2. Fluctuation of Hs-cTnT before and after hemodialysis.

with a mean percentage decrease of 56% ± 3.5% for Nt-pro-BNP and a decrease of 38.3% ±3.9% for hs-cTnT.

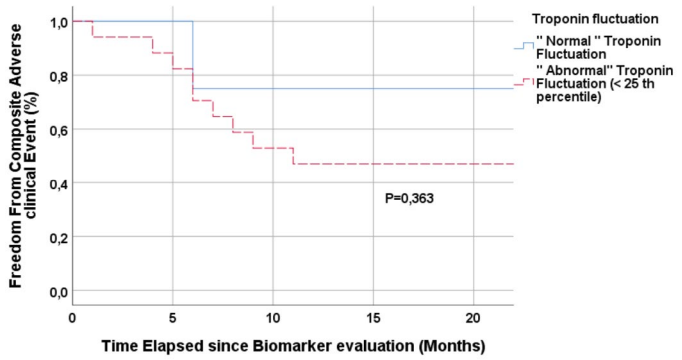

Figure 3. Troponin Peri-dialytic fluctuation and freedom from composite adverse clinical events.

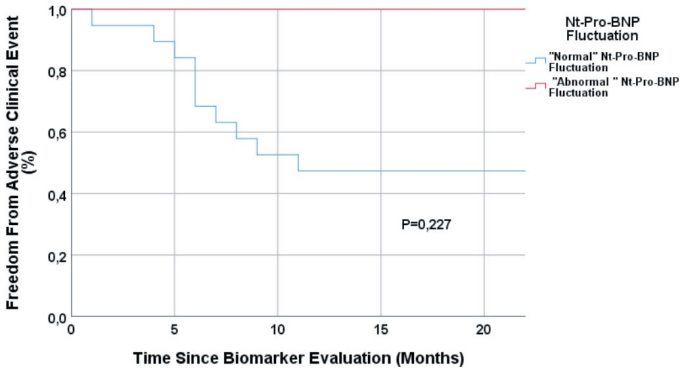

Figure 4. Nt-pro-BNP Peri-dialytic fluctuation and freedom from composite adverse clinical events.

Discussion

This study reports the peri-dialytic fluctuation of Hs-cTnT and Nt-pro-BNP. The serum levels of these biomarkers are influenced acutely by the hemodialytic parameters and by diastolic dysfunction. Hs-cTnT fluctuation demonstrates a fair sensitivity to predict future clinical events, but Nt-pro-BNP has lesser value regarding future clinical events. However, if the two biomarkers are combined in the prediction of clinical events, their specificity and sensitivity could be greatly increased since Hs-cTnT showed good sensitivity and Nt-pro-BNP demonstrated good specificity for adverse clinical events. Post hoc analyses showed a non-statistically significant temporal trend of increased adverse clinical events with the "abnormal" troponin fluctuation and with the "normal" Nt-Pro-BNP fluctuation. This finding has to be interpreted with caution since this analysis was not planned in the initial protocol and is rather exploratory. The fact that the "normal" Nt-Pro-BNP is associated with occurrence of adverse clinical events may be either due to inaccurate starting hypothesis, insufficient occurrence of adverse clinical events during the study or that Nt-Pro-BNP is not strongly associated with prognosis over time as initially thought. Interestingly, the Kt/V showed no association with biomarkers fluctuations, suggesting that the fluctuations of the biomarkers are not due to mere filtration effect. Also, the filter used was of the same kind for every patient, eliminating that variable.

In this study, peri-dialysis hypotension was not associated to biomarker fluctuation, in contrast to previously published papers suggesting that chronic elevation of high sensitivity troponin is associated with peri-dialysis hypotension [6]. The differences in results are most likely due to different definitions of hypotension (relative decrease in reference study vs absolute threshold in this study).

There was a significant association between diastolic dysfunction and lesser decreases in biomarkers. Since nt-pro-BNP and hs-cTnT are typically released in the circulation in relation to myocardial "stretching" and injury, respectively. This could mean the myocardium of those participants is more prone to volume shift and sheer stress during hemodialysis than other patients.

Also, another practical point of this study is that it describes the variation of Hs-c-TnT and Nt-pro-BNP acutely over dialysis sessions which are fairly

reproducible for the same patient over time (standard deviation of 3.5-3.9%). This has not been studied thoroughly over past studies to our knowledge. This will be useful in further studies because it stresses the fact that timing (relative to the hemodialysis sessions) is of utmost importance in the analysis of those biomarkers. For example, one could not compare the biomarkers drawn at the before the first week's session to the biomarkers drawn after the last week's session for there is intrinsic changes after and between hemodialysis sessions. This could also have significant implications for clinicians when assessing patients chronically undergoing hemodialysis for myocardial infarction.

This study leads to the seemingly paradoxical observation that smaller ultrafiltration rates and higher fluid removal lead to smaller biomarker decreases during hemodialysis. This may be explained by a shifting point where the benefit of fluid removal from the cardiovascular system gets offset by the cardiovascular strain of a higher ultrafiltration rate. In fact, one retrospective study that evaluated the effect of ultrafiltration rate on mortality has illustrated that before 13ml/kg/H, the mortality over ultrafiltration rate was relatively flat and It rose in a steeper slope after that specific point [5,10]. One other study to our knowledge has assessed the relationship between high ultrafiltration rates and troponin elevation [10]. The present results of this study are compatible with the findings of the latter study that has shown elevation over a three month's span. The originality of our findings lie in the acuteness of the biomarker fluctuation, in the exploration of other patient specific factors affecting that relationship and in the correlation with cardiovascular prognosis.

One of the strengths of this study is that very few participants were lost to follow up due to preventable circumstances. This was achieved because patients on chronic hemodialysis are usually consistent in the location of their hemodialysis center.

Since our institution is a tertiary center and collaborates with many secondary centers in a region that is relatively vast, this could have introduced a source of error. Clinical events were recorded by reviewing our institution's files but could have missed events that occurred at other institution. This could have decreased the number of clinical events recorded compared to the events that actually happened. Since attending nephrologist records is significant to their clinical history at each visit, this source of error is lessened. Also, about 4% of all blood tests were missing due to clerical and technical issues. This could be seen as a relative weakness, but since blood draws were made by usual hemodialysis ward nurses due to economic reasons and this was an add-on to their usual tasks, this is relatively good.

One of the Relative weaknesses of this study was that a relatively small number of participants was studied making it underpowered for assessment of a link between clinical events and biomarkers variation. However, being a unicentric study, a relatively great proportion of the patients undergoing hemodialysis at our center was screened (total of approximately 70 patients at the time). Only Caucasian patients were recruited which is representative of our local hemodialysis population, which confers a good intrinsic value, but renders the conclusions in this study less applicable to other populations and other healthcare centers. It would be surprising, but not completely excluded, that race had a significant influence on biomarker fluctuations in this setting.

Conclusion

Since increased hs-cTnT are also known to be risk factors associated with increased mortality, it can be reasonably inferred that strategies to decrease hs-cTnT, such as increasing hemodialysis duration, could be used in further clinical studies to help improve prognosis. However, economical and logistic consideration associated with limited hemodialysis periods availability would probably hamper the application of those findings in the real clinical setting. The impact of Nt-Pro-BNP in guiding hemodialysis is less certain because of its limited prognostic value.

The point of this study was to determine which hemodialytic settings influenced biomarkers fluctuation on a relatively small timescale (here and now), so that those settings could be used in further studies to help and improve biomarkers levels and thus prognosis later on. The observations made in this study could be used by future researchers in a randomized controlled trial to determine the exact magnitude of change in the long-term prognosis of these patients.

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Author Contributions

Patrick Prud'homme: Literature review, protocol writing and submitting to the research and ethics committee, participant recruitment, data collection, data interpretation, writing and reviewing of the manuscript.

Hajar El-Kamouni: Literature review, protocol writing, participant recruitment, data collection, data interpretation, reviewing manuscript.

Gabriel Fortin: Literature review, protocol writing, data interpretation, reviewing manuscript.

Anne Marie Côté: Protocol writing and reviewing, data interpretation, reviewing manuscript.

Mélanie Godin: Protocol writing and reviewing, data interpretation, reviewing manuscript.

Michel Nguyen: Protocol writing and reviewing, data interpretation, reviewing manuscript.

Serge Lepage: Protocol writing and reviewing, data interpretation, reviewing manuscript.

Paul Farand: Protocol writing and reviewing, data interpretation, reviewing manuscript.

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