Diagnostic Performance of Echocardiography for the Detection of Acute Cardiac Allograft Rejection: A Systematic Review and Meta-Analysis

Wei Lu, Jun Zheng, Xudong Pan, Lizhong Sun

1 Department of Cardiac surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing, 100029, China, 2 Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, 100029, China

These authors contributed equally to this work.
* lizhongsun@outlook.com

Abstract

Objective

Many studies have addressed the diagnostic performance of echocardiography to evaluate acute cardiac allograft rejection compared with endomyocardial biopsy. But the existence of heterogeneity limited its clinical application. Thus, we conducted a comprehensive, systematic literature review and meta-analysis for the purpose.

Methods

Studies prior to September 1, 2014 identified by Medline/PubMed, EMBASE and Cochrane were examined by two independent reviews. We conducted meta-analysis by using Meta-DiSc 1.4 software. An assessment tool of QUADAS-2 was applied to evaluate the risk of bias and applicability of the studies.

Results

Thirty studies met the inclusion criteria of meta-analysis. The four parameters of pressure half time, isovolumic relaxation time, index of myocardial performance and late diastolic mitral annular motion velocity were included in the meta-analysis, with a pooled diagnostic odds ratio of 10.43, 6.89, 15.95 and 5.68 respectively, and the area under the summary receiver operating characteristic curves value of 0.829, 0.599, 0.871 and 0.685 respectively.

Conclusion

The meta-analysis and systematic review demonstrate that no single parameter of echocardiography showed a reliable diagnostic performance for acute cardiac allograft rejection. A result of echocardiography for ACAR should be comprehensively considered by physicians in the context of clinical presentations and imaging feature.
Introduction

Presently, heart transplantation (HTX) is the only effective treatment modality for end-stage heart diseases. Despite the improvements of prognosis for HTX patients over the past 20 years, acute cardiac allograft rejection (ACAR) remains the most common complication during the first year after transplantation. Approximately 40% of patients will experience at least one episode of ACAR within this period. Furthermore, ACAR contributes to approximately 12% of mortality between 1 and 12 months of post-transplantation, and was an independent risk factor for developing into cardiac allograft vasculopathy (CAV), an irreversible stage to final allograft dysfunction. Even with effective treatments, an episode of ACAR occurring in the first year will increase two-year and four-year fatalities [1]. Therefore, early detecting and curbing ACAR is essential to the survival of HTX patients.

However, clinical features of ACAR are not consistent, for patients usually remain asymptomatic until hemodynamic compromise occurs. Invasive surveillance procedure is obligatory to perform routinely and frequently in order to detect ACAR in an earlier stage. Timely diagnosis following by early immunosuppressive treatment, will prevent rejection from developing into more severe grade, with the aim of achieving better long-term result [1]. Right ventricular endomyocardial biopsy (EMB) still represents the clinical gold standard in monitoring cardiac allograft rejection. Nevertheless, this invasive diagnostic procedure is uncomfortable and concomitant with several, albeit rare, major complications such as carotid artery puncture, cardiac tamponade and permanent heart block. EMB also has a number of limitations like sample error and myocardial scarring[2,3]. Non-invasive but equally accurate technique to detect rejection is highly desirable.

Many promising modalities have been tried to develop a sensitive and specific non-invasive method. Of the many diagnostic techniques, echocardiography is the most ubiquitous tool for monitoring ACAR since it is easily performable, time-saving, and not associated with the risks of the invasive methods [4]. Its versatility allows it to be applied in a wide variety of circumstances during the post-transplant period. Some studies have addressed the diagnostic accuracy of echocardiography to assess the rejection grade of ACAR compared with EMB. But the methodological heterogeneity, such as different parameters and cutoff value, which led to conflicting outcomes among individual studies, limited the clinical application of echocardiography. It is necessary to further assess the diagnostic value of echocardiography for the detection of ACAR. Accordingly, we seek a comprehensive, systematic literature review and meta-analysis for the purpose.

Methods

Study Protocol

The analysis complied with a predetermined protocol [5]. The data were collected according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (S1 PRISMA Checklist).

Data resource and Search strategy

We systematically searched the Cochrance clinical trials database, Medline/Pubmed and EMBASE to identify eligible studies prior to September 1, 2014. No starting date was limited. In addition to database searches, we reviewed the references of included studies and other relevant review articles to obtain a comprehensive list of included studies. Two authors (W.L. and J.Z.) searched and reviewed database independently. Disagreements were resolved by discussion or upon consensus from a third reviewer. We used the following Medical Subject
Headings and search terms: “echocardiography,” “heart transplantation” and “graft rejection.” The searching formula is shown below.

**Medline search formula.** ((("Echocardiography"[Mesh]) OR (echocardiography OR sonography OR ultrasonic OR doppler OR echo OR ultrasound OR ultrasonography)) AND ((("heart transplantation"[MeSH Terms] OR heart transplantation[Text Word]) AND ("graft rejection"[MeSH Terms] OR graft rejection[Text Word]))) OR ((cardiac OR heart) AND (transplantation OR transplant OR allograft OR graft*) AND (rejection OR reject)))

**Embase search formula.** 'Echocardiography' OR 'echocardiography'/exp OR echocardiography OR echo OR ultrasonic OR doppler OR ultrasound AND ('heart' OR 'heart'/exp OR heart OR cardiac) AND ('transplantation' OR 'transplantation'/exp OR transplantation OR transplanted OR transplant OR 'allograft' OR 'allograft'/exp OR allograft) AND (rejection OR reject) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([article]/lim OR [article in press]/lim) AND [english]/lim AND [humans]/lim AND [embase]/lim.

**Study selection**

Selection criteria ☑ for Meta-analysis: (I) Type of study: Diagnostic accuracy test. (II) Population: Underwent HTX with all age spectrums. (III) Index test: echocardiography. (IV) Reference standard: EMB. (V) Language: Published in English. (VI) True-positive (TP), false-positive (FP), true-negative (TN) and false negative (FN) data were available or could be derived from articles.

Selection criteria ☑ for summarization: (I) Type of study: Diagnostic accuracy test. (II) Population: Underwent HTX with all age spectrums. (III) Index test: echocardiography. (IV) Reference standard: EMB. (V) Language: Published in English.

Exclusion criteria: (I) Type of study: Reviews, case reports, editorial, conference presentations or animal researches. (II) Sample size <10 patients. (III) Duplicated data.

**Data extraction and quality assessment**

The following variables were extracted from each study: author, publication year, country, demographics characteristics of study population, study design (prospective or retrospective), recruitment method (consecutive or random), interval between echocardiography and EMB, blind, echocardiographic parameter, cutoff value, rejection grade of detection, reference of histological interpretation for rejection grade, and number of TP, FP, TN and FN. If studies enrolled all of subjects during a certain period, and conducted echocardiography and EMB on them, the recruitment method will be defined as “consecutive”, even if the studies did not describe the method. Two authors extracted the data from eligible studies independently (W.L. and J.Z.). The methodological quality of the eligible studies was assessed by two authors (XD.P. and J.Z.) independently using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2), an assessment tool used in systematic reviews to evaluate the risk of bias and applicability of primary diagnostic accuracy studies [6]. In the same way, disagreements were resolved by discussing together or appealing to a third author.

**Data synthesis and statistical analysis**

Meta-DiSc version 1.4 [7] statistical software was used for our study. Analysis process included four steps as follows. First of all, Spearman correlation coefficient between sensitivity (se) and specificity (sp), and p-value, were computed to explore heterogeneity arising from threshold effect. Subgroup analysis would be conducted according to different threshold variables. Secondly, non-threshold heterogeneity was explored by using inconsistency (I2) value and $\chi^2$ test [8]. I2 value within 25–49%, 50–74% or 75–100% was considered a low, moderate or high degree of
heterogeneity respectively [9]. Subsequently, sensitivity analysis was applied to explore the source in case of the existence of non-threshold heterogeneity, and DerSimonian-Laird random effects model was considered if necessary [10]. Otherwise, pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) with 95% confidence interval (CI) were calculated by using Mantel-Haenszel fixed effects models [8]. The pooled DOR was used for constructing summary receiver operating characteristic curve (SROC), with its Q point representing the maximal joint of sensitivity and specificity [11,12]. We also summarized all of the articles which met the selection criteria ②. If a study showed a certain index correlated with ACAR, the index would be marked as “+”, otherwise, marked as “–”.

Results

Database search and additional citation tracking of review and original articles produced 1391 potentially relevant citations, 683 from Medline/Pubmed, 708 from EMBASE and 0 from Cochrane library. After getting rid of ineligible articles, such as duplicated articles, case reports, reviews or animal researches, we submitted 61 studies for a full text review. Thirty one studies were excluded, in which, 16 articles failed to construct 2×2 table, 4 did not focus on diagnostic test, and 11 were correlated with cardiac allograft vasculopathy. Finally, 30 eligible studies were included in meta-analysis. The selection process is presented in Fig. 1.

Characteristics and quality of included articles

Thirty articles for meta-analysis were published during a long span of time, from 1988 to 2014 [13–42]. Prospective studies account for 73.3% (22/30) of all eligible studies. A total of 2100 patients was included in the analysis. Characteristics of included studies are shown in Table 1. Of all the studies, 15 studies (50.0%) consecutively recruited subjects for research. There are 11 studies (36.7%) complying with double-blind principle when interpreting index test and reference standards. Twenty seven studies (90.0%) performed EMB and echocardiography on the same day. EMB was used as a reference standard in all eligible studies. However, two studies included an additional clinical reference standard that patients presenting hemodynamic compromise, even with a negative histological result, were deemed to have ACAR [15,19]. Eight studies (26.7%) performed echocardiography using a pre-specified threshold value. Seven articles (23.3%) enrolled pediatric patients as research subjects. The risk of bias and applicability of the studies was evaluated based on QUADAS-2 summarized in S1 Fig. and S2 Fig.

Diagnostic information and accuracy

A total of 41 parameters [e.g. Pressure half time (PHT), isovolumic relaxation time (IVRT), index of myocardial performance (IMP), late diastolic mitral annular motion velocity (Am), early diastolic mitral annular motion velocity (Em)] was able to construct 2×2 table. Among them, the parameters of diastolic function accounted for 48.8% (20/41), and 29.2% (12/41) of parameters reflected systolic function. Seven studies supplied se and sp by combining two or more parameters to detect ACAR. Finally, the parameters of PHT, IVRT, IMP and Am were included in the meta-analysis, because the number of eligible studies using the other parameters is less than 3.

PHT

Four studies using PHT for detection of ACAR could construct 2×2 table [16,18,20,26]. Overall diagnostic performance of PHT was shown in Figs. 2 and 3. The Spearman correlation
coefficient was computed as a result of 0.00 with a P value 0.10, which suggested the absence of a threshold effect. For the existence of a high degree of heterogeneity, DerSimonian-Laird random effects model was introduced to pool diagnostic indices. Pooled se, sp, PLR, NLP, DOR and AUC of SROC curve was 0.41 (0.36–0.47), 0.91 (0.90–0.93), 5.26 (1.23–22.44), 0.65 (0.48–0.88), 10.43 (1.75–62.17) and 0.829, respectively. Sensitivity analysis demonstrated the high degree of heterogeneity was consistent after each study was removed, which indicated the heterogeneity might arise from multiple factors.

IVRT

Four studies employing IVRT could construct 2×2 table [16,18,26,38]. Overall diagnostic performance of IVRT was shown in Figs. 4 and 5. The Spearman correlation coefficient was computed as a result of 0.80 with a P value 0.20, which suggested no existence of a threshold effect. Except for the absence of heterogeneity in NLR, the other indices showed a high degree of
Table 1. Characteristics of eligible studies for meta-analysis.

| Study        | Year  | Country | Design | Study population | Enrollment method | Blind | Sample size | Interval Detection of grade | Parameters | Cutoff value |
|--------------|-------|---------|--------|------------------|-------------------|-------|-------------|------------------------------|------------|--------------|
| Angermann    | 1997  | Germany | P      | Adult            | Consecutive       | Single | 52          | ≥IB                          | PWED 2D-IB | 1.5dB²       |
| Asante-Korang| 2003  | USA     | P      | Child            | Consecutive       | Unclear| 20          | ≥IIIA                        | PWED 2D-IB | 5.5dB²       |
| Behera       | 2007  | USA     | R      | Child            | Unclear           | Double | 148         | ≥IB, AMR, clinical rejection| E/Em       | 5            |
| Ciliberto    | 1994  | Italy   | P      | Adult            | Unclear           | Single | 130         | ≥IA                          | PHT, IVRT  | 20ms         |
| Ciliberto    | 1996  | Italy   | P      | Adult            | Unclear           | Single | 30          | ≥IA                          | Multiple parameters |
| Desruennes   | 1988  | France  | P      | Adult            | Unclear           | Unin        | 26          | ≥IA                          | PHT, IVRT  | 20% decrease |
| Dandel       | 2001  | Germany | P      | Adult            | Single            | Unin        | 293         | ≥II, clinical rejection     | Sm,Em    | 10% decrease |
| Fauchier     | 1997  | France  | P      | Adult            | Double            | Unin        | 23          | ≥IA                          | PHT       | 20% decrease |
| Flanagan     | 2013  | USA     | R      | Child            | Unin              | Double     | 80          | <3 days                       | Relative change of IMP | ≥20.4%       |
| Kato         | 2010  | Japan   | P      | Adult            | Unin              | Single     | 35          | ≥IB                          | Systolic strain | −27.4%       |
| Lieback      | 1994  | Germany | P      | Adult            | Unin              | Single     | 23          | ≥II                          | Multiple parameters |
| Leonard      | 2005  | USA     | P      | Child            | Consecutive       | Unclear    | 21          | ≥II                          | IMP       | <0.44        |
| Lunze        | 2013  | USA     | R      | Child            | Consecutive       | Unclear    | 122         | ≥II, AMR                     | Relative change of Sm | 15%b        |
| Mankad       | 1999  | USA     | P      | Adult            | Consecutive       | Double     | 78          | ≥IB                          | Systolic strain | 135mm/s      |
| Moidl        | 1998  | Austria | R      | Adult            | Unclear           | Single     | 94          | ≥II                          | PFR       | <4 EDV/s      |
| Moully-Bandini| 1996 | France  | P      | Adult            | Unclear           | Double     | 23          | ≥IA                          | PHT, IVRT  | 20% decrease |
| Marciniak    | 2007  | Belgium | P      | Adult            | Consecutive       | Single     | 31          | ≥IB                          | Radial strain of LVPW | ≤30%        |
| Moran        | 2000  | USA     | P      | Child            | Consecutive       | Single     | 37          | ≥IIIA                        | Stress velocity index | −2         |
| Paika        | 2005  | Australia| P     | Adult            | Consecutive       | Double     | 44          | ≥IIIA                        | IVRMVG    | >0.1S⁻¹       |
| Patzer       | 2000  | USA     | P      | Child            | Consecutive       | Unclear    | 18          | ≥IIIA                        | ECHO-B score | ≥4         |
| Park         | 1992  | Germany | P      | Adult            | Unclear           | Single     | 96          | ≥II                          | Te        | 20% increase |
| Pan          | 2011  | China   | P      | Adult            | Consecutive       | Single     | 95          | ≥II                          | Tmsv 16-SD% | 1.73        |
| Roshanali    | 2010  | Iran    | P      | Adult            | Unclear           | Double     | 38          | ≥IIIA                        | (PWT + LVMI)-(Lat-S + Sep-TS) | 1           |
| Resende      | 2011  | Brazil  | P      | Adult            | Consecutive       | Double     | 54          | ≥IIIA                        | Am       | 7% decrease |
| Stengel      | 2001  | Switzerland | P | Adult            | Consecutive       | Double     | 41          | ≥IIIA                        | Am       | <8.7cm/s |

(Continued)
heterogeneity. Therefore, DerSimonian-Laird random effects model was used for pooling diagnostic indices. Pooled se, sp, PLR, NLP, DOR and AUC of SROC curve was 0.40 (0.35–0.45), 0.92 (0.90–0.93), 4.54 (1.51–13.62), 0.72 (0.66–0.79), 6.89 (2.31–20.51) and 0.599, respectively. Sensitivity analysis demonstrated the high degree of heterogeneity was consistent after each study was ruled out, which showed the heterogeneity might arise from multiple factors.

### Table 1. (Continued)

| Study          | Year | Country | Design | Population | Enrollment Method | Blind | Sample Size | Interval | Detection of Grade | Parameters | Cutoff Value |
|----------------|------|---------|--------|------------|-------------------|-------|--------------|----------|-------------------|------------|--------------|
| Sera [38]      | 2014 | USA     | R      | Adult      | Unclear           | Unclear| 59           | 0        | ≥IB               | Global longitudinal strain | <14.8%       |
| Sun [39]       | 2005 | USA     | P      | Adult      | Consecutive       | Single| 264          | 0        | ≥IB               | Am         | <9cm/s<sup>a</sup> |
| Sato [40]      | 2011 | Japan   | P      | Adult      | Consecutive       | Single| 32           | 0        | ≥II              | LV systolic torsion         | <90ms<sup>b</sup> |
| Toumanidis [41]| 2003 | Greece  | R      | Adult      | Consecutive       | Double| 24           | 0        | ≥IA              | IMP        | <0.69         |
| Vivekananthan  | 2002 | USA     | R      | Adult      | Unclear           | Double| 40           | 0        | ≥III A           | IMP        | 20% decrease   |

A, late diastolic mitral inflow velocity; Am, Late diastolic mitral annular motion velocity; AMR, antibody mediated rejection; Double, Echo blind to EMB and EMB blind to Echo; E, early diastolic mitral inflow velocity; Em, early diastolic mitral annular motion velocity; IMP, index of myocardial performance; Interval, interval between Echo and EMB; IVRMVG, Peak late isovolumic relaxation myocardial velocity gradient; IVRT, isovolumic relaxation time; LVPW, left ventricular posterior wall; LVMI, LV mass index; Lat-S, LV lateral peak systolic strain; P, Prospective; PWED 2D-IB, Posterior wall End-diastolic 2 dimension-Intergated backscatter; PHT, pressure half time; PFR, left ventricular peak filling rate; PWT, LV posterior wall thickness; R, retrospective; Single, Echo blind to EMB or EMB blind to Echo; Sep-TS, Septum time to systole; sm, systolic mitral annular motion velocity; Te, time interval between maximal posterior wall contraction and the point of peak posterior wall endocardium retraction velocity; Tmsv 16-SD, standard deviation of time to minimum systolic volume of ventricular segment of 16 segments.

<sup>a</sup>, cutoff value corresponding to different rejection grade.

<sup>b</sup>, cutoff value corresponding to different parameters.

**Fig 2. Pooled diagnostic odds ratio of pressure half time for detecting acute cardiac allograft rejection.** Random-effects models were applied to pool effect sizes. Each solid diamond represents a value of pooled diagnostic odds ratio. Sample size is indicated by the size of the square. CI, confidence interval; df, degrees of freedom; OR, odds ratio.

doi:10.1371/journal.pone.0121228.g002
IMP

Four studies applying IMP could construct 2×2 table [21,24,41,42]. Overall diagnostic performance of IMP was shown in Figs. 6 and 7. The Spearman correlation coefficient was computed as a result of 0.20 with a $P$ value 0.80, which suggested the absence of a threshold effect. $I^2$ value of se, sp, PLR, NLR and DOR were 57.1%, 68.5%, 70.9%, 65.2%, and 72.5%, respectively, and

![Symmetric SROC curve](image)

**Fig 3.** Summary receiver operator characteristic of pressure half time. The figure shows a symmetric curve with an area under the curve of 0.8292 and standard error of 0.1762. Each study is represented as a square in the summary receiver operating characteristic. The sample size is shown by the size of the square. AUC, area under the curve; SROC, Summary receiver operator characteristic; SE, standard error.

doi:10.1371/journal.pone.0121228.g003

**Fig 4.** Pooled diagnostic odds ratio of isovolumic relaxation time for detecting acute cardiac allograft rejection. Effect sizes were pooled by random-effects models.

doi:10.1371/journal.pone.0121228.g004
corresponding $P$ value of $\chi^2$ test were 0.07, 0.02, 0.01, 0.03, and 0.01, respectively. These results indicated a moderate degree of heterogeneity, and the source of heterogeneity was explored by sensitivity analysis. After removing the study of Toumanidis et al [41], which including detection for a relatively low grade of ACAR, IA and IB, homogeneity were achieved in se, NLR and DOR. However, sp and PLR still presented a moderate degree of heterogeneity. DerSimonian-Laird random effects model was used for pooling diagnostic indices. Pooled se, sp, PLR, NLP,

Fig 5. Summary receiver operator characteristic of isovolumic relaxation time. The figure shows a symmetric curve with an area under the curve of 0.5997 and standard error of 0.0392.

doi:10.1371/journal.pone.0121228.g005

Fig 6. Pooled diagnostic odds ratio of index of myocardial performance for detecting acute cardiac allograft rejection. Effect sizes were pooled by random-effects models.

doi:10.1371/journal.pone.0121228.g006
DOR and AUC of SROC curve was 0.78 (0.70–0.86), 0.74 (0.66–0.81), 3.27 (1.76–6.06), 0.25 (0.12–0.54), 15.95 (4.06–62.63) and 0.871, respectively.

Am

Four studies applying Am could construct 2×2 table [25,36,37,38]. Overall diagnostic performance of Am was shown in Figs. 8 and 9. The Spearman correlation coefficient was computed...
as a result of −0.40 with a $P$ value 0.60, which suggested the absence of a threshold effect. For the existence of a high degree of heterogeneity, the source of heterogeneity was explored by using sensitivity analysis. After removing the study of Sun et al [38], which included detection of a relatively low grade of ACAR, IB, homogeneity was achieved in NLR and DOR. However, sp still presented a high degree of heterogeneity, and PLR and se showed a moderate heterogeneity. DerSimonian-Laird random effects model was applied for pooling diagnostic indices. Pooled se, sp, PLR, NLP, DOR and AUC of SROC curve was 0.72 (0.66–0.78), 0.60 (0.56–0.63), 2.01 (1.29–3.13), 0.38 (0.20–0.75), 5.68 (1.92–16.78) and 0.685, respectively.

**Major parameters summarization**

A total of 46 articles (include 30 articles for meta-analysis) studied the correlation between a certain index and ACAR were enrolled for summarization [13–58]. The summary of correlation between 13 major parameters and ACAR was shown in Table 2. Among eligible studies, 50% (9/18) articles showed a decrease in PHT or deceleration time (DT) was relevant to ACAR, and 45% (9/20) studies showed a decrease in IVRT was relevant to ACAR. An existence of correlation between IMP and ACAR was supported by 62.5% (5/8) studies, and correlation between Am and ACAR presented in 70% studies (7/10). Only 4 parameters, IMP, Am, Em and Sm, showed more than 50% of correlation with ACAR. Several parameters, such as ejection fraction, fractional shortening and pericardial effusion, which are universally acknowledged as poor diagnostic performance in ACAR, were not included in the summary. Moreover, several...
Table 2. The summary of correlation between some major parameters and ACAR.

| Study                        | PHT or DT | IVRT | IMP | A    | E    | E/A | Am  | Em  | E/Em | Em/Am | Sm  | WT  | LVMI |
|------------------------------|-----------|------|-----|------|------|-----|-----|-----|------|-------|-----|-----|------|
| Angermann et al [13]         |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Asante-Korang et al [14]     |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Behera et al [15]            |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Ciliberto et al [16]         |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Desruennes et al [18]        |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Dandel et al [19]            |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Fauchier et al [20]          |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Flanagan et al [21]          |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Kato et al [22]              |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Leonard et al [24]           |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Lunze et al [25]             |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Moul-Bandini et al [26]      |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Mankad et al [27]            |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Moran et al [29]             |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Marciniak et al [30]         |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Putzer et al [32]            |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Palka et al [33]             |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Roshanali et al [35]         |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Resende et al [36]           |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Stengel et al [37]           |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Sun et al [38]               |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Sato et al [39]              |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Sera et al [40]              |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Toumanidis et al [41]        |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Vivekananthan et al [42]     |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Boyd et al [43]              |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Burgess et al [44]           |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Bader et al [45]             |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Eun et al [46]               |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Fabregas et al [47]          |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Mannaerts et al [48]         |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Miguel et al [49]            |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Neuberger et al [50]         |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Pauliks et al [51]           |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Prakash et al [52]           |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Rosenthal et al [53]         |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Stork et al [54]             |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Spes et al [55]              |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Stempfle et al [56]          |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Valantine et al [57]         |           |      |     |      |      |     |     |     |      |       |     |     |      |
| Valantine et al [58]         |           |      |     |      |      |     |     |     |      |       |     |     |      |
| **Number of “+”**            | 9/18       | 9/20 | 5/8 | 2/11 | 5/19 | 1/9 | 7/10 | 10/18 | 4/10 | 2/4 | 5/8 | 5/18 | 3/13 |
| **Percentage of “+”**        | 50%        | 45.0% | 62.5% | 18.2% | 26.3% | 11.1% | 70.0% | 55.5% | 40.0% | 50.0% | 62.5% | 27.8% | 23.1% |

A, late diastolic mitral inflow velocity; Am, Late diastolic mitral annular motion velocity; DT, deceleration time; E, early diastolic mitral inflow velocity; Em, early diastolic mitral annular motion velocity; IMP, index of myocardial performance; IVRT, isovolumic relaxation time; Sm, systolic mitral annular motion velocity; WT, ventricular wall thickness; +, the parameter correlates with rejection; −, the parameter does not correlate with rejection.

doi:10.1371/journal.pone.0121228.t002
parameters like ventricular wall strain or stress were excluded, since only two or three studies assessed them.

**Discussion**

Due to sampling error of EMB associated with the inhomogeneous nature of ACAR, histological "false negative" ACAR is reported to occur in up to 20% of patients [59]. Furthermore, EMB is an invasive, expensive and uncomfortable procedure to patients. These drawbacks prevent more frequent monitoring and, thus, limit optimal immunosuppressive therapy in time. Despite many imaging modalities have been developed, the noninvasive detection of ACAR remains a clinical challenge.

Acute cardiac allograft rejection is characterized by a series of pathological alterations, including microvascular antigen deposition, myocyte edema, interstitial hemorrhage, inflammatory cellular infiltration, and varying degrees of myocardial necrosis. These alterations will impair myocyte function, especially diastolic function in the early stage [60]. As mentioned in our study, diastolic indices of echocardiography, including PHT, DT, IVRT, early diastolic mitral inflow velocity (E wave), late diastolic mitral inflow velocity (A wave), E/A, Em, Am, E/Em, Em/Am, were the most popular parameters for screening ACAR. When ACAR occurs, diastolic function is impaired as a result of ventricular wall stiffness through inflammatory cellular infiltration and myocardial edema, thus causing a reduction of left ventricular (LV) compliance and reflecting on these indices [18].

PHT is the time interval for the peak pressure gradient to reach its half level and is the same as the interval for the peak velocity to decline to a velocity equal to the peak velocity divided by \( \sqrt{2} \) [61–63]. It is always proportionally related to DT. IVRT is an interval from the closure of the aortic valve to the onset of filling by opening the mitral valve [64]. The two indices can be used to systematically assess LV diastolic function. Decrease of PHT and IVRT in ACAR may reflect a decreased ventricular compliance due to the impairment of distensibility secondary to diffuse interstitial edema and inflammatory cellular infiltrate. Progression of edema and myocardial necrosis may increase the stiffness of elastic elements and shorten the rapid filling period [18]. A brisk increase LV diastolic pressure, which results in a rapid decrease of atrioventricular pressure gradient and premature closure of mitral valve, may lead to the decrease in PHT and IVRT [18]. However, the two diastolic indices, as is shown in our analysis, had a similarly poor performance for diagnosis of ACAR, only 40% of pooled sensitivity and 45% of correlation with rejection grade. Many factors, such as age, heart rate, loading condition, initial left atrial pressure, myocardial contractility and vasoactive agents, are known to affect LV filling [65–68,57]. Consequently, not only PHT and IVRT, but E wave and A wave are influenced secondary to the changes of LV filling. Second, a regional lesion in the early stage may only induce gentle alternation on diastolic indices. Moreover, for lack of autonomic regulation, donor heart will present with constant tachycardia and a restrictive ventricular filling pattern even in the absence of ACAR [37,69]. All these factors could explain the difficulties of these indices in the diagnosis of ACAR.

Am, Em and Sm derived from Doppler tissue motion parameters are new methods for evaluating left ventricular diastolic and systolic function. The myocardial contraction and relaxation velocities at the mitral annulus can more early and accurately detect ventricular dysfunction than PHT, IVRT, E and A wave [70,71]. During diastolic and systolic period, mean and peak motion velocity in different wall segments can be quantitatively acquired through tissue Doppler and pulse wave Doppler techniques. Analyzing the motion velocity of each ventricular wall during different cardiac cycle period might increase the diagnostic sensitivity, because this advantage, in theory, is in accord with the inhomogeneous pattern of
rejection, and this regional index might be superior to the global indices like PHT, IVRT, E and A wave. In our study, 70% (7/10) researches showed the correlation between Am and ACAR. More than 50% articles supported Em and Sm were relevant to ACAR. However, the existence of high heterogeneity and rather poor pooled results indicate these parameters are not sufficient to distinguish rejections. The high degree of heterogeneity may come from clinical diversity (e.g. adults or children), methodological diversity (e.g. cutoff value or rejection grade), and statistical diversity [72]. We explored the source of heterogeneity and found Dendel et al, Resende et al and Lunze et al using a relative cutoff value achieved higher se (81.8% ~ 94.7%) and sp (64.4% ~ 94.1%) than Sun et al, Resende et al and Palka et al using an absolute cutoff value, with se (67% ~ 76.3%) and sp (49% ~ 73.8%). It might be more reasonable to choose relative alternation to baseline as cutoff value compared with absolute value.

IMP, another Doppler-derived index reflecting systolic and diastolic function, is defined as the summation of isovolumic contraction time and isovolumic relaxation time divided by ejection time [73]. This parameter partially fuses E and A wave, and is relatively not influenced by heart rate and ventricular geometry [74,75]. It also seems to be independent of alternations in preload, afterload and mitral regurgitation [76–78]. During an episode of ACAR, especially in the early stage and mild rejections, LV diastolic function may be compromised primarily, and systolic function is usually well preserved. With the development of the disease, systolic dysfunction occurs [57,79]. IMP combining the two indices has a promise to present ideal performance in monitoring rejection. In the meta-analysis, the diagnostic performance of IMP seems to be superior to the other indices, with a DOR of 15.95 and AUC of 0.871. The correlation between IMP and ACAR was supported in 62.5% studies (5/8). Miguel et al discovered IMP in HTX patients with and without rejection were significantly higher than that in healthy control group. In addition, IMP in HTX patients with rejection was higher than that in HTX patients without rejection, but not reaching statistical level, [49]. Burgess et al demonstrated an absence of significant change in IMP between rejection group and Non-rejection group. However, there was a significant increase in IVCT and a significant decrease in IVRT during rejection. It is possible that the decrease of IVRT is counterbalanced by IVCT prolongation, and this may lead to no significant change in IMP [44].

Wall thickness and left ventricular mass index subject to operator dependent errors, are relatively rough parameters in echocardiography [37]. Furthermore, an increase in wall thickness detectable by echocardiography due to myocardial edema is a rather late event [3]. Other indices like ventricular strain, strain rate and two dimensional integrated backscatter have shown more than 85% se and sp. However, the highly technical dependence and low reproducibility limit their application [60].

There were 7 studies testing two or more parameters and significantly improving the diagnostic value on ruling out therapeutically relevant ACAR with a higher sensitivity and negative predictive value (NPV) compared to single parameter test. In view of invasive and “false-negative” nature of EMB, multi-parameter echocardiography may have the potential of non-invasive tool for inclusion of all clinical suspected ACAR. Because parts of sub-clinical ACAR have the tendency to progress into severe rejection, and grade 1B have been combined into grade 2R in the revision of the international society for heart and lung transplantation [80], multi-parameter echocardiography might be considered as an alternative modality for surveillance sub-clinical ACAR. However, due to a small number of studies and methodological diversity, these combined parameters were not able to be evaluated comprehensively by meta-analysis.
Limitations

Similar to other diagnostic meta-analysis, several limitations exist exactly in our study. First, studies ranged from 1988 to 2014, hence results may be affected by the progression of technique and device update. Second, only 4 studies applied 4 parameters in the meta-analysis. Because the number of eligible studies including other parameters is less than 3, hence, we cannot comprehensively evaluate their diagnostic performance. Third, the presence of high degree heterogeneity may have overestimated or under estimated the actually diagnostic accuracy. Moreover, 19 eligible studies did not mention double-blind principle, thus, it might increase the possibility of review bias; only 15 studies were confirmed to have enrolled patients consecutively that might cause selection bias; patients with atrial fibrillation or arrhythmia were excluded from some researches might also generate selection bias; all of eligible study published in English that could result in publication bias. Finally, the sample size of meta-analysis is relatively small. A larger sample size could acquire more reliable results.

Conclusion

Although the existence of limitations, to our knowledge, this is the first meta-analysis to explore the diagnostic value of echocardiography in ACAR. The meta-analysis and systematic review demonstrate that no single parameter of echocardiography was able to provide a reliable performance in diagnosing ACAR. A result of echocardiography for ACAR should be comprehensively considered by physicians in the context of clinical presentations and imaging feature. Multi-parameter screening and several new techniques still need to be evaluated in the future.

Supporting Information

S1 PRISMA Checklist.

(TIF)

S1 Fig. Assessment of methodological quality according to QUADAS-2.

(TIF)

S2 Fig. Summary of methodological quality according to QUADAS-2.

(TIF)

Author Contributions

Conceived and designed the experiments: LZS. Performed the experiments: WL JZ. Analyzed the data: WL JZ. Contributed reagents/materials/analysis tools: XDP. Wrote the paper: WL JZ XDP LZS. Checked the manuscript before submission: LZS XDP. Assessment of methodological quality: XDP JZ. Resolved disagreements when necessary: LZS XDP.

References

1. Stehlik J, Edwards LB, Kucheryavaya AY, Aurora P, Christie JD, Kirk R, et al. The registry of the international society for heart and lung transplantation: Twenty-seventh official adult heart transplant report–2010. J Heart Lung Transplant. 2010; 29:1089–1103. doi:10.1016/j.healun.2010.08.007 PMID: 20870164

2. Baraldi-Junkins C, Levin HR, Kasper EK, Rayburn BK, Herskowitz A, Baughman KL. Complications of endomyocardial biopsy in heart transplant patients. J Heart Lung Transplant. 1993; 12:63–67. PMID: 8443204

3. Spiegelhalter DJ, Stovin PG. An analysis of repeated biopsies following cardiac transplantation. Stat Med. 1983; 2:39–40. PMID: 6359316
4. Mena C, Wencker D, Krumholz HM, McNamara RL. Detection of heart transplant rejection in adults by echocardiographic diastolic indices: a systematic review of the literature. J Am Soc Echocardiogr. 2006; 19(10):1295–300. PMID: 17000376

5. Deeks JJ. Systematic reviews in health care: Systematic reviews of evaluations of diagnostic and screening tests. BMJ. 2001; 323: 157–162. PMID: 11463691

6. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; 155:529–36. doi: 10.7326/0003-4819-155-8-201110180-00009 PMID: 22007046

7. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006; 6:31. PMID: 16836745

8. Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. Stat Med. 2002; 21:1525–37. PMID: 12111918

9. Ferreira ML, Smeets RJ, Kamper SJ, Ferreira PH, Machado LA. Can we explain heterogeneity among randomized clinical trials of exercise for chronic back pain? A meta-regression analysis of randomized controlled trials. Phys Ther 2010; 90:1383–403. doi:10.2522/ptj.20090332 PMID: 20671101

10. Copas J, Shi JQ. Meta-analysis. funnel plots and sensitivity analysis. Biostatistics. 2000; 1(3):247–62. PMID: 12933507

11. Irwig L, Macaskill P, Glasziou P, Fahey M. Meta-analytic methods for diagnostic test accuracy. J Clin Epidemiol. 1995; 48: 119–30; discussion 131–2. PMID: 7853038

12. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med. 1993; 12: 1293–1316. PMID: 8210827

13. Angermann CE, Nassau K, Stempiel HU, Krüger TM, Drewello R, Junge R, et al. Recognition of acute cardiac allograft rejection from serial integrated backscatter analyses in human orthotopic heart transplant recipients. Comparison with conventional echocardiography. Circulation. 1997; 95(1):140–50. PMID: 8994429

14. Asante-Korang A, Fickey M, Boucek MM, Boucek RJ Jr, et al. Diastolic performance assessed by tissue Doppler after pediatric heart transplantation. J Heart Lung Transplant. 2004; 23(7):865–72. PMID: 15261182

15. Behera SK, Trang J, Feeley BT, Levi DS, Alejos JC, Drant S. The use of Doppler tissue imaging to predict cellular and antibody-mediated rejection in pediatric heart transplant recipients. Pediatr Transplantation. 2008; 12:207–214. doi: 10.1111/j.1399-3046.2007.00812.x PMID: 18307670

16. Ciliberto GR, Mascarello M, Gronda E, Bonacina E, Anjos MC, Danzi G, et al. Acute rejection after heart transplantation: noninvasive echocardiographic evaluation. J Am Coll Cardiol. 1994; 23(5): 1156–61. PMID: 8179380

17. Ciliberto GR, Pingitore A, Mangiavacchi M, Alberti A, Paterni M, Picano E. The clinical value of blunting of cyclic gray level variation for the detection of acute cardiac rejection: A two-dimensional, doppler, and videodensitometric ultrasound study. J Am Soc Echocardiogr. 1996; 9(3):306–13. PMID: 8736015

18. Desruennes M, Corcos T, Cabrol A, Gandjbakhch I, Pavie A, Léger P, et al. Doppler echocardiography for the diagnosis of acute cardiac allograft rejection. J Am Coll Cardiol. 1988; 12(1):63–70. PMID: 3288679

19. Dandel M, Hummel M, Müller J, Meyer R, Solowojowa N, Ewert R, et al. Reliability of tissue Doppler wall motion monitoring after heart transplantation for replacement of invasive routine screenings by optimally timed cardiac biopsies and catheterizations. Circulation. 2001; 104(12 Suppl 1):I184–91. PMID: 11568053

20. Fauchier L, Sirinelli A, Aupart M, Babuty D, Marchand M, Pottier JM. Performances of Doppler echocardiography for diagnosis of acute, mild, or moderate cardiac allograft rejection. Transplant Proc. 1997; 29(5):2442–5. PMID: 9270803

21. Flanagan R, Cain N, Tatum GH, Debrunner MG, Drant S, Feingold B. Left ventricular myocardial performance index change for detection of acute cellular rejection in pediatric heart transplantation. Pediatr Transplant. 2013; 17(8):782–6. doi: 10.1111/petr.12153 PMID: 24118848

22. Kato TS, Oda N, Hashimura K, Hashimoto S, Nakatani T, Ueda HI, et al. Strain rate imaging would predict sub-clinical acute rejection in heart transplant recipients. Eur J Cardiothorac Surg. 2010; 37 (5):1104–10. doi: 10.1016/j.ejcts.2009.11.037 PMID: 20031437

23. Lieback E, Meyer R, Nawrocki M, Bellach J, Hetzer R. Noninvasive diagnosis of cardiac rejection through echocardiographic tissue characterization. Ann Thorac Surg. 1994; 57(5):1164–70. PMID: 8179380
24. Leonard GT Jr, Fricker FJ, Pruett D, Harker K, Williams B, Schowengerdt KO Jr. Increased myocardial performance index correlates with biopsy-proven rejection in pediatric heart transplant recipients. J Heart Lung Transplant. 2006; 25(1):61–6. PMID: 16399532

25. Lunze FI, Colan SD, Gauvreau K, Perez-Atayde AR, Smith RN, Blume ED, et al. Tissue Doppler imaging for rejection surveillance in pediatric heart transplant recipients. J Heart Lung Transplant. 2013; 32(10):1027–33. doi: 10.1016/j.healun.2013.06.016 PMID: 23937884

26. Mouly-Bandini A, Vion-Dury J, Viout P, Mesana T, Cozzone PJ, Montiès JR. Value of Doppler echocardiography in the detection of low-grade rejections after cardiac transplantation. Transpl Int. 1996; 9(2):131–6. PMID: 8639254

27. Mankad S, Murali S, Kormos RL, Mandarino WA, Gorcsan J 3rd. Evaluation of the potential role of color-coded tissue Doppler echocardiography in the detection of allograft rejection in heart transplant recipients. Am Heart J. 1999; 138(4 Pt 1):721–30. PMID: 10502219

28. Moidl R, Chevthich O, Simon P, Grimm M, Wieselthaler G, Ullrich R, et al. Noninvasive monitoring of peak filling rate with acoustic quantification echocardiography accurately detects acute cardiac allograft rejection. J Heart Lung Transplant. 1999; 18(3):194–201. PMID: 10328144

29. Moran AM, Lipshultz SE, Rifai N, O’Brien P, Mooney H, Perry S, et al. Non-invasive assessment of rejection in pediatric transplant patients: serologic and echocardiographic prediction of biopsy-proven myocardial rejection. J Heart Lung Transplant. 2000; 19(8):756–64. PMID: 10967269

30. Marciniak A, Erogul E, Marciniak M, Sirbu C, Herbots L, Drooghe W, et al. The potential clinical role of ultrasonic strain and strain rate imaging in diagnosing acute rejection after heart transplantation. Eur J Echocardiogr. 2007; 8(3):213–21. PMID: 16716752

31. Park JW, Warnecke H, Deng M, Schüller S, Heinrich KW, Hetzer R. Early diastolic left ventricular function as a marker of acute cardiac rejection: a prospective serial echocardiographic study. Int J Cardiol. 1992; 37(3):351–9. PMID: 14688191

32. Putzer GJ, Cooper D, Keehn C, Asante-Korang A, Boucek MM, Boucek RJ Jr. An improved echocardiographic rejection-surveillance strategy following pediatric heart transplantation. J Heart Lung Transplant. 2000; 19(12):1166–74. PMID: 11124486

33. Palka P, Lange A, Galbraith A, Duhig E, Clarke BE, Parsonage W, et al. The role of left and right ventricular early diastolic Doppler echocardiographic indices in the evaluation of acute rejection in orthotopic heart transplant. J Am Soc Echocardiogr. 2005; 18(2):107–15. PMID: 15682046

34. Pan C, Wang C, Pan W, Shu X, Chen H. Usefulness of real-time three-dimensional echocardiography to quantify global left ventricular function and mechanical dyssynchrony after heart transplantation. Acta Cardiol. 2011; 66(3):365–70. PMID: 21744707

35. Roshanali F, Mandegar MH, Bagheri J, Sarzaeem MR, Chitsaz S, Alaeddini F, et al. Echo rejection score: new echocardiographic approach to diagnosis of heart transplant rejection. Eur J Cardiothorac Surg. 2010; 38(2):176–80. doi: 10.1016/j.ejcts.2009.12.045 PMID: 20356757

36. Resende MV, Vieira ML, Bacal F, Andrade JL, Stolf NA, Bocchi EA. Tissue doppler echocardiography in the diagnosis of heart transplantation rejection. Arq Bras Cardiol. 2011; 97(1):8–16. PMID: 21584480

37. Stengel SM, Allemann Y, Zimmerli M, Lipp E, Kucher N, Mohaci P, et al. Doppler tissue imaging for assessing left ventricular diastolic dysfunction in heart transplant rejection. Heart. 2001; 86(4):432–7. PMID: 11559685

38. Sun JP, Abdalla IA, Asher CR, Greenberg NL, Popović ZB, Taylor DO, et al. Non-invasive evaluation of orthotopic heart transplant rejection by echocardiography. J Heart Lung Transplant. 2005; 24(2):160–5. PMID: 15701431

39. Sato T, Kato TS, Komamura K, Hashimoto S, Shishido T, Mano A, et al. Utility of left ventricular systolic torsion derived from 2-dimensional speckle-tracking echocardiography in monitoring acute cellular rejection in heart transplant recipients. J Heart Lung Transplant. 2010; 30(5):536–43. doi: 10.1016/j.healun.2010.10.014 PMID: 21183361

40. Sera F, Kato TS, Farr M, Russo C, Jin Z, Marboe CC, et al. Left ventricular longitudinal strain by speckle-tracking echocardiography is associated with treatment-requiring cardiac allograft rejection. J Card Fail. 2014; 20(5):359–64. doi: 10.1016/j.cardfail.2014.02.006 PMID: 24561182

41. Toumanidis ST, Papadopoulou ES, Saridakis NS, Kalantaridou AT, Apagitos EV, Nanas JN, et al. Evaluation of myocardial performance index to predict mild rejection in cardiac transplantation. Clin Cardiol. 2004; 27(6):352–8. PMID: 15237696

42. Vivekananthan K, Kalapura T, Mehran M, Lavie C, Milani R, Scott R, et al. Usefulness of the combined index of systolic and diastolic myocardial performance to identify cardiac allograft rejection. Am J Cardiol. 2002; 90(5):517–20. PMID: 12208413
43. Boyd SY, Mego DM, Khan NA, Rubal BJ, Gilbert TM. Doppler echocardiography in cardiac transplant patients: allograft rejection and its relationship to diastolic function. J Am Soc Echocardiogr. 1997; 10 (5):526–31. PMID: 9203492

44. Burgess MI, Bright-Thomas RJ, Yonan N, Ray SG. Can the index of myocardial performance be used to detect acute cellular rejection after heart transplantation? Am J Cardiol. 2003; 92(3):308–11. PMID: 12888141

45. Bader FM, Islam N, Mehta NA, Ray SG. Noninvasive diagnosis of cardiac allograft rejection using echocardiography indices of systolic and diastolic function. Transplant Proc. 2003; 43(10):3877–81. doi: 10.1016/j.transproceed.2011.09.039 PMID: 22172863

46. Eun LY, Gajarski RJ, Graziano JN, Ensing GJ. Relation of left ventricular diastolic function as measured by echocardiography and pulmonary capillary wedge pressure to rejection in young patients (< or = 31 years) after heart transplantation. Am J Cardiol. 2005; 96(6):857–60. PMID: 16169377

47. Fábregas RI, Crespo-Leiro MG, Muñiz J, Regueiro M, Rodríguez JA, Álvarez N, et al. Usefulness of pulsed Doppler tissue imaging for noninvasive detection of cardiac rejection after heart transplantation. Transplant Proc. 1999; 31(6):2545–7. PMID: 10500710

48. Miguel GA, Rojas SS, Vieira RW, Silva JP, Abensur H. Role of echocardiography in the ventricular assessment of the transplanted heart versus heart rejection. Arq Bras Cardiol. 2012; 99(5):1031–9. PMID: 23138670

51. Prakash A, Printz BF, Lamour JM, Addonizio LJ, Glickstein JS. Myocardial performance index in pediatric patients after cardiac transplantation. J Am Soc Echocardiogr. 2004; 17(5):439–42. PMID: 15122183

52. Prakash A, Printz BF, Lamour JM, Addonizio LJ, Glickstein JS. Myocardial performance index in pediatric patients after cardiac transplantation. J Am Soc Echocardiogr. 2004; 17(5):439–42. PMID: 15122183

58. Valantine HA, Hatle LK, Appleton CP, Gibbons R, Popp RL. Variability of Doppler echocardiographic indexes of left ventricular filling in transplant recipients and in normal subjects. J Am Soc Echocardiogr. 1990; 3(4):276–84. PMID: 2206544

59. Tang ZY, Kobashigawa J, Raffel M, Stern LM, Hamilton M. The natural history of biopsy-negative rejection after heart transplantation. J Transplant. 2013; 2013:236720. doi: 10.1155/2013/236720 PMID: 24490053

60. Miller CA, Fildes JE, Ray SG, Doran H, Yonan N, Williams SG, et al. Non-invasive approaches for the diagnosis of acute cardiac allograft rejection. Heart. 2013; 99(7):445–53. doi: 10.1136/heartjnl-2012-302759 PMID: 23257172

61. Libanoff AJ, Rodbard S. Atrioventricular pressure half-time. Measure of mitral valve orifice area. Circulation. 1968; 38(1):144–50. PMID: 11712283
62. Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. Circulation. 1979; 60(5):1096–104. PMID:487543

63. Thomas JD, Weyman AE. Doppler mitral pressure half-time: a clinical tool in search of theoretical justification. J Am Coll Cardiol. 1987; 10(4):923–9. PMID:3309007

64. Bloch KE, Jugoon S, Sackner MA. Inductance cardiography (thoracocardiography): a novel, noninvasive technique for monitoring left ventricular filling. J Crit Care. 1999; 14(4):177–85. PMID:10622752

65. Choong CY, Herrmann HC, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. J Am Coll Cardiol. 1987; 10(4):800–8. PMID:2958532

66. Ishida Y, Meisner JS, Tsujioka K. Left ventricular filling dynamics: influence of left ventricular relaxation and left atrial pressure. Circulation. 1986; 74(1):187–96. PMID:3708773

67. Louie EK, Rich S, Brundage BH. Doppler echocardiographic assessment of impaired left ventricular filling in patients with right ventricular pressure overload due to primary pulmonary hypertension. J Am Coll Cardiol. 1986; 8(6):1296–306. PMID:3782636

68. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol. 1988; 12(2):426–40. PMID:3392336

69. Rodriguez L, Garcia M, Ares M, Griffin BP, Nakatani S, Thomas JD. Assessment of mitral annular dynamics during diastole by Doppler tissue imaging: comparison with mitral Doppler inflow in subjects without heart disease and in patients with left ventricular hypertrophy. Am Heart J. 1996; 131:982–7. PMID:8615320

70. Sutherland GR, Stewart MJ, Groundstroem KW, Moran CM, Fleming A, Guell-Peris FJ, et al. Color Doppler myocardial imaging: a new technique for the assessment of myocardial function. J Am Soc Echocardiogr. 1994; 7:441–58. PMID:7986541

71. Palka P, Lange A, Fleming AD, Sutherland GR, Fenn LN, McDicken WN. Doppler tissue imaging: myocardial wall motion velocities in normal subjects. J Am Soc Echocardiogr. 1995; 8:659–68. PMID:9417209

72. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available: www.cochrane-handbook.org.

73. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol. 1995; 26:135–136. PMID:7674144

74. Poulsen SH, Nielsen JC, Andersen HR. The influence of heart rate on the Doppler derived myocardial performance index. J Am Soc Echo. 2000; 13:379–384.

75. Eidem B, Tei C, O’Leary P, Cetta F, Seward JB. Nongeometric quantitative assessment of right and left ventricular function: Myocardial performance index in normal children and in patients with Ebstein anomaly. J Am Soc Echo. 1998; 11:949–856. PMID:9758376

76. Molier J, Poulsen S, Egstrup K. Effect of preload alterations on a new Doppler echocardiographic index of combined systolic and diastolic performance. J Am Soc Echo. 1999; 135:1065–1072.

77. Tei C, Nishimura R, Seward J, Tajik J. Noninvasive Doppler-derived myocardial performance index: Correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echo. 1997; 10:169–178. PMID:9083973

78. Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ, et al. New index of combined systolic and diastolic myocardial performance: A simple and reproducible measure of cardiac function—a study in normals and dilated cardiomyopathy. J Cardiol. 1995; 26:357–366. PMID:8558414

79. Amende I, Simon R, Seegers A. Diastolic dysfunction during acute cardiac allograft rejection. Circulation. 1990; 81(supplIII):III-66–III-70. PMID:2297863

80. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant. 2005; 24:1710–20. PMID:16297770