Chapter 20

Effect of cardiac resynchronization therapy on cerebral blood flow

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ABSTRACT

Background: Decreased cerebral blood flow is frequently observed in patients with heart failure and this may be the result of impaired cardiac systolic function. Cardiac resynchronization therapy (CRT) improves cardiac function and heart failure symptoms in selected patients. The effects of CRT on cerebral blood flow have not been evaluated before.

Methods: In this study, left ventricular (LV) systolic function and cerebral blood flow were assessed in 35 heart failure patients, before and 6 months after CRT. Additionally, 15 heart failure patients, not being candidates for CRT were included as a control group. Peak-systolic velocity (PSV), end-diastolic velocity (EDV), mean velocity and pulsatility index (PI = [PSV-EDV] / mean velocity) were obtained with the use of transcranial Doppler (TCD) from the right middle cerebral artery from the temporal window in all subjects. Response to CRT was defined as a reduction in LV end-systolic volume (LVESV) ≥15%.

Results: At 6 months follow-up, PSV significantly increased from 83±20 cm/s to 100±20 cm/s ($p = 0.001$), EDV increased from 29±7 cm/s to 37±8 cm/s ($p<0.001$) and mean velocity increased from 47±10 cm/s to 58±11 cm/s ($p<0.001$), only in responders to CRT. Conversely, no significant changes in cerebral blood flow were observed in non-responders and controls.

Conclusions: CRT induces an increase in cerebral blood flow in heart failure patients. This increase in cerebral blood flow is related to the improvement in LV systolic function.

INTRODUCTION

Transcranial Doppler (TCD) has been validated as a reliable non-invasive technique to measure cerebral blood flow and is widely used.[1-4] In the current study, cerebral blood flow was measured with TCD in heart failure patients before cardiac resynchronization therapy (CRT) implantation and at 6 months follow-up. The aim of the study was to evaluate whether cerebral blood flow is altered after CRT, and whether changes in cerebral blood flow are related to improvement in cardiac systolic function after CRT.

METHODS

Study population and protocol

Thirty-five patients scheduled for CRT were evaluated in this study. The study was approved by the local ethics committee and written informed consent was obtained in all patients. The selection criteria for CRT included advanced symptoms of heart failure (New York Heart Association [NYHA] functional class III or IV), left ventricular ejection fraction (LVEF) <35%, sinus rhythm and a wide QRS complex (>120 ms).[5] Patients with recent myocardial infarction (<3 months), decompensated heart failure, history of ischemic stroke/transient ischemic attack or known carotid stenosis were not included. Etiology of heart failure was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in 1 or more of the major epicardial coronary arteries) and/or a history of myocardial infarction or prior revascularization.

Before CRT device implantation, clinical status including NYHA class, 6-minute walking distance and Minnesota Living with Heart Failure Questionnaire (MLHFQ] score was assessed. Cognitive function was specifically evaluated with the psychometric sub-score of the MLHFQ (MLHFQ-PS). This psychometric properties sub-score has recently been validated against the more extensive Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).[6, 7]

In addition, left ventricular (LV) volumes and LVEF were measured using real-time three-dimensional echocardiography (RT3DE). Cerebral blood flow was evaluated with the use of TCD. At 6 months follow-up, the abovementioned measurements were repeated to assess the effect of CRT on cerebral blood flow, cognitive function and LV performance. Patients with a reduction ≥15% of LV end-systolic volume (LVESV), reflecting improvement in LV systolic function, were considered responders to CRT.[8, 9]

Finally, 15 heart failure patients matched for age, gender, NYHA class and LV function, not being candidates for CRT according to current guidelines (QRS duration <120 ms), were included as a control group. These patients underwent the same clinical, echocardiographic

and transcranial Doppler assessment as the CRT recipients. All patients were on stable heart failure medication and medical therapy was unchanged during the study.

Echocardiography and Transcranial Doppler assessment

Complete echocardiographic methods have been described previously.[10] In brief, patients were imaged in the left lateral decubitus position with a commercially available system (iE33, Philips Medical Systems, N.A., Bothell, Washington, USA) equipped with a X3, fully sampled matrix transducer. RT3DE data sets were stored digitally and quantitative analysis of the 3D dataset was performed off-line using a semi-automated contour tracing algorithm (Q-Lab, version 6.0, Philips Medical Systems) over a complete heart cycle.

LV systolic performance was quantified by measuring the LV outflow-tract velocity-time integral (LVOT VTI) using pulsed-wave Doppler, during end-expiratory apnea.

Transcranial Doppler images were acquired after the patient was in supine position for a minimum of 10 minutes, with the same system used for the echocardiographic examinations (iE33, Philips Medical Systems, N.A., Bothell, Washington, USA), equipped with a broadband pure wave S5-1 transducer. All TCD measurements were taken from the right middle cerebral artery from the temporal window. Blood flow velocities were measured by placing a sample volume of 2.5 mm in the bloodstream at a depth (range 40 – 65 mm) giving the highest values. The software (HighQ) automatically calculated peak-systolic velocity (PSV), end-diastolic velocity (EDV), mean velocity and pulsatility index (PI = [PSV-EDV] / mean velocity) using automatic trace of the Doppler spectrum. For each patient, blood flow velocities were obtained from a minimum of 10 cardiac cycles.

Statistical analysis

Continuous data are presented as mean±SD, and dichotomous data are presented as numbers and percentages. Comparison of continuous data between 2 groups was performed using the Mann-Whitney U-test. For comparison between more than 2 groups, the Kruskal-Wallis test with manual Bonferroni post-hoc testing was performed. Fisher's exact tests or χ^2 tests were used to compare dichotomous data. Comparison of continuous data within patient groups (at baseline and 6 months follow-up) was performed with the Wilcoxon test. Additionally, linear regression analysis was performed to evaluate the relation between reduction in LVESV and increase in mean TCD velocity. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study population

Adequate visualization of the middle cerebral artery was not feasible in 3 patients in the CRT group and in 1 control patient. These patients were excluded from further analysis and therefore the final study population consisted of 32 CRT recipients and 14 control patients. Baseline characteristics of the study population are summarized in Table 1. By definition, CRT patients and controls were comparable in terms of age, gender, NYHA class and LV function. Control patients had a significantly shorter QRS duration (110±8 ms vs. 152±25 ms, p<0.001). No differences in baseline TCD measurements (depth, number of samples, PSV, EDV, mean velocity and PI) were observed between CRT patients and controls.

Table 1. Baseline characteristics of the study population (n = 46)

Variable	Patients (n = 32)	Controls (n = 14)	p-value
Men / Women	25 / 7	11 / 3	0.648
Age (years)	68 ± 10	66 ± 10	0.583
Etiology of heart failure			
Ischemic	16 (50%)	10 (71%)	0.153
Non-ischemic	16 (50%)	4 (29%)	
QRS duration (ms)	152 ± 25	110 ± 8	**<0.001**
Systolic blood pressure (mmHg)	123 ± 15	121 ± 12	0.696
Diastolic blood pressure (mmHg)	71 ± 10	73 ± 7	0.349
NYHA class	3.0 ± 0	2.9 ± 0.3	0.132
Medication			
ACE-inhibitors/AII-blockers	30 (94%)	13 (93%)	1.000
B-blockers	24 (75%)	13 (93%)	0.240
Diuretics	29 (91%)	10 (71%)	0.176
Spironolactone	20 (63%)	6 (43%)	0.333
Echocardiography			
Heart rate	70 ± 17	68 ± 13	0.558
LV end-diastolic volume (ml)	189 ± 68	158 ± 32	0.272
LV end-systolic volume (ml)	137 ± 55	109 ± 24	0.073
LV ejection fraction (%)	29 ± 6	32 ± 4	0.101
LV outflow-tract VTI (cm)	13 ± 4	14 ± 3	0.510

ACE = angiotensin converting enzyme; LV = left ventricular; NYHA = New York Heart Association; VTI = velocity time integral

Clinical and echocardiographic changes at 6 months follow-up

At 6 months follow-up, mean NYHA class improved in the CRT group from 3.0±0 to 2.3±0.7 (p<0.001). In addition, MLHFQ score decreased from 32±16 to 24±20 (p = 0.010) and MLHFQ-SP decreased from 7.1±5.3 to 4.8±5.1 (p = 0.031), while 6-minute walking distance increased

from 333±89 m to 374±114 m (p = 0.024). Furthermore, a significant LV reverse remodeling was observed with a decrease in LVESV from 137±55 ml to 120±50 ml (p = 0.001) and an improvement in LVEF from 29±6% to 35±8% (p<0.0001). Finally, there was a significant increase in LVOT-VTI from 13±4 cm to 14±4 cm (p = 0.027).

In contrast, control patients did not show any change in echocardiographic parameters (LVESV from 109±24 ml to 111±25 ml [p = 0.314], LVEF from 32±4% to 32±3% [p = 0.810] and LVOT-VTI from 14±3 cm to 15±2 cm [p = 0.180]).

CRT responders vs. non-responders

At 6 months follow-up, 16 patients (50%) demonstrated response to CRT. There were no differences in baseline clinical characteristics between responders and non-responders, except for non ischemic etiology of heart failure, which was more frequently observed in responders. Baseline echocardiographic characteristics were comparable between the 2 groups (Table 2). Only responders showed a significant decrease in both the MLHFQ (from 31±12 to 16±12, p = 0.005) and the MLHFQ-PS (from 6.8±4.4 to 3.6±3.3, p = 0.043) reflecting an improvement in quality of life and cognitive functions.

At follow-up, responders demonstrated not only a significant reduction in LVESV (by definition) when compared to non-responders, but also a significant increase in LVEF and LVOT VTI, indicating improvement in cardiac performance (Table 2).

Insonation depth and number of samples acquired for TCD assessment were comparable between baseline and follow-up in responders, non-responders and controls. At follow-up, peak-systolic velocity significantly increased in responders from 83±20 cm/s to 100±20 cm/s (p = 0.001). Similarly, EDV increased from 29±7 cm/s to 37±8 cm/s and mean velocity increased from 47±10 cm/s to 58±11 cm/s (both p<0.001, Figure 1). The mean value of PI showed no significant change from baseline to follow-up.

Conversely, in non-responders and controls, no significant changes in any of the TCD velocities were observed (Figure 1). An example of a CRT patient that demonstrated a marked improvement in cerebral blood flow is shown in Figure 2. Linear regression analysis revealed a strong correlation (r = 0.78, p<0.001) between reduction in LVESV and increase in mean TCD velocity, demonstrating that improvement in cardiac function resulted in a significant increase in cerebral blood flow (Figure 3).

Table 2. Clinical and echocardiographic characteristics of responders and non-responders (n = 32)

Variable	Responders n = 16)	Non-responders n = 16)	p-value
Men / Women	12 / 4	13 / 3	1.000
Age (years)	67 ± 10	69 ± 10	0.317
Etiology of heart failure			
Ischemic	12 (75%)	4 (25%)	**0.012**
Non-ischemic	4 (24%)	12 (75%)	
QRS duration (ms)	159 ± 25	145 ± 24	0.105
NYHA class	3.0 ± 0	3.0 ± 0	1.000
MLHFQ			
baseline	31 ± 12	35 ± 20	0.755
follow-up	16 ± 12*	32 ± 24	0.088
MLHFQ-PS			
baseline	6.8 ± 4.4	7.4 ± 6.2	0.909
follow-up	3.6 ± 3.3*	6.1 ± 6.3	0.413
Echocardiography			
LV end-diastolic volume (ml)			
baseline	188 ± 67	190 ± 70	0.836
follow-up	186 ± 74	180 ± 59	0.880
LV end-systolic volume (ml)			
baseline	148 ± 65	126 ± 43	0.429
follow-up	114 ± 55‡	127 ± 46	0.214
LV ejection fraction (%)			
baseline	28 ± 8	30 ± 4	0.557
follow-up	40 ± 8‡	30 ± 4	**<0.001**
LV outflow-tract VTI (cm)			
baseline	12 ± 3	14 ± 4	0.187
follow-up	14 ± 4†	14 ± 4	0.598

MLHFQ = Minnesota Living with Heart Failure Questionnaire; MLHFQ-PS = Minnesota Living with Heart Failure Questionnaire - Psychometric Sub-score. Rest of abbreviations as in Table 2

* $p<0.05$, baseline vs. follow-up, † $p = 0.001$, baseline vs. follow-up, ‡ $p<0.0001$, baseline vs. follow-up

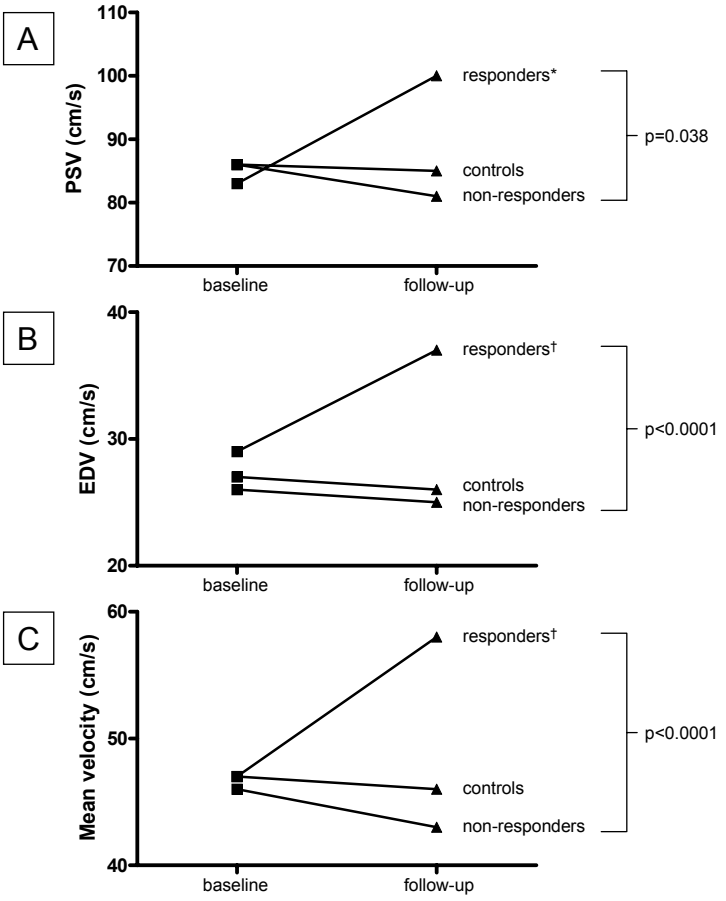

Figure 1. Changes from baseline to follow-up in cerebral blood flow; responders, non-responders and controls.
A significant increase in peak systolic velocity (PSV, panel A), end-diastolic velocity (EDV, panel B) and mean velocity (panel C) was observed in responders, while no changes were observed in both non-responders and control patients. Provided p-values are from the Kruskal-Wallis test for comparison of follow-up data between the 3 groups.
*$p = 0.027$, responders vs. non-responders.
†$p<0.01$, responders vs. non-responders and controls.

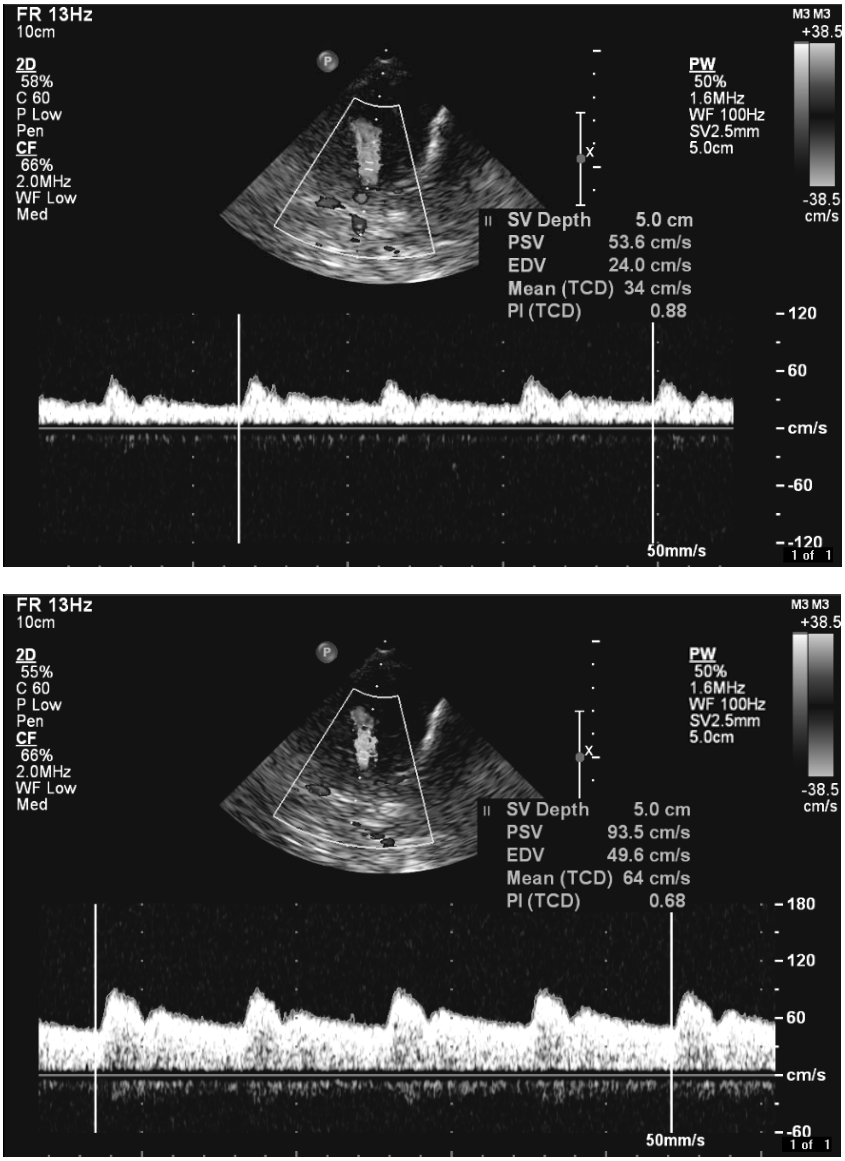

Figure 2. Example of improvement in cerebral blood flow after 6 months CRT.

(Upper panel) Before CRT, velocities are low and a dicrotic waveform can be seen. (Lower panel) After 6 moths CRT, the dicrotic waveform is still present, but velocities have increased significantly, indicating increase in cerebral blood flow.

EDV = end-diastolic velocity; PI = pulsatility index; PSV = peak-systolic velocity; SV = sample volume; TCD = transcranial Doppler.

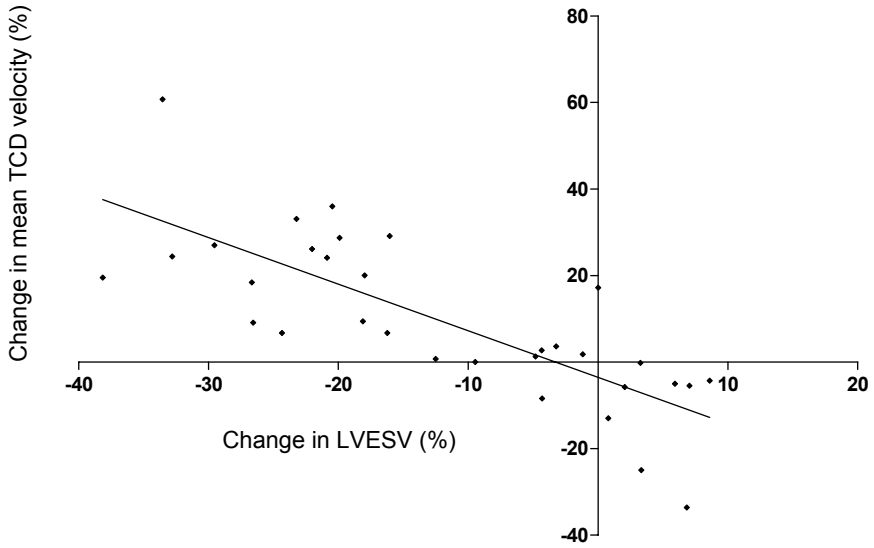

Figure 3. Relation between change in LVESV and chance in mean TCD velocity (y = -3.3 – 1.1x, n = 32, r = 0.78, p<0.0001).
LVESV = left ventricular end-systolic volume; TCD = transcranial Doppler.

DISCUSSION

The findings of the present study can be summarized as follows: 1) cardiac resynchronization therapy improves cerebral blood flow in patients with heart failure; and 2) this improvement in cerebral blood flow is related to the improvement in LV systolic function following CRT.

Cerebral blood flow is decreased in symptomatic heart failure patients and this may contribute to the impaired cognitive performance frequently observed in these patients.[11-13] Choi et al reported significantly lower values for cerebral blood flow in 52 patients with heart failure secondary to idiopathic dilated cardiomyopathy, in comparison to 10 healthy controls.[13] Additionally, Vogels and co-workers noted reduced cerebral blood flow in 43 heart failure patients in comparison to 33 patients with a history of ischemic cardiac disease without symptoms of heart failure and an LVEF >55%, and 22 healthy controls.[12] Cardiac resynchronization therapy improves heart failure symptoms, quality of life, LV systolic function, and prognosis in patients with moderate or severe heart failure.[14-16] More recent studies have also linked the improvement in LV systolic function to systemic improvements.[17, 18] The first study to show an association between CRT and improvement in cognitive function was reported by Conti and co-workers.[19] The authors found significant improvements in quantitative neurocognitive measures of attention and information processing at 3 months follow-up in 10 heart failure patients treated with CRT (Digit Span increased from 50±5 to 57±7, p = 0.04 and Symbol Digit from 39±9 to 49±15, p = 0.04). Although, the precise mechanism underly-

ing this improvement is not clear, it could be related to increase in cerebral blood flow as result of the increased cardiac systolic function.

An increase in cerebral blood flow has been previously reported in patients undergoing heart transplantation.[2, 20] Gruhn et al studied 12 healthy controls and 12 patients with severe heart failure (NYHA class III-IV) of whom 5 underwent cardiac transplantation.[20] In the patients who underwent transplantation, cerebral blood flow normalized to the level of the controls at 1 month follow-up. Similar findings were described by Massaro and co-workers in a series of 14 patients who underwent cardiac transplantation.[2] The currently observed improvement of 23.4% in mean cerebral blood flow is a significant improvement, which may translate into a substantial clinical benefit in these patients.[21] The MLHFQ and the MLHFQ-PS scores reduced significantly only in patients that showed response to CRT, probably related to the significant increase in cerebral blood flow observed in these patients. The last observation further strengthens the assumption that in patients with heart failure, increase in cerebral blood flow is the key mechanism in improvement in cognitive function.

A limitation of this study is the single-centre, non randomized, observational design. To counterbalance the absence of randomization, a control group with similar baseline characteristics, but without an indication for CRT (since these control patients did not have a wide QRS complex) was included. Still, a multi-centre, randomized trial should be performed to confirm the current findings. Second, the study sample was relatively small, and finally, no other neurological tests were performed besides the MLHFQ-PS. Therefore, a direct relation between improvement in cerebral blood flow and improvement in cognitive function could not be shown.

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