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Coronary sinus Reducer implantation results in improved oxygen kinetics at cardiopulmonary exercise test in patients with refractory angina

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Short Title: Improved oxygen kinetics after coronary sinus reducer implantation.

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Abstract

Aims. Refractory angina is still a major public health problem. The Coronary Sinus Reducer (CSR) has recently been introduced as an alternative treatment to reduce symptoms in these patients. Aim of this study is to investigate objective improvements in effort tolerance and oxygen kinetics as assessed by cardiopulmonary exercise testing (CPET) in patients suffering from refractory angina undergoing CSR implantation.

Methods and Results. In this multicentre prospective study, patients with chronic refractory angina undergoing CSR implantation were scheduled for CPET before the index procedure and at 6-month follow-up. Main endpoints of this analysis were improvements in VO_2 max and in VO_2 at anaerobic threshold (AT). Clinical events and improvements in symptoms were also recorded. A total of 37 patients formed the study population. CSR implantation procedure was successful and without complications in all. At follow-up CPET significant improvement in VO_2 max (+0.97 ml/kg/min [+11.3%], 12.2±3.6 ml/kg/min at baseline vs 13.2±3.7 ml/kg/min, p=0.026), and workload (+12.9[+34%]; 68±28 W vs 81±49W, p=0.05) were observed, with *non-significant differences in* VO_2 at AT (9.84±3.4 ml/kg/min vs 10.74±3.05 ml/kg/min, p=0.06). Canadian Cardiovascular Society (CCS) grade improved from a mean of 3.2±0.5 to 1.6±0.8 (p<0.01), and significant benefits in all Seattle Angina Questionnaire variables were shown.

Conclusions. In patients with obstructive coronary artery disease suffering from refractory angina, the implantation of CSR was associated *with objective improvement in exercise capacity and oxygen kinetics at CPET, suggesting a possible reduction of myocardial ischemia.*

Key Words: Other technique; Prior CABG; Prior PCI; Stable angina

Condensed Abstract

The clinical benefits of the coronary sinus reducer (CSR) have so far been limited to angina relief. In this study we investigate the improvements in oxygen kinetics at cardiopulmonary exercise test (CPET) after CSR implantation in 37 patients with refractory angina. Six-months after CSR implantation, overall improvements at CPET were observed, including VO_2 max (+0.97 ml/kg/min[+11.3%], 12.2±3.6 ml/kg/min at baseline vs 13.2±3.7 ml/kg/min, p=0.026), VO_2 at AT (9.84±3.4 ml/kg/min vs 10.74±3.05 ml/kg/min, p=0.06) and workload (+12.9[+34%]; 68±28W vs 81±49W, p=0.05). The adoption of CSR in patients suffering from refractory angina results *in improved effort tolerance and potentially reduced myocardial ischemia.*

Abbreviation List

AT: anaerobic threshold

CRS: coronary sinus reducer

CPET: cardiopulmonary exercise test

LAD: left anterior descending

LCx: left circumflex

RCA: right coronary artery

Introduction

Available data from large registries suggests that the number of patients suffering from refractory angina is constantly increasing. It is estimated that 5-10% of patients with a history of ischaemic heart disease suffer from angina, refractory to medical and interventional therapies, and 30% of patients following revascularization suffer from persistent angina [1-4]. These patients present with recalcitrant angina symptoms despite optimal medical treatment, with lack of revascularization options. In addition, they are considered at higher risk for new hospitalizations and increased incidence of adverse cardiac events [1]. The coronary sinus Reducer (CSR) was recently introduced as a therapeutic option in patients with refractory angina who are not candidates for coronary revascularization. This hourglass balloon-expandable mesh is implanted in the coronary sinus (CS), creating, once completely covered by ingrowth of tissue, an iatrogenic narrowing with augmented backwards pressure. The narrowing forces re-distribution of coronary flow from the non-ischemic sub-epicardial areas to the ischemic sub-endocardial layers of the myocardium, thus relieving ischemia and angina symptoms [5]. Benefits in terms of angina relief and improvements in quality of life have been demonstrated in the majority of patients by the first randomized trial and from "real life" registries[6-7]. In addition, data showing improvement in objective evidence of myocardial ischemia - as shown by enhanced myocardial perfusion at cardiac MRI - , in diastolic function, as well as very long term follow up safety and efficacy data have been published. [8-14]

Nevertheless, more robust evidence of effect of the CSR on myocardial ischemia is required. Cardiopulmonary exercise test (CPET) detects myocardial ischemia with higher sensitivity than conventional ECG-stress test [15]. Indeed patients with exercise-induced silent or symptomatic ischemia have been found to have lower peak-VO_2 and oxygen pulse compared with non-ischemic controls, also in absence of ECG changes [15]. In addition, decreased VO_2 at anaerobic threshold (AT) has also been consistently shown to be related to the presence [15-19] and the extent [20] of myocardial ischemia. The aim of this study was to investigate objective improvement in effort tolerance and in oxygen kinetics parameters by CPET in patients with refractory angina treated with CSR implantation.

Methods

This is a prospective, 2-center, international registry conducted at Antwerp Cardiovascular Center, Ziekenhuis Netwerk Antwerpen (ZNA) Middelheim (Antwerp, Belgium) and Tel Aviv Medical Center, Tel Aviv University Medical School (Tel Aviv, Israel). All consecutive patients referred to the study centres for evaluation for CSR implantation were considered for cardiopulmonary exercise test before the procedure and scheduled for a follow-up CPET at 6 months when eligible. All patients had evidence of reversible myocardial ischemia at non-invasive imaging stress-tests, left ventricular ejection fraction of more than 25%, and no option for revascularization according to the local heart team decision. Indication for CSR implantation included age>18 years, obstructive coronary artery disease with chronic refractory angina, Canadian Cardiovascular Society (CCS) grade II to IV despite maximally tolerated antianginal medical therapy for at least 30 days before screening. Medical therapy included beta-blockers, calcium-channel blockers, nicorandil, ivabradine, and short-acting/long-acting nitrates used at maximum tolerated doses. Clinical outcome was established with variation in CCS score and in quality of life as assessed with the Seattle Angina Questionnaire (SAQ). By protocol, the same anti-angina medical treatment was maintained before CSR implantation and at follow-up, to avoid possible confounders in clinical/CPET benefits.

Device and implantation procedure

The Reducer's mechanism of action and implantation technique were described in details elsewhere[5]. In short, the Reducer is a stainless steel balloon-expandable mesh designed to establish narrowing of the CS. It's available in a single size, adaptable to the tapered anatomy of the CS by the balloon inflation pressure (diameter 3 mm in the mid portion, 7-13 mm at both ends). The procedure consists of selectively cannulating the CS from the right internal jugular vein, generally achieved with a diagnostic multi-purpose catheter. A dedicated 9-F guiding catheter is exchanged over a wire and used to deliver the Reducer. Implantation is performed by inflating the semi-compliant balloon in order to conform adequately to the CS anatomy. A final angiogram is always performed to confirm proper positioning of the device.

Dual antiplatelet therapy was maintained for 6 months after the implantation.

Cardiopulmonary Exercise Test

Cardiopulmonary exercise testing was carried out on an electromagnetic bicycle ergometer (Ergo-metrics 800S, Sensormedics, Yorba Linda, CA, USA), using a standardized protocol in the two study centres. Each patient was examined with the same protocol in the pre-implantation evaluation and at 6 month follow-up. Breath-by-breath minute ventilation (VE), carbon dioxide production (VCO_2), and oxygen consumption (VO_2) were measured using a Medical Graphics metabolic cart (ZAN, nSpire Health Inc, Germany). Peak-VO_2 was defined as the highest averaged 30-second VO_2 during exercise. Whenever possible, the test was conducted, by protocol, until patient's exhaustion.

The AT is calculated according to the modified V-slope method. The slope of the ventilation vs. volume of exhaled carbon dioxide (VCO_2) relationship (VE/ VCO_2 slope) was evaluated, excluding, when present, its final nonlinear portion due to acidotic ventilatory drive. Heart rate reserve was calculated as the difference between the predicted maximal heart rate, based on age, and the measured heart rate at peak VO_2. The O_2 pulse was determined by dividing the VO_2 by the simultaneously measured heart rate. Blood pressure was measured at rest and every two minutes during the exercise and recovery phases.

Statistical Analysis

Baseline and outcome data were analysed using descriptive statistics. Numerical values were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Categorical variables were expressed as percentages. Comparisons of measured outcomes were performed using the Fisher exact test to compare binary and categorical variables and paired student t-test for continuous variables. A two tailed probability value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPPS version 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

During the study period, a total of 94 patients underwent CSR implantation in the two study centres. Of these, 37 patients were eligible to participate and were included in the present study (13 in the centre of Antwerp and 24 in the centre of Tel Aviv). Most of the patients treated with CSR were referred to us from different hospitals, and this represented the major reason for not participating in the present study; other reasons consisted of incapability of performing the CPET and presence of a pacemaker.

Demographic baseline characteristics of the study population are shown in detail in Table 1. Briefly, the majority of patients were males, with a mean age of 68±9 years, history of previous CABG in more than 70% of cases. All suffered from chronic angina CCS class III (73%) or IV (24.3%), except one (2.6%) who was in CCS grade II (see Table 2). The implantation procedure was successful and uncomplicated in all patients.

Clinical Outcome

All patients presented at the scheduled 6-month follow-up visit. Improvement in angina symptoms was observed in 32 patients (86.5%), with a mean improvement in CCS grade at follow up of 1.6±0.8 (see Table 2 for complete details). As per protocol, only very limited differences in anti-anginal medications were recorded, with a mean of 1.9±1.1 drugs per patient at baseline vs 1.8±1.1 at follow-up (p=0.77; see Table 1 and 2 for additional information). In particular, the rate of use of beta-blockers was comparable at baseline and at follow-up. No adverse cardiovascular events were reported during the follow-up period. Baseline and follow-up Seattle Angina Questionnaires for assessment of quality of life were available for 31 patients (84%), and showed consistent and significant improvement in all variables of the questionnaire (all p<0.01, see Table 2 for further details).

Cardiopulmonary Exercise Test (CPET)

All patients performed the CPET with the same protocol at baseline and at 6-month follow-up. Full results of the CPETs are available in Table 3. Both at baseline and follow-up, the exercise was interrupted due to physical exhaustion in 64% of patients, while the onset of anginal symptoms was the reason for the test interruption in the remaining 36% *(p=NS)*. Significant ST-segment changes suggestive of ischemia were detected in 43% of baseline CPETs, while 28% were positive at the follow-up test (p=NS).

An overall better performance was observed at follow-up CPET, with significant improvements in terms of exercise workload (+12.9[+34%]; 68±28 W at baseline vs 81±49W at follow-up, p=0.05), VO_2 max (+0.97 ml/kg/min [+11.3%], 12.2±3.6 ml/kg/min at baseline vs 13.2±3.7 ml/kg/min at follow-up, p=0.026, see Figure1) and VCO_2 at AT (0.64±0.29 L/min at baseline vs 0.79±0.24 L/min at follow-up, p=0.04). Of note, improvements in VO_2 max and VO_2 at AT occurred in 78.4% of patients. An illustrative case of CPET performance at baseline and after CSR implantation is shown in Figure 2.

However, improvement in VO_2 at AT resulted non-significant (9.84±3.4 ml/kg/min vs 10.74±3.05 ml/kg/min, p=0.06). No significant changes were detected for the other parameters in the CPET, including respiratory exchange ratio (see Table 3 for further details).

CPET in patients without clinical benefits

A sub-analysis of the CPET outcomes was performed in the 4 patients who reported lack of CCS improvements at follow-up. Consistently with this, non-significant improvement was observed in VO_2 kinetics parameters at follow-up CPET. More specifically, VO_2 at AT improved from 9.22±1.99 to 11.2±2.75 ml/kg/min (p=0.07), VO_2 max from 11.3±3.11 to 13.22±3.73 ml/kg/min (p=0.11) and workload remained substantially stable (45±20 vs 46±22 W, p=0.93). All other parameters remained essentially unchanged. An additional sensitivity analysis was performed on responder-patients and presented in the Supplementary Table 1.

Discussion

This is the first report on a significant improvement of CPET parameters supporting objective reduction in myocardial ischemia after CRS implantation. Indeed, the increased effort tolerance (exercise workload +34.8% compared with baseline) and the higher VO_2-max (+11.3%), together with *a borderline non-significantly* higher VO_2 at anaerobic threshold, support overall improved oxygenation kinetics during maximal effort after CSR implantation. In addition, these benefits are accompanied by consistent improvement in symptoms as expressed by CCS and SAQ assessments. Of note, these results were registered in conditions of stable medical treatment before and after CSR implantation (in particular, with a very high percentage of patients consuming beta-blockers and calcium-channel blockers, which explain the sub-maximal HR observed, see Table 2).

Data on beneficial effects from the "trans-venous" treatment of myocardial ischemia by means of Reducer implantation have been investigated in previous studies. Indeed increases in SAQ parameters and improvements of CCS-class reported in our study are consistent with those of previously published experiences [6,7,10]. However, the mechanisms of its anti-ischemia effect remain at least in part unknown. In a physiological study by Ido et al, the authors described a significant increase in regional myocardial blood flow toward more ischemic sub-endocardial areas following intermittent occlusion of the CS [22]. *Additional insights supporting reduction in ischemia after CSR have been provided in the unique investigation by Giannini et al. According to their results, in fact, CSR implantation resulted in improved myocardial perfusion in all LV layers as investigated with cardiac-MRI*[8]. *Consistently with those findings, w*e hypothesize that the observed re-distribution in flow to the ischemic myocardium is linked not only to a better perfusion of ischemic sub-endocardial area, but also to an overall improved myocardial performance during exercise [23-24]. *This is confirmed by the improvements in VO2 max and VO2 at AT observed during CPET after CSR implantation. VO2 at AT, in particular, is less influenced by patients' motivation and performance, and may suggest an overall improved condition independently from the maximal exercise reached during a single effort.* Ongoing investigations with cardiac MRI after CSR implantation from our group will be able to further explore the nature and mechanisms of these reported benefits.

Furthermore, the improvements we describe here are in line with those historically shown in patients with stable angina undergoing percutaneous revascularization. In their original investigation, Adachi and colleagues observed the variation in performance at CPET in a population of relatively young patients (average age 55 years) undergoing, mostly, simple single-vessel PCI[25]. They reported an increase in VO_2-max of nearly 14% (from 23.1±3.5 to 26.5±3.2 mL/min/kg), which is similar to the 11.3% observed with the CSR. Of note, the population enrolled in the present study comprises complex patients suffering from refractory angina, of older age (68±9 years old), with common history of previous multiple myocardial revascularization procedures (including CABG in almost 75% of cases) and presence of symptoms despite maximized anti-ischemic medical therapy in absence of other therapeutic options. For this reason, the increments reported here represent a valuable improvement and have to be considered in the context of a relatively complex pool of patients with advanced coronary artery disease.

Our findings may suggest potentially relevant prognostic implications. In fact, a significant body of evidence has linked the performance at CPET with clinical outcome in patients with chronic heart failure [26-29]. In a recent article, specific cut-offs of VO_2-max have been identified to predict worse clinical outcome (including cardiac death), which varied during the last decades, but constantly showed that a reduction in absolute VO_2-max is associated with lower survival [30]. The effects of physical training on CPET performance were investigated in a study from Hambrecht et al [31], where 22 patients with HF and impaired LV function (mean EF 26±9%) were randomized to 6 months of training program versus physical inactivity. At 6 months, patients undergoing physical training showed significant improvements in peak-VO_2 (+ 31%, $p<0.01$ vs. control group) and VO_2 at AT (+23%, $p<0.01$ vs. control group). Moreover, in the HF-ACTION trial, a dedicated rehabilitation program was applied to heart failure patients, showing consistent improvement in VO2. Of interest, the exercise-training induced increases in peak-VO_2 were closely correlated with a better prognosis. For every 6% increase in peak VO_2 (+0.9 ml/kg/min) there was an associated 5% lower risk of the primary endpoint (time to all-cause mortality or all-cause hospitalization, $p<0.001$) and an associated 8% lower risk of combined cardiovascular mortality and CHF hospitalizations ($p<0.001$)[32]. Thus, even a small increase in VO_2 max as observed with CPET may translate to clinically significant improvement.

Finally, recent evidence supports possible benefits in diastolic function after CSR implantation [14]. Diastolic dysfunction has been linked to reduced VO_2 max, which appeared negatively impacted by increased LV-end diastolic filling pressures [33].

Our observations (in particular the average absolute +34.8% increased workload capacity and +0.97 ml/kg/min[+11.3%] in VO_2 max) suggest that a significant proportion of patients undergoing CSR implantation experience also relevant improvement in their general clinical condition, with higher effort-tolerance and a more physiological oxygen kinetics. Possible reduction in the incidence of adverse cardiac events may therefore be expected, even though they remain, at least at present, only speculative. Dedicated trials – with larger sample sizing and a control group– are needed to further confirm these hypotheses.

Limitations

The present study has some limitations that need to be acknowledged. First of all, this is not a randomized trial, and no control group was available to support the described outcomes and avoid any possible bias in the analysis. *Consistently, no independent and centralized laboratory was commissioned to analyse the CPET data*. Another limitation is the relatively small number of patients included in the analysis. A larger cohort of subjects enrolled would probably offer additional analysis, and, in our view, potentially confirm those increments with borderline statistical significance (such as the improvements in VO_2 at AT). In addition, insights on the interaction between anti-ischemic agents (such as beta-blockers) and CPET outcomes would merit deeper investigation, provided a sufficient sample size. In addition, relative new parameters of oxygen kinetics were not available in our analysis [34-35]. Finally, despite no specific instruction for any physical rehabilitation program was given after CSR implantation, the potential impact of any autonomous physical activity performed by the enrolled subjects on the CPET outcome cannot be excluded.

Conclusions

The application of the Coronary Sinus Reducer in patients with refractory angina is associated with significant clinical benefits and with objective improvements in VO_2 kinetics and efforts tolerance, as assessed by

cardiopulmonary exercise testing. Further dedicated studies are needed to confirm our findings and to assess their impact on long-term clinical outcome.

Impact on clinical practice

Coronary sinus reducer (CSR) implantation represents an emerging treatment option to reduce symptoms in patients with refractory angina. This the first description of improved effort tolerance and oxygen kinetics after CSR implantation as assessed with cardiopulmonary exercise test. *CSR implantation should be considered in the clinical practice not only to improve quality of life of patients with refractory symptoms, but also with the potential to reduce ischemic burden and improve clinical conditions.*

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Conflict of interest: P. Agostoni and S. Verheye are consultants for Neovasc Inc.; S. Banai is medical director of Neovasc Inc. The other authors have no relevant conflicts of interest to disclose.

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Figure Legends

Figure 1 (Central illustration). Distribution and improvements of VO_2 max (panel A) and VO_2 at AT (panel B) in the study population, before and after CSR implantation. Red lines indicate patients with lower values of VO_2 max or VO_2 at AT at follow-up if compared with baseline values, while black lines show the improvements in these parameters.

Figure 2. Illustrative case of CPET before CSR implantation (left panel) with reduced effort tolerance (280 seconds, 52 W), limited VO_2-max (14.6 ml/kg/min) and evident change in VO_2 slope after the anaerobic threshold, with stable increase in VCO_2. This is typical of cardiac-limited CPET, where VO_2 increases with a stable $\Delta VO_2/\Delta WR$ slope until the myocardium reaches its ischemic threshold. Then, the $\Delta VO_2/\Delta WR$ slope abruptly decreases while the $\Delta VCO_2/\Delta WR$ slope continues to rise relatively steeply (see left panel).

Results from CPET after CSR in the same patient (right panel), with slightly higher effort tolerance (342 seconds, 75 W), higher VO_2 max (18.1 ml/kg/min) and more physiologic change in VO_2 slope. Consistent improvements in CCS were observed (from CCS IV to CCS I).

Table 1. Demographic baseline characteristics of the study population.

	Total Population (n=37)
Age	68±9
Male gender	27(71.1%)
BMI	26.1±4.3
Hypertension	31(81.6%)
Diabetes	23(60.5%)
Current or Previous Smoking	20(52.6%)
Hypercholesterolemia	34(89.5%)
Previous PCI	10(26.3%)
Previous MI	20(52.6%)
Previous CABG	28(73.7%)
Previous Stroke	4(10.5%)
Peripheral Vascular Disease	9(23.7%)
Left Ventricular Ejection Fraction	55±11

BMI: body mass index; CABG: coronary artery bypass graft; MI: myocardial infarction; PCI: percutaneous coronary interventions;

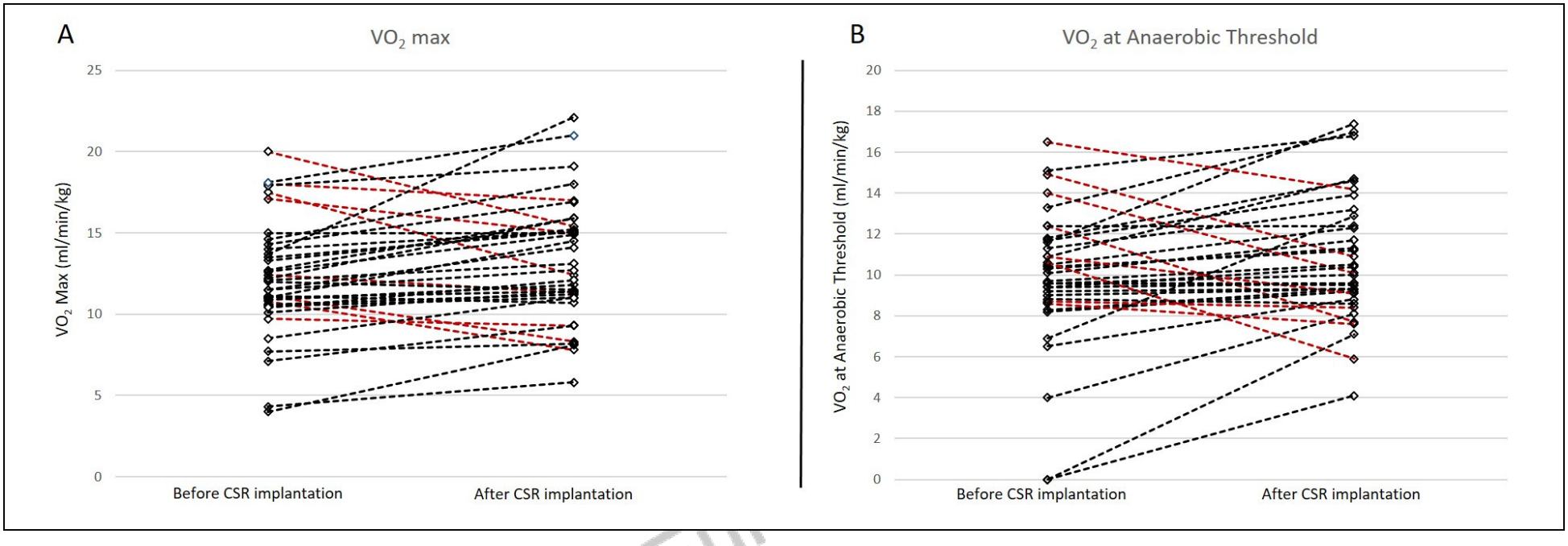
Table 2. Clinical characteristics after CSR implantation in the study population.

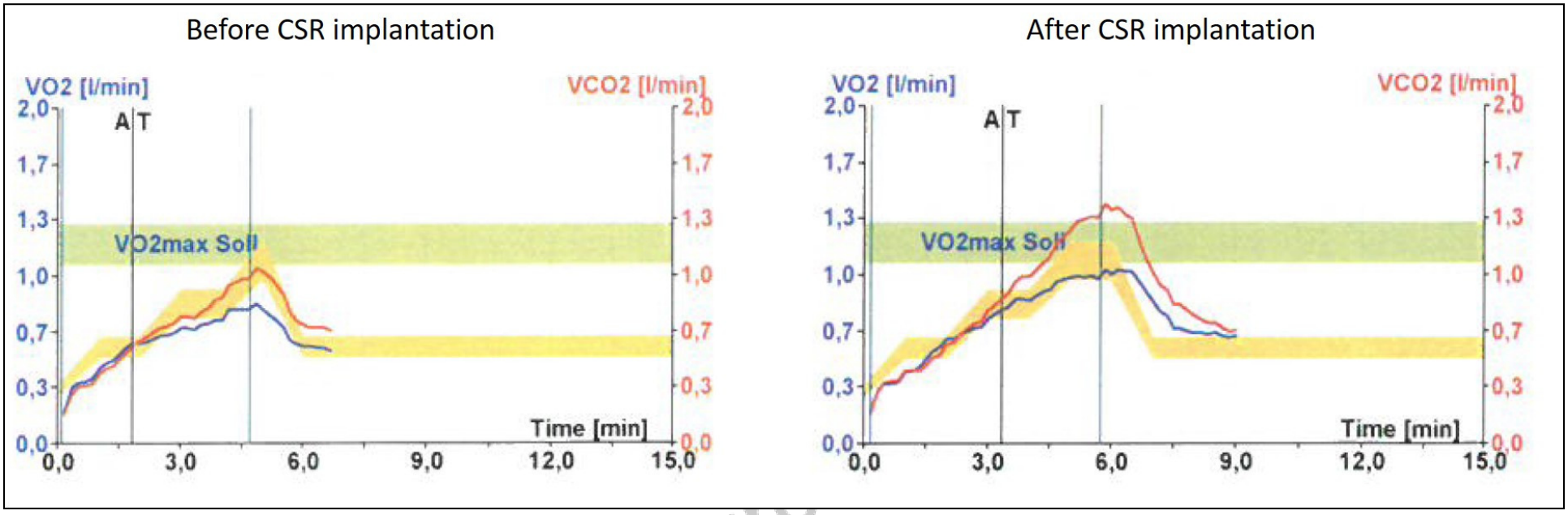
	Baseline (n=37)	Follow-up (n=37)	p Value
Canadian Cardiovascular Society class	3.2±0.48	1.6±0.8	<0.01
I	-	20(54.1%)	
II	1(2.6%)	10(27%)	
III	27(73%)	7(18.9%)	
IV	9(24.3%)	-	
Seattle Angina Questionnaire			
Physical Limitation	44.39±21.78	63.66±21.53	<0.01
Angina Stability	30.11±25.75	58.75±36.57	<0.01
Angina Frequency	42.15±30.06	69.65±29.02	<0.01
Treatment Satisfaction	54.65±26.08	79.74±21.21	<0.01
Quality of Life	26.52±17.37	52.43±23.64	<0.01
Anti-anginal medication			
Beta-blockers	24 (64.9%)	26 (70.3%)	
Calcium Channels Blockers	17 (45.9%)	16 (43.2%)	
Nitrates	26 (70.3%)	25 (67.6%)	
Ivabradine	4(10.8%)	3 (8.1%)	
Ranolazine	-	-	
Number of Anti-anginal medications	1.9±1.1	1.8±1.1	0.77
0	2 (5.4%)	1(2.7%)	
1	11 (29.7%)	14 (37.8%)	
2	13 (35.1%)	11 (29.7%)	
3	10 (27%)	10 (27%)	
>3	1(2.7%)	1(2.7%)	

Table 3. Cardiopulmonary exercise test results in the study population.

	pre - CSR	post - CSR	p-Value
Work Load (W)	68±28	81±49	0.05
Exercise Time (s)	309±84	335±101	0.26
VO_2 at AT (L/min)	0.78±0.31	0.83±0.23	0.16
VO_2 at AT (ml/kg/min)	9.84±3.4	10.74±3.05	0.06
VO_2 max (L/min)	0.96±0.32	1.02±0.28	0.09
VO_2 max (ml/kg/min)	12.2±3.6	13.2±3.7	0.026
VCO_2 at AT (L/min)	0.64±0.29	0.79±0.24	0.04
VCO_2 at AT (ml/kg/min)	8.95±3.99	11.04±3.2	0.05
VCO_2 max (L/min)	1.06±0.37	1.1±0.37	0.56
VCO_2 max (ml/kg/min)	13.51±4.41	14.60±4.97	0.07
Respiratory Exchange ratio	1.08±0.13	1.09±0.13	0.57
HR at max effort (bpm)	101±21	106±21	0.16
HR at AT (bpm)	98±16	90±17	0.13
Heart Rate Reserve	50±23	45±22	0.16
O_2 pulse (ml/beat)	9.8±4.5	9.7±3	0.86
O_2 pulse at AT (ml/beat)	7.31±2	8.4±2.1	0.02
Workload at AT	47±18	61±16	0.03
VE/VCO_2 slope	29.6±9.8	32.1±7.5	0.09

Data are expressed as Mean±SD, T-student test applied. AT: anaerobic threshold; CSR: Coronary Sinus Reducer;





Supplementary Table 1.

Sensitivity Analysis of responder patients

A sensitivity analysis was conducted to further explore the characteristics and outcome of patients responding to Coronary Sinus Reducer (CSR) implantation with clinical improvement.

Out of the 37 patients forming the study population, improvements in angina symptoms were observed in in 32 patients (86.5%), with a mean improvement in CCS grade at follow up of 1.6±0.8. All patients with at least 1 point of improvement in CCS class were included in the present analysis. Results at CPET of this sub-population are shown in the following table. On average, slightly higher improvements are observed in terms of effort tolerance and higher parameters of VO_2 kinetics. However significant differences are limited to the maximal Work Load tolerated, while borderline p-values are observed for VO_2 max. Many limitations need to be acknowledged, starting from the small number of patients enrolled in the main analysis (that makes a sub-group investigation even weaker). In addition, despite all these patients were clinical responders (defined as CCS improvement ≥1), this parameter remains relatively subjective and may not necessarily indicate the only patients where benefits at level of myocardial perfusion occurred. For these reasons, we cannot entirely consider this small group of patients as the only beneficiary of CSR implantation.

	pre - CSR	post - CSR	p-Value
Work Load (W)	71±28	85±49	0.05
Exercise Time (s)	316±100	343±95	0.36
VO_2 at AT (L/min)	0.80±0.32	0.84±0.23	0.27
VO_2 at AT (ml/kg/min)	9.91±3.6	10.7±3.1	0.14
VO_2 max (L/min)	0.99±0.33	1.05±0.28	0.13
VO_2 max (ml/kg/min)	12.3±3.6	13.2±3.8	0.07
VCO_2 at AT (L/min)	0.66±0.32	0.81±0.25	0.11
VCO_2 at AT (ml/kg/min)	9.01±4.2	10.8±3.1	0.15
VCO_2 max (L/min)	1.09±0.38	1.1±0.38	0.83
VCO_2 max (ml/kg/min)	13.6±4.45	14.4±4.85	0.25
Respiratory Exchange ratio	1.08±0.14	1.08±0.12	0.96
HR at max effort (bpm)	101±21	105±21	0.28
HR at AT (bpm)	97±13	91±16	0.19
Heart Rate Reserve	49.9±22.9	45.9±21.9	0.28
O_2 pulse (ml/beat)	10.2±4.6	10±3.1	0.86
O_2 pulse at AT (ml/beat)	7.55±2.23	8.55±2.36	0.08
Workload at AT	52±17	66±13	0.07
VE/VCO_2 slope	29.6±10.2	32.2±7.8	0.11

Data are expressed as Mean±SD, T-student test applied. AT: anaerobic threshold; CSR: Coronary Sinus Reducer;