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Sublingual Tissue Perfusion Improves during Emergency Treatment of Acute Decompensated Heart Failure

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Keywords

Heart Failure; Perfusion; Microcirculation

Introduction

Acute decompensated heart failure (ADHF) accounts for over 1,000,000 Emergency Department (ED) visits annually that result in a high rate of inpatient admission.¹ The ED diagnosis of ADHF centers on global assessment of cardiac function, namely, serum B-type natriuretic peptide (BNP) measurement, physical exam, and chest radiographs, all of which have limitations.^{2–5}

One evolving concept is to approach heart failure from a tissue perfusion perspective, viewing the disease as a state of chronic hypo-perfusion that is exacerbated in the acutely decompensated state. Prior studies assessing heart failure with global tissue perfusion parameters (cardiac index and systemic oxygen delivery) demonstrated impaired systemic oxygen delivery⁶ and utilization.⁷ Sidestream darkfield imaging differs from this earlier perfusion work in ADHF because it measures perfusion on a regional microvascular level through quantitative analysis of perfused capillary density (PCD), as opposed to a more global assessment. It is a noninvasive technology that has been shown to estimate heart

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failure severity⁸ and treatment response⁹ in severe disease and cardiogenic shock. Approaching ADHF in the ED setting from a regional microvascular perfusion perspective has not previously been reported, although the technology has been used in the ED sepsis population.¹⁰ This study measured PCD to assess the behavior of microvascular perfusion during ED treatment of ADHF as a potential objective means to evaluate the course of treatment.

Methods

This was an observational, prospective study that enrolled patients from October 2006 to January 2009. The study protocol was approved by our medical center's Institutional Review Board, and written informed consent was obtained from all patients or their legally authorized representative prior to enrollment.

Patients were a random sample taken from those presenting to an urban ED that has an annual census of 75,000 patients. Patients presenting with complaints suggestive of ADHF were approached for enrollment after being screened by research personnel when the monitor cart was available. Inclusion criteria were designed to identify patients who had a high likelihood of having isolated ADHF,¹¹⁻¹³ namely a serum BNP measurement greater than 100 ng/mL measured with an ADVIA Centaur BNP Assay (Bayer AG, Leverkusen, Germany) and a score greater than or equal to 8 on the Boston Heart Failure Criteria (see Appendix 1) once the subject was evaluated by the ED attending physician and the chest radiograph was reviewed. The Boston Criteria was chosen because it can be applied in a uniform manner and has been previously validated.^{14, 15}

Exclusion criteria limited factors that could alter microvascular flow dynamics: hypothermia (oral temperature < 35°C) or hyperthermia (oral temperature > 38°C), a history or physical evidence of severe peripheral vascular disease, the presence of sepsis, hemorrhagic shock, or those who received ADHF treatment prior to enrollment.

Patients underwent PCD measurement with a MicroScan imaging system (MicroVision Medical, Amsterdam, The Netherlands), which recorded digital images of sublingual microcirculatory blood flow using technology that illuminates the tissue of interest with green light (540-550 nm), allowing erythrocytes within tissue arteries, arterioles, venules and capillaries to be visualized (Figure 1).

For each patient encounter, two separate, 20-second video sequences were recorded on the mucosal surface of the sublingual tissue and later analyzed by three independent scorers after the sequences were stripped of specific patient and time identifiers. Images were obtained in multiple areas of the sublingual tissue and were not recorded unless elimination of secretions, minimal tissue compression, adequate focus and optimal contrast adjustment could be obtained. Repeat PCD measurements were made 2 hours after the initial assessment.

The PCD was calculated by measuring the total length of perfused capillaries divided by the image area. Capillaries were considered perfused if they had sluggish, continuous or hyperdynamic flow by visual inspection. For purposes of analysis, capillaries were defined as vessels less than or equal to a width of 20 micrometers based on prior studies utilizing sidestream darkfield imaging technology.^{8, 9} Each scorer independently identified and scored two 2 to 5 second steady state segments using a semi-automated computer image analysis program (AVA 3.0, MicroVision Medical, Amsterdam, The Netherlands) that has been previously validated.^{9, 16} The PCD values from each monitoring session were averaged for each scorer. For final analysis, the average of the three scores was used.

Bedside mean arterial pressure (MAP), both serum hemoglobin and BNP measurements were recorded during each imaging session. Past medical history, including hypertension, coronary artery disease, diabetes mellitus and hypercholesterolemia, were recorded for analysis along with patient gender, age and ethnicity. The heart failure etiology and ejection fraction (EF), if done, were determined from prior records or subsequent inpatient workup. As patients underwent ED treatment, the medication class used and route of delivery were recorded for later analysis.

To evaluate ADHF severity in a uniform quantitative manner that reflects current clinical practice, two visual analogue scale (VAS) assessments were administered during each monitoring session (Appendix 2). The first part of the VAS asked patients to rate their present degree of dyspnea and level of activity using a 100 mm scale (0 mm represented no difficulty; 100 mm represented severe dyspnea or decreased activity). The second part of the VAS was completed by the researcher administering the assessment to record how diaphoretic and dyspneic the subject appeared, using a 100 mm scale (0 represented no obvious distress; 100 represented severe dyspnea or diaphoresis). When possible the same observer was used for all VAS administrations for that specific subject.

Measurements

PCD (mm/mm^2) was reported as an absolute number with median and 25th and 75th interquartile ranges (IQR). Continuous data, such as patient age, PCD, serum BNP (ng/dL) and hemoglobin (g/dL), were reported as means $\pm$ standard deviation if found to be normally distributed, otherwise, median and IQR were reported. A medical record review after discharge provided the ED length of stay, length of hospitalization and death within 6 months of discharge.

Data Analysis

For continuous data, normal distribution was determined by analysis with quantile plotting. To determine if PCD changed during ED treatment, the pre- and post-treatment values were analyzed with a paired student *t*-test (JMP version 8.0, SAS, Inc., Cary, NC), as was MAP. The VAS pre- and post-treatment scores were analyzed as ordinal data with Wilcoxon Sign-Rank analysis (JMP version 8.0, SAS, Inc., Cary, NC). To determine if changes in PCD correlated with changes in MAP, the length of time to reassessment, **or change in VAS scores**, logistic regression compared change in PCD to the pre-and post-treatment changes in these respective parameters (JMP version 8.0, SAS, Inc., Cary, NC).

Reliability of PCD scores for the mean of *k* raters was assessed using Shrout and Fleiss's ICC(2,*k*), an intraclass correlation coefficient (ICC), which measures the reliability of the *k* ratings, assuming that all subjects are rated by same *k* raters who are assumed to be a random subset of all possible raters.¹⁷ An ICC > 0.9 was considered as excellent reliability, 0.8 – 0.9 as good reliability, and 0.7– 0.8 as modest reliability (SAS version 9.2, SAS, Inc. Cary, NC). A *p* < 0.05 was considered statistically significant for all tests.

Sample size calculations were based on prior data describing PCD in ADHF¹⁸ suggesting a change of 2 mm/mm^2 was clinically significant and on data demonstrating a standard deviation of 3.5.¹⁹ Thirty six patients would be required for 90% power for a 2-sided test with an alpha of 0.05.

Results

Sixty seven patients were screened for enrollment, but 7 declined participation and 17 received EMS or ED treatment prior to enrollment. Enrollment continued until 36 patients

met the discharge criteria and had complete data. Of the 43 patients enrolled, 2 were discharged with a diagnosis other than ADHF and 5 had incomplete data, leaving 36 patients for data analysis (Table 1 and Appendix 3). **The 6-month mortality was 13%.**

The time between the pre- and post-treatment PCD measurements was 138 $\pm$ 59 minutes while the hospital length of stay once admitted was 4.0 $\pm$ 4.1 days. Patients underwent treatment with diuretics (89.9%), angiotensin converting enzyme inhibitors (5.4%), inotropes (16.2%), digoxin (2.7%) as well as with topical (70.0%), intravenous (10.0%) and sublingual (20.0%) nitroglycerin.

The mean pre- and post-treatment PCD (Figure 2), MAP, as well as the patient-based and observer-based VAS scores were normally distributed. The ICC(2,k) for PCD was 0.954, indicating there was excellent reliability for raters' PCD scores. The PCD (Figures 3 and 4) increased between the pre- and post-treatment measurements ($p = 0.004$) with a difference of 1.32 m/mm² (95% CI: 0.4 – 2.1). The patient and observer VAS values decreased over this time period ($p < 0.001$ for both), as did mean arterial pressure ($p = 0.002$) (Table 2). The change in PCD (Figures 5 and 6) did not correlate with changes in MAP ($R^2 = 0.01$, $p = 0.54$), time ($R^2 = 0.02$, $p = 0.47$), patient-scored VAS ($R^2 = 0.09$, $p = 0.09$) or observer-scored VAS ($R^2 = 0.04$, $p = 0.26$) (Figures 7a and 7b).

Discussion

With the exception of serum BNP, current ADHF assessment in the ED setting is still based on global parameters such as: physical exam findings, vital signs, chest radiographs, urine output and patient symptoms. These have moderate to poor accuracy in determining ADHF severity and response to treatment.^{2, 4, 20, 21} Serum BNP also has been studied for its ability to guide treatment with lackluster results.²² Although ED-specific clinical decision rules have been developed,¹² they still rely on global parameters that are not fully refined.²³

It is in the ED setting that a quantitative ADHF assessor would prove most useful, as initiation of treatment early in the ADHF presentation has been found to impact outcomes,²⁴⁻²⁶ but modalities such as echocardiography or pulmonary artery catheters are not usually available. The evaluation and treatment rendered in the ED has been found to impact the overall length of stay and costs as well.²⁷

As in previous studies evaluating severe heart failure and cardiogenic shock,^{8, 28} we demonstrated diminished sublingual microvascular perfusion in ADHF patients. This is the first study to examine the ED population, which often represents a wide range of heart failure severity, ranging from mild fluid overload resulting in an observation unit short stay to fulminate cardiogenic shock requiring an ICU admission. This differs from previous studies that have investigated PCD in patients with more severe disease or cardiogenic shock in the intensive care unit setting.

We also observed microvascular perfusion increased after ED treatment, a finding consistent with prior studies that measured PCD before, during, and after cardiogenic shock treatment. Nitroglycerin in particular has been shown to improve perfusion in the ADHF population,^{9, 16} most likely due to its mediation of nitric oxide in endothelial dysfunction.

The PCD values we measured improved as patients received standard of care ADHF treatment, namely, diuretics, nitrates and inotropes,¹³ and were monitored over a reasonable time period for these interventions to take effect. Although there was variation in the follow-up assessment time, reassessment time did not correlate with changes in PCD.

Symptomatic heart failure occurs from the combination of diminished cardiac output, peripheral vasoconstriction, fluid overload and endothelial dysfunction, all of which make it a difficult and complex disease to evaluate and treat. Traditional assessors of disease severity focus on the former three processes from a global perspective, delineating clinical assessment into profiles based on evidence of congestion and hypo-perfusion,³⁰ which has not proven to be a reliable indicator of ADHF severity in advanced disease.³¹ There is limited clinical data on endothelial dysfunction in ADHF,^{32, 33} most likely from a lack of bedside assessors that could assess the behavior of the microvasculature. Our finding that an increased PCD did not correlate with the decreases in the VAS scores suggests that changes in the regional microvasculature may not be reflected in a global assessment parameters such as dyspnea or diaphoresis. Since global assessment is known to have poor accuracy in ADHF assessment, PCD may be a better assessor of disease severity and response to treatment despite not correlating with the current clinical parameters. Because these global assessors are currently the only clinical means to assess ADHF and its response to treatment, determining if PCD truly reflects disease severity and response to treatment may prove challenging. This study will help in the design of these future studies.

Sidestream darkfield imaging first made its debut in the trauma³⁴ and sepsis³⁵ populations with limited use in the cardiogenic shock population.⁸ This early work was limited by a lack of uniform measurement and reporting characteristics, as well as the cumbersome process of recording and analyzing the images. Since then, a consensus has emerged on how best to obtain, report and interpret SDI data,³⁶ and computer software has become available that has accelerated analysis.³⁷ Both of these advances have been incorporated into our analysis, in which three investigators independently selected images, isolated vessels less than 20 micrometers, determined the absence or presence erythrocyte flow and then used the imaging software to generate a PCD score while demonstrating excellent reproducibility.

The PCD in both the pre- and post-treatment periods (12.8 and 14.1 m/mm², respectively) were lower than those found in the non-ADHF population, which had an average PCD of 14.8 m/mm².³⁸ Based on correlation analysis, the behavior of PCD appeared to be statistically independent of MAP, but overall, as MAP decreased between pre- and post-treatment, the PCD increased. This increase in PCD may have resulted from decreased afterload, decreased endothelial dysfunction or increased vessel dilation known to occur with ADHF treatment.

As opposed to peripheral circulation that may be subject to vasoconstriction, the sublingual PCD is of particular interest because it may represent blood flow in the central splanchnic region given that the tongue shares a common embryogenic origin with the gut and that prior studies have reported good correlation between sublingual and gastric mucosal carbon dioxide pressures.³⁹ More recent work in the cardiogenic shock and severe ADHF population has demonstrated significant alterations in microvascular perfusion, and more importantly, these values appear to change with afterload reduction.^{9, 16} Our study is the first to examine the application of microvascular tissue perfusion measurement to the ED population, who often are evaluated and treated based on global assessment alone. SDI may represent a bedside technology that holds promise to assist clinicians in tailoring therapy to the individual.

Limitations

Although we argue that physical exam, chest radiographs and patient symptoms are less than ideal assessors of ADHF, these markers are the currently the only guides clinically available. In our subject population, we used the VAS to assess patient response to treatment and subjective physical exam findings to provide a quantitative measure, as has been used

previously in the ADHF population,¹⁵ and found an improvement in patient symptoms during treatment. However, there is the possibility of measurement bias in each patient measuring their own VAS if each individual assessed their complaints differently. Our study was not designed to detect this phenomenon.

Another significant limitation was the lack of control over the ADHF treatment. This limited our ability to draw conclusions about the effects of specific medications, although the overall effect of ED treatment demonstrated a significant improvement in PCD. However, sublingual nitroglycerin, which may have caused local vasodilation where PCD was measured, may have affected our results and is a limitation of this study. Future studies will investigate ADHF medications, specifically nitroglycerin, in order to address this limitation. Nitroglycerin also is of great interest because it has previously been shown to improve microvascular perfusion in the cardiogenic shock population.⁹

Our sample size calculations were based on a difference of 2 mm/mm² but the actual difference was 1.3 mm/mm². This may limit the validity of our conclusions, although the 95% confidence intervals around the mean difference demonstrated adequate significance.

Because of the inner city urban location of our medical center, the majority of patients were African American. This may matter because differences in response to various medication classes among race has been previously reported,⁴⁰ and we did not control for racial differences to account for this potential confounder. Because African Americans have a 53% higher ED visit rate for ADHF compared to whites but a 13% lower hospitalization rate,⁴¹ this technology may be particularly helpful in this subgroup of ADHF patients if found to be a predictor of which patients need more aggressive treatment or hospital admission. Because the Boston heart failure criteria were validated in predominantly white HF patients¹⁴ and our population was overwhelmingly African-American, the accuracy of this scoring system may be limited. However, only two patients were excluded from the study because of an initial inaccurate HF diagnosis, making the inclusion criteria we employed fairly accurate.

While most parameters were measured during the monitoring period or hospitalization after enrollment, some EF values used in analysis were found upon chart review, values that were weeks or months old. We only used this measure to determine the etiology of ADHF. However, in the elapsed time between the last measurement and enrollment, it is possible that the EF may have significantly changed. Future studies will allow for a dedicated determination of EF and possibly other echocardiography parameters such as cardiac power.

Lastly, enrolling only 44 patients over 2 years may suggest selection bias. However, the SDI monitor was often in use by other concurrent studies that were applying this technology to other disease entities, limiting our ability to enroll on a regular basis. The lack of the monitor cart availability also impacted our two hour reassessments in some patients.

Conclusions

Sublingual tissue perfusion, as measured by PCD, is decreased in ED patients with acutely decompensated heart failure but increases after treatment. Measuring sublingual PCD has greater ease than prior technologies, and may represent a quantitative way to evaluate ADHF in the ED setting.

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Appendix

Table 3
Appendix 1: Boston Inclusion Criteria

• <u>Patient History:</u>	4	Dyspnea at rest
	4	Orthopnea
	3	Paroxysmal nocturnal dyspnea
	2	Dyspnea while walking on level area
	1	Dyspnea while climbing stairs
	Total: ____	
• <u>Physical Exam Findings:</u>		<u>Heart Rate</u>
	1	If 91 to 110 beats per minute
	2	If more than 110 beats per minute
		<u>Jugular Venous Distention</u>
	2	> 6 cm H ₂ O
	3	> 6 cm H ₂ O plus hepatomegaly or edema
		<u>Chest Exam</u>
	1	Basilar crackles
	2	If crackles auscultated more than basilar
	3	Wheezing
	3	Third heart sound
		Total: ____
• <u>Chest Radiograph Findings:</u>	4	Alveolar pulmonary edema
	3	Interstitial pulmonary edema
	3	Bilateral pleural effusion
	3	Cardiothoracic ratio greater than 0.50
	2	Upper zone flow redistribution
	Total: ____	
Grand Total: ____ (Note: Only a maximum of 4 points from each category allowed.)		

Appendix

Table 4
APPENDIX 2: Subject Visual Analogue Scale

Patient: Please mark on the following scale how you feel:		
1. Patient-reported Dyspnea		
0 mm		100 mm
<hr/>		
"I can breath as I normally do"		"I cannot breath at all"
2. Patient-reported Level of Activity		
0 mm		100 mm
<hr/>		
"I can move around as I normally do"		"I am short of breath just sitting here"
Observer: Rate the following observations:		

3. Observer-reported Dyspnea:

0 mm

100 mm

No respiratory distress

Needs intubation

4. Observer-reported Diaphoresis

0 mm

100 mm

Skin is dry.

Dripping with sweat

Appendix

Table 5

Appendix 3: The individual characteristics of patients, in which ejection fraction (EF), pre- and post treatment observer (Pre-Tx OBS VAS and Post-Tx OBS VAS, respectively), pre- and post treatment patient (Pre-Tx PT VAS and Post-Tx PT VAS, respectively), pre- and post treatment perfused capillary density (Pre-Tx PCD and Post-Tx PCD, respectively) and mortality are listed. For medications received, nitroglycerin (NTG), furosemide (FUR), natreacor (NAT), digoxin (DIG), Dobutamine (DOB) and angiotensin-converting enzyme inhibitor (ACEI) are listed

Patient	EF (%)	Pre-Tx OBS VAS	Post-Tx OBS VAS	Pre-Tx PT VAS	Post-Tx PT VAS	Pre-Tx PCD	Post-Tx PCD	Died	Medications Received
HF0048	17	86	32	123	14	12.6	18.2	N	NTG, FUR
HF0051	40	112	3	139	19	17.5	15.3	N	NTG, FUR, NAT
HF0052	20	-	-	-	-	7.1	8.2	N	NTG, FUR
HF0054	20	36	2	122	4	9.6	12.6	N	FUR
HF0055	35	84	4	162	37	7.3	9.0	N	NTG
HF0056	10	14	2	165	25	9.6	9.0	N	NTG, FUR
HF0057	-	-	-	-	-	8.4	10.4	N	FUR
HF0058	10	56	4	138	17	6.8	8.0	N	NTG, FUR, NAT
HF0060	35	139	19	108	16	6.5	10.0	N	NTG, DIG
HF0061	20	159	150	172	180	9.4	10.7	N	DOB, FUR
HF0065	25	61	65	164	57	10.9	13.3	N	FUR
HF0067	25	54	2	164	55	10.3	12.1	N	NTG, FUR
HF0071	15	14	38	72	88	12.2	12.4	N	NTG, FUR, NAT
HF0078	15	99	-	146	20	14.8	18.7	Y	FUR
HF0082	35	39	4	96	25	16.8	14.6	N	NTG, FUR
HF0108	30	8	6	63	9	12.8	14.5	N	FUR
HF0109	16	28	8	157	32	17.7	13.1	N	NTG, FUR, ACEI
HF0119	40	65	3	120	4	16.8	14.5	N	FUR

Patient	EF (%)	Pre-Tx OBS VAS	Post-Tx OBS VAS	Pre-Tx PT VAS	Post-Tx PT VAS	Pre-Tx PCD	Post-Tx PCD	Died	Medications Received
HF0121	59	62	56	120	27	17.8	18.9	N	NTG, FUR
HF0122	30	59	24	136	118	15.9	18.3	N	NTG, FUR
HF0123	35	35	17	110	34	16.0	19.4	N	NTG, FUR
HF0126	20	102	-	151	-	15.4	18.3	Y	FUR
HF0129	25	97	3	18	3	14.1	11.9	N	NTG, FUR, ACEI
HF0131	40	72	2	141	53	16.4	16.5	N	NTG
HF0132	60	99	43	111	118	10.3	13.5	N	NTG, FUR
HF0133	25	23	18	90	0	14.4	21.2	N	FUR
HF0143	60	97	120	0	0	13.0	15.5	N	NTG, FUR
HF0146	25	4	17	134	31	14.5	13.3	N	FUR
HF0149	25	13	0	59	28	16.3	17.9	N	FUR
HF0150	50	6	1	129	1	6.9	14.3	N	FUR
HF0151	60	9	12	174	16	13.0	12.7	N	FUR
HF0153	-	-	-	26	-	13.8	13.9	N	FUR, DOB
HF0154	40	59	4	101	96	15.2	15.7	Y	-
HF0155	15	96	-	180	-	10.7	11.5	Y	DOB
HF0156	20	76	1	149	73	12.8	12.0	N	NTG, FUR
HF0157	30	17	0	43	1	18.6	18.2	N	NTG, FUR

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Figure 1. Sidestream darkfield imaging in acute decompensated heart failure, ranging from larger venules and arterioles to smaller capillaries in which single file erythrocytes move through sublingual tissue.

Figure 2.

The pre- and post-treatment perfused capillary density measurement distributions, with the median denoted by the horizontal bar, and the 25th and 75th interquartile ranges represented by the lower and upper boundaries of the rectangle, respectively.

Figure 3.

Pre- and post-treatment perfused capillary density (PCD) with standard error in patients undergoing ED treatment of acute decompensated heart failure (ADHF). The change from pre- to post-treatment PCD is shown for each patient.

Figure 4.

The change from pre- to post-treatment perfused capillary density (PCD) for each patient undergoing ED treatment of acute decompensated heart failure (ADHF).

Figure 5. Bivariate fit ($R^2 = 0.016$, $p = 0.47$) of change from pre- and post-treatment PCD (Delta PCD) by time between measurements (ED Time).

Figure 6. Bivariate fit ($R^2 = 0.013$, $p = 0.54$) of change from pre- and post-treatment PCD (Delta PCD) by pre- and post-treatment mean arterial pressure measurements (Delta MAP).

Figures 7a and 7b.

Bivariate fits of the patient-scored (Delta PT VAS) visual analogue scale score ($R^2 = 0.09$, $p = 0.09$) and the observer-scored (Delta OBS VAS) visual analogue scale score ($R^2 = 0.04$, $p = 0.26$) versus the change in perfused capillary density (Delta SDI) over the treatment period.

Table 1

Patient demographics (SD =standard deviation).

Age (mean years +/- SD)	61.2 +/-12.1
Gender (%):	
Female	14(39)
Male	22 (61)
Race (%):	
Black	32 (89)
Hispanic	1 (3)
White	3 (8)
ADHF Etiology (%)	
Hypertension	15 (41.3)
Ischemic	14 (38.9)
Pulmonary Hypertension	4 (11.2)
Valvular	1 (2.9)
Unknown	2 (5.7)
ADHF Classification (%):	
Preserved LV Function	6 (16.7)
Reduced LV Function	30 (83.3)
Ejection Fraction (n = 34)	30.2 +/- 14.5 %
Co-morbidities (%)	
Diabetes Mellitus	9 (25.7)
Hypertension	34 (97.1)
Coronary Artery Disease	20 (57.1)
Hypercholesterolemia	24 (68.6)
Hemoglobin (g/dL) +/- SD	12.0 +/-1.8
BNP (ng/dL) +/- SD	1530.9 +/- 1392.5

Table 2

Pre- and post-treatment values for perfused capillary density (PCD), mean arterial pressure (MAP) and the patient and observer based visual analogue scale (VAS). SD = standard deviation and 95% CI = 95% confidence intervals. The asterisk denotes statistical significance.

	Pre-Treatment (+/- SD)	Post-Treatment (+/- SD)	Difference (+/- 95% CI)	Significance
PCD (m/mm²)	12.8 +/- 3.8	14.1 +/- 3.6	1.3 (0.4 – 2.1)	0.004*
MAP (mm Hg)	104.7 +/- 24.2	97.0 +/- 16.7	12.3 (6.5 – 18.1)	0.002*
Patient VAS (mm)	122.4 +/- 45.3	34.5 +/- 33.7	86.5 (68.0 – 105.1)	< 0.001*
Observer VAS (mm)	60.0 +/- 40.7	17.6 +/- 26.5	35.0 (20.4 – 49.6)	<0.001*