A Network Meta-analysis and Systematic Review of Left Bundle Branch Pacing, His Bundle Pacing, Biventricular Pacing or RV Pacing in Patients Requiring Permanent Pacemaker

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Research Article

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Abstract

Background: Cardiac dyssynchronization is the proposed mechanism for pacemaker-induced cardiomyopathy. The standard of treatment is biventricular pacing. Left bundle branch pacing and His bundle pacing are novel interventions that imitate the natural conductionof the heart with, theoretically, less interventricular dysynchrony. One of the surrogate markers of interventricular synchrony is QRS duration. Our study aimed to compare the change of QRS duration before and after implantation between types of cardiac implantable electronic device (CIED): left bundle branch pacing versus His bundle pacing versus biventricular pacing and conventional right ventricular pacing.

Methods: A literature search for studies that reported an interval change of QRS duration after CIED implantation was conducted utilizing the MEDLINE, EMBASE, and Cochrane databases. All relevant work through September 2020 from these databases was included in this analysis. A random-effects model network meta-analysis was used to analyze QRS duration changes (i.e., electrical cardiac synchronization) across different CIED implantations.

Results: The mean study sample size, from 16 included studies, was 185 subjects. According to SUCRA analysis for the studies analyzed, the His bundle pacing intervention resulted in the most dramatic decline in QRS duration (mean difference -53 ms, 95% CI -67, -39), followed by left bundle branch pacing (mean difference -46 ms, 95% CI -60, -33) and biventricular pacing (mean difference -19 ms, 95% CI -37, -1.8), when compared to conventional right ventricle apical lead placement.

Conclusion: Our network meta-analysis found that His bundle branch pacing devices have the greatest effect on QRS duration reduction after implantation, followed by left bundle branch pacing. Physiologic pacing interventions result in improved electrocardiography markers of cardiac synchronicity, narrower QRS duration, and might lower electromechanical dyssynchrony.

Introduction

Pacemaker-induced cardiomyopathy (PCM) is defined as a fall in left ventricular ejection fraction (LVEF) of more than 10 percent from the baseline after other differential diagnoses are excluded (1). More than 20% of right ventricular (RV) pacing has been found to be highly associated with an increased incidence of heart failure (2). The prevalence of PCM has been reported to be up to 9% in chronic RV pacing patients (3).

The key pathophysiology in PCM is the hemodynamic effect of pacing-induced cardiac dyssynchrony. RV pacing results in delayed activation of cardiac muscle cells, causing abnormal contraction and a negative inotropic effect in mammals (4). This phenomenon has also been confirmed by histological changes in cardiac muscle cells, in which myofibril disarrays have been observed (5).

The main objective of PCM therapy is to restore cardiac synchronicity. The gold standard treatment is to upgrade from conventional RV pacing, placing a ventricular lead in the RV apex, to biventricular pacing, synonymously called cardiac resynchronized therapy (CRT). CRT is associated with lower mortality, fewer urgent care visits for acute heart failure, and improved LV end-systolic volume index (6). Other methods of resynchronization are His bundle pacing and left bundle branch pacing, so-called physiologic pacing. These techniques differ in the success rates of implantation and clinical outcomes across studies; however, there have been no studies comparing the benefits and effects of these interventions. In the present study, we aim to investigate the effect of these different pacing techniques on cardiac synchronization.

Methods

Literature review and Search Strategy

The protocol for this network meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD 42020210277). A systematic literature search of MEDLINE (1946 to November 2020), EMBASE (1988 to November 2020), and the Cochrane Database of Systematic Reviews (1993 to November 2020) was conducted to compare the following outcomes: electromechanical desynchrony, as represented by QRS duration, following CIED implantation between His bundle pacing; left bundle branch pacing; biventricular pacing; and conventional RV pacing treatments.

The systematic literature review was undertaken independently by two investigators (R.C. and N.T.) applying a search approach that incorporated the terms of “His bundle pacing”, “Left bundle branch pacing”, “Biventricular pacing”, “Cardiac resynchronization therapy”, and “Right ventricular pacing” in combination. The results of this search are provided in **online supplementary data 1**. A manual search for conceivably relevant studies was also performed using references of the included articles. No language limitation was applied. This study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) (7) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (8).

Selection criteria

Data from observational studies (cohort, case-control, or cross-sectional studies) and randomized studies were utilized for this analysis. Eligible studies included those that provided data on the clinical characteristics, type of CIEDs, and QRS duration prior to and after device implantation. Inclusion was not limited by study size. Retrieved articles were individually reviewed for their eligibility by R.C. and N.T. Discrepancies were discussed and resolved by a third researcher (N.P.). The Newcastle-Ottawa quality assessment scale was used to appraise the quality of study for case-control studies and outcomes of interest for cohort studies (9). The modified Newcastle-Ottawa scale was used for cross-sectional studies (10). The Cochrane Collaboration’s tool was used to assess the risk of bias for randomized trials, as shown in **Table 1Figure 7 and Figure 8**.

Data abstraction

A structured data collection form was utilized to derive the following information from each study: title, year the study was conducted, name of the first author, publication year, country where the study was conducted, demographic and characteristic data of CIED devices, and QRS duration before and after implantation.

Statistical analysis

Analyses were performed using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Adjusted point estimates from each included study were combined by the generic inverse variance approach of DerSimonian and Laird, which designated the weight of each study based on its variance (11). Given the possibility of between-study variance, we used a random-effects model rather than a fixed-effect model network meta-analysis model. To assess the magnitude of heterogeneity, we performed a comparison of the posterior distribution of the estimated heterogeneity variance with its predictive distribution. Surface Under Cumulative Ranking Curve (SUCRA) was used to rank the treatment for all outcomes.(12)

We evaluated consistency (agreement between direct and indirect evidence) statistically using a design by node splitting test as show in **Figure 5.** This consistency test allowed us to confirm that the selection, or non-selection, of specific comparisons is not related to an actual effect size of that comparison (13, 14).

Cochrane Handbook for Systematic Reviews of Interventions was used as reference for risk of bias assessment. Also, Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was performed to assess if the certainty of information accounted for the network estimates of the main outcomes from individual studies (15).

We assessed if the primary outcomes, QRS duration changes, remained statistically significant in subgroup analysis based on sample size and study year of individual studies (16). Brooks-Gelman Rubin diagnostic was performed to assess convergence of models. **Figure 6**

Sensitivity analysis was performed by comparing the results between Frequentist Network Meta-Analysis approach and Bayesian Netowork Meta-Analysis approach. Level of study biases was also included in the sensitivity analysis.

Results

A total of 707 potentially eligible articles were identified using our search strategy. After the exclusion of duplicate articles, case reports, correspondences, review articles, *in vitro* studies, pediatric patient population, or animal studies, 34 articles remained for full-length review. 18 were excluded from the full-length review as the QRS duration changes were not reported.

Thus, the final analysis included 16 studies (8 randomized studies and 8 observational studies; 17-32), including 2,967 patients. The literature retrieval, review, and selection process are illustrated in **Figure 1.** The characteristics and quality assessment of the included studies are presented in **Table 1 and Figure 2**.

The mean study sample size was 185 subjects. For individual implantation, 835 patients were assigned to conventional right ventricular apex implantation, 224 for biventricular pacing, 361 for left bundle branch pacing (LBBP), and 590 for His Bundle Pacing (HBP). When compared to conventional RV pacing, HBP patients had the greatest QRS narrowing with a mean difference of -53 ms (95% CI -67, -39), followed by left bundle branch pacing with a mean difference of -46 ms (95% CI -60, -33), and biventricular pacing with a mean difference of -19 ms (95% CI -37, -1.8) (**Figure 3**). The result of SUCRA is illustrated in **Figure 4**

Sensitivity analysis was performed by comparing the results of NMA between Bayesian method and Frequentist method. Categorization of studies according to degree of bias was also used to perform the sensitivity analysis. The results were consistent and showed that HBP, and LBBP provided the most change in QRS narrowing.

Meta-regression to exclude study biases was performed and once again demonstrated the most dramatic decline of QRS duration with His bundle pacing and left bundle branch pacing.

Discussion

This study demonstrates that physiologic pacing interventions, both HBP and LBBP, maintain normal physiology of cardiac conduction systems, as shown in the electrocardiogram (ECG) of patients requiring a permanent pacemaker. Further, these results support the hypothesis that pacemakers that use physiologic pacing cause less cardiac desynchrony compared to traditional RV pacing, consistent with a previous study that showed the HBP technique could improve cardiac function by maintaining myocardial segment electrical activation (4). In patients with preexisting bundle branch block, the long helix His bundle lead may penetrate distally to the level of cardiac conducting system blockage and normalize the QRS complex. While many theories have tried to explain this QRS normalization, functional longitudinal dissociation between bundle branches is believed to be the fundamental physiology of the change (33).

QRS duration is a powerful marker for cardiac dyssynchrony. The prolongation of QRS complex to ≥ 120 ms is associated with more advanced myocardial disease, poorer prognosis, and higher all-cause mortality compared to a normal QRS complex duration (34). In patients with an LVEF < 30%, QRS prolongation is associated with increased mortality and sudden cardiac death. Further, in patients with an LVEF of 30-40%, QRS prolongation is associated with increased mortality (35). QRS duration is the major determinant for cardiac resynchronization therapy according to current guidelines (36). The results from our study showed a significantly narrower QRS duration in patients with HBP and LBBP compared to BiV; thus, physiologic pacing can be translated into better cardiac performance by restoring normal interventricular electrical activation pattern.

The current guidelines recommend RV pacing- or BiV pacing-based interventions in patients with chronic atrial fibrillation and heart failure who underwent AV node ablation due to inadequate control of heart rate by medications (37). However, several studies have shown no benefit in patients with previously narrow QRS complex, which could be explained by remaining electrical dyssynchrony after BiV pacing (38, 39).

The implantation of His bundle pacing comprises delivery of the RV lead into the area of His Purkinje system with a 3830 pacing lead and C315 His non-deflectable sheath (40). Once the area of His signal is obtained, the lead is then screwed into myocardium (40, 41). The success rate of this procedure has been reported as up to 92% in experienced centers (42), and was found not to be different from the success rate of BV pacing (43). The issues with His bundle pacing that concern most operators are long-term lead stability and ventricular capture threshold. Primarily, the pacing output threshold, the least electrical energy delivered that triggers electrical depolarization, would increase overtime; 6.7% of patients required lead revision over 5 years of follow-up (42, 44). Another unresolved issue with HBP interventions is increased battery drainages secondary to higher ventricular capture thresholds (41). The implantation of left bundle branch pacing is similar to the HBP implantation procedure, with the same type of lead and sheath, as well as methods of delivering the lead, used in both implantation processes. The difference between LBBP and HBP procedures is that once the His bundle electrogram is obtained, the tip of pacing lead is moved 1.5-2 cm toward the ventricular apex on the right anterior oblique fluoroscopic projection, and pace-mapping is performed to secure lead in the ideal position (45). The successful LBBP would result in right bundle branch morphology with a QRS duration of less than 130 milliseconds. The issues with HPB (increased pacing and sensing threshold) do not occur in LBBP (23, 46).

Current evidence has pointed toward higher success rates and lower pacing thresholds in LBBP compared to HBP (47, 48). Although both techniques appear to be relatively safe in short-term follow-up and, theoretically, advantageous over conventional pacing, many questions remain to be answered in the clinical setting. For example, the mortality benefit and rate of heart failure hospitalization remain unknown for both procedures. Nevertheless, the results of the present study provided additional evidence to support that physiologic pacing, both HBP and LBBP, is associated with narrower QRS duration compared to conventional pacing. Narrowing of QRS duration is related to a lower electromechanical desynchrony, and thus, HBP and LBBP may confer lower incidence of adverse cardiac events from pacing-induced cardiomyopathy.

Limitations

QRS duration was the only parameter analyzed in our study. Other markers of synchronous contraction were not specified in included studies, precluding further analysis. Nevertheless, many studies have suggested QRS duration is the best surrogate marker for cardiac synchronicity (34, 49). Since physiologic pacing, particularly LBBP, has been in the early phase of trials, the lack of clinical endpoints is inevitable. Further studies are required to establish health impacts among patients receiving either HBP or LBBP. Secondly, half of the studies we included in our analysis were observational studies. Thus, residual biases cannot be completely excluded. Despite this caveat, NOS criteria were adopted to stratify biases risks as well as study qualities, suggesting robust analysis. Thirdly, the total number of patients in our study was small, possibly leading to an underestimation of the actual effects. Lastly, almost all the studies were done in centers with expertise in physiologic pacing. Therefore, the success rates and results might not be applicable to general or low volume clinical settings. Despite these limitations, this study is the first network meta-analysis to provide the most updated comparison of the performance of physiologic pacing compared to conventional pacing.

Conclusion

Our study has demonstrated that HBP and LBBP result in narrower QRS duration compared to biventricular pacing and conventional RV pacing. Although clinical outcomes were not studied, these results suggest the advantage of near-normal ventricular depolarization in physiologic pacing interventions. Further analysis should be done to demonstrate the clinical benefit of physiologic pacing. We believe that new battery systems, delivery tools, and lead technologies being developed in the near future will be the key to improved feasibility and success rate of physiologic pacing interventions.

Abbreviations

BBB: Bundle Branch Block

BiV: Biventricular pacing

CRT: Cardiac resynchronization therapy

CIED: Cardiac implantable electronic device

HBP: His bundle pacing

LBBP: Left bundle branch pacing

NMA: Network Meta-Analysis

PCM: Pacemaker induced cardiomyopathy

RV: Right Ventricle

Declarations

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Table

Table 1

Author	Year	Study type	Population	Pacing indication	RV	CRT	His pacing	LBBP	Outcome	Quality assessment
Abdelrahman	2018	Observational study	765	Sinus node dysfunction and AV node dysfunction	Y	N	Y	N	QRS duration	Good quality (0)
Albertsen	2008	Randomized	679	AV block	Y	Y	N	N	QRS duration	
Cai	2019	Observational study	78	Sinus node dysfunction	Y	N	N	Y	QRS duration	Good quality (0)
Chan	2011	Randomized controlled trial	177	Sinus node dysfunction and AV node dysfunction	Y	Y	N	N	QRS duration	
Guarav	2019	Randomized controlled trial	41	CRT indication	N	Y	Y	N	QRS duration	
Hou	2019	Observational study	59	Sinus node dysfunction and AV node dysfunction	Y	N	Y	Y	QRS duration	Good quality (0)
Hu	2020	Observational study	50	AV block	N	N	Y	Y	QRS duration	Good quality (0)
Hua	2020	Observational study	224	Sinus node dysfunction and AV node dysfunction	N	N	Y	Y	QRS duration	Good quality (0)
Lustgarten	2015	Randomized crossover	29	CRT indication	N	N	Y	Y	QRS duration	
Occhetta	2006	Randomized crossover	16	AV node ablation for AF	Y	N	Y	N	QRS duration	
Sharma	2014	Observational study	192	Sinus node dysfuntion and AV node dysfunction	Y	N	Y	N	QRS duration	Good quality (0)
Stockburger	2011	Randomized	108	Sinus node dysfunction and AV node dysfunction	Y	Y	N	N	QRS duration	
Wang	2019	Randomized	131	Sinus node dysfunction and AV node dysfunction	Y	N	N	Y	QRS duration	
Wang	2020	Observational study	40	CRT indication	N	Y	N	Y	QRS duration	Fair quality (1)
Wu	2020	Observational study	137	CRT indication	N	Y	Y	Y	QRS duration	Good quality (0)
Zhang	2020	Randomized	235	Sinus node dysfunction and AV	Y	N	N	Y	QRS duration	

		node dysfunction	

Figures

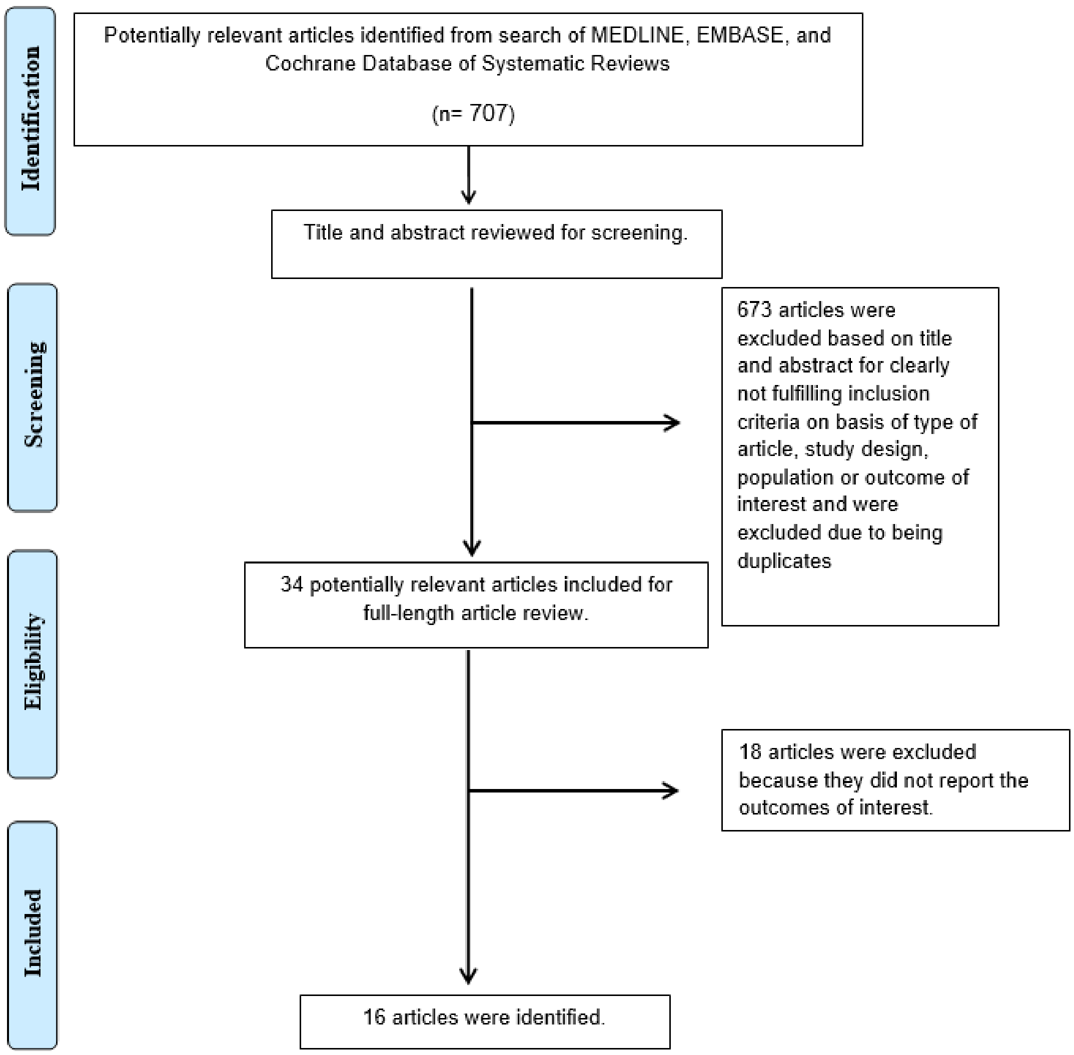

Figure 1

The literature retrieval, review and selection process

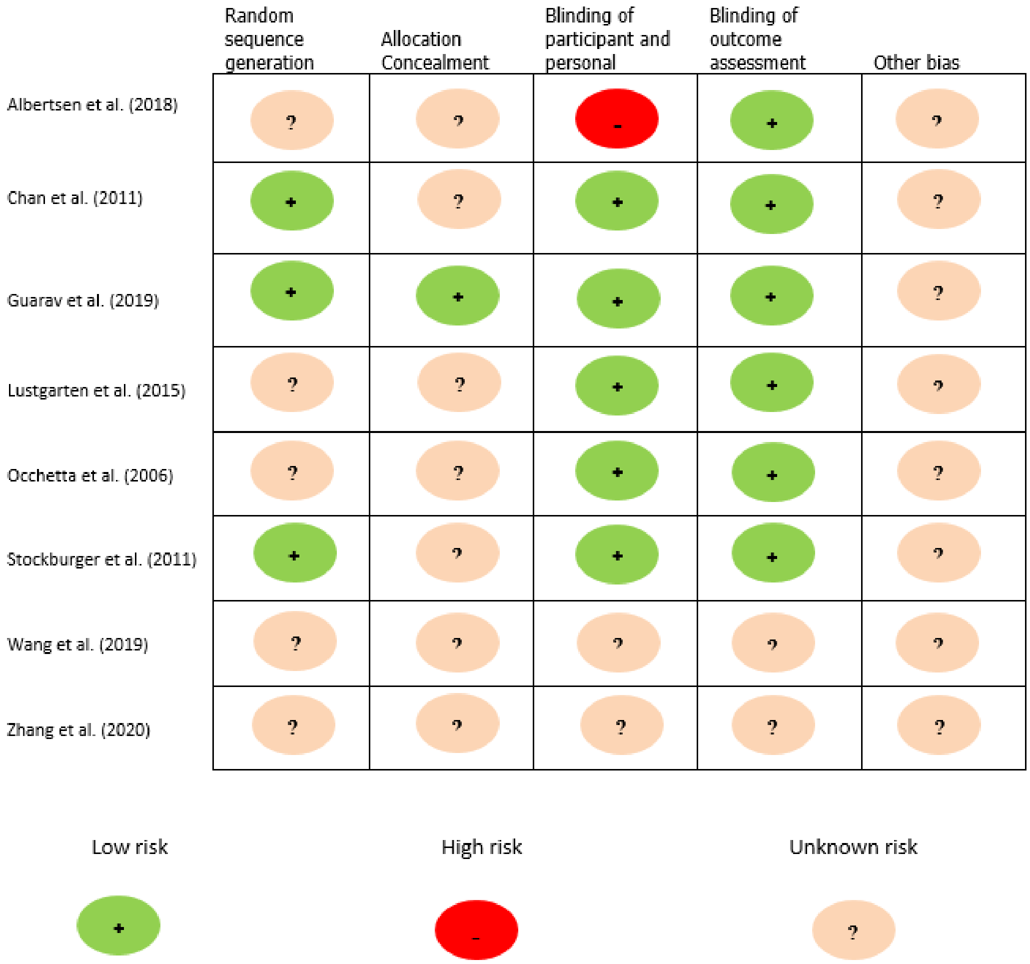

Figure 2

Cochrane risk of bias assessment

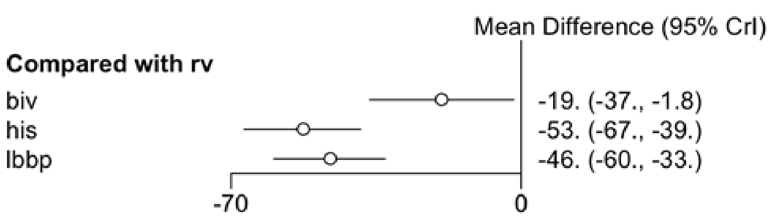

Figure 3

Forest plot demonstrating relative effect size compared to those with conventional RV pacing.

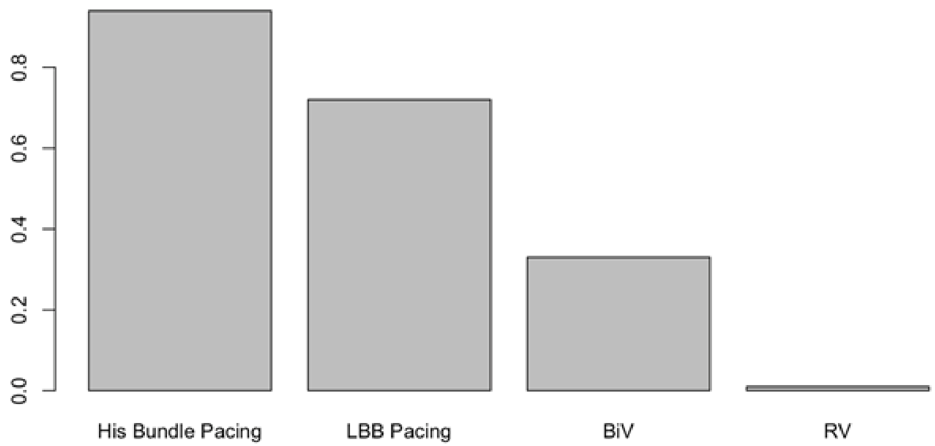

Figure 4

SUCRA ranking plot

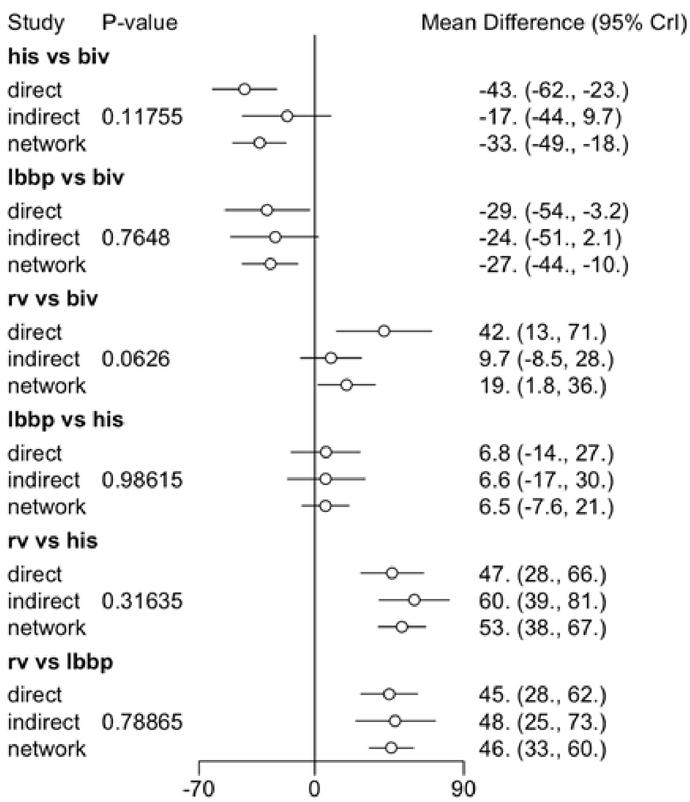

Figure 5

Node Splitting

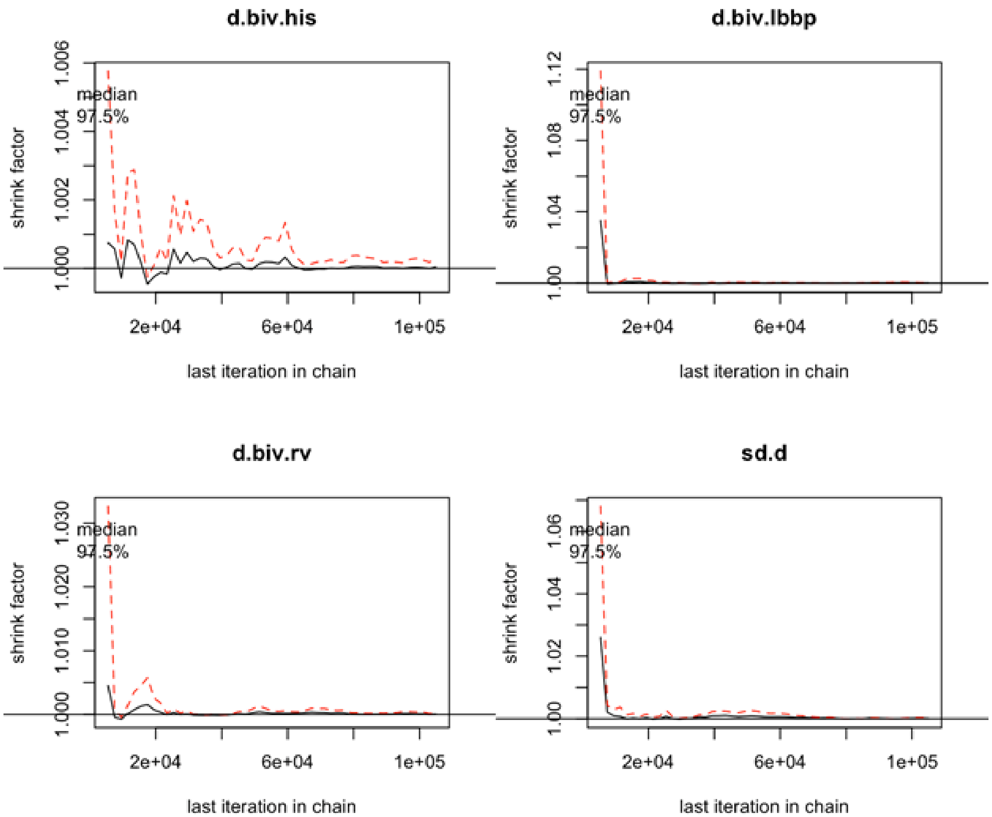

Figure 6

Gelman plot

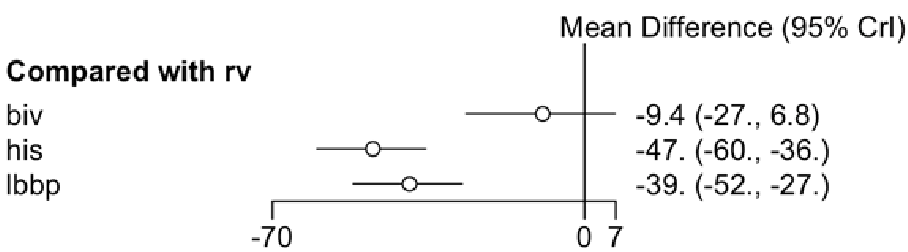

Figure 7

Low risk of biases studies

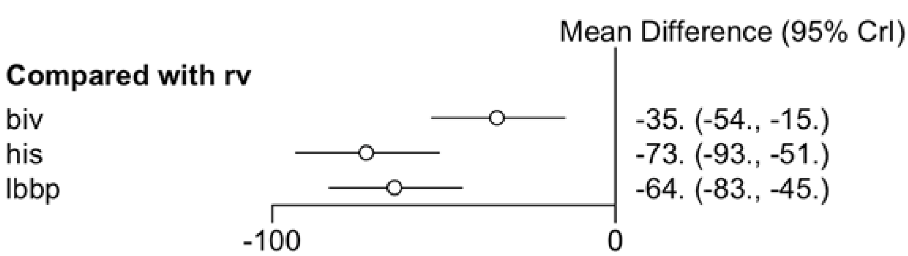

Figure 8

High risk of biases studies

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Onlinesupplementdata1.docx