Septal flash as a predictor of cardiac resynchronization therapy response: A systematic review and meta-analysis

Running title: Septal flash and CRT response

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Abstract

Background: Cardiac resynchronization therapy (CRT) in heart failure patients has been shown to improve patient outcomes in some but not all patients. A few studies have identified that septal flash on imaging is associated with response to CRT but there has yet to be systematic review to evaluate consistency of the finding across the literature.

Methods: A search of MEDLINE and EMBASE was conducted to identify studies which evaluate septal flash and its association with CRT response. Studies that met the inclusion criteria were statistically pooled with random-effects meta-analysis and heterogeneity was assessed using the I^2 statistic.

Results: A total of nine studies were included with 2,307 participants (mean age 76 years, 67% male). Septal flash on imaging before CRT implantation was seen in 53% of patients and the proportion of CRT responders from the included studies varied from 52% to 77%. In patients who were CRT responders, septal flash was seen in 40% of patients compared to 10% in those deemed to be CRT non-responders. Meta-analysis of the eight studies suggests that the presence of septal flash at pre-implant was associated with an increased likelihood of CRT response (RR 2.55 95%CI 2.04-3.19, $p<0.001$, $I^2=51\%$). Septal flash was also reported to be associated with left ventricular reverse remodeling but the association with survival and symptomatic improvement was less clear.

Conclusions: Septal flash is a well-defined and distinctive contraction pattern which is consistently associated with CRT response and should be evaluated when assessing for appropriateness of CRT device.

Introduction

Heart failure (HF) affects approximately 1-2% of the adult population, rising to over 10% in those aged 70 years and above.[1] Despite significant advances in drugs and therapeutics used to treat heart failure, it continues to be associated with poor quality of life,[2] and patient outcomes.[3] In patients with heart failure and cardiac dyssynchrony, cardiac resynchronization therapy (CRT) is designed to restore synchronous electromechanical contraction, resulting in improved cardiac output and favorable LV remodeling. Data from large scale randomized studies has consistently demonstrated that, in patients with a broad left bundle branch block (LBBB) conduction patterns and severe left ventricular systolic dysfunction, CRT improves hard outcomes, including mortality and heart failure hospitalization. Furthermore, it is associated with improved exercise capacity, symptoms and quality of life.[4] However, it is also recognized that some patients fail to respond to CRT (non-responders) whilst others exhibit negative-response to CRT.[5] The *a priori* identification of patients who are likely to be responders, would enable superior patient selection criteria for patients potentially being considered for CRT implantation. However, to date, this remains an area of primary research. It has been proposed that assessment of ventricular/mechanical dyssynchrony prior to CRT could improve patient selection and identify those likely to respond to CRT irrespective of LVEF or QRS duration.[6,7,8]

Septal flash, as first described by Dillion et al in 1974,[9] is a sign of intra-ventricular dyssynchrony, easily recognizable on cardiac imaging including echocardiography and cardiac magnetic resonance (CMR) imaging. It is defined as an abnormal and rapid leftward motion of the interventricular septum during the isovolumetric phrase of ventricular contraction. It relies on pattern recognition; it does not require additional measurements and is easily incorporated in a pre-implant report. Septal flash has become an increasingly investigating parameter as a potential predictor of CRT response with various studies identifying the presence of septal flash prior to CRT implantation is able to predictor CRT response with the presence of septal flash being able to predict both reverse left ventricular remodelling,[10] benefits in symptomatic status[11] and improved survival rates.[12] Unlike many other echocardiographic parameters used, with variable success, it is a simple observation which does not require additional analysis time, but does requires pattern recognition

To the best of our knowledge there has been no previous systematic review to determine if the association between septal flash and CRT response is consistent across the literature and the strength of the association. Therefore, we conducted a systematic review and meta-analysis of septal flash and response after CRT implantation.

Methods

This systematic review and meta-analysis was conducted in accordance to the PRISMA guidelines.

Eligibility criteria

We selected studies that evaluated septal flash and the response rate to CRT. There were no restrictions on how septal flash was quantified and imaging modalities included 2D and 3D echocardiography and/or CMR imaging. There was no restriction based on study design, cohort type or language of the report but original data had to be presented. We excluded studies identified as conference abstracts, editorials, articles without original data such as reviews, case studies/case series and animal studies.

Search strategy

We searched MEDLINE and EMBASE using OVID with no date or language restriction on 26th October 2020. The exact search terms were: “cardiac dyssynchrony”, "septal flash" and "septal dyssynchrony". We reviewed the bibliography of relevant studies and reviews for additional studies that met the inclusion criteria.

Study selection and data extraction

Two reviewers (SB and JT) independently screened all titles and abstracts retrieved from the search for studies that met the inclusion criteria. The studies that potentially met the inclusion criteria were reviewed and the final decision to include or exclude studies was made by consensus. The data extraction was carried out by SB and checked by CSK and JT independently. Data was collected on study design, country of study origin, year, sample size, mean age, percentage of male participants and inclusion criteria. Imaging modality used, definition and assessment of septal flash and definition of CRT response. Follow-up duration, pertinent results of each study along with an overview of the usefulness of septal flash in predicting CRT response was provided.

Risk of bias assessment

Methodological quality assessment of the included studies was based on the risk of bias assessment with consideration of the following: i) prospective study, ii) reliable ascertainment of septal flash, ii) reliable outcome ascertainment, iii) low missing data/loss to follow up, iv) adjustments for confounders in the estimate for septal flash and response in CRT and v) generalizability of the cohort. This assessment was done by one reviewer (SB) and checked independently by two other reviewers (CSK and JT).

Data analysis

Data was extracted into pre-designed tables which collected data on study design, the country where it took place, the year when the study took place, sample size, mean age, percentage of the cohort that was male, percentage of the cohort that had ischemic cardiomyopathy and inclusion criteria. We also collected data on the definition for septal flash for each study and the results including CRT response and its definitions. Using the inverse variance method, random effects meta-analysis of septal flash and response in patients with CRT was undertaken on Review Manager (Version 5.3, The Cochrane Collaboration, 2014). Where available the most adjusted risk or odds estimates were collected and pooled in meta-analysis. For studies which only reported crude results, we calculated the risk ratio using the Mantel-Haenszel method in a random effects model. Statistical heterogeneity was considered with the I^2 statistic where 30-60% represents a moderate level of heterogeneity[13] and leave-on-out sensitivity analysis was performed to evaluate the source of statistical heterogeneity. Publication bias was assessed by asymmetry testing with funnel plots if the dataset contains more than 10 studies and there is no evidence of significant heterogeneity.[14]

Results

Study selection and description of included studies

Our search initially yielded 543 potential inclusions which, after detailed screening and review yielded total of nine studies that met the inclusion criteria.[,10,11,14,15,16,17,18,19,20]

The description of the included studies is shown in Table 1. There were four retrospective studies and four prospective studies while one study was of unclear design. The studies took place between 2009 and 2017 and majority of studies took place in Europe. Overall, there were 2,307 participants and the average age across the eight studies which reported mean age was 76 years. The proportion of male patients in the included studies as 67% and 42% of all patients had ischemic heart failure. Five studies reported percentage of LBBB among participants, the average was 77%. The mean QRS duration across all studies ranged from 155 to 170 ms.

The definitions for septal flash used in each study are presented in Table 2. All studies used either 2D or 3D transthoracic echocardiography to assess for the presence of septal flash. One study[20] used a combination of echocardiography and CMR. Although all nine studies indicated the imaging modality of how septal flash was assessed which included, only seven had reliable methods of detecting and quantifying the presence of septal flash.

Study quality assessment

Quality assessment of the included studies in shown in Table 3. Exposure and ascertainment of outcomes were both reliably assessed for in all studies. Outcomes measures included echocardiographic parameters (improvement in LVEF and a reduction in LV volumes) and clinical characteristics (improvement in NYHA classification and survival rates at follow-up). Outcomes were assessed with evaluation of echocardiograms, CMR or events from medical records. With respect to missing data, eight studies had no significant (<10%)

missing data or loss to follow up data.[10,11,14,15,17,18,19,20] The percentage of missing data/lost to follow-up was not clear in the remaining included study.[16] Only three studies used some form of adjustment in the analysis which evaluated the association of septal flash in predicting CRT response.[11,16,20] Only one study only including heart failure patients with atrial fibrillation.[11] all remaining studies including heart failure patients with sinus rhythm[10,12,15,16,17,18,19,20]

Results for septal flash in predicting overall CRT response

Six of the nine studies had clearly defined echocardiographic criteria for the assessment of CRT response. This was characterized as either a ≥10% [19] or ≥15% [10-12,15,18] reduction in left ventricular end systolic volumes. The percentage of CRT responders from the included studies varied from 52% to 77%. All studies reported that septal flash was present in a greater proportion for patients who were reported as CRT responders compared to those who were deemed CRT non-responders. In patients who were deemed CRT responders, septal flash was seen in approximately 40% (n=865/2174) of patients compared to only 10% (n=232/2174) who were classed as CRT non-responders.

Results for septal flash in predicting LV reverse remodeling

Doltra et al reported that patients with septal flash at baseline had an echocardiographic response rate of 80.2%, which included a reduction in LV end systolic volumes and LVEF. CRT corrected the septal flash abnormality in 93% of patients.[10] Gabrillei et al found that septal flash was the only independent predictor for significant LV reverse remodeling (OR 5.24 95%CI 1.95–14.1, p<0.01).[11] Gasior et al found that septal flash at baseline was associated with significant improvements in LVEF, LV systolic and diastolic volumes.[17] Of the 87 patients who were identified as having septal flash at baseline by Parsai et al, 88% of these showed resolution of septal flash following CRT implantation and improvements in LV volumes were also noted, though no significant improvement in overall LVEF was observed.[19] Sohal et al reported that septal flash without scar was able to predict reverse remodeling with a sensitivity 78% 95%CI 67-89% and specificity 88% 95%CI 79-97%.[20]

Results for septal flash in predicting survival rates

Only one study by Stankovic et al assessed the presence septal flash at baseline on survival rates. In this study, septal flash at baseline had significantly higher survival rates that those without septal flash (multivariable HR 0.456 95%CI 0.342-0.608, p<0.0001).[12]

Results for septal flash in predicting NYHA classification

Only two studies Mada et al, assessed for improvement in NYHA classification in patients with and without septal flash.[18] Here, patients with septal flash compared to patients without septal flash were more likely to have a reduction by at least one NYHA class at 6 months follow-up (92% Vs 64%; P=0.02). Gasior reported no significant change in NYHA classification amongst patients with and without septal flash (P=0.06).[17] Similar results were also reported in Gabrielli et al where baseline NYHA classification did not significantly improve at 12 months follow-up between patients with and without septal flash (2.21 ±0.51 vs 2.54±0.67, p=0.36).[11] When considering NYHA classification improvement in only septal flash patients, Gabrielle also reported no significant improvement between baseline and follow-up NYHA classification (3.21±0.54 Vs 2.88±0.83, p=0.44).[11]

Pooled results for septal flash CRT response

Eight studies in the review were included in the pooled meta-analysis to quantify the association between septal flash and CRT response (Figure 2). The presence of septal flash at baseline was associated with an increase in CRT response (RR 2.55 95%CI 2.04-3.19, $p<0.001$, $I^2=51\%$). The moderate statistical heterogeneity was explored and sequential evaluation of I^2 after exclusion of each study, did not reduced the statistical heterogeneity lower than 42%.

Discussion

Our review and meta-analysis has several key findings. First, septal flash is common and present in more than half of HF patients undergoing CRT therapy. Secondly. when septal flash is present there is more than two-fold increase in the response to CRT, with further suggestion that septal flash is associated with positive left ventricular remodeling after CRT implantation. Thirdly, most studies assess the presence of septal using transthoracic echocardiography and there are limited studies evaluating septal flash on CMR imaging. These findings suggest that in the workup for potential CRT implantation patients should have imaging to assess for septal flash as this finding is associated with response to therapy.

Septal flash has been reported to occur in approximately 45-63% of patients with LBBB leading to studies suggesting that septal flash may prove to be an additional marker alongside a prolonged QRS duration which may assist in selecting patient who are more likely to benefit from CRT.[11] Our review suggests that among the population with CRT device implantation with an LVEF ≤35% with a QRS duration ≥120msec, 53% have septal flash on baseline imaging. Although there have been previous articles providing comprehensive overviews on septal flash,[8] CRT non-response causes[21] and opinion pieces on selection criteria for CRT,[22] this is the first systematic review and meta-analysis which has been undertaken assessing the significance of septal flash in predicting CRT response in patients with HF. Although all studies examined used inclusion criterion of QRS duration ≥120ms, overall the mean duration was 163 ms. This is important as, it highlights that, beyond assessment of LVEF, assessment of septal flash retains its relevance in a contemporary population as part of the pre-implant work up of patients for CRT.

The mechanistic between septal flash and associated CRT response are relatively unknown and remain an area of primary research. In LBBB, asynchronous electrical activation results in impaired cardiac output secondary to prolonged right to left transseptal activation. The early activation of the inter-ventricular septum causes a delayed elevation of intracavity pressure which subsequently leads to delayed activation of the lateral left ventricular wall, of which the latter, occurs when the inter-ventricular septum is entering its relaxation phase.[23] Septal flash however is more challenging to pinpoint its exact mechanism of activation and research into this area is lacking. A computer simulated study by Walmsley et al,[24] indicated that septal flash was not purely the result of LBBB and was not associated with alterations to the pressures gradients as seen in LBBB. Instead, they indicated that premature contraction of the right ventricular free wall results in an unopposed increase in wall stress. This imbalance, results in a hinging motion to occur at the attachment points between the right ventricle and interventricular septum. Furthermore, the results of Duckett et al, indicated there to be functional lines of conduction block which slowed conduction propagation and subsequently delayed contraction of the postero-lateral left ventricular wall.[25] This was attributed to premature contraction of the right ventricle. Although the underlying mechanism of septal flash is associated with improved CRT response is not fully understood, from the research discussed above it is likely that septal flash results from a mechanical abnormality Involving both left and right ventricles, therefore representing an inter-ventricular dyscoordination, in addition to well-documented intra-ventricular dyssynchrony in the presence of LBBB alone. It is probable that re-established inter-ventricular organization contributes toward positive left ventricular re-modelling which may be amenable to correction by the use of CRT.

The benefits of CRT in patients with heart failure are well known and include positive LV remodeling, improved symptomatic status and a reduced mortality rates.[24] However approximately one third of CRT patients do not show a clinical improvement.[27] Thus, there is a potentially a large cohort of patients receiving expensive therapies which require long term follow-up with no clear clinical benefit associated with it. Although there are well defined international guidelines for the use of CRT in heart failure patients which include LBBB morphology and QRS duration of ≥130msec,[4] there are several studies which indicate that prolonged QRS duration is not a precise and specific marker of true ventricular dyssynchrony.[,28,29] This was seen in Gebrielle et al also where they concluded that QRS duration had no independent prognostic value in assessing CRT response.[11] It is also thought that in a cohort of patients, mechanical dyssynchrony can occur with shorter QRS durations of <120msec.[30]

Various echocardiographic dyssynchrony parameters have been investigated previously which were thought to better reflect mechanical dyssynchrony. These included septal to posterior wall motion delay, longitudinal velocities and differences in left ventricular to right ventricular ejection timing intervals.[31] These parameters have been used in large multicenter trials including PROSPECT to assess for CRT response, however these measurements were hindered with poor reproducibility, as such they were thought to be unreliable to assist in the selective criteria of patients for CRT in mainstream clinical practice.[,31,32] This is not unexpected as many of the parameters involve complex and time consuming timing interval calculations. The assessment of septal flash overcomes the limitations due to its distinctive and recognizable pattern of motion which, as seen in this review can be easily be assessed by the routine use of 2D transthoracic echocardiography. The evaluation of septal flash is advantageous as most patients have 2D echocardiography in order to assess the LVEF when considering whether patients met CRT implantation guidelines. Furthermore, inter-observer agreement in two studies in this review were shown to be high in Doltra et al (100% agreement - kappa=1, misclassification=0)[10] and Mada et al (k=0.9, P=0.01).[18] Therefore, the clinical implications of this review is that there should be greater awareness among reporters of imaging about the significance of identifying septal flash especially among patients with heart failure who may benefit from CRT.

The limitations of this review include the small number of studies investigating the use of septal flash of which, five were retrospective in nature. The underlying mechanisms of action of septal flash remains relatively unknown as such, a better understanding of the pathophysiology would enable a more targeted approach of patients when being considered for CRT. Furthermore, this may lead to improved understanding in how LBBB, septal flash and LVEF are interrelated. All of the included studies used CRT indications of LBBB duration of >120miliseconds and an LVEF ≤35%, however new international guidelines now require a LBBB duration of >130mseconds. Due to the date of the included studies of this review, these new guidelines were not implemented. Although it must be noted that in the included studies, the overall averaged QRS duration is still in keeping with the new guidelines of >130msec.While our review provides some evidence that septal flash is consistently associated with CRT response, large prospective trials are needed to assess the utility of septal flash in selecting patients for CRT. More research on quality of life measurements, cardiac event rates such as recurrent hospitalization with heart failure and mortality are required to assess the association of septal flash and its potential impact on mortality rates as data in this area is lacking. Patients in atrial fibrillation are increasingly offered CRT, they represent a particularly challenging group for management, outcome measurement and suitability for this therapy. The presence or absence of septal flash in this sub-group deserves further studies, although hard-end points such as LV volumes require averaged values and subject to errors in sampling, further than those in sinus rhythm.

Conclusions

Septal flash is a well-defined and distinctive contraction pattern which is easily recognizable to 2D transthoracic echocardiography. The results of this systematic review suggests that septal flash is consistently associated with CRT response and should be evaluated in the patients that are considered for CRT device.

Acknowledgements: None

List of Figures and Tables

Figure 1: Flow diagram of study inclusion

Caption: Flow diagram to illustrate the study selection process and the reason for study exclusion.

Figure 2: Meta-analysis of septal flash and response in CRT

Caption: Pooled results from 8 studies suggest a 2.5-fold increase in response in patients with CRT who have septal flash compared to no septal flash.

Table 1: Study design, patient characteristics and inclusion criteria

Table 2: Definitions for septal flash

Table 3: Results of included studies

Supplementary Table 1: Study quality assessment

Figure 1: Flow diagram of study inclusion

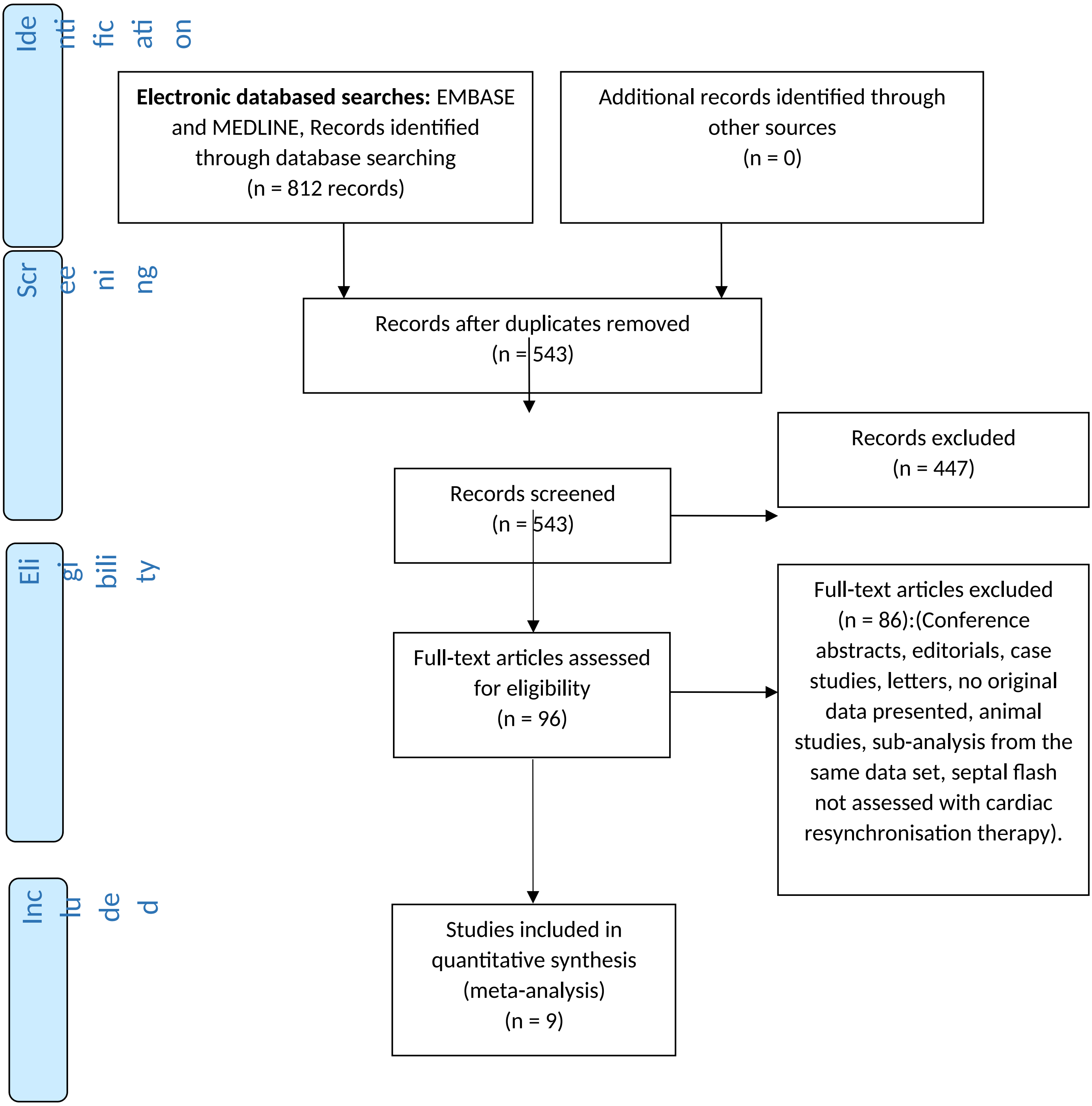

Figure 2: Meta-analysis of septal flash and response in CRT

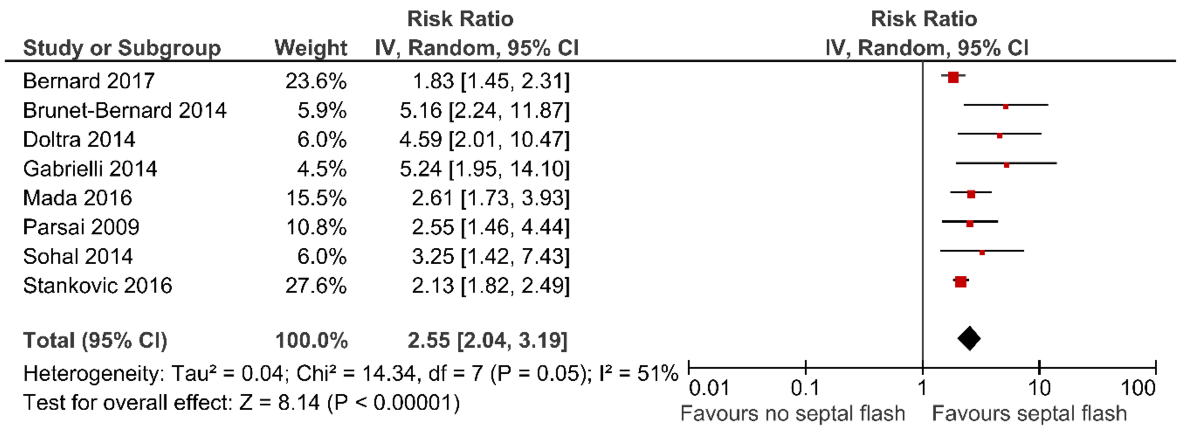

Table 1: Study design, patient characteristics and inclusion criteria

Study ID	Study design; Country; Year	Sample size	Age	% Male	Ischemic etiology (%)	% Left bundle branch block at baseline	QRS duration	Patient inclusion criteria
Bernard 2017	Retrospective cohort study; France; 2016.	275	67	70	65	73	161±26msec	Patients with HF requiring a CRT device according to international guidelines (LVEF ≤35%, QRS duration ≥120msecs).
Brunet-Bernard 2014	Retrospective cohort study; France; 2010-2012.	207	66	70	35	69	161±25msec	Patients with HF requiring a CRT device (LVEF ≤35%, QRS duration ≥120msecs), with adequate ultrasound acoustic windows
Doltra 2014	Retrospective cohort study; Spain; 2005-2009.	200	67.3	77	40	70	169±30msec	Patients with HF requiring a CRT device according to international guidelines (LVEF ≤35%, QRS duration ≥120msecs), who were not awaiting heart transplantation or without significant comorbidity that would shorten life expectancy.
Gabrielli 2014	Prospective cohort study; Spain; 2013.	94	69	79	28	85	166±35msec	Patients with HF and long standing atrial fibrillation (≥3 months) who required a CRT device according to international guidelines (LVEF ≤35%, QRS duration ≥120msecs).
Gasior 2016	Prospective cohort	133	63	77	51	Not stated	165±25msec	Patients enrolled onto the ViaCRT study and

	study; Poland; 2009-2012.							who met standard indications for a CRT device (LVEF ≤35%, QRS duration ≥120msecs).
Mada 2016	Retrospective cohort study; Belgium and Germany; unclear.	125	63	71	54	Not stated	170±26msec	Patients with HF requiring a CRT device according to international guidelines (LVEF ≤35%, QRS duration ≥120msecs) with good echocardiographic windows.
Parsai 2009	Prospective cohort study; France and Netherlands; 2008.	161	66	80	51	Not stated	156±21msec	Patients with HF requiring a CRT device according to international guidelines (LVEF ≤35%, QRS duration ≥120msecs).
Sohal 2014	Prospective cohort study; UK; 2014.	52	65	88	48	Not stated	155±24	Patients with HF requiring a CRT device according to international guidelines (LVEF ≤35%, QRS duration ≥120msecs).
Stankovic 2016	Retrospective cohort study; Europe; 1999-2012.	1060	64	76	43	88	170±29	Heart failure patients enrolled on PREDICT-CRT study requiring a CRT device according to international guidelines (LVEF ≤35%, QRS duration ≥120msecs).

HF=heart failure, CRT=cardiac resynchronization therapy, LVEF: Left ventricular ejection fraction.

Table 2: Definition of septal flash / dyssynchrony and CRT response

Study ID	Imaging modality used	Definition of SF	Assessment of SF	Definition of CRT response
Bernard 2017	2D echocardiography.	Early septal thickening/thinning within the isovolumetric contraction period.	Visual and m-mode assessment.	Reduction of > 15% in LVESV at 6-month follow-up and/or occurrence of major cardiovascular event.
Brunet-Bernard 2014	2D echocardiography.	Leftward displacement of the interventricular septum during pre-ejection, followed by rightward (paradoxical) motion.	Visual and m-mode assessment.	Not clear.
Doltra 2014	2D echocardiography.	Fast contraction and relaxation (inward/ outward motion) of the septum occurring during the isovolumetric contraction period (within the QRS width).	Visual and m-mode assessment.	Reduction of ≥ 15% in LVESV at follow-up on echocardiogram. Clinically defined as: alive, without heart transplantation, and with improvement of ≥20% in the 6-min walk test or of at least 1 NYHA functional class.
Gabrielli 2014	2D echocardiography.	Early fast inward/outward motion of the interventricular septum within the isovolumetric contraction period and the QRS complex duration. The presence of SF was confirmed with an excursion >1 mm and corrected SF at 12-month follow-up was defined by the disappearance of SF or a reduction of the excursion ≥3 mm.	Visual or color tissue Doppler M-mode assessment.	Reduction of ≥15% in LVESV at follow-up.
Gasior 2016	2D echocardiography.	Not stated.	Not stated.	Not clear.
Mada	2D & 3D	Not stated.	Visual assessment.	Reduction of ≥ 15% in LVESV.

2016	echocardiography.			
Parsai 2009	2D echocardiography.	The presence of an early septal thickening/thinning within the isovolumetric contraction period.	Visual or color tissue Doppler M-mode assessment.	Reduction of >10% in LVESV. Reduction in NYHA class by ≥1 class.
Sohal 2014	MRI & 2D echocardiography.	MRI definition: inward septal motion within the first 15 % of the cycle measured by the software platform Echo definition: early inward and outward motion within the isovolumetric contraction period.	MRI: time volume curves and visual assessment. Echocardiography: visual and m-mode assessment	Changes in NYHA, 6 min walk distance and Minnesota Living questionnaire.
Stankovic 2016	2D echocardiography.	Short inward motion of the septum in early systole (within the QRS width).	Visual assessment.	Reduction of ≥15% in LVESV at follow-up.

2D=2-dimensional, 3D=3-dimensional, CRT=cardiac resynchronization therapy, LVESV=left ventricular end systolic volumes, MRI=magnetic resonance imaging, NYHA=New York Heart Association

Table 3: Results of included studies

Study ID	Follow-up	Results	Septal flash a useful parameter in CRT response?
Bernard 2017	Median 720 days	CRT response rate: 172/275 (62.5%). Responders vs non-responders: Septal flash: 140/172 (84%) Vs 43/97 (46%), p<0.001. LVEF: 31±10 vs 28±8, p=0.005. Major cardiovascular events: 21/275 (8%) Cardiovascular mortality: 16/275 (6%).	Yes, Septal flash is associated with CRT response.
Brunet-Bernard 2014	6 months	Responders vs non responders: Derivation cohort: 76/98 (78%) vs 28/64 (44%), p<0.0001. Validation cohort: 24/32 (77%) vs 4/13 (31%). Combined: 100/130 (77%) vs 32/77 (42%). Multivariate predictor of good response with septal flash: OR 5.16 95%CI 2.24-11.86, p=0.0001. LVEF: Derivation cohort 27±6 vs 27±6, p=0.67. Validation cohort: 27±3 vs 24±3, p=0.003.	Yes, Septal flash is associated with CRT response.
Doltra 2014	12 months	Septal flash: 106/200 (53%). Echo response at 12 months: septal flash 85/106 (80%). Proportion with septal flash: Death or no clinical response and LVESV reduction: <6.8%: 5/37 (13.5%) Clinical response and LVESV reduction: <6.8%: 12/40 (30.0%) LVESV reduction of 6.8% to 26.68%: 37/62 (59.7%) LVESV reduction >26.68%: 52/61 (85.2%) Septal-to-lateral delay and echocardiographic response: univariate OR 1.00 95%CI 0.99-1.01, p=0.583. Septal-to-lateral delay and cardiovascular mortality: univariate OR 1.00 95%CI 0.99-1.01, p=0.563.	Yes, Septal flash is associated with CRT response.
Gabrielli 2014	12 months	CRT responders: 56/94 (59%). Responders vs non-responders:	Yes, Septal flash was associated with CRT response.

		Septal flash: 74.1% (41/56) vs 25.9% (10/38), p<0.01. Significant reverse remodelling and response with septal flash: multivariate OR 5.24 95%CI 1.95-14.11, p<0.01). LVEF: 24±6 vs 29±10, p=0.04.	
Gasior 2016	12 months	Septal flash: 24/87. Septal flash (n=24) vs no septal flash (n=63) ΔLVEDV: -46±10 vs -32±7, p<0.05 ΔLVESV: -63±10 vs -36±6, p<0.05 ΔLVEF: 14±2 vs 8±1, p<0.05 ΔNYHA: -1.1 vs -0.8, p=0.06	No, unable to comment on septal flash and its associated with CRT response.
Mada 2016	6 months	CRT responders: 77/125 (61.6%). Septal flash: 83/125 (66.4%). Responders vs non-responders: Septal flash: 67/77 (87.0%) vs 16/48 (33.3%), p<0.001. LVEF at baseline: 24±6 vs 27±7, p=0.07.	Yes, Septal flash was associated with CRT response.
Parsai 2009	1,3 and 6 months	CRT responders: 121/161 (75%). Septal flash: 84/161 (54%). Responders vs non-responders: Septal flash: 77/121 (64%) vs 10/40 (25%). Septal flash in clinical responders 77/121, volume responders 73/92 and non-responders 22/40. Septal flash sensitivity 64% 95%CI 54-72%, specificity 55% 95%CI 39-70%, PPV 81% 95%CI 71-88%, NPV 33% 95%CI 23-46%.	Yes, Septal flash was associated with CRT response.
Sohal 2014	6 months	CRT responders: 27/52 (51.9%). Septal flash: 24/52 (46.1%). Responders vs non-responders: Echo septal flash: 21/27 (78%) vs 5/20 (20%), p=0.001. CMR septal flash: 21/27 vs 3/25, p=0.001. Degree of CMR septal flash: 18.5±7.7 vs 8.9±2.7, p=0.003. LVEF with septal flash vs no flash: 33.9±8.9 vs 30.0±10.2, p=0.18.	Yes, Septal flash was associated with CRT response.

		Septal flash and reverse remodelling: sensitivity 78% 95%CI 67-89%, specificity 88% 95%CI 79-97%. No scar and septal flash and reverse remodelling: sensitivity 52% 95%CI 38-66%, specificity 96% 95%CI 90-100%. Scar and septal flash and reverse remodelling: sensitivity 24% 95%CI 12-36%, specificity 86% 95%CI 76-96%. Septal flash and as a predictor of CRT response: multivariate prevalence ratio 3.25 95%CI 1.42-7.42.	
Stankovic 2016	Median 48 months	CRT response: 58% Septal flash: 438/677 (65%) Responders vs non-responders: Septal flash: 329/396 (83%) vs 109/279 (39%), p<0.001. Septal flash and all-cause mortality: multivariable HR 0.456 95%CI 0.342-0.608, p<0.0001.	Yes, Septal flash was associated with CRT response.

CRT=cardiac resynchronisation therapy, PPV=positive predictive value, NPV=negative predictive value, LBBB=left bundle branch block, RVP=right ventricular pacing, CMR=cardiac magnetic resonance, LVEF=left ventricular ejection fraction, LVEDV=left ventricular end diastolic volume, LVESV=left ventricular end systolic volume, NYHA=New York Heart Association.

Supplementary Table 1: Study quality assessment

Study ID	**Prospective design**	**Reliable septal flash ascertainment**	**Reliable outcome ascertainment**	**Low missing data/lost to follow up**	**Adjustments for confounders**	**Generalizable cohort**
Bernard 2017	No, retrospective.	Yes, assessment by echocardiography.	Yes, echocardiographic parameters and MACE.	Yes, 6 (2.8%) lost to follow-up.	No, unadjusted.	Yes, heart failure patients requiring a CRT device.
Brunet-Bernard 2014	Not clear.	Yes, assessment by echocardiography.	Yes, echocardiographic parameters and clinical characteristics.	Yes, 5 (2.4%) excluded for missing data.	Yes, adjusted for LBBB, non-ischemia HF, >70 years, LVEDD <40mm/msq.	Yes, heart failure patients requiring a CRT device.
Doltra 2014	No, retrospective.	Yes, assessment by echocardiography.	Yes, echocardiographic parameters and clinical characteristics.	Yes, no loss to follow up/missing data described.	No, unadjusted.	Yes, heart failure patients requiring a CRT device.
Gabrielli 2014	Yes, prospective.	Yes, assessment by echocardiography.	Yes, echocardiographic parameters and clinical characteristics.	Yes, 6 (6.3%) excluded for missing data.	Yes, adjusted but unclear what variables.	No, patients with atrial fibrillation and heart failure requiring a CRT device.
Gasior 2016	Yes, prospective.	Yes, assessment by echocardiography.	Yes, echocardiographic parameters and clinical characteristics.	Unclear, sub analysis of a larger study.	No, unadjusted.	Yes, heart failure patients requiring a CRT device.
Mada 2016	No, retrospective.	Yes, assessment by echocardiography.	Yes, echocardiographic parameters and clinical characteristics.	Yes, no loss to follow up/missing data described.	No, unadjusted.	Yes, heart failure patients requiring a CRT device.
Parsai 2009	Yes, prospective.	Yes, assessment by echocardiography.	Yes, echocardiographic parameters and clinical characteristics.	Yes, no loss to follow up/missing data described.	No, unadjusted.	Yes, heart failure patients requiring a CRT device.
Sohal 2014	Yes, prospective.	Yes, assessment by MRI and echocardiography.	Yes, MRI and echocardiographic parameters and clinical characteristics.	Yes, no loss to follow up/missing data described.	Yes, adjusted prevalence ratios for myocardial scar, QRS duration,	Yes, heart failure patients requiring a CRT device.

					echo derived SDI and presence of septal flash.	
Stankovic 2016	No, retrospective.	Yes, assessment by MRI and echocardiography.	Yes, MRI and echocardiographic parameters and clinical characteristics.	Yes, 2 (0.2%) excluded for missing data.	No, unadjusted.	Yes, heart failure patients requiring a CRT device.

MACE=Major adverse cardiac events, MRI=magnetic resonance imaging, LBBB=left bundle branch block, HF=heart failure, LVEDD=left ventricular end diastolic diameter, LV=Left ventricle, LVESD=left ventricular end systolic diameter, SDI=systolic dyssynchrony index, CRT=cardiac resynchronization therapy.

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