THORACIC ELECTRICAL BIOIMPEDANCE

Prepared for:
Agency for Health Care Research and Quality
U.S. Department of Health and Human Services
2101 East Jefferson Street
Rockville, MD 20852
http://www.ahrq.gov

Contract No. 290-97-0019
Task Order #10
EPC Technical Support of the CPTA Technology Assessment Program

Prepared by Tufts-New England Medical Center AHRQ Evidence-based Practice Center

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July 2, 2002 (rev. November 27, 2002)

Document must be viewed in “Page Layout” mode for all figures to display.

TABLE OF CONTENTS

Abstract

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Purpose: Thoracic electrical bioimpedance (TEB) is an alternative to invasive monitoring of hemodynamic parameters including cardiac output, stroke volume, and cardiac index. The Centers for Medicare and Medicaid Services (CMS) requested a technology assessment by the Agency for Health Care Research and Quality (AHRQ) to evaluate data on the clinical effectiveness of thoracic electrical bioimpedance (TEB) for several cardiovascular applications. The Tufts-New England Medical Center was asked to conduct a technology assessment on the literature published since an earlier report published in 1992 by the Agency for Health Care Policy and Research (now AHRQ).

Materials and Methods: We conducted a systematic review and meta-analysis of the TEB literature. We searched MEDLINE® using synonyms for “impedance cardiography;” the search strategy was restricted to the English language, to human subjects, and was conducted for the period from 1966 through January 2002. This search yielded more than 8000 articles. An updated search was performed on July 22, 2002. Inclusion criteria for articles included date of publication 1991 and onward, reporting on the methodology of TEB as a diagnostic and/or monitoring tool or TEB in comparison to another diagnostic technique for the clinical indications of interest. Seventy-seven articles were included in the evidence tables of this report.

We performed meta-analyses by constructing subgroups (i.e., inpatient, outpatient, emergency department, and years of publication – to account for most recent technology) for selected comparison techniques, equations used by the devices and hemodynamic parameters --- cardiac output, cardiac index, and stroke volume.

Results:

1. Accuracy of bioimpedance devices
The overwhelming majority of studies reported only the correlation coefficient of bioimpedance when compared to alternative techniques, such as thermodilution (TD). Correlation coefficients were in the range of -0.01 to 0.97. Correlation coefficients have serious limitations when used to summarize diagnostic test data, and there are no methodologic crosswalks which can allow correlation coefficients to reflect well-established parameters of accuracy, such as sensitivity

and specificity. There was significant between-study heterogeneity due to factors other than the factors that we used to stratify studies. The majority of the studies were done on the NCCOM device, a device that is no longer commercially produced. There is wide variation in results across the instruments; the variation could be due to differences in instrument performance, but there is not enough data available on any one instrument to draw conclusions about this. We also reported the bias (systematic error) and limits of agreement (random variation) in studies of TEB. The test for heterogeneity across studies was statistically significant for bias and limits of agreement for cardiac output for TD, suggesting that there may be patient populations where TEB measurements can be much farther from the TD measurement than the combined limits of agreement indicate.

Errors in placement of the leads, and clinical factors such as patient weight and presence of pulmonary edema, have been reported to affect results of measurements. Data on the effect of these factors have not been adequately reported in published literature with currently available commercial devices on the outpatient population of interest.

2. Clinical Results

A. MONITORING IN PATIENTS WITH SUSPECTED OR KNOWN CARDIOVASCULAR DISEASE

No studies provided information on health outcomes, patient management, or on clinical endpoints to address the usefulness of TEB in monitoring or management.

B. ACUTE DYSPNEA:

No studies were found that evaluated the clinical impact on patient management and/or improved health outcomes from the use of TEB monitoring for the differentiation of cardiogenic from pulmonary causes of acute dyspnea.

C. PACEMAKERS:

There were no well-designed studies for this indication that provided information on the clinical impact on patient management or improved health outcomes. For example, since none of the studies reported health outcomes after adjustment of the atrioventricular delay (AV) setting, the evidence is insufficient to conclude whether TEB optimization of the AV delay improves health outcomes.

D. INOTROPIC THERAPY:
No studies were found that evaluated the clinical impact on patient management and/or improved health outcomes from the use of TEB monitoring of patients in need of inotropic therapy.

E. POST-HEART TRANSPLANT EVALUATION:
Only one study reported sensitivity and specificity of TEB as a diagnostic test. In this study, TEB had a sensitivity and specificity of 71% and 100%, respectively, for detecting rejection in heart transplant patients, suggesting that, if this finding were replicated, TEB might be a useful adjunct to the standard test, myocardial biopsy.

F. CARDIAC PATIENTS WITH A NEED FOR FLUID MANAGEMENT:
Several studies were identified which assessed congestive heart failure patients with a need for fluid management with whole body impedance, but no such studies involving TEB were found.

G. HYPERTENSION:
Only one study reported patient outcomes, and this was a randomized study of the use of TEB compared to specialist care in guiding management of patients with resistant hypertension. In this study, patients who were monitored with TEB had a small, but statistically significant, lower blood pressure at the end of the study, compared to patients treated using clinical judgment. Blood pressure is a well-accepted intermediate result for health outcomes of interest such as lower rates of stroke. Despite the randomized design, the TEB group had a lower average blood pressure at the beginning of the study. The difference in blood pressure between groups at the end of the study was not much larger than the difference at the beginning. Patients in both the control and TEB groups had large reductions in blood pressure compared to their starting pressures, suggesting that the majority of the benefit may have been due to intensive management by expert specialists. The results may not be generalizable to community practice.

Conclusion: Due to limitations in the studies, no meaningful conclusions can be drawn about the accuracy of TEB, compared to alternative measures of hemodynamic parameters. There is also little conclusive evidence regarding TEB's usefulness in the specific clinical areas addressed. This was largely due to the lack of focus on clinical outcomes by researchers in this area. The clinical reports on the use of TEB for a variety of clinical indications in reports published from 1991 onwards suggested that this non-invasive method is of interest and may potentially support some of these indications, but there is little evidence that directly addressed how this monitoring technique can affect patient outcomes.

1. INTRODUCTION

Indicators of cardiac function, measured through invasive techniques such as pulmonary artery catheters, are often used for applications such as peri-operative monitoring of surgical patients. Thoracic electrical bioimpedance (TEB) cardiography is a noninvasive technology for cardiac output monitoring. TEB has been suggested as a replacement for invasive techniques in critically ill and surgical patients; due to the noninvasive nature of TEB, other applications have also been suggested in the outpatient setting. These applications include optimizing hemodynamic parameters in patients with congestive heart failure, patients with pacemakers, patients needing fluid management, and patients with other conditions.

TEB devices measure a variety of hemodynamic parameters, including

- Cardiac output --- the volume of blood pumped each minute by the heart (Tate, Seeley, Stephens, et al., 1994). Cardiac output is a function of the heart rate (pulse) and the stroke volume (amount of blood pumped by each ventricle of the heart in one contraction).

- Cardiac index --- although this measure is not widely used in practice, it is theoretically more useful than cardiac output, because it adjusts for patient weight and height.
- Ejection fraction --- this important indicator of cardiac function denotes the proportion of total blood in the ventricle pumped out of the heart in one contraction.

A variety of methods and devices have been developed to measure these parameters, and some of these are more invasive than others. Invasive techniques such as cardiac catheterization subject the patient to increased risk, are more complex and costly, and require more training. Another disadvantage of invasive techniques is that they are impractical in the outpatient setting (De Maria and Raisinghani, 2000). Non-invasive techniques that decrease risk but which provide the same or greater accuracy would be of great benefit.

The following table briefly describes several invasive and non-invasive measurement techniques. The techniques are ranked roughly in order of their usefulness as reference standards for the current analysis. (An asterisk indicates that the material is extracted from De Maria and Raisinghani (2000):

	Technique	Inva-sive?	Description
1.	Direct Fick*	Yes	• Estimates cardiac output through direct measurement of mixed venous blood oxygen concentrations • Gold standard but usually confined to the cardiac catheterization lab and research settings
2.	Indirect Fick*	Yes	• Similar to direct Fick but uses pulse oximetry assessment of arterial oxygen content
3.	Thermo-dilution*	Yes	• Estimates cardiac output by measuring change in temperature of a solution injected into the right atrial chamber • Large measurement variability • Most widely used in clinical practice
4.	Dye dilution	Yes	• Similar to thermodilution. Dye is injected into pulmonary artery and its concentration is measured at a peripheral site
5.	Radio-nuclide angiography or ventriculo-graphy	Yes	• Estimates cardiac output by dynamic sampling of left ventricular radioactive counts.
6.	Echocardio-gram/Dopp-ler	No	• Measures stroke volume and provides a complementary estimation of systolic function by providing velocity values as well as two-dimensional images
7.	Echocardio-gram/non-Doppler*	No	• Measures ejection fraction (and therefore stroke volume) by using two-dimensional images of the left ventricle to estimate its volume • Under-estimates left ventricular volume

TEB is one of a variety of methods used to measure cardiac output, cardiac index, stroke volume, and ejection fraction. TEB takes advantage of the fact that resistance to electrical current in the thorax (the area between the neck and abdomen) varies in relation to the amount of blood in the aorta. It works by introducing a low voltage alternating current between sets of electrodes (leads) placed on the skin surface over the thorax. The difference between the voltage that is introduced by the device and that which the device senses moving through the thorax indicates the amount of resistance (impedance) that the electrical current encounters. The impedance, in conjunction with electrocardiographic results and an equation, are used to estimate stroke volume, from which other cardiac measures may be computed (De Maria and Raisinghani, 2000). Cardiac index is another cardiac parameter that can be calculated from bioimpedance measurements. While ejection fraction can also be calculated, TEB has not been viewed as a substitute for echocardiography or radionuclide ventriculography.

1.1 Requests by the Centers for Medicare and Medicaid Services

The Centers for Medicare & Medicaid Services (CMS) requested a technology assessment by the Agency for Health Care Research and Quality (AHRQ) to address a number of issues regarding the value of TEB.

These issues include:

1. A review of the diagnostic test performance of electrical bioimpedance for measurement of cardiac output, stroke volume, thoracic fluid content, and other physiological parameters including the following elements:

- Comparison to the diagnostic test performance of alternative tests
- A review of information from clinical trials (if any) on any factors (for example, placement of leads, experience of the operator, comorbid conditions) that may affect the test performance of electrical bioimpedance and the limitations that these factors would place on clinical utility.

2. A review of the clinical trial literature on the use of electrical bioimpedance for the following seven indications, with a focus on data demonstrating changes in patient management and/or improved health outcomes from the use of the device. The first six indications are taken from CMS' existing national coverage policy on the use of TEB:

- Noninvasive diagnosis or monitoring of hemodynamics in patients with suspected or known cardiovascular disease.
- Differentiation of cardiogenic from pulmonary causes of acute dyspnea.
- Optimization of atrioventricular interval for patients with A/V sequential cardiac pacemakers.
- Patients with need of determination for intravenous inotropic therapy.
- Early identification of rejection in post heart transplant myocardial biopsy patients.

- Cardiac patients with a need for fluid management (Excluding patients on dialysis and with cirrhosis of the liver).
- Management of hypertension.

3. A review of the setting of the clinical trials of bioimpedance (inpatient vs. outpatient) and issues related to generalizability of data from the inpatient to the outpatient setting.

4. A review of any information available in the clinical trials on training of the persons using the devices and any issues related to this training (e.g., must monitoring data be interpreted only by a cardiologist; can nonphysicians collect the data?)

In 1992, the Agency published a technology assessment that examined the accuracy of measuring cardiac functions with TEB using literature published up to 1992 (Handelsman, 1992). The following excerpt from that report summarizes the findings: "…There continues to be lack of persuasive data derived from rigorous clinical trials supporting the use of [T]EB determinations of cardiac output for the clinical management of any subset of patients… Although many investigators have concluded that [T]EB yields satisfactory results…their reliance on correlation coefficients as the main evidence supporting their stance appears to provide necessary but insufficient evidence of clinical utility in either hospital or outpatient settings…"

The present report is a systematic review of studies that have assessed TEB since the 1992 review. Issues in the assessment of a diagnostic technology include test performance in diagnosing disease, test performance relative to alternatives, and clinical impact. Issues in the assessment of individual research studies include the need for clear definitions, appropriate reference standards, and appropriate statistical analyses. In the following section we describe our systematic review methodology.

2. METHODS

2.1 Assessment Approach

AHRQ, CMS, and T-NEMC staff jointly developed an analytic framework for the assessment of TEB (Figures 2.1 – 2.3). TEB may be used in three different ways: diagnosis, guiding interventions, and monitoring. An example of the diagnostic application of TEB is the differentiation of cardiogenic from pulmonary causes of dyspnea. Examples of guiding interventions and monitoring are monitoring patients' status in the critical care setting and early diagnosis of rejection in post-heart transplant patients.

As shown in the analytic framework, the primary purpose of this technology assessment is to find evidence directly demonstrating that the use of TEB leads to changes in patient management that in turn lead to better health outcomes for patients. Adverse effects of TEB and any information about alternative technologies that are directly compared to TEB in clinical trials are also included in the technology assessment. The technology assessment also includes studies of the correlation of TEB with other diagnostic tests such as thermodilution (TD), but most of these studies do not report whether changes in patient management were made, or provide information on health outcomes.

The report on “Recommendations for Evaluating Effectiveness; Executive Committee Working Group Medicare Coverage Policy” (Executive Committee Working Group, 2001) stated that:

“…Few studies have directly measured the effects of a diagnostic or screening test on health outcomes (studies of occult blood testing for colon cancer represent one such exception). Typical studies that evaluate the effectiveness of diagnostic, screening, or monitoring tests focus either on technical characteristics (e.g., does a new radiographic test produce higher resolution images?) or effects on accuracy (does it distinguish between patients with and without a disease better than another test?)…” These points apply to TEB. Few well-designed studies evaluate the impact of this test on clinical outcomes.

Our assessment approach therefore relied on three components and was driven largely by the study design and measurements reported in the literature. The assessments we were able to perform included:

- Assessment of the correlation between TEB and other techniques (high correlation implies that measurements using one method move in the same direction --- upwards or downwards ---as measurements derived from the method being compared)

- Assessment of the bias and limits of agreement of TEB compared to other techniques (tests may have high correlation coefficients while still having systematic differences from the reference test or large random variation for individual measurements; bias and the limits of agreement are one way to measure these variations)
- Qualitative assessment of studies on the use of bioimpedance in clinical situations. Our analyses of these studies are presented in narrative form.

2.2 Literature Search

Using the OVID search engine on January 9, 2002, we conducted a broad search of Medline® & PreMedline® (Table 2.1). Filters and limitations were used to eliminate inappropriate publications. The search yielded 8330 citations. The search was conducted for the period from 1966 through January, 2002. The search strategy was restricted to English language publications about human subjects and consisted of the terms *impedance, bioimpedance, cardiography, impedance cardiography, electrical impedance*. Synonyms for bioimpedance include: electrical bioimpedance, thoracic electrical bioimpedance (TEB), bioelectrical impedance, electrical impedance tomography, bioimpedance spectroscopy, single or multifrequency bioimpedance, and impedance cardiography. Technical experts were consulted, and references in published meta-analysis and selected review articles were examined to identify additional articles. An updated search performed on July 22, 2002 yielded 213 additional abstracts which were identified and screened. Three additional studies qualified and were included in this report.

2.3 Selection Criteria

All abstracts were reviewed to identify full articles that met the criteria. Those articles reporting on the methodology of TEB as a diagnostic and/or monitoring tool, or TEB in comparison to another diagnostic technique (such as TD, dye dilution, direct or indirect Fick methods, echocardiographic techniques, or radionuclide angiography) in the following seven clinical situations were retrieved: cardiovascular disease, dyspnea, pacemakers, intravenous inotropic therapy, heart transplant, fluid management, hypertension. Both studies that explicitly compared bioimpedance to other techniques (comparative studies) and studies using other types of assessment (noncomparative, qualitative studies) were included. (See 'Assessment Of Methodological Issues' below). After discussions with CMS, studies were excluded if they involved: animals, pediatric or obstetric populations, healthy volunteers, patients on dialysis, patients with acromegaly, cystic fibrosis, AIDS, Crohn's disease, obesity solely to determine body composition, patients subjected to laparoscopic cholecystectomy, and patients with cirrhosis of the liver who were on fluid management. In addition, related technologies such as electrical impedance tomography (EIT) were excluded. If the article did not specifically say that *thoracic* impedance was measured, or if non-thoracic electrode placement was used (i.e. whole body impedance), the studies were rejected. Subsequent discussions with CMS further narrowed the inclusion criteria from the initial indication of "cardiac patients with a need for fluid management" to only CHF patients with such a need.

Approximately 275 full articles were retrieved and examined, including five meta-analyses (De Maria and Raisinghani, 2000; Fuller, 1992; Handelsman, 1992; Raaijmakers, Faes, Scholten, et al., 1999; Critchley and Critchley, 2000); one of these was a Technology Assessment report by AHCPR that included studies through part of 1992. All titles in bibliographies of these articles were also reviewed and retrieved, if pertinent. In addition, several lists of articles compiled by CardioDynamics sent to CMS were reviewed.

Because so few articles were obtained for certain conditions, we included articles containing studies with a minimum of 5 subjects for the evaluation of diagnostic test performance or for studies that report correlation with important physiologic parameters.

At the request of CMS, our analyses include only articles published from 1991 onward. This ensures coverage of articles published late in 1991 since the earlier review by AHCPR covered articles prior to that time (Handelsman, 1992). Seventy-seven articles are included in the evidence tables.

Abstracts not published as full articles were not reported in the Results section, were not included in the evidence tables, and were not included in any meta-analyses. In the section entitled “Further Consideration Of Certain Material” some abstracts and allusions to future research were discussed.

2.4 Data Extraction

We noted the following elements for each study: primary purpose of the study, clinical situation, reference standard in the comparison tests, design of study, characteristics of the population including setting and funding source, demographics and extended description of the patients enrolled in the study, inclusion and exclusion criteria, description of the equipment and methods of TEB including model and year, manufacturer, calibration and details of the test, placement of leads and procedure followed, quality of the data, method of data analysis, and results. The opinions and conclusions of the authors were quoted where appropriate. Furthermore, the following questions were posed:

- Is the diagnostic test performance compared with a reference standard?
- Does the TEB measurement correlate with clinical measurements?
- Do the authors of the study conclude that TEB is useful, accurate, reliable?
- Are there data to suggest that TEB improves patients' outcomes or affects clinical management?
- Do the authors conclude that TEB improves patients' outcomes or affects clinical management?
- Does this paper discuss the training and experience of the operator? If so, what…
- Does this paper address any problems encountered in operating the device? If so, what…

2.5 Assessment of Methodological Issues

The studies were classified into two groups. *Comparative* studies explicitly compared TEB to another technique. *Non-comparative* studies examined a relevant aspect of TEB as a diagnostic technique but did not provide data comparing TEB to an alternate technique. For the non-comparative studies, the outcomes and results were described in narrative form.

Four criteria that specifically related to the scope of this report were used to assess major methodological issues regarding the articles included. These criteria pertained to the subject studied (i.e. medical or surgical condition of patients enrolled and inclusion/exclusion criteria) and the apparatus used (manufacturer of the device and specific equation used to calculate cardiac parameters from measured impedance variables). For both types (i.e. comparative and non-comparative) of studies, four yes or no questions were developed and applied. These four questions were:

1. Does the study provide a description of the device that was used to measure TEB (including manufacturer and model)?
2. Does the study describe the equation used to calculate impedance measurements? (researchers using an off-the-shelf clinical system might not know the equations used)
3. Does the study include a description of the patients in the study, with inclusion and exclusion criteria?

4. Does the study include a description of the indication for the use of TEB in the patients enrolled?

The results of this classification are presented in the final column of each evidence table (see below). The criteria were neither used as inclusion criteria nor to provide a detailed assessment of the methodological quality, but rather describe a minimum set of methodological standards that should be applied to the included reports. For studies that measured cardiac output and used TD as the comparison, we added an additional quality measure: the number and appropriate analysis of measurement replications. This is important because researchers have measured variation of 10-20% in repeat TD measurements (Handelsman, 1992); therefore measurement replication is essential to obtain an accurate measurement. We graded each study (A, B, C, where A was highest) according to the methodology employed for obtaining the TD and TEB measurements:

A. At least three TD measurements were made (Stetz, Miller, Kelly, et. al. 1982), with variability between the TD measures less than 20% (by discarding those poor measurements, or excluding those patients with poor measurements from the analysis). Means of the TD and TEB measurements were used in the analysis.

B. Taking only single measurements for both TD and TEB, (or some other data collection problem), but not inappropriately analyzing the results, as in “C” below.
C. Inappropriately treating multiple measurements taken on one patient as if they were “independent” in the statistical analysis.

Both of the above grading approaches focus on key aspects of the measurement process that could be readily inferred from the Methods sections of the articles.

2.6 Evidence Tables

The detailed information extracted from the articles along with assessment of methodological issues are included in two evidence tables. Because the types of information extracted from the comparative and non-comparative studies differ in some respects, Evidence Table 1 contains comparative studies, and Evidence Table 2 contains non-comparative studies.

2.7 Meta-analysis Methods

Under certain circumstances, an overall estimate of key results is desirable, because such an estimate is more precise than any individual finding. Meta-analysis provides a means of obtaining such an estimate of the results through systematic statistical procedures. While this approach has benefits, it is important to exercise interpretive caution when combining highly variable data, and to consider other information in addition to the quantitative results.

Our meta-analytic framework identified key measures, comparison techniques, and subgroups. Figures 3.1 and 3.2 show the number of studies for each comparison technique as well as the analytic approach, which resulted in the following meta-analyses when there were three or more studies within a subgroup:

- Measures of cardiac function: cardiac output, cardiac index, stroke volume
- Comparison techniques: TD
- Subgroups: setting (inpatient, outpatient, emergency department), study year (1991-1996 vs. 1997-2002), and ‘quality’

While many studies were excluded from the meta-analyses, they were reviewed for relevant qualitative material which was, when appropriate, included in the narrative sections. Following is a summary of the article selection and analysis process:

Step 1	Step 2	Step 3	Step 4
Number of Articles Identified by Literature Searches	Number of Articles Included After Title & Abstract Screening	Number of Articles Included After Full-Text Screening	Final Number of Articles Included in Meta-analyses
Initial search: 8330 Updated search: 213	TEB articles: 271 Review articles: 5	Non-comparative studies: 17*	Correlation Coefficients: 22[‡]
		Correlation Coefficients: 49[†]	
		Bias: 36[†]	Bias: 9[‡]
Total: 8543	**276**	**77**[†]	**22**[†*]

[†] There is some overlap between correlation studies and bias studies.
[‡] Some articles provide more than one comparison (study); therefore the sums of the studies in the analytic frameworks (Figures 3.1 and 3.2) are larger then the number of articles included in the meta-analyses.
* Non-comparative studies were not in meta-analyses.

Random effects model meta-analyses were performed on studies that compared TEB against alternative methods for the measurement of cardiac function. These studies provided the correlation coefficient and/or the average bias for TEB vs. other techniques, but several analytic issues arose regarding potential duplication of information. To address these issues, the following rules were developed and applied:

1. Whenever a study provided not only data for the whole sample but also for subgroups of patients, only the one entry from the entire sample was used to avoid double counting. Similarly, when a study provided information about the same patients for different conditions (e.g. at rest vs. active) as well as

aggregated, only the aggregated data were used. If aggregated data were not provided, the data were averaged across conditions. Averaging such results made the analysis of these studies more comparable to other studies that did not perform subgroup analyses. This avoided over-weighting but, of course, some information was lost.

2. When the study protocol specified repeated measurements on each patient, we replaced the number of paired measurements with the number of patients in the correlation meta-analyses to provide the appropriate weighting.

3. The equations used by the TEB device may impact the results (See below). We therefore only used meta-analysis on groups of studies using the same equation. Because of the number of studies threshold we applied, meta-analyses could only be done with studies that used the Sramek-Bernstein equation.

The software used to conduct the correlation meta-analyses was Comprehensive Meta-analysis Version 1.0.23 (www.Meta-Analysis.com). The bias analyses were done using a web site calculator (http://department.obg.cuhk.edu.hk/ResearchSupport/MetaEffectSize.asp) verified against a standard random effects model formula (Sutton, Abrams, Jones et al., 2000) programmed into a spreadsheet.

2.8 Statistical Analysis

The most commonly reported statistic was the correlation between the various cardiac function metrics as measured by TEB vs. the same metrics measured by the various comparison techniques. For example, cardiac output as measured by TD was frequently compared by a correlation coefficient to cardiac output as measured by TEB. Correlation coefficients were therefore an important component of the meta-analysis, despite their limitations. These limitations include:

- the dependence of the correlation on the distribution of true cardiac output levels in the study sample
- the fact that even when the correlation coefficient is close to one, there can be large systematic differences or random variations in individual measurements. (Bland and Altman, 1986).

For correlation coefficients, formal tests for the presence of heterogeneity (gross variation in the size of the correlation coefficients) across studies were performed. The combined estimates of the correlation coefficients and their confidence intervals were derived from random-effects models. These models incorporated both “within” and “between” study variability into the calculations, which generally increases the variability of the combined estimates and produces wider, more conservative confidence intervals and fewer statistically significant findings.

Correlation coefficients measure the correlation of one diagnostic test to another, but do not provide any information about the clinical utility of the diagnostic test. There is no straightforward method of translating the magnitude of correlation coefficients into a statement that reflects the clinical impact of TEB on a population. While such comparisons cannot be translated into clinical impact, it is possible to compare correlations across diagnostic studies to provide a context for interpreting them (De Maria and Raisinghani, 2000). In a later section of this report, we provide some comparative data to provide this context.

The method of Bland and Altman (1986) is commonly used to measure the bias (systematic error) and limits of agreement (random variation) in comparison studies of diagnostic tests. One researcher has pointed out that there is a “…notable lack of consistency in how results of bias and precision statistics are presented…” in studies of methods of measuring cardiac parameters (Critchley, 1999). This, combined with incorrect collection of TD data as reported by some authors (see Results), limits the number of studies for which the bias can be analyzed, but we analyzed bias data where feasible. Finally, we reported bias as (TEB minus comparison) to ensure that the ‘sign’ of the bias was consistent.

2.9 Meta-analysis Displays

The meta-analysis displays show:

- Abbreviated name of the effect/metric being analyzed (e.g. CO for cardiac output)
- Article citation (author and year)
- Number of patients used in the comparison
- Graphic description of the individual effects and 95% confidence intervals
- Measurement conditions applying to the comparisons (see Evidence Table 1 for detail)
- Combined random effects model estimate and its confidence bounds

3. RESULTS

In this section we address the issues raised by the key study questions described in the Introduction. We organize the questions around the seven clinical indications:

(1) hemodynamic monitoring

(2) acute dyspnea

(3) pacemakers

(4) inotropic therapy

(5) heart transplants

(6) fluid management

(7) hypertension

Within each indication, we examine evidence regarding:

1. Clinical impact on patient management and/or improved health outcomes from the use of TEB,
2. TEB performance compared to alternative technologies for monitoring cardiac output, cardiac index, and stroke volume,
3. TEB performance compared to alternative technologies for the measurement of other physiologic parameters,

4. Factors that may affect performance of the measurement (e.g. lead placement, operator experience, comorbid conditions)
5. Potential limitations in the use of the technology relating to the setting (i.e. inpatient, outpatient, emergency), and
6. Training needs.

3. 1: INDICATION 1: Demonstration of changes in patient management and/or improved health outcomes from the use of the device for noninvasive diagnosis or monitoring of hemodynamics in patients with suspected or known cardiovascular disease.

3.1.1 Clinical impact on patient management and/or improved health outcomes from the use of TEB

No studies provided information on health outcomes, patient management, or on clinical end-points to address the usefulness of TEB in monitoring or management. In what follows, however, we discuss results of studies that indirectly offer some insight into the *potential* uses of TEB.

Three non-comparative studies investigated uses of TEB monitoring in patients with cardiovascular and/or pulmonary disease and related complications

(Greenberg, Hermann, Pranulis, et al., 2000; Scherhag, Pfleger, de Mey, et al., 1997; Zerahn, Jensen, Olsen, et al., 1999). These were preliminary studies designed to measure ranges of values and reproducibility of TEB in specific clinical populations.

Zerahn, Jensen, Olsen, et al. (1999) aimed to determine the relationship between improvement in lung function and changes in TEB after thoracocentesis in patients with pleural effusions due to heart failure or malignancy. They found that the relative impedance at baseline was twice as high in patients with cancer as compared with that in heart failure patients. They also found correlation between TEB and the "drying effect" of lung fluid aspiration in respiratory functional variables (FEV1, FVC, VC, TLC). Baseline impedance measurements did not change at the end of thoracocentesis and ten minutes later.

Greenberg, Hermann, Pranulis, et al. (2000) found that TEB provided reproducible hemodynamic measurements in the outpatient setting in 62 ill patients with clinically stable heart failure, with no reporting of adverse reactions on the procedures associated with TEB.

Scherhag, Pfleger, de Mey, et al. (1997) reported on the computerized impedance cardiographic monitoring of 50 outpatients with suspected coronary artery disease (CAD) during pharmacological stress testing with dobutamine or dipyridamole. The researchers found varying responses of the hemodynamic parameters to the different pharmacologic agents, but no comparative test was used to validate this data.

Kasznicki and Drzewoski (1993) performed a study to compare the effect of chemotherapy on cardiac indices in 30 patients with hematological malignancies divided into two groups ---those with and those without cardiac risk factors. They found that chemotherapy had some effect on some hemodynamic parameters in some patients, but these measurements were not validated through comparison with other methods. Finally, it should be noted that one of the electrodes was placed on the forehead.

While the following two studies were not as directly relevant to the hemodynamic indication as the others, they are nonetheless included because they reported some hemodynamic data. Raaijmakers, Faes, Meijer, et al. (1998) investigated the effects of non-cardiogenic edema (accumulation of protein and extracellular fluid) on thoracic impedance. One study component involved 13 ICU patients with acute respiratory failure and found a poor correlation (r = -0.24) between single frequency impedance measurement and extravascular lung water measured by the double indicator dilution method. These findings may be applicable to the differential diagnosis of cardiogenic versus non-cardiogenic pulmonary edema where extravascular lung water volumes may differ. These results, however, are very preliminary and were derived from a very small heterogeneous sample of patients.

Tatevossian, Shoemaker, Wo et al. (2000) performed an uncontrolled, observational study in a series of consecutive trauma and ICU patients to evaluate whether early noninvasive monitoring using TEB may reveal early circulatory deficiencies that lead to the development of acute respiratory distress syndrome (ARDS). They used both invasive (pulmonary thermodilution catheter) and non-invasive (TEB) methods to record the time course of hemodynamic and tissue perfusion patterns in 60 severely injured postoperative patients to assess hemodynamic parameters in survivors and non-survivors of ARDS. In a subgroup analysis they observed significantly lower cardiac index and transcutaneous oxygen tension, and higher transcutaneous carbon dioxide tension beginning with the early stage in those patients who developed ARDS compared with those who did not. They concluded that early noninvasive monitoring in the emergency department, operating room, and ICU can disclose patterns of reduced cardiac and tissue perfusion in patients who subsequently develop ARDS which may help identify patients at higher risk for developing ARDS, a rather strong inference, given the limitations of their study design.

These data suggest that TEB may help in the early identification of ARDS in trauma patients. This has potentially important implications in the management of ARDS and reduction of its associated morbidity and mortality.

In summary, the studies summarized in this section provide preliminary data indicating that TEB may be able to detect clinically significant changes in hemodynamic parameters in a variety of clinical situations. However, the studies do not provide adequate evidence of TEB's clinical utility due to study design issues such as not providing a comparison group and not reporting changes in patient management and health outcomes.

3.1.2 TEB performance compared to alternative technologies for monitoring cardiac output, cardiac index, and stroke volume

Assessment of diagnostic performance requires information on how well a test identifies a disease or some aspect of a disease. We did not identify any studies that used TEB to diagnose a disease or condition, so in this section we can only compare ‘agreement’ between TEB and alternatives. Most of the data available on TEB report correlations with reference tests; correlation coefficients have serious limitations when used to summarize diagnostic test data. There were 49 comparisons in 45 articles that paired TEB with other techniques and reported correlation coefficients (Table 3.1; some articles contained more than one ‘study.’). The majority of these comparisons were to TD, with a small number of comparisons to the two Fick methods, echocardiogram, and radionuclide methods. The greatest amount of data were provided for the cardiac output and cardiac index metrics, with the least provided on stroke volume and left ventricular ejection fraction. The meta-analyses described below therefore focus on the comparisons of TEB cardiac output and cardiac index to TD, according to the analytic framework presented in Figure 3.1. The results are presented below for various subgroups.

3.1.4.1 Factors that may affect test performance (e.g. lead placement, operator experience, comorbid conditions)

Most studies did not investigate any of these factors. No studies reviewed have analyzed the influence of operator experience; TEB measurements were typically obtained as part of routine care. The evidence tables describe the co-morbidities of patients in each study. In the large majority of studies, no separate data were provided on the agreement of TEB compared with another technique for patients with a specific comorbid condition.

3.1.4. Leads and Equations

Overall Lead Positioning

The principle of TEB is based on measuring the impedance in the thorax when an alternating current is applied. Electrodes are used to apply the current and measure the impedance. Several equations, lead configurations, and combinations of equations and lead configurations have been described in the literature.

There are three principal equation types (Fuller, 1992; De Maria and Raisinghani, 2000; Handelsman, 1992). These equations can be summarized as follows:

- Kubicek’s equation was described in 1966 as part of NASA's effort to develop TEB as a non-invasive cardiac output monitoring system. The equation for estimating stroke volume uses measurements obtained from four circumferential aluminum strip electrodes, two around the neck and two around the torso (See below and Appendix 2 for electrode detail). The stroke volume is calculated as a function of the blood resistivity (hematocrit dependent), distance between electrodes, baseline thoracic impedance, ventricular ejection time, and the maximum rate of reduction of thoracic impedance during systole. The volume of electrically participating tissue is assumed to be a cylinder.

- Sramek modified Kubicek's equation in 1981 and replaced circumferential electrodes with four pairs of electrocardiogram (ECG)-type electrodes (see below and Appendix 2 for electrode detail). The volume of electrically participating tissue is assumed to be a cone; parameters in the equation include circumference of the thorax and the average distance between sensing electrodes, while the blood resistivity variable was eliminated.

- Bernstein (Sramek-Bernstein) modified the Kubicek and Sramek equations in 1986 by correcting for both height and weight.

Several electrode configurations linked to the equations are described by van der Meer, Woltjer, Sousman (1996):

- The original Kubicek et al. configuration used bands of circular electrodes at four levels of the thorax --- two at the neck and two just below the xyphoid. (Appendix 2)

- The lateral spot configuration consists of eight spot electrodes placed at four levels of the thorax--- two pairs inject current and two pairs measure the voltage (Appendix 2). One pair of voltage measuring electrodes is placed on the left and right mid-axillary lines at the xiphoid level. The second pair of voltage measuring electrodes is placed at the base of the neck, parallel to the first pair of measuring electrodes. The current injecting electrodes are placed on the same lines as the voltage measuring ones --- one pair is placed just below the voltage measuring electrodes at the xiphoid level, and the other pair is located just above those at the neck. This configuration is used in many currently available commercial devices.
- The semicircular spot electrode configuration consists of sixteen spot electrodes--- four pairs inject current and four pairs measure the voltage. The pattern is similar to the lateral spot placement, with two rather than four pairs of electrodes at each level. This configuration is electrically equivalent to the circular electrode configuration of Kubicek. Krasznicki and Drzewoski (1993) developed a modification of this electrode placement that included a forehead placement.

Balestra, Malacrida, Leonardi, et al. (1992) studied the accuracy of bioimpedance measurements using a prototype 7 mm diameter esophageal probe with four applied electrodes introduced via a conventional oro-gastric tube in 10 critically ill ICU patients. The use of these internal electrodes yielded high correlation (r= .989) with very little bias. The authors pointed out that this technique was less invasive than TD. It was not very practical, however, for routine use in the outpatient setting, as it was invasive and required position confirmation with radiography.

Woltjer, Bogaard, Scheffer et al. (1996) compared a modified semi-circular (MSC) array (the semicircular array with an additional current injecting electrode on the forehead with the same voltage detecting electrodes as the eight spot configuration) to the lateral spot array among patients undergoing coronary bypass surgery. They found that the Sramek-Bernstein equation was valid only with the lateral spot electrode array for calculating stroke volume, and the Kubicek equation worked well only with the modified semi-circular spot electrode array. They found a higher correlation coefficient to TD with the Kubicek equation/modified MSC electrode configuration compared to the Sramek-Bernstein/lateral spot electrode configuration.

Demeter, Parr, Toth et al. (1993) compared the estimation of cardiac output by TEB and TD in ten stable, non-ventilated male coronary artery bypass patients in an open heart recovery unit. These investigators calculated the blood resistivity for the Kubicek equation from actual hematocrits, and compared the correlation (but not bias) of cardiac output estimated from TEB vs. TD to that obtained using a ‘constant’ value. Because they found superior results using the calculated hematocrits, these investigators concluded that this approach would be most important in situations where the hematocrit is not normal, for example among the type of patients in their study.

Van der Meer, Woltjer, Sousman, et al. (1996) reported that systems using the equations which adjust for height and weight (Sramek-Bernstein and adjusted Kubicek) with the appropriate lead placement had similar performance; this performance was superior to systems using the older equations that did not adjust for height and weight (Sramek and the original Kubicek equation) in mechanically ventilated patients in intensive care settings.

There were an insufficient number of studies using similar enough equations to conduct a meta-analysis comparing equation types.

Effects of Electrode Type and Errors in Electrode Placement

Jewkes, Sear, Verhoeff, et al. (1991) concluded that a main source of TEB observer error "…relates to the placement of the electrodes and the electrode type… " These authors found that different electrode types (RedDot™ and Medicotest™) resulted in significant differences in measurement of thoracic fluid index, but they did not observe significant differences in average stroke volume and cardiac output. Changing electrode position in the diagonal or frontal positions, or decreasing the effective inter-electrode position by 5 cm movement of the cervical electrodes yielded only small changes (< 5%) in thoracic fluid index and stroke volume. Large changes (39.8% increase for thoracic fluid index and 15.8% decrease for stroke volume) were observed when inter-electrode difference was increased by 10 cm.

Balestra, Malcrida, Leonardi et al. (1992) studied the effects of displacing the xiphoid voltage sensing electrodes by 3 cm in the caudal direction, which led to a change in cardiac output from 7.1 +/- 1.2 to 5.8 +/- 1.3 L/min ($p < 0.001$) in the lateral spot electrode configuration using Sramek-Bernstein equations in healthy volunteers (another group of critically ill ICU patients were studied in another part of this article; see above). Statistically significant increases in cardiac output were also measured when the electrodes were moved 3 and 6 cm in the cranial direction.

Other Factors

One study designed to investigate the influence of pulmonary edema (13 ICU patients with lung injury or adult respiratory distress syndrome) on the accuracy of cardiac output as measured by TEB found that Kubicek's equation correlated better with TD than when the Sramek-Bernstein equation was used (Raaijmakers, Faes, Kunst, et al., 1998). These authors provided a theoretical basis for their empirical findings and postulated that Kubicek's equation is 'edema-independent' due to its modeling assumptions. They also hypothesized that mechanical ventilation's impact among patients with respiratory failure on the accuracy of TD measurements but not on those of TEB could result in measurement error being incorrectly attributed to TEB.

The performance of TEB during mechanical ventilation is also a factor of interest. Castor, Klocke, Stoll, et al. (1994) studied 10 patients with Swan-Ganz catheterization during neurosurgical removal of intracranial tumor or aneurysm. They concluded that compared to TD, TEB "… slightly overestimates cardiac output in the normal range during spontaneous ventilation and during intermittent positive pressure ventilation (IPPV)…" They reported overestimation of cardiac output in increased cardiac output states with spontaneous ventilation and underestimation of cardiac output during IPPV.

Being overweight has been suggested as a factor that might affect the performance of TEB. Van Der Meer and co-workers prospectively investigated the influence of being overweight on TEB measurements of cardiac output among forty critically ill post-cardiac surgery patients (Van der Meer, de Vries, Schreuder WO, et al., 1997). These investigators compared cardiac output measurements obtained by TEB with those obtained through the use of TD. All patients were mechanically ventilated. Three patients were excluded from the final analysis due to increased variability in cardiac output measurements obtained by the TD method and one due to dysrhythmia. In the remaining thirty-seven patients (n=37) a correlation coefficient for cardiac output of 0.60 (bias +/- 2 standard deviations = -0.06 +/- 1.25) was found between the TEB and TD methods. In a subgroup analysis the authors excluded patients with more than 15% deviation from ideal weight and calculated a correlation coefficient of 0.85 (bias +/- 2 standard deviations = 0.09 +/- 0.96) for the remaining twenty-five patients. The authors discuss potential reasons for their finding mainly in relation to the body geometry factor in the Sramek-Bernstein formula.

In another report on the same patient sample, Woltjer, Bogaard, and van der Spoel (1996) focus on stroke volume rather than cardiac output. The correlation and bias +/- 2 standard deviations was r=0.90; bias = 2.0 +/- 17.7 ml using Kubicek's equation for normal weight patients and r=0.80; bias = -2.7 +/- 14.4 for obese patients. Using Sramek and Bernstein, the correlation and mean difference +/- 2 standard deviations was r=0.63, md= -0.8 +/- 30.8 ml and r=0.43, md= -7.7 +/- 26.2 for obese patients. In this analysis, the authors concluded that "…weight significantly influences the calculation of stroke volume when Sramek and Bernstein's method is applied and that the weight correction factor is not valid to adjust this. Kubicek's method, however, is not seriously biased by weight and appears to be more accurate than Sramek and Bernstein's method in patients after coronary bypass surgery…"

Both of the above analyses suggest that larger scale investigations are needed to compare TEB with other methods in patients with abnormal anthropometric characteristics such as being overweight. The discussion of the implications of the findings about equation use adds further support to the proposition that equation type may be important.

Summary of Equation and Lead Placement

Many currently available commercial devices use the lateral spot electrode configuration; many devices use proprietary equations. Errors in placement of the leads and clinical factors such as patient weight and presence of pulmonary edema have been reported to affect results of measurements; data on these factors have not been adequately reported in published literature with currently available commercial devices on the outpatient population of interest.

3.1.5 Potential limitations relating to test performance setting (i.e. inpatient, outpatient, emergency)

3.1.5.1 Correlation Coefficients

Most of the studies on bioimpedance are performed on an inpatient population; many of these patients are critically ill. Results for these patients might not be generalizable to the outpatient population of interest in this TA. In this section, we report results of separate meta-analyses for data collected in different settings.

One study directly compared TEB for measuring cardiac output between thirteen critically ill and fifteen non-critically ill patients and found no statistically significant difference in cardiac output results (Weiss, Calloway, Cairo, et al., 1995). The authors do not assess the statistical power of their design, so it is difficult to assess whether the lack of statistical significance results from true equivalence or merely lack of power. Additionally, these authors concluded that TEB measurement variability limits its use to monitoring relative changes in cardiac metrics rather than estimating absolute values of these metrics.

Table 3.2 shows meta-analyses of inpatient, outpatient, and emergency department studies comparing TEB to TD for either cardiac output or cardiac index. Since the TEB equation used might influence results, and because at least three studies was our cutoff for analysis, we restricted our analyses to studies using the Sramek-Bernstein equation. Figures 3.2.a and 3.2.b show individual study results and in what follows, when statistical significance is reported, the level was $p<.0001$, unless otherwise indicated. Overall (not just those studies in the meta-analysis) the correlation coefficients ranged from -0.01 to 0.97. In seventeen studies (396 patients) of cardiac output for inpatients using TD as the comparison, the combined r = 0.693 (95% CI, 0.578-0.781), with significant heterogeneity. In three studies (75 patients) of cardiac index for inpatients using TD as the comparison, the combined r = 0.349 (95% CI: 0.122-0.540), without significant heterogeneity.

In studies of outpatients using TD as the comparison, there were three studies (40 patients) using cardiac output with combined r = 0.879 (95% CI: 0.642-0.962), without significant heterogeneity. There were no studies meeting the criteria for an analysis of outpatient cardiac index.

There were three studies (793 patients) of cardiac index in the emergency department comparing TEB to TD with combined r=0.848 (95% CI: 0.827-0.866), without significant heterogeneity. There were no studies for a meta-analysis of cardiac output in the ED.

3.1.5.2 BIAS

As mentioned earlier, it is preferable to analyze the 'bias' and limits of agreement rather than the correlation coefficient, when they were reported and the methodology for obtaining them was correct. Of 36 studies that reported bias and limits of agreement, only 12 used the correct methodology for obtaining the data. Most comparisons were to TD, with a small number of comparisons to the direct Fick method, and only one to the pulsed Doppler method. The greatest amount of data was provided for the cardiac output metrics, with the least provided on cardiac index and stroke volume. Table 3.3 summarizes all studies reporting bias and Figure 3.2 shows the analytic framework used to analyze the bias. Due to the limited number of comparisons among outpatients, our meta-analyses focus on the test agreement between TEB cardiac output and stroke volume with TD.

Fourteen studies correctly (single measurement or average of multiple measurements per patient) reported cardiac output for a comparison between TEB and TD among inpatients using the Bland and Altman method. Table 3.4 shows the bias, limits of agreement (+/- 2 standard deviations of the difference), and measurement conditions (another indicator of the quality of measurement) for the eight studies. Individual study results may be interpreted as follows: About 95% of patients would be expected to have the cardiac metric measured by bioimpedance (i.e. cardiac output) within ±2 standard deviations (i.e. the limits of agreement) of the bias. A good test should have a bias as close to zero as possible. Bias near zero and clinically acceptable limits of agreement would imply a favorable comparison of TEB to the alternative. For example, the bias of one study was 0.10, with limits of agreement of –1.90 to 2.10 L/min (van der Meer, deVries, Schreuder, 1997). This suggests that 95% of patients would be expected to have bioimpedance derived cardiac output measurements between –1.90 lower to 2.10 L/min higher than the results derived from TD. This finding would be most useful when the clinical implications of an interval this wide could be assessed.

The combined bias and the combined limits of agreement of the bias for cardiac output in the 8 studies were 0.006 and –2.87 to 2.89. If these results were not heterogeneous, the implication would be that 95 percent of inpatients might be expected to have TEB cardiac output limits of agreement of –2.87 to 2.89. The test of heterogeneity across studies was statistically significant, however, for both bias and limits of agreement. This suggests that there may be patient populations where TEB measurements can be much further from the TD measurements than the combined limits of agreement indicate.

Table 3.5 shows that the combined bias and the combined limits of agreement of the bias for stroke volume in these studies were -1.86 and –28.30 to 24.74, respectively. While the test of heterogeneity for the combined limits of agreement was not statistically significant (p=0.59), the test for the bias was.

3.1.6 Training Needs

For the time frame reviewed, no studies were identified that adequately addressed this issue. One study, however, (Belardinelli, Ciompini, Costantini et al., 1996) stated in its Discussion section that it examined the 'reproducibility' of TEB by 2 independent and experienced cardiologists on TEB measurements on patients in sinus rhythm with CAD and a previous myocardial infarct either at rest or during exercise on 2 tests separated by 1 week. The authors state that the coefficient of variation was similar for the 2 observers and for the 2 tests; but the results were not presented clearly.

3. 2 Indication 2: bioimpedance use for the differentiation of cardiogenic from pulmonary causes of acute dyspnea

3.2.1 Patient Management and Health Outcomes

Acute dyspnea has a variety of causes, including cardiogenic and pulmonary causes. Patient management is determined by diagnosis of the underlying cause. No studies, however, were found that evaluated the clinical impact on patient management and/or improved health outcomes from the use of TEB monitoring for differentiation of cardiogenic from pulmonary causes of acute dyspnea (but see also Conclusions section).

3.2.2-3.2.6 Other Issues

No studies were found that addressed the following issues regarding this indication:

- TEB performance compared to alternative diagnostic tests for monitoring cardiac output, cardiac index, stroke volume, or other physiologic parameters
- factors that may affect test performance
- potential limitations regarding test performance setting
- factors regarding training.

3.3 Indication 3: Applicability of bioimpedance in the optimization of atrioventricular interval for patients with AV sequential cardiac pacemakers

3.3.1 Patient Management and Health Outcomes

Some researchers have suggested that finding the optimal atrioventricular (AV) delay is important in maximizing cardiac output in patients with AV sequential pacemakers. We found no well-designed studies for this indication that provide information on the clinical impact on patient management or improved health outcomes after treatments that would be useful in addressing the issues of TEB applicability that have been published to date. Some preliminary studies have been published that measure ranges of values and reproducibility of TEB measurements in patients with pacemakers; these offer some insight into the potential uses of TEB.

Five studies evaluated various aspects of applicability of impedance cardiography-derived cardiac measurements in patients with pacemakers (Haennel, Logan, Dunne, et al., 1998; Ovsyshcher, Gross, Blumberg, et al., 1992; Ovsyshcher, Gross, Blumberg, et al., 1993; Ovsyshcher, Zimlichman, Katz, et al., 1993: Kindermann, Frohlig, Doerr et al. 1997). Two similar studies by the same authors found a mean coefficient of variation of 4% during dual chamber pacing and 6% when the ventricular pacing mode was used to calculate cardiac indices (cardiac and stroke index) from serial (consecutive and non-consecutive) impedance measurements suggesting a high level of reproducibility of the technique at rest during sinus rhythm (Ovsyshcher, Gross, Blumberg, et al., 1992; Ovsyshcher, Gross, Blumberg, et al.,1993). Another study by the same authors evaluated the use of impedance cardiography to optimize pacing (AV) delay in 11 patients (8 with complete heart block and 3 with sick sinus syndrome) with DDD pacemakers or during VVI pacing (3% and 6% respectively) (Ovsyshcher, Zimlichman, Katz, et al., 1993). The authors defined the best programmed AV delay as the setting that produced the highest cardiac index, but they did not validate this measurement with an alternative technique or with data on health outcomes. They found that the correlation coefficient between two consecutive measurements of the cardiac index was 0.94 ($p<.0001$) in the DDD mode and 0.82 ($p<0.0001$) in the VVI mode and concluded that "hemodynamic measurements obtained with impedance cardiography can facilitate optimal programming of pacemaker variables."

Haennel and colleagues used impedance cardiographic monitoring in 10 pacemaker-dependent patients to assess the effects of three different exercise sensing modes on the cardiovascular response to graded exercise (Haennel, Logan, Dunne, et al., 1998). While the study was not designed to assess the accuracy of TEB in this context, the authors stated that "…impedance cardiography provides a simple and reliable means of obtaining repeated hemodynamic data during upright exercise that allows for sequential measurements during a single exercise bout and permits a beat-to-beat examination of the relative contribution of both stroke volume and overall heart rate to cardiac output…"

Kindermann, Frohlig, Doerr et al. (1997) performed a prospective study in 53 patients with high degree AV block to evaluate a new method for the determination of the optimal AV delay using pulsed Doppler echocardiography. These investigators correlated the optimal AV delay using serial TEB determinations of the cardiac index after different settings of AV delay with the optimal delay estimated in the same set of patients. They found a moderate but significant correlation of the AV delay determined with the two methods. It is important to note that in this study TEB-determination of the optimal AV delays of pacemakers was considered the standard and it was compared to an alternative technique. This study did not report health outcomes in two groups of patients in which AV delay optimization was performed using different methods so it is unknown which method of setting the delay is optimal.

Some of the above evidence suggests that TEB is potentially useful in patients with pacemakers and one of these studies compares TEB with an alternative method for optimization of the AV delay setting. None of the studies reported health outcomes after adjustment of the AV delay, so the evidence is insufficient to conclude whether TEB optimization of the AV delay improves health outcomes.

3.3.2-3.3.6 Other Issues

No studies were found that addressed the following issues regarding this indication:

- TEB performance compared to alternative diagnostic tests for monitoring cardiac output, cardiac index, stroke volume, or other physiologic parameters
- Factors that may affect test performance
- potential limitations regarding test performance setting
- factors regarding training.

3. 4 Indication 4: Bioimpedance use in patients with need of determination for intravenous inotropic therapy

3.4.1 Health Outcomes and Patient Management

Non-invasive serial hemodynamic measurements of cardiac parameters might be useful to monitor the effects of parenteral inotropic agents such as dobutamine or milrinone. No studies, however, were found evaluating the clinical impact on patient management and/or improved health outcomes from the use of TEB monitoring of patients in need of inotropic therapy (but see Conclusions section).

3.4.2-3.4.6 Other Issues

No studies were found that addressed the following issues regarding this indication

- TEB performance compared to alternative diagnostic tests for monitoring cardiac output, cardiac index, stroke volume, or other physiologic parameters
- factors that may affect test performance
- potential limitations regarding test performance setting
- factors regarding training.

3.5 Indication 5: Bioimpedance use in early identification of rejection in post heart transplant myocardial biopsy patients

3.5.1 Patient Management and Health Outcomes

The current standard of care for patients with heart transplant includes a regularly scheduled series of cardiac biopsies. Some researchers have suggested that a non-invasive monitoring technique could potentially supplement cardiac biopsies in the early identification of transplant rejection. Weinhold Reichenspurner, and Fulle et al. (1993) assessed the usefulness of TEB in early diagnosis of rejection in 35 heart transplant recipients during the immediate postoperative period and during the outpatient follow-up. These investigators used TEB to measure the stroke volume index, ejection fraction and the acceleration index. They found that average value of the acceleration index during 17 rejection episodes was significantly lower when compared with the non-rejection average. They also found that in their study the diagnostic sensitivity and specificity of the acceleration index for rejection in these patients was 71% and 100% respectively. The authors concluded that TEB is ideal for use "in the outpatient setting to supplement myocardial biopsies."

This study did not provide data on the clinical impact on patient management or improved health outcomes after treatment. These preliminary findings might be useful if replicated. The fact that we found no other report published on this indication since this study was published almost 10 years ago suggests that the approach has not been widely adopted.

3.5.2-3.5.6 Other Issues

No studies were found that addressed the following issues regarding this indication:

- TEB performance compared to alternative diagnostic tests for monitoring cardiac output, cardiac index, stroke volume, or other physiologic parameters

- factors that may affect test performance
- potential limitations regarding test performance setting
- factors regarding training.

3.6 Indication 6: Bioimpedance use in cardiac patients with a need for fluid management

3.6.1 Patient Management and Health Outcomes

This indication might include monitoring and diagnosis of pulmonary edema or peri-operative monitoring of patients following various types of surgery. Several studies employing a similar technology --- whole body impedance—were found that assessed congestive heart failure patients with need for fluid management; however, we found no study of TEB for this indication.

3.6.2-3.6.6 Other Issues

No studies were found that addressed the following issues regarding this indication.

- TEB performance compared to alternative diagnostic tests for monitoring cardiac output, cardiac index, stroke volume, or other physiologic parameters
- Factors that may affect test performance

- Potential limitations regarding test performance setting
- Factors regarding training.

3.7 Indication 7: Bioimpedance use in the management of hypertension

3.7.1 Patient Management and Health Outcomes

TEB has been used to monitor the efficacy of antihypertensive medications. One study compared TEB-based drug selection to physician management without the support of TEB. Taler, Textor, Augustine, et al. (2002) described a controlled trial involving 104 resistant hypertension patients without a secondary cause or who were to be treated medically. Patients were randomized to hemodynamic-based drug selection or hypertension-specialist-directed drug selection. TEB was used to calculate stroke volume, cardiac output, systemic vascular resistance index, and markers of cardiopulmonary volume. The authors reported that patients with chronic hypertension who were treated using a treatment algorithm and serial hemodynamic measurements obtained by TEB had a small but statistically significant greater decrease in blood pressure compared to patients treated with clinical judgment alone.

Certain methodological weaknesses of this study should be noted. The details of the randomization method are not reported, and it is unclear whether or not all patients were blinded to the use of TEB in their care. There was a small difference in average blood pressure between the “specialist care” and “hemodynamic” monitoring group (4/4 mm Hg difference); this difference was similar in magnitude to the difference between the groups at the end of the study (8/7 mm Hg difference). The blood pressure control rate achieved by the hemodynamic treatment group (56%) was significantly higher than the control rate achieved for the specialist care group (33%). Also, the authors noted that significantly more frequent changes in medications and dosages were made in the hemodynamic group as compared to the specialist care group, while it is unclear how many opportunities for such a change were offered in each study arm. The authors commented that the specialist care group was comprised of nationally certified hypertension specialists with special expertise in the treatment of resistant hypertension, and suggested that monitoring with TEB would have a greater benefit when the alternative was management with a community physician. However, it is also possible that the small improvement in the hemodynamic monitoring group was due to the increased number of specialist visits. It is, therefore, not known what the benefit of TEB would be in community practice with treatment decisions made by generalists.

3.7.1 Other Issues

No studies were found that addressed the following issues regarding the following situations:

- TEB performance compared to alternative diagnostic tests for monitoring cardiac output, cardiac index, stroke volume, or other physiologic parameters.
- Factors that may affect test performance.
- Factors regarding training.

The study by Taler, Textor, Augustine, et al. (2002) described above has a serious limitation regarding test performance setting. As noted above, the specialists in the study were national experts, and the results might not be generalizable to a community setting.

3.8 Additional Material Regarding Some Of The Indications

While not among the original questions, peer review comments and discussions with AHRQ suggested further analyses.

3.8.1 Year of Publication

First, it is of interest to examine whether year of publication affected the results. Advances in technology such as new signal processing algorithms may lead to increased accuracy of bioimpedance over time. Figure 3.3 shows correlation coefficients arrayed by year; no trend toward higher correlation in more recent years is apparent in these graphs. In order to quantitatively estimate whether there has been an improvement in correlation in recent years, we compared an estimate of correlation in the period 1991-1996 to the period 1997 and later. There were twelve studies (305 patients) using cardiac output in the period 1991-1996 comparing TEB among inpatients to TD. The combined correlation coefficient for this group was 0.756 (95% CI: 0.639-0.838), with significant heterogeneity. For the five studies (91 patients) published in 1997 and later, the combined r = 0.487 (95% CI: .299-.640), without significant heterogeneity. The magnitude of the combined correlation coefficient from earlier studies was somewhat higher than that of the coefficient from more recently published studies.

3.8.2 Quality

There were a sufficient number of studies using the Sramek-Bernstein equation involving a comparison of TEB and TD to conduct a meta-analysis comparing one dimension of quality of measurement --- that relating to appropriate analysis of number of measurement replications. There were five studies (148 patients) using cardiac output with a quality grade of “A” with combined r=0.612 (95% CI: 0.422-0.751). There were four studies (88 patients) with a quality grade of “B” with combined r=0.691 (95% CI: 0.333-0.874). There were eight studies (160 patients) with a quality grade of “C” with combined r=0.738 (95% CI: 0.545-0.856). These results, for which there was not significant heterogeneity, do not suggest that this definition of quality is related to the size of the correlation coefficient. Table 3.6 displays quality grades by study.

3.9 Summary of Results

Despite the large amount of observational data generated on TEB, almost all of the studies did not use a design that would allow for meaningful comparisons of patient outcomes of care and thus provide evidence to address the questions. In several of these reports the authors anecdotally stated in their discussion sections that they found the method to be clinically useful and helpful for managing patients under various critical circumstances (or the opposite); however, these inferences were not based on randomized or other comparative designs where a group of patients was monitored by TEB and contrasted with a control group. The authors’ conclusions are included in the evidence table.

4. FURTHER CONSIDERATION OF CERTAIN RELEVANT ABSTRACTS AND OTHER MATERIAL

For some of the indications and some of the material discussed in the Results section, some additional material beyond that previously presented merits comment. In this section we mention several abstracts, none of which appear to have been published as full articles (the earliest was first presented in 1998). It is difficult to adequately evaluate these reports, because this type of publication provides limited information. They are included, however, to provide relevant information about work in progress.

4.1 Comparisons to alternative technologies for monitoring

Several abstracts that could not be evaluated for the reasons described above involved comparisons of TEB to alternative techniques. Yung, Fletcher, Fedullo, et al. (1999) reported comparing TEB to TD and Fick on 33 ambulatory patients with echocardiographic evidence of pulmonary hypertension. Based on the correlation coefficients and measures of bias and precision against TD and Fick that they obtained, the authors suggested that, for measuring CI in patients with pulmonary hypertension, TEB may be a convenient, less costly alternative to TD.

An abstract by Milzman, Napoli, Gerace et al. (2000) reported studying whether the use of TEB monitoring of 58 heart failure patients in the ED (stratified by whether or not their CI improved after one hour of therapy in the ED) affected total hospital stay and charges. They concluded that TEB was helpful identifying patients likely to show an early response to therapy and to incur lower total costs, but they also observed that the device had limitations when certain arrhythmias occurred and that the lack of central pressure monitoring could be problematic.

In another abstract Kzanegra, Barcarse, Chen et al. (2002) reported investigating whether TEB measurements, combined with knowledge of B-type natriuretic peptide (BNP) levels, improved physicians' ability to diagnose congestive heart failure (CHF) in 98 patients in an emergency setting. They concluded that TEB enabled better diagnosis of CHF by rapidly distinguishing systolic from diastolic dysfunction and by assessing severity of illness.

4.2 Acute Dsypnea

Diagnosing the cause of dyspnea can be difficult and TEB has been proposed as a tool that is potentially useful for the differential diagnosis of cardiogenic and pulmonary causes of dyspnea in an abstract by Marrocco, Eskin,Nashed et al. (1998). They studied the sensitivity and specificity of hemodynamic parameters measured by TEB to distinguish between cardiogenic and pulmonary causes of dyspnea. Only patients with "clinically clear" diagnoses were included, and only moderate sensitivity and specificity were achieved with TEB. This suggests that the diagnostic performance of TEB would be unacceptable when all patients are considered, including patients with mixed or uncertain diagnoses that were excluded from this study. Since this report was in abstract form, it is impossible to assess the quality of the study and its usefulness.

No studies on the use of TEB for differential diagnosis of dyspnea were found in a search of Medline®. This search was supplemented with a search for abstracts published at the annual meetings of the American Academy of Emergency Medicine. Two relevant abstracts presented in the last three years were found, and a reviewer suggested an additional abstract. Han, Lindsell, Tsurov et al. (2002) found a significant correlation in hemodynamic parameters measured by TEB in the presence of congestive heart failure as determined by follow-up over the next two months, but no information was given about whether the use of TEB would lead to changes in management. Another abstract (Aisiku, Ander, Knoepp et al., 2000) did not find a correlation between hemodynamic parameters measured with TEB and subjective improvement in dyspnea following treatment for heart failure. These studies suggest that changes in hemodynamic parameters may be measured in patients with dyspnea, but the interpretation and clinical utility of these measurements is not known at the present time. The abstract suggested by the reviewer described a study of 45 dyspneic and hypotensive patients in which TEB was compared with an ED physician's clinical judgment to determine whether the cause of the dyspnea and hypotension was cardiogenic (Springfield, Sebat, and Sebat, 2002). The authors concluded that TEB yielded a quicker assessment and equal accuracy, which could enable earlier intervention. Again, since these reports were in abstract form, it is impossible to assess their quality and usefulness.

4.3 Atrioventricular Delay

A narrative review article by Belott (1999) asserted that finding the optimal AV delay is valuable to maximize cardiac output and prevent mitral regurgitation, but that most pacemakers are left at the default setting because of the difficulty of finding the optimum value. The article also stated that newer pacemakers have internal systems that work on a similar principle to bioimpedance (minute ventilation) for automatic parameter adjustment, but that possibly harmful interactions can occur with these systems and TEB, so TEB would be contraindicated for patients with these pacemakers.

The proposed benefit of TEB is based on an analytic framework with three steps:

1. TEB can measure changes in cardiac output in response to programming changes in the AV delay in pacemakers.
2. The optimal AV delay can be found based on the information provided by TEB.
3. Adjusting the AV delay would potentially improve clinical outcomes.

The Ovsyshcher, Gross, Blumberg (1992) article cited above only addressed the first part of this analytic framework (without a confirmatory technique). The Ovsyshcher, Gross, Blumberg (1993b) article addressed the second, but did not have any independent confirmation (such as echocardiogram) that the values found were objectively optimal. The Kindermann, Frohlig, Doerr et al. (1997) study is a step in this direction.

In another abstract related to this subject that was suggested by a reviewer, Trupp, Voegtlin, Abraham et al. (2002) studied 15 patients before discharge to determine whether TEB could better determine optimal inter-ventricular settings during biventricular pacing than echocardiography. The results presented by these authors were unclear, although they concluded that TEB "…may provide an alternative noninvasive method to echo…"

Finally, one case study has been reported where a single patient had resolution of symptoms of heart failure after optimization of atrioventricular delay with TEB (Young, Smart, and Ventura, 1999). The currently available evidence, however, is not adequate to demonstrate a benefit in health outcomes with the use of TEB.

4.4 Intravenous Inotropes

There were no original studies that directly addressed TEB's usefulness for this indication. One author, however, argued in a case report for the use of TEB for this indication (Lasater, 1999), but rigorous studies of TEB for this application are needed.

4.5 Cardiac Patients With a Need for Fluid Management

With respect to use for congestive heart failure, the American College of Cardiology and American Heart Association in their 2001 "ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult" (ACC website: http://www.acc.org/clinical/guidelines/failure/iii%5Fassessment.htm) makes the following statement about TEB for use in patients with chronic heart failure: "…Although hemodynamic measurements can also be performed by non-invasive methods such as transthoracic bioimpedance, routine use of this technology cannot be recommended at the present time because the accuracy of bioelectrical parameters has not been defined in patients with chronic HF and it has not been shown to be more valuable than routine tests, including the physical examination. Moreover, it is not clear whether serial noninvasive hemodynamic measurements can be used to gauge the efficacy of treatment or to identify patients most likely to deteriorate symptomatically during long-term follow-up …"

4.6 Adverse Events

TEB does not require the skills and expertise needed for the use of invasive techniques, and only one study reported a death due to pacemaker malfunction associated with TEB use (Critchley, 1998). It is unclear, however, whether such information would have been routinely reported in these types of studies, but the FDA MAUDE database (voluntary adverse event reporting) indicated no reports related to TEB.

4.7 Lead Placement and Equations

Additional comments about lead placement are merited. Although they do not present evidence for their observation, Castor, Klocke, Stoll, et al. (1994) point out that small changes in the position of TEB electrodes impact measurement of cardiac output by as much as 10 percent. They suggest that decreased distance leads to overestimation of cardiac output and vice versa. These authors further suggest that "…incorrect input of height and weight of the patient in the computerized system..." can lead to error. They provide theoretical but not empirical evidence for this assertion.

While the lead placements described in the results were those most frequently encountered in this review, Critchley (1998) mentions that new electrode placement schemes have been proposed. He also mentions that the esophageal probe method described by Balestra, Malacrida, Leonardi, et al. (1992) was withdrawn because of "...fears of oesophaeal perforation with surgical diathermy and defibrillation." However, no specific reference was provided.

We report above that Demeter, Parr, Toth et al. (1993) inferred that the Kubicek equation performs well when the resistivity term is calculated from measured hematocrit rather than from an assumed constant. Fuller's (1992) TEB review also indicated that previous studies had found improved correlations when calculated hematocrit was used. In contrast, Handelsman's 1992 review referred to Sramek's removal of the blood resistivity term from the Kubicek equation and characterization of this parameter as inconsequential in the context of total resistivity. Similarly, in a study of cardiac output among nineteen patients with chronic obstructive pulmonary disease, Bogaard, Hamersma, Horsch, et al. (1997) concluded that measured hematocrit resulted in only a small improvement in validity. These contrasting findings raise the issue of whether more research on this issue may be needed.

The reporting of equations in studies reviewed was not always complete, and for some devices the equations may be proprietary by the manufacturer of the device and not known to the researcher. For example, three recent studies with a total of 95 patients (Spiess, Patel, and Soltow, 2001; Drazner, Thompson, Rosenberg, et al., 2002; Sageman, Riffenburgh, and Spiess, 2002) reported using "BioZ" equipment (Cardiodynamics International Corporation, San Diego, CA), but these studies did not describe which equation was used. The correlation coefficients measured in these three studies range from 0.61-0.93. The combined correlation coefficient for these three studies is r=0.788; 95% CI: 0.466-0.926; which is somewhat higher than the correlation coefficient we calculated only for studies which indicated that the Sramek-Bernstein equation was used. These three studies illustrate the large number of variables between the studies that make it difficult to combine the studies in a single meta-analysis (see Evidence Table I for details). For example, in one study patients are critically ill but in another patients are hospitalized but not critically ill.

Furthermore, the different studies measure different hemodynamic parameters. In this technology assessment, we present results of separate meta-analyses for patient setting, hemodynamic parameter measured, equation used and quality of thermodultion measurements; these meta-analyses show that there is significant between-study heterogeneity, suggesting that many other factors in addition to the factors that we have identified from the studies are important. Further studies are needed to identify all the sources of heterogeneity in TEB measurements --- especially studies that characterize the performance of TEB in the outpatient population of interest for the questions addressed in this technology assessment.

4.8 Electrical Disturbance

Balestra, Malacrida, Leonardi et al. (1992) observed that "… simultaneous measurement of TEB and Doppler ultrasound leads to prolonged disturbance of the impedance signal…" They explained that the Doppler transducer absorbs a large portion of the current, reducing the signal and thereby decreasing the cardiac output measurement. This effect was not mentioned in other articles, but if confirmed, it does raise concerns about simultaneous Doppler vs. TEB comparisons.

4.9 Manufacturers

Figure 3.4 shows correlation coefficients for cardiac output as measured by TEB for the different manufacturers' instruments, showing results for critically ill patients (including CCU, ICU and critically ill inpatients), inpatients who were not identified as critically ill, and outpatients.

The majority of the studies were done on the NCCOM device (#9), which is no longer commercially produced. There is wide variation in the correlation coefficient measured with this device, which is no longer commercially produced. The manufacturers attribute the variation to problems with the signal processing algorithms (letter to CMS). Other possible causes of the variation include factors that are identified in the TA, such as specifics of lead placement and clinical characteristics (overweight, pulmonary embolism) that affect accuracy of the devices or other factors that have not been studied.

There is wide variation in the results across the instruments. Several factors could account for this such as variation in lead placement and clinical characteristics. The variation could also be due to differences in instrument performance; however, not enough data is available on any one instrument except the NCCOM to draw conclusions about this. Unfortunately, most of the research literature focuses on machines no longer made, and there are few data available on currently manufactured devices.

5. PREVIOUS SYSTEMATIC REVIEWS

Five systematic reviews (Fuller, 1992; De Maria and Raisinghani, 2000; Handelsman, 1992; Raaijmakers, Faes, Scholten, et al., 1999; Critchley and Critchley, 2000) have examined whether the measurement of cardiac output by TEB is comparable to measures obtained by other technologies. The conclusions reported in these systematic reviews are summarized below:

Fuller (1992):

- "…A moderately good correlation exists between impedance cardiac output measurement and other techniques, although correlation is not so good when ICU patients are studied…"

Raaijmakers, Faies, Scholten et. al. (1999):

- " …The overall r^2 value of .67 indicates that thoracic impedance cardiography might be useful for trend analysis of different groups of patients. However, for diagnostic interpretation, a value of .53 might not meet the required accuracy of the study…Great care should be taken when thoracic impedance cardiography is applied to the cardiac patient…"

De Maria and Raisinghani (2000):

- "…impedance cardiography has the potential to make routine assessment and trending of cardiac output a viable alternative to assist in the management of both chronically and acutely ill patients, including those with heart failure…"

Critchley and Critchley (1999):

"…Using our revised criteria for the acceptance of limits of agreement of less than +/- 28.3%, the results of many of the studies performed in the early 1990's using Doppler ultrasound and bioimpedance methods would still support the rejection of either of the newer techniques in favor of TD. This is particularly true of studies involving impedance cardiography in critically ill patients… however apart from this specific <critical care> situation our present review of the literature suggests that the bioimpedance method is more accurate than current Doppler techniques…." They conclude by suggesting technological improvements be made to improve the accuracy of both.

6. DISCUSSION

Fineberg, Bauman, Soman et al. (1977) suggested five criteria for evaluating diagnostic technologies:

- Technical capacity (feasibility and reproducibility),
- Diagnostic accuracy (test performance, i.e. sensitivity, specificity),
- Diagnostic impact (influence on the pattern of subsequent diagnostic testing and replacement of other tests or procedures)
- Therapeutic impact (influence the selection and delivery of therapy), and
- Patient outcome (contribution to improved health).

The majority of the studies on TEB address only the first issue, technical capacity. One study on heart transplant patients addressed the second issue, sensitivity and specificity for diagnosing a specific condition (in this case rejection of the transplant); but this study did not quantify the potential diagnostic impact, therapeutic impact or patient outcome. One study on the use of TEB in resistant hypertension addressed the fifth issue, patient outcome compared to a standard treatment (in this case management by a specialist).

While we did not conduct a systematic review of other diagnostic tests, several additional reports regarding TD are relevant. One systematic review of 1,610 patients from 12 randomized controlled trials “ …examined the incidence of major morbidity in critically ill patients managed with pulmonary artery catheters … and found a statistically significant reduction in morbidity using pulmonary artery catheter-guided strategies…” (Ivanov, Allen, Calvin, 2000). In contrast, another review (of studies of less ill patients) of four randomized prospective studies found that “…in moderate risk vascular surgery patients routine preoperative pulmonary artery catheterization is not associated with improved outcomes…” (Barone, Tucker, Rassias, et al., 2001).

It should also be noted that the parameter most useful in patient management obtained from catheterization is pulmonary artery wedge pressure, which cannot be directly measured by TEB. Furthermore, Drazner, Thompson, Rosenberg, et al. (2002) found that thoracic fluid content obtained via TEB did not correlate well with this cardiac parameter.

There has been considerable debate about the value of right heart catheterization (using TD), with concern not only about lack of demonstrated benefit, but also about possible harm. Potential reasons that have been suggested to explain negative outcome include complications of the procedure itself or, possibly harmful, aggressive interventions (e.g. inotropic therapy) initiated in response to catheterization findings. (Connors, Speroff, Dawson et al., 1996; Hall, 2000; Polanczyk, Rohde, Goldman et al., 2001). One review concluded that inotropic (e.g. dobutamine, milrinome) therapy has "… beneficial hemodynamic effects…" (Felker and O'Connor, 2001). These authors, however, also described a "negative impact on survival in patients with heart failure" and concluded that the evidence for the impact of this type of therapy on improving quality of life is "mixed".

This debate about TD is only indirectly related to the key objective of this TA of evaluating the use of TEB. It warrants consideration, however, because evaluating TEB using existing literature requires comparison to TD, since much of the literature compares TEB to thermodilution in inpatient and intensive care unit settings. Due to the extensive use of TD implied by the large number of comparisons, the accuracy of TEB relative to TD is relevant. The controversy about the value of TD (beyond the issue of its accuracy) results from outcomes studies of that procedure. The fact that outcomes studies raise these issues strengthens the point made repeatedly in this TA --- without more such studies of TEB, conclusions about its usefulness in patient care must remain limited.

The most important limitation in addressing the questions raised in this review is the almost complete absence of studies examining clinical outcomes in a methodologically sound manner. It is for this reason that each of the Results sections repeatedly emphasizes this. This limits the interpretation of the quantitative and non-quantitative results that follows. Additionally, as mentioned previously, many of the studies reviewed have serious methodological flaws beyond this basic one.

First, to best evaluate diagnostic test performance, comparisons of one test versus another should be made on each test's ability to diagnose a specific clinical condition. Studies that take this approach are almost non-existent, so a sound answer to the study question regarding this issue is impossible to provide. We therefore had to rely solely on comparisons of TEB to various other tests, and this presented another problem. The Fick method is, in a sense, a "gold standard" but is not and cannot be commonly used in outpatient practice. In fact, none of the tests commonly used in actual practice are likely to qualify as a gold standard, and their usefulness could only be assessed by a systematic review of those other tests.

Another review article attempts to address this problem. Critchley and Critchley (1999) quotes the accuracy of TD as +/- 10 to 20%, and suggests that +/- 20 to 30% limits of agreement would be acceptable for patients with certain indications. While our review was not designed to estimate the prevalence of the use of this alternative technique, TD was the most frequently used comparative technique in the literature. Our meta-analyses therefore heavily rely on this technique for most comparisons.

Correlation coefficients are poor summary indicators of the relative performance of diagnostic tests. At least one researcher (Critchley and Critchley, 1998) describes their use as 'inappropriate.' Interpreting the correlation coefficient is complicated further by the difficulty in translating its magnitude into a clinically meaningful statement. While the scope of this review did not include a review of how comparison techniques compare among themselves on this measure, we do have limited information which may help to put the correlation results into context. For example, Handelsman (1992) reported that the correlation of TD with Fick ranged from .89 to .96, but that " … intra-subject TD measurements, depending on the clinical situation, is stated to be in the range of 15% to 20%…" or even higher during mechanical ventilation.

Looking at TEB performance within subgroups is clinically more meaningful than combining coefficients across the various cardiac metrics, equations, and practice settings. This approach, however, trades off the higher statistical power that would result from collapsing across some of these categories. Correlations as high as .879 for TD measurement of cardiac output compared to TEB using the Sramek-Bernstein equation appear encouraging, but the wide confidence interval (.642 - .962) based on only three studies limits the inferences that can be made. Similarly, the low correlation of .349 (.122 to .541) for CI using the Sramek–Bernstein equation is tempered by the scarcity of data. In summary, there is great variability in the results reporting correlation coefficients.

Critchley and Critchley (1999) point out that with their data, for one subset of patients, the difference between TD and TEB is not much greater than the difference between different measurements of TD itself. That paper also points out that the repeatability of bioimpedance is 4 to 8%--better than TD.

A better measure than correlation coefficients (Critchley and Critchley, 1999; Bland and Altman, 1986) is the “bias” and limits of agreement. We, like Critchley and Critchley, found that the bias is infrequently reported, and when present, it is sometimes based on inappropriate measurements. The three studies with the largest bias in cardiac output (Balestra, Malcrida, Leonardi et al., 1992; Ng, Coleman, Walley, et al., 1993); Critchley, Calcroft, Tan, et al., 2000) shared a common characteristic. These authors used only a single measurement or averages of the multiple measurements without controlling for the variability of the measurements. Lack of controlling for the variability of TD measurements may be one explanation for these results (Stetz, Miller, Kelly, et al., 1982).

Nonetheless, we did identify 12 articles (thirteen studies) for which the measurement method justified further analysis. The implications of these results depend upon the “clinical interpretability” of the limits of agreement. It is difficult to interpret such results, however, without data on clinical outcomes. In addition, the issue of the adequacy of the reference “standard” (in this instance TD) remains in doubt.

Finally, the scarcity of suitable data placed limits on what could be quantitatively analyzed. For example, combinations of equations and electrode configurations, which some of the studies suggested may be important, were not analyzed.

6. Conclusion

The clinical reports on the use of TEB for a variety of clinical indications by reports published since 1991 suggested that this non-invasive method is of interest and may potentially support some of these indications, but there is little evidence that directly addressed how this monitoring technique can affect patient outcomes. A conceptual model that captures the essential clinical aspects of the use of this technique for clinical management and therapeutics, such as the CMS analytic model described in the Introduction, will aid the design of such studies.

There was little conclusive evidence regarding TEB's usefulness in the specific areas addressed, and this was largely due to the lack of focus of researchers in this area on clinical outcomes. One study (Taler, Textor, Augustine, et al., 2002) is an example of the type of study that needs to be done; it evaluated the use of TEB for managing patients with resistant hypertension and examined hypertension, an important outcome, that is a well-accepted surrogate for other important health outcomes. The Taler, Textor, Augustine, et al. (2002) study demonstrates the importance of a control group. In that study patients in the TEB and the control group both experienced large reductions in blood pressure; therefore, the majority of the effect in the study is attributed to other factors that are common to both the control group and the intervention group such as access to the expert specialists. The results may not be generalizable in a community setting.

In conclusion, using the Fineberg, Bauman, Sosman et al. criteria described above, the following table summarizes TEB performance based on available studies:

FINEBERG, BAUMAN, SOSMAN ET AL. CRITERION	TEB Performance
Technical capacity (feasibility and reproducibility)	Variable results
Diagnostic accuracy (test performance, i.e. sensitivity, specificity)	Insufficient data
Diagnostic impact (influence on the pattern of subsequent diagnostic testing and replacement of other test or procedures)	Insufficient data
Therapeutic impact (influence the selection and delivery of therapy), and	Insufficient data
Patient outcome (contribution to improved health).	Insufficient data

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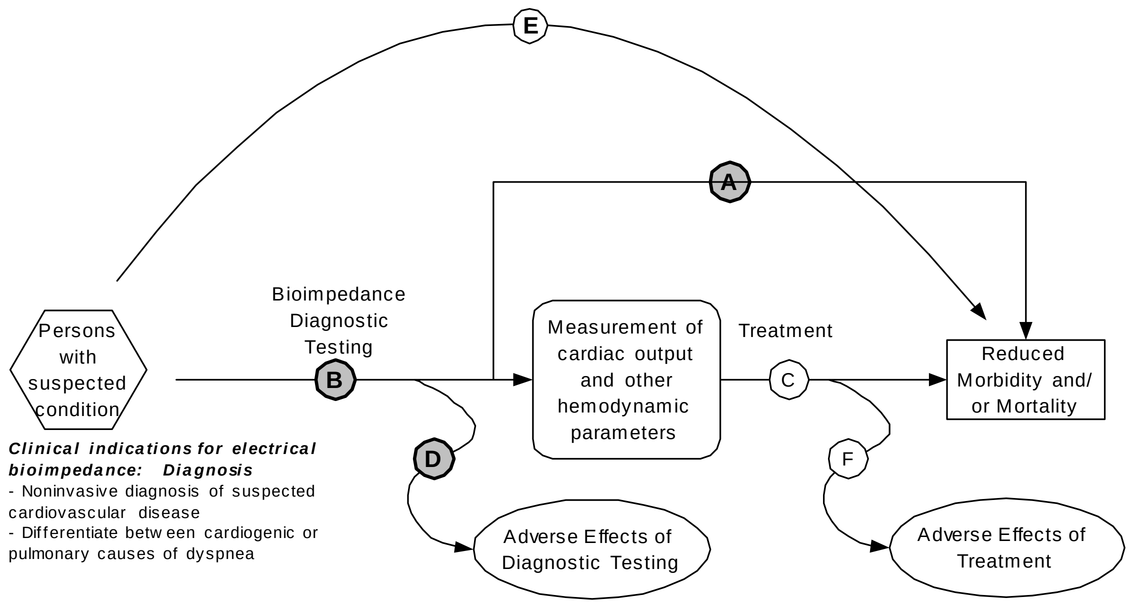
Figure 2.1

Analytic Framework- Electrical Bioimpedance for Diagnosis



Clinical indications for electrical bioimpedance: Diagnosis
- Noninvasive diagnosis of suspected cardiovascular disease
- Differentiate betw een cardiogenic or pulmonary causes of dyspnea

A ***Clinical impact of bioimpedance diagnostic testing***
Question #2

B ***Ability of bioimpedance to measure cardiac output:***
Question #1
-Sensitivity and specificity of bioimpedance to measure cardiac output
-False Positives
-False Negatives
Question #3
-Inpatient vs. Outpatient settings for meaurement
Question #4
- Training and experience of operator

C ***Treatment strategies***

D ***Adverse Effects of Diagnostic Testing***
Any direct adverse effects w ill be noted

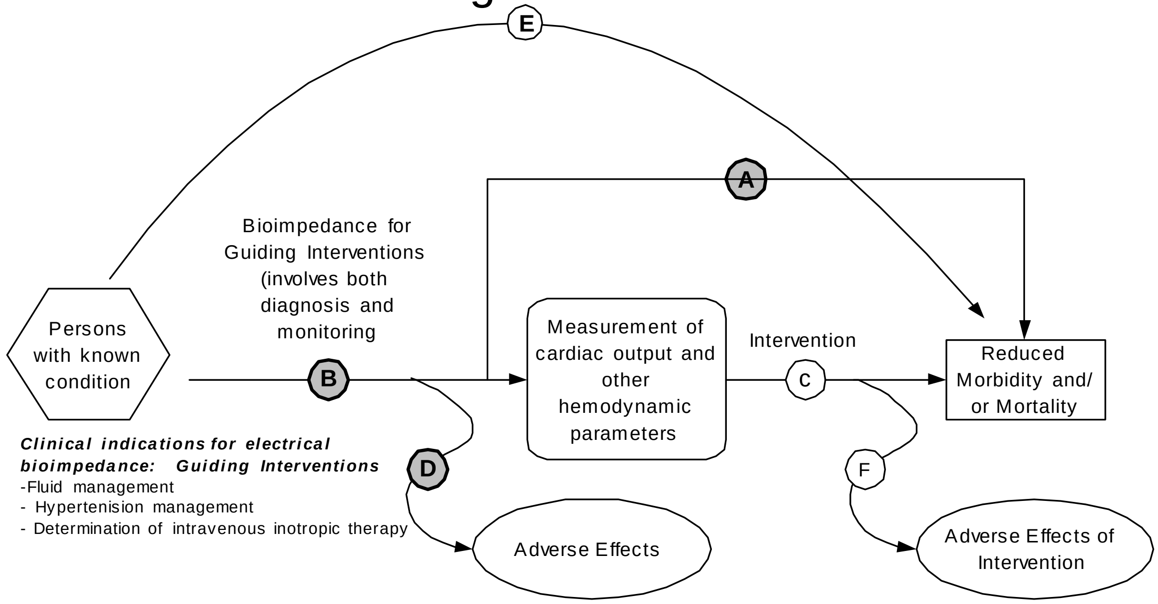
E ***Other diagnostic procedures*** may be used to measure cardiac output and/or determine management strategies for patient- include w hen comparison is made against electrical bioimpedance in a clinical trial

F ***Adverse Effects from Treatment***

For diagnostic testing, the sensitivity and specificity of bioimpedance to measure cardiac output or other physiological parameter compared to reference methods will be reviewed (link B). Any direct adverse events of testing mentioned in the studies will be noted. The effects of false positives and false negatives on morbidity/mortality will be reviewed if mentioned in the studies (link D). Any studies that directly demonstrate a change in patient management or a reduction in morbidity/mortality will be reviewed (link A). It is outside the scope of this technology assessment to include other diagnostic strategies except when compared with bioimpedance in clinical studies.

Figure 2.2

Analytic Framework- Electrical Bioimpedance for Guiding Interventions



Clinical indications for electrical bioimpedance: Guiding Interventions
-Fluid management
- Hypertenision management
- Determination of intravenous inotropic therapy

A ***Clinical impact of bioimpedance for guiding interventions***
Question #2

B ***Ability of bioimpedance to measure cardiac output:***
Question #1
-Sensitivity and specificity of bioimpedance to measure cardiac output
Question #3
-Inpatient vs. Outpatient settings for meaurement
Question #4
- Training and experience of operator

C ***Intervention strategies***

D ***Adverse Effects***

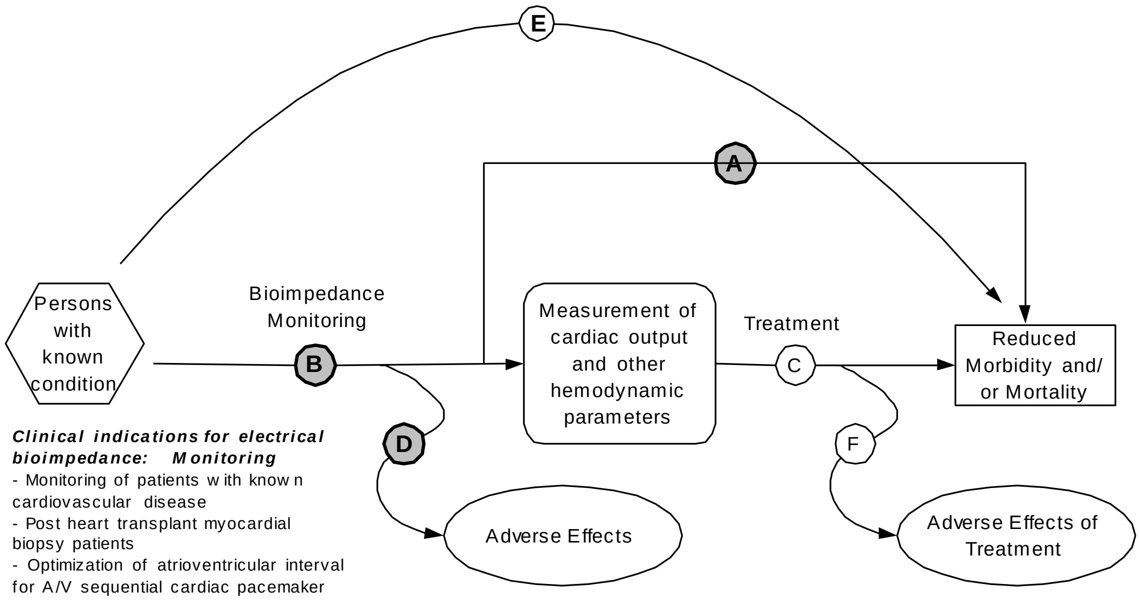
E ***Other intervention guidance procedures***may be used to measure cardiac output and/or determine management strategies for patient- include w hen comparison is made against electrical bioimpedance in a clinical trial

F ***Adverse Effects of intervention***

For use in guiding interventions, the sensitivity and specificty of bioimpedance for measuring cardiac output or other physiological parameters compared to reference methods will be reviewed (link B). Any direct adverse effects cited in the studies will be noted (link D). Studies that directly link a change in patient strategy or a reduction in morbidity/mortality to the use of bioimpedance for guiding interventions will be reviewed (link A). It is outside the scope of this technology assessment to review other intervention guidance strategies except to review these strategies when compared to bioimpedance in clinical studies.

Figure 2.3

Analytic Framework- Electrical Bioimpedance for Monitoring



Clinical indications for electrical bioimpedance: Monitoring
- Monitoring of patients with known cardiovascular disease
- Post heart transplant myocardial biopsy patients
- Optimization of atrioventricular interval for A/V sequential cardiac pacemaker patients

A ***Clinical impact of bioimpedance monitoring***
Question #2

B ***Ability of bioimpedance to measure cardiac output:***
Question #1
-Sensitivity and specificity of bioimpedance to measure cardiac output
Question #3
-Inpatient vs. Outpatient settings for meaurement
Question #4
- Training and experience of operator

C ***Treatment strategies***

D ***Adverse Effects***

E ***Other monitoring procedures*** may be used to measure cardiac output and/or determine management strategies for patient- included when comparison is made against electrical bioimpedance in a clinical trial

F ***Adverse Effects from Treatment***

For monitoring, the correlation of bioimpedance to reference methods will be reviewed (link B). Any direct adverse effects of bioimpedance monitoring cited in the studies will be noted (link D). Any studies that directly demonstrate a change in patient management or a reduction in morbidity/mortality will be reviewed (link A). It is outside the scope of this technology assessment to review other monitoring strategies except when compared to bioimpedance in clinical studies.

Table 2.1 Bioimpedance literature search strategy using OVID to search MEDLINE and PREMEDLINE databases on January 2002

		# Citations
1	bioimpedance.mp. [mp=ti, ab, rw, sh]	633
2	impedance.mp. [mp=ti, ab, rw, sh]	10735
3	exp cardiography, impedance/	1042
4	exp electric impedance/	3114
5	exp thermodilution/	1495
6	teb.tw.	109
7	1 or 2 or 3 or 4 or 5 or 6	13977
8	limit 7 to human [Limit not valid in: Pre-MEDLINE; records were retained]	10434
9	limit 8 to english language	8846
10	Case Report/	1031559
11	9 not 10	8597
12	limit 11 to (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschrift or interview or lectures or legal cases or letter or news or periodical index)	267
13	11 not 12	8330
14	exp hypertension/	152540
15	hypertens$.tw.	159472
16	high blood pressure.tw.	4698
17	14 or 15 or 16	204979
18	13 and 17	330
19	13 not 18	8000

	Table 3.1: Summary of studies reporting correlation coefficients*									
	Study	Ref. Test	Para-meter	Setting	Equation	Manufacturer of TEB	Disease	Corr.	N	Measurement Condition
1	Balestra 1992	TD	CO	IN	SB	NCCOM-4	CV	0.74	10	External electrodes
2	Barin 2000	TD	CO	OUT	K	Rheo-Graphic	Lab	0.86	47	Suspected cardiac disease
3	Barry 1997	TD	CO	IN	SB	NCCOM-3	Mixed ICU	0.10	7	
4	Belardinelli 1996a	TD	CO	OUT	SB	NCCOM-7	CAD	0.90	10	Normal LV @exercise
								0.98	10	Normal LV @rest
	1996b							0.90	15	isch cardiomyo @exercise
								0.94	15	isch cardiomyo @rest
5	Clancy 1991	TD	CO	IN	SB	NCCOM-7	mixed ICU	0.91	17	
6	Critchley 1996	TD	CO	IN	SB	NCCOM-7	mixed ICU	0.60	8	
7	Critchley 2000	TD	CO	IN	SB	NCCOM-7	Sepsis	0.39	24	
8	Demeter 1993	TD	CO	IN	K	Minnesota 304B	CABG	0.84	10	Supine 1
								0.90	10	45 degrees
								0.97	10	Supine 2
9	Doering 1995	TD	CO	IN	ND	NCCOM-3	cardiac surg	0.22	34	Postextubation
								0.28	34	Normothermia
								0.46	34	24h ICU
								0.48	34	ICU admission
10	Drazner 2002	TD	CI	IN	ND	BioZ	heart failure	0.64	50	
			CO					0.76	50	
11	Genoni 1998	TD	CO	IN	SB	NCCOM-7	lung injury	0.30	10	ZEEP
								0.60	10	PEEP
12	Horstmann 1993	TD	CO	OUT	K	Diefenbach	Lab	-0.01	35	at rest
								0.45	35	at exercise
13	Jewkes 1991	TD	CO	IN	SB	NCCOM-3	mixed ICU	0.72	16	
			SV					0.83	16	
14	Marik 1997	TD	CO	OUT	ND	Renaissance-IQ	CHD	0.08	24	
15	Ng 1993	TD	CO	IN	SB	NCCOM-7	mixed ICU	0.87	37	
16	Perrino 1994	TD	CO	IN	SB	NCCOM-7	noncardiac surgery	0.84	43	
17	Pickett 1992	TD	CO	IN	K	HDC	mixed ICU	0.86	43	SM with means of multiples
18	Raaijmakers 1998a	TD	CO	IN	SB	ND	sepsis	0.42	13	
19	Sageman 1993	TD	CO	IN	SB	NCCOM-7	CABG	0.48	50	
20	Sageman 2002	TD	CI	IN	ND	BioZ	CABG	0.93	20	
21	Shoemaker 1994	TD	CI	ED	ND	Renaissance-IQ	mixed ED	0.86	68	
22	Shoemaker 1998	TD	CI	ED	ND	Renaissance-IQ	mixed ED	0.85	680	

	Table 3.1: Summary of studies reporting correlation coefficients*									
	Study	Ref. Test	Para-meter	Setting	Equation	Manufacturer of TEB	Disease	Corr.	N	Measurement Condition
23	Shoemaker 2000	TD	CI	ED	ND	Renaissance-IQ	mixed ED	0.78	45	
24	Shoemaker 2001	TD	CO	ED	ND	Renaissance-IQ	mixed ED	0.91	151	
25	Spiess 2001	TD	CI	IN	ND	BioZ	CABG	0.87	47	Postanesthesia
								0.56	45	Chest closed
								0.73	45	Chest open
								0.76	47	after bypass
26	Thangathurai 1997	TD	CO	IN	ND	IQ 101	surgery	0.89	23	
27	Van der Meer 1996	TD	CO	IN	SB	IPG-104	CABG	0.83	21	
28	Van der Meer 1997	TD	CO	IN	SB	IPG-104	CABG	0.60	37	
29	Velmahos 1998	TD	CI	ED	ND	Renaissance-IQ	CV accidents	0.82	17	
30	Weiss 1995	TD	CO	OUT	SB	NCCOM-7	lab	0.69	15	Stable pts
							MICU	0.81	13	Unstable pts
31	Woltjer 1996b	TD	SV	IN	SB	IPG-104	CABG	0.64	37	
32	Woltjer 1997	TD	SV	OUT	K	IPG-104	lab	0.69	24	
33	Wong KL 1996	TD	CO	IN	SB	NCCOM-7	CABG	0.86	18	
34	Zacek 1999	TD	CI	IN	SB	HotmanAH-HHC	cardiac surgery	0.26	28	
35	Zubarev 1999	TD	CO	IN	mod K	BPCS	AMI	0.91	11	
36	Woo 1992	TD	CO	IN	SB	NCCOM-3	heart failure	0.51	44	
37	Yakimets 1995 Tr2	TD	CI	IN	SB	NCCOM-7	cardiac surgery	0.40	28	2-4h postsurgery
								0.45	28	Immed postsurgery
			CO					0.51	28	2-4h postsurgery
								0.55	28	Immed postsurgery
38	Young 1993	TD	CI	IN	SB	NCCOM-6	sepsis	0.36	19	
39	Belardinelli 1996	Dir Fick	CO	OUT	SB	NCCOM-7	CAD	0.93	15	isch cardiomyo @exercise
								0.85	15	isch cardiomyo @rest
								0.89	10	Normal LV @exercise
								0.95	10	Normal LV @rest
40	Yakimets 1995 Tr1	Dir Fick	CI	OUT	SB	NCCOM-7	lab	0.26	17	at exercise
								0.62	17	at rest
			SV					0.43	17	at exercise
								0.76	17	at rest
41	Drazner 2002	Dir Fick	CI	IN	ND	BioZ	heart failure	0.61	28	
			CO	IN	ND	BioZ	heart failure	0.73	28	
42	Bogaard 1997	Ind Fick	CO	OUT	K	IPG-104	COPD	0.92	14	
43	Antonicelli 1991	Pulsed Doppler	SV	OUT	K	ND	HBP	0.95	14	
44	Van der Meer 1999	Echo Doppler	CO	OUT	SB	IPG-104	lab	0.85	26	

	Table 3.1: Summary of studies reporting correlation coefficients*									
	Study	Ref. Test	Para-meter	Setting	Equation	Manufacturer of TEB	Disease	Corr.	N	Measurement Condition
45	Summers 2001	Echo-cardiog	LVEF	ED	ND	Sorba	mixed ED	0.89	15	Capan method
								0.89	15	Weissler method
46	Bowling 1993	Angio-graphy	LVEF	OUT	ND	NCCOM-7	Cancer	0.74	20	
47	Marik 1997	Angio-graphy	LVEF	OUT	ND	Renaissance-IQ	CAD	0.02	24	
48	Mattar 1991	Angio /nucl steth	LVEF	IN	SB	NCCOM-7	mixed ICU	0.69	17	
49	Thomas SH 1992b	Angio-graphy	CO	IN	SB	NCCOM-7	CHD	0.25	34	
			SV					0.65	34	

Note: Some articles report more than one 'study.'
*Abbreviations:
TD=Thermodilution
CO=Cardiac input
CI=Cardiac Index
SV=Stroke volume
IN=Inpatient
OUT=Outpatient
ED=Emergency Dept.
SB=Sramek-Bernstein
K=Kubicek
ND=No data

Table 3.2: Combined correlation coefficients for cardiac output and cardiac index by care setting: inpatient, outpatient, emergency room (TEB compared to TD using Sramek-Bernstein equation)

	Inpatient	**Outpatient**	**ED**
Cardiac Output	**.693**	**.879**	-
95% Confidence Interval	.578 - .781	.642 - .962	-
# Studies / # Patients	17/396	3/40	-
Cardiac Index	**.349**	-	**.848**
95% Confidence Interval	.122 - .540	-	.827 - .866
# Studies / # Patients	3/75	-	3/793

Figure 3.2.a : Combined correlation coefficients for cardiac output by care setting: inpatient, outpatient, emergency room (TEB compared to TD using Sramek-Bernstein Equation) Individual Study Results

	Setting	Citation	Effect	NTotal	Manufacture
	IN	Clancy 1991	.910	17	NCCOM-7
	IN	Jewkes 1991	.720	16	NCCOM-3
	IN	Balestra 1992	.740	10	NCCOM-4
	IN	Woo 1992	.510	44	NCCOM-3
	IN	Ng 1993	.870	37	NCCOM-7
	IN	Sageman 1993	.480	50	NCCOM-7
	IN	Perrino 1994	.840	43	NCCOM-7
	IN	Weiss 1995	.810	13	NCCOM-7
	IN	Yakimets 1995 Tr2	.530	28	NCCOM-7
	IN	Van der Meer 1996	.830	21	IPG-104
	IN	Critchley 1996	.600	8	NCCOM-7
	IN	Wong KL 1996	.860	18	NCCOM-7
	IN	Van der Meer 1997	.600	37	IPG-104
	IN	Barry 1997	.100	7	NCCOM-3
	IN	Genoni 1998	.450	10	NCCOM-7
	IN	Raaijmakers 1998	.420	13	ND
	IN	Critchley 2000	.390	24	NCCOM-7
Random	**IN (17)**		**.693**	**396**	
	OUT	Weiss 1995	.690	15	NCCOM-7
	OUT	Belardinelli 1996 a	.940	10	NCCOM-7
	OUT	Belardinelli 1996 b	.920	15	NCCOM-7
Random	**OUT (3)**		**.879**	**40**	
Random	**Combined (21)**		**.744**	**587**	

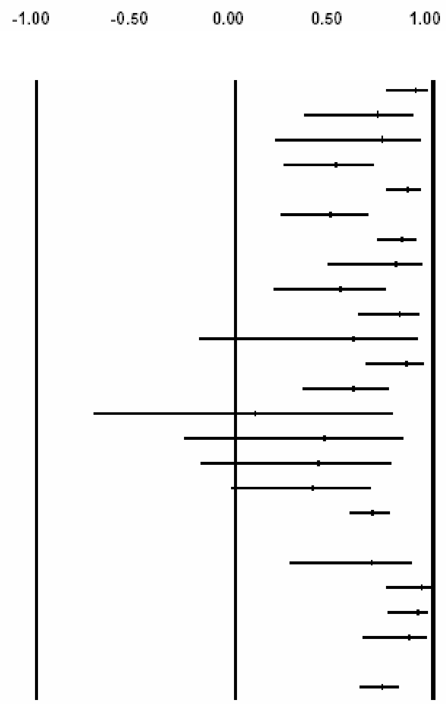


Figure 3.2.b: Combined correlation coefficients for cardiac index by care setting: inpatient, outpatient, emergency room (TEB compared to TD using Sramek-Bernstein Equation) individual study results

	Setting	Citation	Effect	NTotal	Manufacture
	ED	Shoemaker 1994	.860	68	Renaissance-IQ
	ED	Shoemaker 1998	.850	680	Renaissance-IQ
	ED	Shoemaker 2000	.780	45	Renaissance-IQ
Random	**ED (3)**		**.848**	**793**	
	IN	Young 1993	.360	19	NCCOM-6
	IN	Yakimets 1995 Tr2	.425	28	NCCOM-7
	IN	Zacek 1999	.260	28	HotmanAH-HHC
Random	**IN (3)**		**.349**	**75**	
Random	**Combined (6)**		**.675**	**868**	

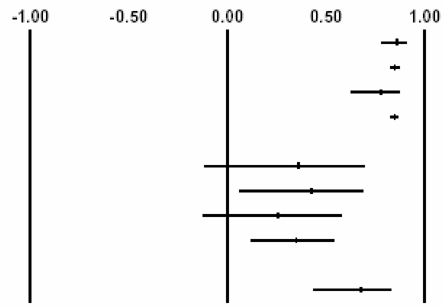


Table 3.3: Summary of studies reporting bias								
Study	N	Ref. Test	Test	D	SD	Unit	Measurement conditions	Replication of measurements
Antonicelli 1991	14	Pulsed Doppler	SV	-0.7	8.5	ml		Yes
Atallah 1995	5	TD	CI	0.69	0.66	L/min.m^2		Yes
Balestra 1992	30	TD	CO	1.99	2.20	L/min	external electrodes	No
Barin 2000	47	TD	CO	-0.18	0.78	L/min		Yes
Barry 1997	7	TD	CO	-1.60	1.16	L/min		Yes
Belardinelli 1996	15	TD	CO	-0.10	0.17	L/min	at rest	Yes
	15	TD	CO	-0.12	0.15	L/min	at rest 25%	
	15	TD	CO	-0.14	0.20	L/min	at rest 50%	
	15	TD	CO	-0.16	0.40	L/min	at rest 75%	
	15	TD	CO	-0.22	0.22	L/min	at rest 100%	
	10	TD	CO	0.04	0.10	L/min	peak exercise	
	10	TD	CO	-0.05	0.20	L/min	peak exercise 25%	
	10	TD	CO	-0.08	0.20	L/min	peak exercise 50%	
	10	TD	CO	-0.10	0.30	L/min	peak exercise 75%	
	10	TD	CO	-0.30	0.40	L/min	peak exercise100%	
	15	Fick	CO	-0.03	0.24	L/min	at rest	
	15	Fick	CO	-0.09	0.13	L/min	at rest 25%	
	15	Fick	CO	-0.12	0.30	L/min	at rest 50%	
	15	Fick	CO	-0.10	0.40	L/min	at rest 75%	
	15	Fick	CO	-0.31	0.42	L/min	at rest 100%	
	10	Fick	CO	-0.01	1.43	L/min	peak exercise	
	10	Fick	CO	-0.04	0.25	L/min	peak exercise 25%	
	10	Fick	CO	-0.02	0.20	L/min	peak exercise 50%	
	10	Fick	CO	-0.20	0.30	L/min	peak exercise 75%	
	10	Fick	CO	-0.50	5.53	L/min	peak exercise100%	
	15	TD	SV	1.78	2.48	ml	at rest	
	15	TD	SV	0.50	2.50	ml	at rest 25%	
	15	TD	SV	-1.10	3.00	ml	at rest 50%	
	15	TD	SV	-1.80	4.00	ml	at rest 75%	
	15	TD	SV	-3.00	3.40	ml	at rest 100%	
	10	TD	SV	1.90	0.65	ml	peak exercise	
	10	TD	SV	1.10	3.00	ml	peak exercise 25%	
	10	TD	SV	0.50	4.00	ml	peak exercise 50%	
	10	TD	SV	-1.20	4.50	ml	peak exercise 75%	
	10	TD	SV	-1.97	0.40	ml	peak exercise100%	

Table 3.3: Summary of studies reporting bias

Study	N	Ref. Test	Test	D	SD	Unit	Measurement conditions	Replication of measurements
Bogaard 1997	19	Indir. Fick	CO	-11.7	11.05	L/min	At rest	No*
	10	Indir. Fick	CO	-7.45	9.3	L/min	Prior to t3	
	14	Indir. Fick	CO	3.98	12.8	L/min	Prior to t4	
	19	Indir. Fick	CO	3.45	9.0	L/min	Prior to t5	
	19	Indir. Fick	CO	6.85	8.85	L/min	Highest work intensity	
	19	Indir. Fick	SV	-1.05	0.955	ml	At rest	
	10	Indir. Fick	SV	-0.67	0.89	ml	Prior to t3	
	14	Indir. Fick	SV	0.33	1.24	ml	Prior to t4	
	19	Indir. Fick	SV	0.35	0.985	ml	Prior to t5	
	19	Indir. Fick	SV	0.87	1.195	ml	Highest work intensity	
Clancy 1991	17	TD	CO	0.23	0.56	L/min		Yes
Critchley 2000	24	TD	CO	-1.49	2.08	L/min		No
Doering 1995	34	TD	CI	0.21	0.53	L/min.m^2	ICU admission	No
	34	TD	CI	0.02	0.72	L/min.m^2	Normothermia	
	34	TD	CI	0.04	0.86	L/min.m^2	Postextubation	
	34	TD	CI	0.18	0.76	L/min.m^2	24 hrs ICU	
Drazner 2002	50	TD	CI	0.01	0.60	L/min.m^2		No
	28	Fick	CI	0.40	0.60	L/min.m^2	Subset of the 50 patients	
	50	TD	CO	0.03	1.10	L/min		
	28	Fick	CO	0.74	1.10	L/min	Subset of the 50 patients	
Genoni 1998	10	TD	CO	-1.81	1.07	L/min		Yes
Hirschl 2000	29	TD	CI	-0.61	0.74	L/min.m^2		Yes
Jewkes 1991	16	TD	CO	0.86	0.87	L/min		No
	16	TD	SV	13.00	11.10	ml		
Ng 1993	27	TD	CO	-1.40	1.40	L/min		No
	27	TD	SV	-14.00	13.40	ml		

Table 3.3: Summary of studies reporting bias

Study	N	Ref. Test	Test	D	SD	Unit	Measurement conditions	Replication of measurements
Perrino 1994	43	TD	CO	-0.40	1.00	L/min		Yes
Pickett 1992	201	TD	CO	-0.13	1.03	L/min		Yes
Raaijmakers 1998a	30	TD	CO	-2.40	2.80	L/min	SB equation	Yes
Sageman 1993	50	TD	CO	0.33	1.70	L/min		No
Sageman 2002	20	TD	CI	-0.07	0.20	L/min.m^2		Yes
Shoemaker 1998	680	TD	CI	-0.12	0.75	L/min.m^2		Yes
Shoemaker 2000	45	TD	CI	-0.16	0.95	L/min.m^2		No
Spiess 2001	47	TD	CI	-0.28	0.70	L/min.m^2		Yes
Thangathurai 1997	23	TD	CO	0.10	1.00	L/min		Yes
Thomas AN 1991	28	TD	CO	-1.08	0.96	L/min	<12 hrs	Yes
	28	TD	CO	0.09	0.54	L/min	12-24 hrs	Yes
Thomas SH 1992a	15	TD	CO	-0.55	0.83	L/min		Yes
	15	TD	SV	-8.10	13.20	ml		
Van der Meer 1996	21	TD	CO	0.15	0.96	L/min	SB equation	No
Van der Meer 1997**	25	TD	CO	0.10	1.00	L/min		No
Weiss 1995	15	TD	CO	0.23	2.19	L/min	stable patients	Yes
	13	TD	CO	0.03	2.33	L/min	unstable patients	
Woltjer 1996a	37	TD	SV	-2.70	14.65	ml		No
Woltjer 1997	24	TD	SV	0.10	11.40	ml		No
Wong KL 1996	18	TD	CO	-0.66	0.915	L/min		Yes
Yakimets 1995 Tr1	17	Fick	CI	-0.56	0.78	L/min.m^2	at rest	No
	17	Fick	CI	-0.75	1.12	L/min.m^2	at exercise	
	17	Fick	CO	-1.05	1.53	L/min	at rest	
	17	Fick	CO	-1.51	2.24	L/min	at exercise	
	17	Fick	SV	-13.5	20.9	ml	at rest	
	17	Fick	SV	-16.7	24.3	ml	at exercise	
Yakimets 1995 Tr2	28	TD	CI	-0.18	0.70	L/min.m^2	immed after surgery	No
	28	TD	CI	-1.40	0.67	L/min.m^2	2-4 hrs post-op	
	28	TD	CO	-0.43	1.33	L/min	immed after surgery	
	28	TD	CO	-0.36	1.24	L/min	2-4 hrs post-op	
	28	TD	SV	-3.19	13.97	ml	immed after surgery	

Table 3.3: Summary of studies reporting bias								
Study	N	Ref. Test	Test	D	SD	Unit	Measurement conditions	Replication of measurements
	28	TD	SV	-3.69	12.49	ml	2-4 hrs post-op	
Young 1993	19	TD	CI	1.69	1.24	L/min.m^2		Yes
Zacek 1999	28	TD	CI	-0.07	1.11	L/min.m^2		Yes

*Aggregated data was with replication, but data at each time point was without replication.

**Bias and SD were estimated from the plot (not reported in the text)

Table 3.4: Bias and limits of agreement in studies comparing test agreement between TEB (Sramek-Bernstein equation) And TD cardiac output (L/Min) in inpatients

Study	N	Bias	Limits of Agreement		Measurement Conditions	Measurement Procedure	
			Lower	Upper		TD	TEB
Balestra 1992	30	1.99	-2.41	6.39	external electrodes	M:1	M:1
Critchley 2000	24	-1.49	-5.65	2.67		A set of “nested reading” = mean [3 TDs] + mean [3 TEBs]. Mult. nests per patient	
Jewkes 1991	16	0.86	-0.88	2.60		M:3, V<10%, aver taken	M:3, aver taken
Ng 1993	27	-1.40	-4.2	1.4		M:3, aver taken	Not clear. One measure used. “Poor quality” signals were excluded.
Sageman 1993	50	0.33	-3.07	3.73		M:3~5, V<15%, aver taken	M:5, aver taken
Van der Meer 1996	21	0.15	-1.77	2.07		M:4, V<15%, aver taken	M:6, V<15%, aver taken
Van der Meer 1997*	25	0.10	-1.90	2.10		Multiple, V<15%, assume aver taken	Multiple, V<15%, assume aver taken
Yakimets 1995 Tr2	28**	-0.43	-3.09	2.23	immed after surgery	Not clear	Not clear
	28**	-0.36	-2.84	2.12	2-4 hrs post-op		
Random-effects model combined estimate	191	0.006	-2.87	2.89			

*Bias and SD were estimated from the plot (not reported in the text)

**Same patients. Biases in the two conditions were averaged and the mean was taken for meta-analysis.

Table 3.5: Bias and limits of agreement in studies comparing test agreement between TEB (Sramek-Bernstein equation) and TD stroke volume (ml) in inpatients

Study	N	Bias	Limits of Agreement		Measurement Conditions
			Lower	Upper	
Jewkes 1991	16	13.00	-9.2	35.20	
Ng 1993	27	-14.00	-40.8	12.80	
Yakimets 1995 Tr2	28*	-3.19	-31.13	24.81	immed after surgery
	28*	-3.69	-28.67	21.29	2-4 hrs post-op
Woltjer 1996	37	-2.70	-32.0	26.60	
Random-effects model combined estimate	108	-1.86	-28.30	24.74	

*Same patients. Biases in the two conditions were averaged and the mean was taken for meta-analysis.

Table 3.6: Summary of quality of measurements for studies comparing TEB cardiac output and/or cardiac input to TD among inpatients

Study	Reference standard	Test	Setting	Equation	Manufacturer	TD measures	TEB measures	Analysis of correlation	Bias reported?	Quality
Balestra 1992	TD	CO	IN	SB	NCCOM-4	M:1	M:1	Correlate single measure	Yes	B
Barry 1997	TD	CO	IN	SB	NCCOM-3	Multiple	Multiple	Correlate multiple measures	Yes	C
Clancy 1991	TD	CO	IN	SB	NCCOM-7	M:3	M:3	Correlate multiple measures	Yes	C
Critchley 1996	TD	CO	IN	SB	NCCOM-7	A set of "nested reading" = mean [3 TDs] + mean [3 TEBs]. Mult. nests per patient.		Correlate multiple "nests"	Yes*	C +
Critchley 2000	TD	CO	IN	SB	NCCOM-7	M:3, aver taken	M:3, aver taken	Correlate means	Yes	A -
Demeter 1993	TD	CO	IN	K	Minnesota 304B	M:5, discard high & low values, mean [M:3] taken	M:3, aver taken	Correlate means	No	A
Doering 1995	TD	CI CO	IN	ND	NCCOM-3	M:3, V<10%, aver taken	M:3, corresp. measures, aver taken	Correlate means	Yes	A
Drazner 2002	TD	CI CO	IN	ND	BioZ	M: 3~5, V<10%, assume aver taken	Multiple, aver taken	Correlate means	Yes	A
Genoni 1998	TD	CO	IN	SB	NCCOM-7	M:3, V<10%	M:5, discard 2 extreme values	Correlate multiple measures	Yes	C+
Jewkes 1991	TD	CO	IN	SB	NCCOM-3	M:3, V<10%, aver taken	M:3, aver taken	Correlate means	Yes	A

Table 3.6: Summary of quality of measurements for studies comparing TEB cardiac output and/or cardiac input to TD among inpatients

Study	Reference standard	Test	Setting	Equation	Manufacturer	TD measures	TEB measures	Analysis of correlation	Bias reported?	Quality
Ng 1993	TD	CO	IN	SB	NCCOM-7	M:3, aver taken	Not clear. One measure used. “Poor quality” signals were excluded.	Correlate mean [TDs] with TEB	Yes	B
Perrino 1994	TD	CO	IN	SB	NCCOM-7	M:3/epoch, V<15%, aver taken/epoch, 6 epoch/patient	Corresp. measures	Claim mean [TDs/epoch] was used. In plot, mult. measures were used.	Yes	C
Pickett 1992	TD	CO	IN	K	HDC	M:4~5, V<20%, both mult measures and aver were used	Corresp. measures	Correlate both mult. measures and means, separately	Yes	A
Raaijmakers 1998a	TD	CO	IN	SB	ND	M:5, aver taken	Not clear. Mean was used.	Not sure why 32 measures in 13 patients.	Yes	B
Sageman 1993	TD	CO	IN	SB	NCCOM-7	M:3~5, V<15%, aver taken	M:5, aver taken	Correlate means	Yes	A
Sageman 2002	TD	CI	IN	ND	BioZ	Multiple	Multiple	Correlate mult. measures	Yes	C
Spiess 2001	TD	CI	IN	ND	BioZ	M: 3, V<10%, aver taken	Multiple, aver taken	Correlate means**	Yes	B
Thangathurai 1997	TD	CO	IN	ND	IQ 101	Multiple	Multiple	Correlate mult. measures	Yes	C

Table 3.6: Summary of quality of measurements for studies comparing TEB cardiac output and/or cardiac input to TD among inpatients

Study	Reference standard	Test	Setting	Equation	Manufacturer	TD measures	TEB measures	Analysis of correlation	Bias reported?	Quality
Van der Meer 1996	TD	CO	IN	SB	IPG-104	M:4, V<15%, aver taken	M:6, V<15%, aver taken	Correlate means	Yes	A
Van der Meer 1997	TD	CO	IN	SB	IPG-104	Multiple, V<15%, assume aver taken	Multiple, V<15%, assume aver taken	Assume correlate means	Yes	A-
Weiss 1995	TD	CO	IN	SB	NCCOM-7	Multiple	Multiple	Correlate multiple measures	Yes	C
Wong KL 1996	TD	CO	IN	SB	NCCOM-7	7~8 pairs of TD & TEB measures per patient		Correlate multiple measures	Yes	C
Woo 1992	TD	CO	IN	SB	NCCOM-3	TD&TEB- M:3, aver taken. "A set" = a pair of mean [TDs] and mean [TEB]. 1~2 sets per patient.		Correlate multiple mean values	No	C+
Yakimets 1995 Tr2	TD	CI CO	IN	SB	NCCOM-7	Not clear	Not clear	Correlate sing measure / aver mult measures	Yes	B
Young 1993	TD	CI	IN	SB	NCCOM-6	Multiple	Multiple	Correlate multiple measures	Yes	C
Zacek 1999	TD	CI	IN	SB	HotmanAH-HHC	M: 4, V<10%	Corresp. measures	Correlate multiple measures	Yes	C
Zubarev 1999	TD	CO	IN	mod K	BPCS	Multiple	Multiple	Correlate multiple measures	No	C

*Log values were used for estimation of bias
**The aggregated correlation coefficient for the 4 conditions was using multiple measurements per patient, but that for each condition was correlating means. The aggregated correlation coefficient was dropped, and the average correlation coefficient of the 4 conditions was used in the meta-analyses of correlation coefficients.

Figure 3.1: Analytic framework for correlation meta-analysis

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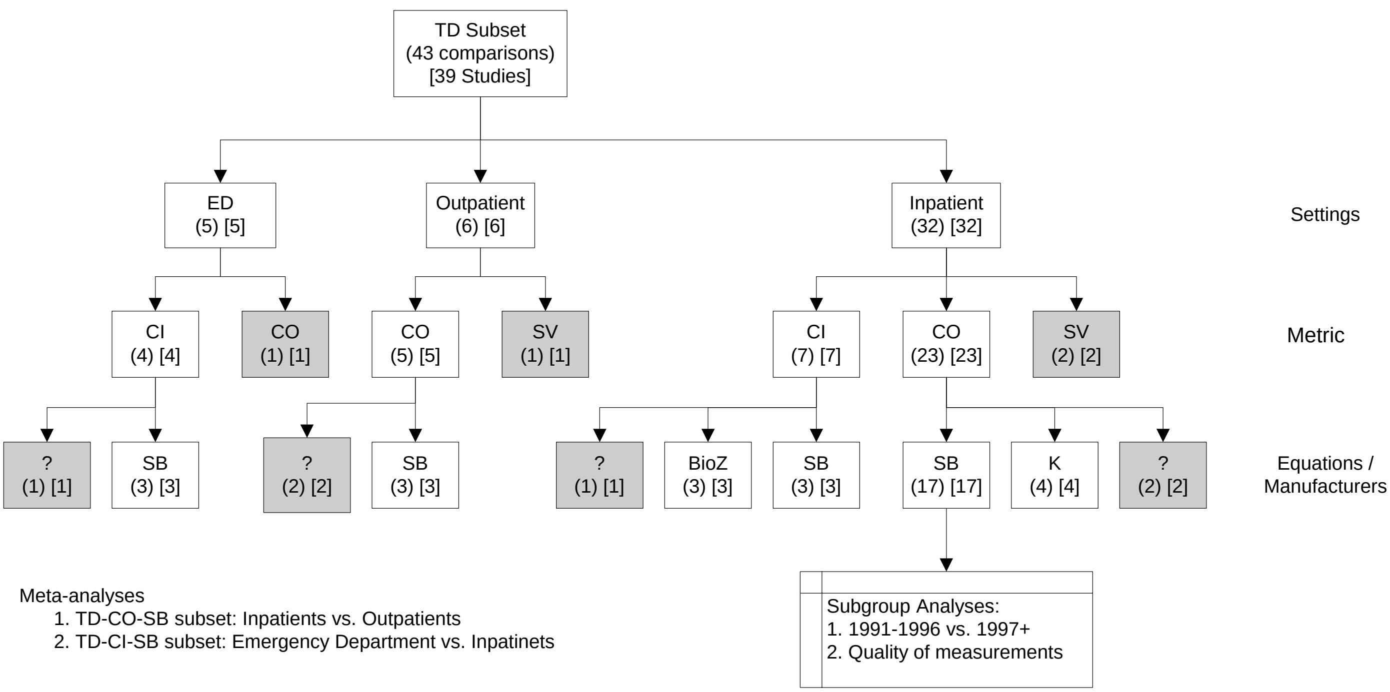
Number of Comparisons of TEB to Other Standards in A Total of 49 Studies

		Echocardio (Doppler)	Echocardio (non-Doppler)	Direct Fick	Indirect Fick	Radio-nuclide	TD
TEB	CI	-	-	3	-	-	11
	CO	1	-	-	1	1	27
	SV	1	-	2	-	1	3
	LVEF	-	1	-	-	3	-



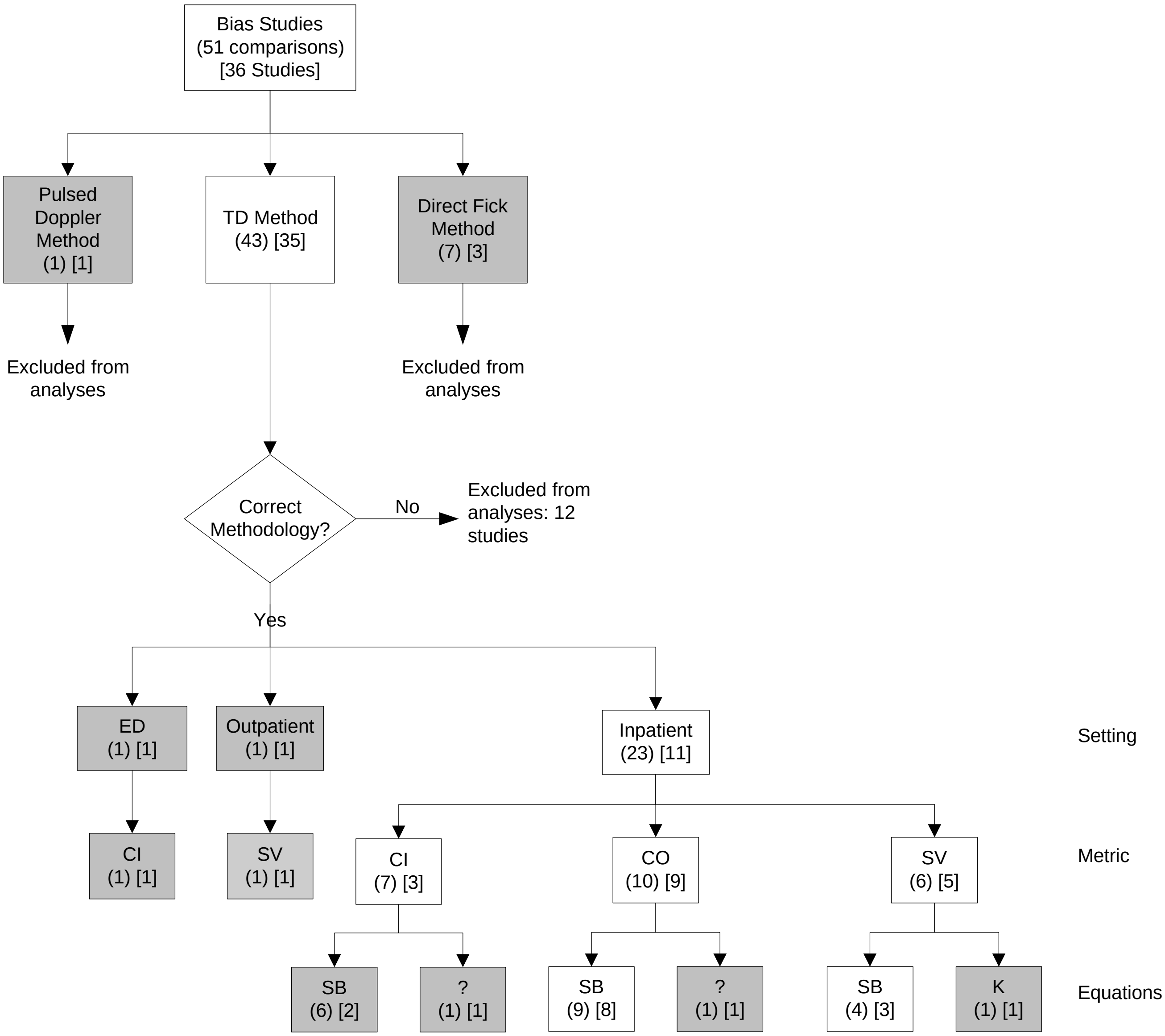
Equation abbreviations: SB= Sramek-Bernstein; K=Kubicek

Notes:

Gray shading indicates studies excluded from meta-analysis.

Studies may not sum to total due to analysis of more than one cardiac metric per study

Figure 3.2: Analytic framework for meta-analyses of bias and limits of agreement



Equation abbreviations: SB= Sramek-Bernstein; K=Kubicek
Notes:
Gray shading indicates studies excluded from meta-analysis.
Studies may not sum to total due to analysis of more than one cardiac metric per study.

Figure 3.3: Chronological array of correlation coefficients for cardiac output in the inpatient setting chronologically arrayed (TEB vs. TD for Sramek-Bernstein)

	YrCutoff	Citation	Effect	NTotal	Manufacture
	early	Jewkes 1991	.720	16	NCCOM-3
	early	Clancy 1991	.910	17	NCCOM-7
	early	Woo 1992	.510	44	NCCOM-3
	early	Balestra 1992	.740	10	NCCOM-4
	early	Sageman 1993	.480	50	NCCOM-7
	early	Ng 1993	.870	37	NCCOM-7
	early	Perrino 1994	.840	43	NCCOM-7
	early	Yakimets 1995 Tr2	.530	28	NCCOM-7
	early	Weiss 1995	.810	13	NCCOM-7
	early	Wong KL 1996	.860	18	NCCOM-7
	early	Van der Meer 1996	.830	21	IPG-104
	early	Critchley 1996	.600	8	NCCOM-7
Random	**early (12)**		**.756**	**305**	
	new	Van der Meer 1997	.600	37	IPG-104
	new	Barry 1997	.100	7	NCCOM-3
	new	Raaijmakers 1998	.420	13	ND
	new	Genoni 1998	.450	10	NCCOM-7
	new	Critchley 2000	.390	24	NCCOM-7
Random	**new (5)**		**.487**	**91**	
Random	**Combined (17)**		**.693**	**396**	

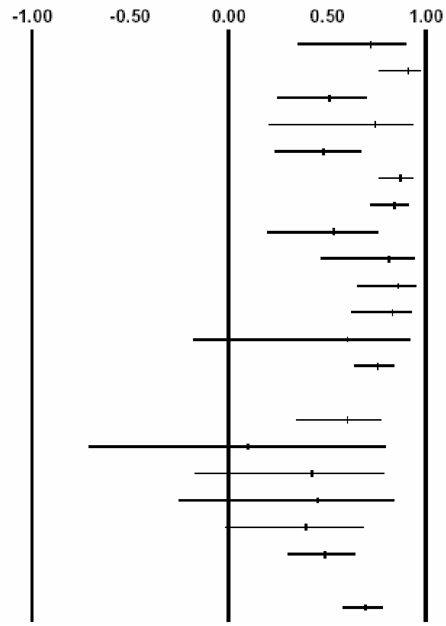
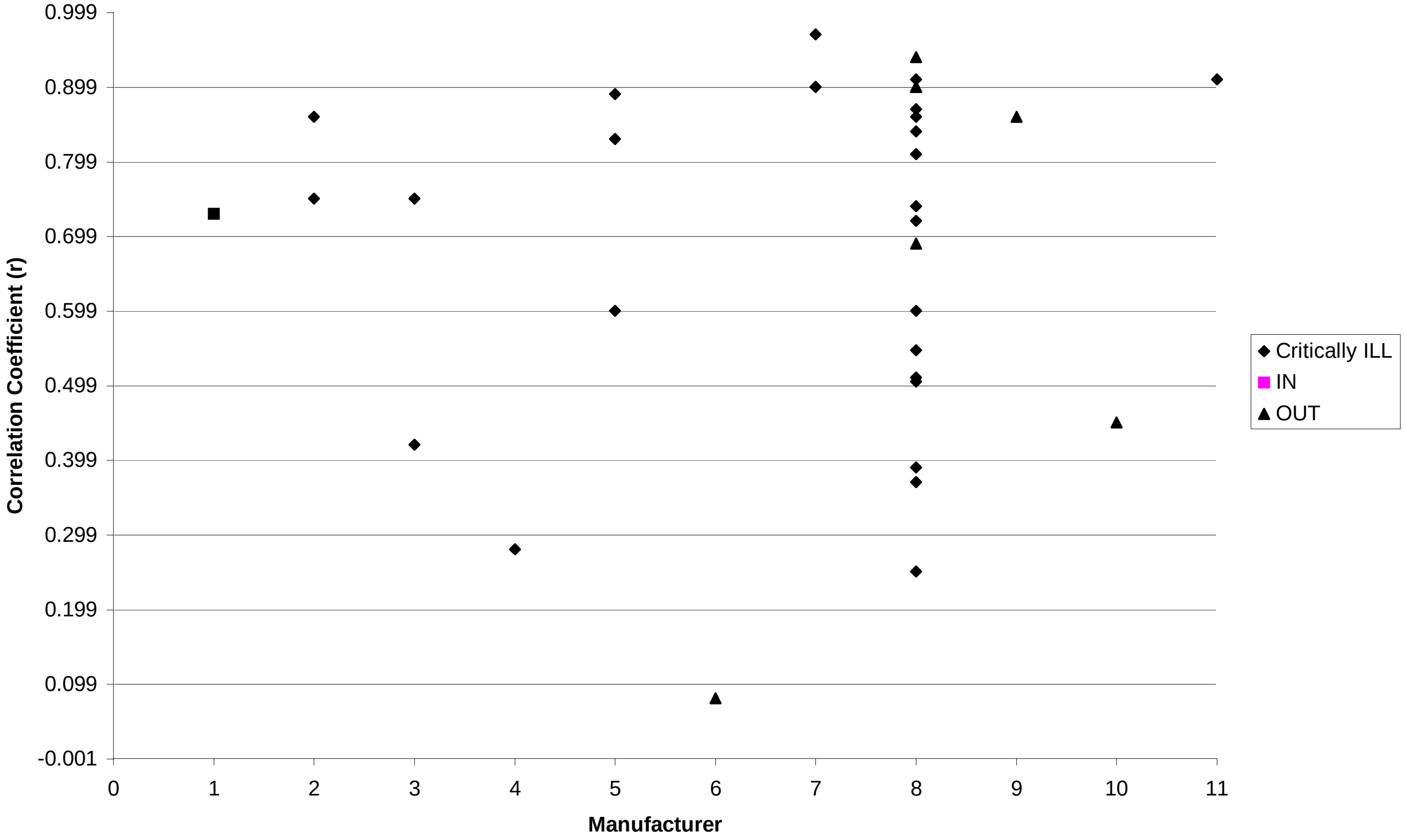


Figure 3.4 TEB Correlation Coefficients for Cardiac Output by Manufacturer

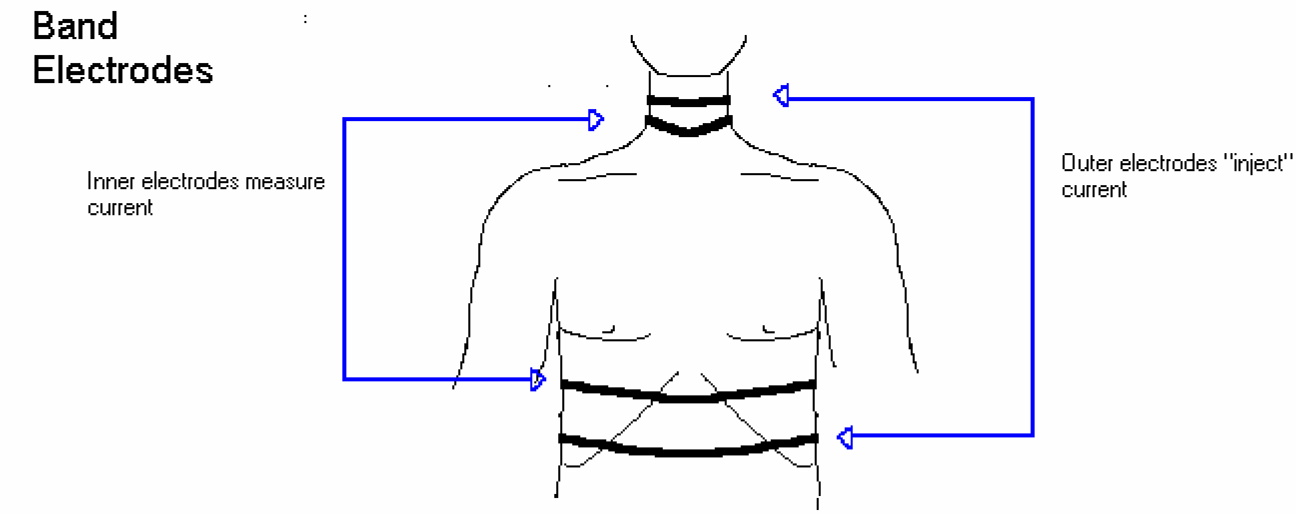


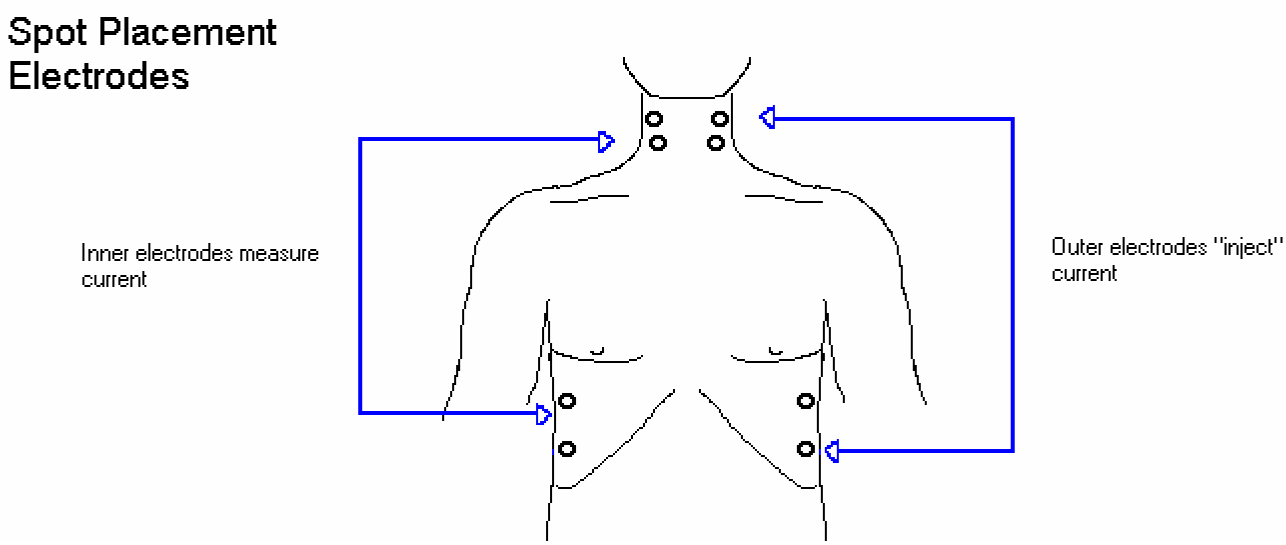
1= Bioz
2= HDC
3= Custom-built
4= Hotman
5=IG101 and IPG-104
6=IQ
7= Minnesota Impedance Cardiograph
8= NCCOM-3
9=RheoCardioMonitor
10=Tetrapolar Impedance
11=Wantagh

	Appendix 1: Evidence Table Acronyms and Abbreviations
A/V	Atrioventricular
AF	Atrial Fibrillation
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Respiratory Failure
BBB	Bundle Branch Block
BMI	Body Mass Index
BPCS	Bioimpedance Polyrheocardiographic System
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCU	Critical Care Unit
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Cardiac Index
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CPB	Cardiopulmonary Bypass
CV	Cardiovascular
CVD	Cardiovascular Disease
D	Bias (against gold standard)
ECG	Electrocardiography
ECW	Extracellular Water
ED	Emergency Department
EF	Ejection Fraction
FEV	Forced Expiratory Volume (in 1 second)
FVC	Forced Vital Capacity
HBP	High Blood Pressure
ICU	Intensive Care Unit
IHD	Ischemic Heart Disease
IPD	Individual Patient Data
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVET	Left Ventricular Ejection Time
MAP	Mean Arterial Pressure
MI	Myocardial Infarction
MICU	Medical Intensive Care Unit
MVR	Mitral Valvular Regurgitation
ND	No Data
OR	Operating Room
PAC	Pulmonary Artery Catheter

	Appendix 1: Evidence Table Acronyms and Abbreviations
PCWP	Pulmonary Capillary Wedge Pressure
PEEP	Positive End-expiratory Pressure
r	Correlation Coefficient
r^2	Multivariate Coefficient of Determination
RM	Repeated Measure
RZ	Time between R wave of ECG and dZ/dt
SAH	Subarachnoid Hemorrhage
SD	Standard Deviation
SI	Stroke Index
SM	Single Measurement
STI	Systolic Time Intervals
SV	Stroke Volume
TBW	Total Body Water
TD	Thermodilution
TEB	Thoracic Electrical Bioimpedance
TFI	Thoracic Fluid Index
TLC	Total Lung Capacity
TS	Tricuspid Stenosis
VC	Vital Capacity
VEPT	Volume of Electrically Participating Tissue
WMS	Wall Motion Score
ZEEP	Zero End Respiratory Pressure
Z_o	Baseline Impedance

Appendix 2: Electrode Placement





Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Antonicelli 1991 91368949	Double-blind crossover	Location: Italy Setting: outpatient Mean age: (66-77) % Male: ND Enrolled: 14	Hypertension Non-critically ill	Elderly hypertensives on cadralizine	Mild or moderate arterial essential HBP--reliable echo required	obesity, pulmonary emphysema
Atallah 1995 95398907	Prospective	Location: Egypt Setting: hospital Mean age: ND % Male: ND Enrolled: 5	Hemodynamics Critically ill	5 radical cystectomy	ND	<20 years old, grossly obese or overweight, cardiac arrhyth-mias, valvular heart lesions, abnormal thoracic anatomy
Balestra 1992 92103922	Prospective	Location: Switzerland Setting: ICU Mean age: 63.4 % Male: 80 Enrolled: 10	Hemodynamics Critically ill	CV and/or respiratory illness	ND	ND
Barin 2000 20214491	Prospective	Location: Australia Setting: lab Mean age: 62.7 % Male: 66 Enrolled: 47	Hemodynamics Non-critically ill	Routine cardiac catheterization for suspected cardiac disease	ND	Severe lung disease, severe valve insuf-ficiency or stenosis, pulmonary con-gestion, pleural effusions, AV shunts, amyloi-dosis, cardiac arrhythmias, frequent ectopic activity, severe organ failure, advanced malignancy

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Barry 1997 11056698	Observational	Location: UK Setting: ICU Mean age: 63 % Male: ND Enrolled: 7	Hemodynamics Critically ill	1 acute pancreatitis; 2 emergency repair of aortic aneurysm; 1 appendix abscess; 1 pulmonary embolism; 1 cholangitis; 1 respiratory failure	Patients requiring PAC	ND
Belardinelli 1996 96259436	Prospective	Location: Italy Setting: lab Mean age: 48.6 % Male: 80 Enrolled: 25	Hemodynamics Non-critically ill	CAD	Consecutive patients in sinus rhythm with documented CAD and prior MI	Unstable angina, MI<2 months, chronic heart failure, COPD, significant valvular heart disease, uncon-trolled HBP, hypotension, arthritis, other orthopedic peripheral vas-cular or neuro-logic disease that limits the ability to exercise
Bogaard 1997 98075787	Prospective	Location: Holland Setting: Lab Mean age: 57 % Male: ND Enrolled:19	Hemodynamics Fluid management Routine	COPD	Clinical diagnosis of COPD; FEV/VC>80%, normal ECG	Any pathology interfering with exercise; CV meds
Bowling 1993 94007883	Prospective	Location: US Setting: outpatient Mean age:56.8 % Male: 50 Enrolled: 20	Hemodynamics Non-critically ill	15/20 patients treated with anthracycline chemo for various malignancies	Ambulatory adults scheduled for radionuclide angiography	Evidence of ongoing myocardial injury, tchysdysrhythmia or significant valvular heart disease

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Castor 1994 94153663	Prospective	Location: Germany Setting: ICU Mean age: (35-65) % Male: 40 Enrolled: 10	Hemodynamics Critically ill	Surgical removal of intracranial tumor or aneurysm	ND	ND
Clancy 1991 91341839	Cross-sectional	Location: US Setting: ICU, OR Mean age: (17-83) % Male: ND Enrolled:17	Hemodynamics Critically ill	5 trauma, 5 post-CABG, 5 post-abdominal surgery, 2 cardiopulmonary	ND	ND
Critchley 1996 96338592	Prospective	Location: Hong Kong Setting: ICU Mean age: ND % Male: ND Enrolled: 8	Hemodynamics Critically ill	2 partial hepatectomies; 5 radical cystectomies + ileal conduit; 1 abdominal aortic aneurysm repair	Patients requiring PAC	ND
Critchley 2000 20399480	Prospective	Location: Hong Kong Setting: ICU Mean age: (13-87) % Male: 70 Enrolled:24	Hemodynamics Fluid management Critically ill	13 Sepsis, 5 fluid balance problems, 6 cardiothoracic problems	Patients in whom PAC was used to measure CO	ND
Demeter 1993 94032793	Cross-sectional	Location: USA Setting: CCU Mean age: 59 % Male: 100 Enrolled: 10	Hemodynamics Critically ill	CABG	Stable, non-ventilated CABG in open heart recovery	ND
Doering 1995 96019885	Prospective, Longitudinal Repeated measures	Location: US Setting: ICU Mean age: 66.7 % Male: 88 Enrolled: 34	Hemodynamics Critically ill	Elective cardiac surgery	PAC in place	Aortic insufficiency, aortic valve replacement scheduled

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Drazner 2002 21947433	Prospective	Location: USA Setting: hospital Mean age: 52 % Male: 74 Enrolled: 50	Hemodynamics non-critically ill	Heart failure	Right-sided cardiac catheterization	Electrical interference, difficulty with venous catheterization, uncertain diagnosis, no pulmonary arterial wedge pressure.
Genoni 1998 98373881	Prospective	Location: Italy Setting: ICU Mean age: 63 % Male: 80 Enrolled: 10	Hemodynamics Critically ill	Acute lung injury with mechanical ventilation	ND	Thoracic surgery, chest tube, or vasoactive drugs
Hirschl 2000 20346676	Prospective	Location: Austria Setting: CCU Mean age: 60.9 % Male: 72 Enrolled: 29	Hemodynamics Critically ill	Critically ill patients requiring monitoring: 18 CV, 2 pulmonary, 4 infectious, 2 toxicological, 3 neurological diseases	Admission to ED or CCU for circulatory disorders	Ongoing cardio-pulmonary resuscitation, hypothermia, heart valve dys-function by ECHO, evidence of pleural effu-sion, mitral regurgitation, failure of tricuspid valve
Horstmann 1993 94328978	Prospective	Location: Germany Setting: lab Mean age: ND % Male: 97 Enrolled: 35	Hemodynamics Non-critically ill	Patients undergoing heart catheterization and supine bicycle exercise for CHD	ND	ND

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Jewkes 1991 92118578	Cross-sectional	Location: UK Setting: ICU Mean age: ND % Male: ND Enrolled: 16	Hemodynamics Critically ill	Patients in ICU after aortic surgery, abdominal surgery, acute respiratory failure	aortic surgery, abdominal surgery, acute respiratory failure	Septic shock, severe arrhythmias, or too unstable
Kerkkamp 1999 99300751	Prospective	Location: Holland Setting: critical care Mean age: 65.4 % Male: 54 Enrolled: 28	Hemodynamics Non-critically ill	Heart disease (uncomplicated CAD, cardiomyopathy)	ND	ND
Kindermann 1997 98023345	Prospective	Location: Germany Setting: inpatient Mean age: 63 % Male: 40 Enrolled: 53	Pacemaker Non-critically ill	High degree A/V block	ND	ND
Kizakevich 1993 94032797	Prospective	Location: US Setting: critical care Mean age:59 % Male:100 Enrolled:26	Hemodynamics Non-critically ill	Chest pain – patients admitted for elective coronary angiography	Ambulatory, reasonable expectation of exercise to moderate workload	Valvular heart disease
Marik 1997	Prospective	Location: US Setting: lab Mean age: 67 % Male: 80 Enrolled: 30	Hemodynamics Non-critically ill	CAD	Consecutive patients undergoing elective right and left heart catheterization	Valvular heart disease, AF
Mattar 1991 92036473	Prospective	Location: Brazil Setting: ICU Mean age: 54.3 % Male: 83 Enrolled: 17	Hemodynamics Critically ill	Subgroup from mixed ICU: 13 pts with abnormal diastolic function, 4 with normal left ventricular function	ND	ND

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Mehlsen 1991 92119899	Prospective	Location: Denmark Setting: Lab Mean age: ND % Male: ND Enrolled: 25	Hemodynamics Non-critically ill	Unmedicated patients with ischemic heart disease	Ischemic heart disease	ND
Ng 1993 94907300	Prospective	Location: UK Setting: ICU Mean age: 60 % Male: 74 Enrolled: 31	Hemodynamics Critically ill	Hemodynamically stable intensive care patients incl 11 post laparotomy, 5 post femoral artery surgery, 4 cardiopulmonary disease, 3 ARF	Selected consecutively depending on availability of drs and patients	Hemodialysis, hemofiltration, or pts with intracardiac shunts
Perrino 1994 94220628	Prospective	Location: USA Setting: critical care Mean age: 67.9 % Male: ND Enrolled: 50	Hemodynamics Critically ill	Noncardiac surgery, predominantly elderly with cardiac disease	Consecutive patients scheduled for noncardiac surgery and PAC	History consistent with valvular heart disease or intracardiac shunts, unsatisfactory TEB signals
Pickett 1992 92264297	Prospective	Location: US Setting: ICU Mean age: 65 % Male: 33 Enrolled: 43	Hemodynamics Critically ill	8 AMI, 17 CHF, 13 pleural effusion, 6 pericardial effusion, 6 sepsis, mitral regur-gitation, 7 AF, 11 HBP, 3 arterio-fistula	PAC in place <24 hr; TD CO values agree ± 20%; ≥4 TD CO; satisfactory EC waveforms; L/Zo ratio≤165% and ≥70%	Aortic insufficiency, intracardiac shunts
Raaijmakers 1998a 99079379	Prospective	Location: Holland Setting: ICU Mean age: 50 % Male: 77 Enrolled: 13	Hemodynamics Critically ill	7 acute lung injury and 6 ARDS--all caused by sepsis	ND	ND

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Raaijmakers 1998b 99214718	Prospective	Location: Holland Setting: ICU Mean age: 50 % Male: 77 Enrolled: 13	Hemodynamics Critically ill	7 acute lung injury and 6 ARDS--all caused by sepsis	Lung injury score	ND
Sageman 1993 93339081	Retrospective, longitudinal	Location: USA Setting: inpatient Mean age: 63 % Male: 58 Enrolled: 50	Hemodynamics Critically ill	CABG	All patients with CABG enrolled between Nov 1990-July 1991	Hemodynamically unstable requiring pressors, vasodilators, intropes, liquid boluses, evidence of significant valvular disease, evidence of left BBB or AMI
Sageman 2002 21843329	Prospective	Location: USA Setting: ICU Mean age: ND % Male: ND Enrolled: 20	Hemodynamics critically ill	CABG or valve replacement surgery	Pts undergoing CPB who enrolled between Dec 1998- April 1999	Significant post-op valvular pathology
Shoemaker 2001 21393819	Prospective	Location: USA Setting: ED/ICU Mean age: 36.6 % Male: 87 Enrolled: 151	Hemodynamics Critically ill	Major trauma patients admitted to ED	Consecutively monitored patients	ND
Shoemaker 2000 21021875	Prospective	Location: USA Setting: ED Mean age: 60.5 % Male: 47 Enrolled: 45	Hemodynamics Critically ill	Acutely ill sepsis and septic shock patients in ED: evidence of infection	Consecutively monitored patients	ND

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Shoemaker 1998 99087206	Prospective	Location: USA Setting: critical care Mean age: 57 % Male: 69 Enrolled: 680	Hemodynamics Critically ill	Acutely ill patients after admission to hospital: 139 severely injured or hemorrhaging, 129 nontrauma, 274 high risk surgical patients	Consecutively monitored patients	ND
Shoemaker 1994 95079738	Prospective	Location: USA Setting: critical care Mean age: 45 % Male: 68 Enrolled: 68	Hemodynamics Critically ill	Severely ill patients who required PAC	Consecutively monitored patients	ND
Spiess 2001 11687996	Prospective	Location: USA Setting: ICU Mean age: 64 % Male: 66 Enrolled: 47	Hemodynamics Critically ill	First-time CABG	No other planned cardiac surgery	Known vascular heart disease
Summers 2001 21233995	Retrospective	Location: USA Setting: ED Mean age: ND % Male: ND Enrolled: 15	Hemodynamics Critically ill	All ED patients from 1997-98 whose hemodynamics were assessed: MI, CHF, HBP, cocaine ingestion	ND	ND
Thangathurai 1997 97331660	Prospective	Location: USA Setting: critical care Mean age: (31-86) % Male: 70 Enrolled: 23	Hemodynamics Critically ill	Patients undergoing extensive surgical procedures with anticipated major blood loss and significant fluid shifts incl 8 radical cystecomy, 3 esophagectomy, 2 prostatectomy	ND	ND

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Thomas AN 1991 92129741	Prospective	Location: UK Setting: ICU Mean age: 56.8 % Male: 93 Enrolled: 28	Hemodynamics Critically ill	CABG	Consecutive patients 24 hours post-CABG	ND
Thomas SH 1992 93152372 (Trial 1)	Prospective	Location: UK Setting: ICU Mean age: 58 % Male: 53 Enrolled: 15	Hemodynamics Critically ill	ICU pts including 2 AF, 4 COPD	ND	Valvular stenosis or regurgitation
Thomas SH 1992 93152372 (Trial 2)	Prospective	Location: UK Setting: ICU Mean age: 57 % Male: 100 Enrolled: 34	Hemodynamics Critically ill	Coronary heart disease	CHD documented by coronary angiography and contrast LV within 6 wks	Use of beta-blockers, patients who changed during treatment between angio-graphy and TEB
Van der Meer 1999 99161702	Prospective, cross-sectional	Location: Holland Setting: Critical care Mean age: 56.6 % Male: 81 Enrolled: 26	Hemodynamics Critically ill	Pts scheduled for echocardiography due to suspected CAD, valve pathology, ventricular septum defect	Consecutive patients	Continuous dysrhythmias; aortic valve pathology, heart rate difference <5% between ED and TEB, ideal body weight deviation <15%
Van der Meer 1999 99151080	Prospective	Location: Holland Setting: lab Mean age: 51.3 % Male: 88 Enrolled: 8	Hemodynamics Non-critically ill	Angiographically documented CAD; 7/8 showed hx of recent MI	CAD	ND

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Van der Meer 1997 97385315 Woltjer 1996a 97034589 Woltjer 1996b 97166939	Prospective	Location: Holland Setting: ICU Mean age: (34-70) % Male: 78 Enrolled: 37	Hemodynamics Critically ill	Mechanically ventilated patients after cardiac surgery incl 36 CABG	Pts <70 years	Hemodynamically unstable patients, cardiac arrhythmias, variation in measurements <15% mean values
Van der Meer 1996 97081838	Prospective	Location: Holland Setting: ICU Mean age: 57.5 % Male: 81 Enrolled: 21	Hemodynamics Critically ill	CABG, aortic valve replacement	Cardiac surgery	Nonstable cardiac status, age<70, weight deviation >15% ideal body wt, cardiac dys-rhythmias, variations >15% mean TEB signals
Van der Meer 1996 96310167	Prospective	Location: Holland Setting: lab Mean age: 45 % Male: 33 Enrolled: 24	Hemodynamics Non-critically ill	Patients who used cardiotoxic chemotherapy or suffered from cardiac failure	ND	cardiac dysrhythmias
Velmahos 1998 98347548	Prospective	Location: USA Setting: ED Mean age: 61.5 % Male: 76 Enrolled: 17	Hemodynamics Critically ill	Acute thrombotic cerebrovascular accidents	Consecutive patients arriving at ED with hemodynamic instability from cerebrovascular accidents	ND

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Weiss 1995 96071685 (stable pts)	Prospective	Location:US Setting: outpatient Mean age: 44.1 % Male: 40 Enrolled: 15	Hemodynamics Non-critically ill	Stable non-critically ill patients undergoing diagnostic heart catheterization	ND	Improperly applied electrodes, or interference with standard patient care
Weiss 1995 96071685 (unstable pts)	Prospective	Location: US Setting: ICU Mean age:50.7 % Male:36 Enrolled:14	Hemodynamics Critically ill	Unstable patients admitted to MICU with conditions requiring CV monitoring	CY monitoring	Improperly applied electrodes, or interference with standard patient care
Woltjer 1997 97468636	Prospective	Location: Holland Setting: outpatient Mean age: 61.6 % Male: ND Enrolled: 24	Hemodynamics Non-critically ill	Pts incl: 23 CAD; 3 aortic stenosis, 2 stenosis+aortic regurgitation; 3 mitral regurgitation; 1 idiopathic cardiomyopathy; 9 HBP; 2 diabetes	Pts who underwent diagnostic heart catheterization	Aortic valve pathology; mitral regurgitation
Woo 1992 91302095	Prospective	Location: USA Setting: CCU Mean age: 53.7 % Male: 84 Enrolled: 44	Heart transplant Critically ill	Heart failure	Individuals in CCU with ischemia or idiopathic cardiomyopathy with functioning PAC	Pacemaker, mechanical ventilation, intraortic balloon pump therapy, renal failure, ambiguous ECG signals
Wong KL 1996 97238198	Prospective	Location: Taiwan Setting: CCU Mean age: (39-64) % Male: 67 Enrolled: 18	Hemodynamics Critically ill	CABG	Consecutive patients with hemodynamic instability from cerebrovascular accidents	Prior severe arrhythmias or aortic insufficiency

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
World 1996 96318217 (Trial 1)	Prospective	Location: UK Setting: ICU Mean age: (40-76) % Male: 62 Enrolled: 21	Hemodynamics Critically ill	Pts admitted to ICU requiring right heart catheterization	Patients collected over 3 years: which incl 7 CHF, 8 IHD	Sepsis, severe dysrhythmia, aortic incompetence
World 1996 96318217 (Trial 2)	Prospective	Location: UK Setting: CCU Mean age: (18-82) % Male: 72 Enrolled: 50	Hemodynamics Critically ill	Routine orthopedic surgery	Tourniquet applied to lower limb to prevent arterial blood flow	Sepsis, severe dysrhythmia, aortic incompetence
Yakimets 1995 95347996 (Trial 1)	Prospective, convenience sample	Location: Canada Setting: lab Mean age: 54.4 % Male: 71 Enrolled: 17	Hemodynamics Non-critically ill	Heart disease with routine cardiac catherization incl 7 CAD, 3 angina, 2 dilated cardiomyopathy	ND	ND
Yakimets 1995 95347996 (Trial 2)	Prospective, convenience sample	Location: Canada Setting: inpatient Mean age: 57.8 % Male: 68 Enrolled: 28	Hemodynamics Critically ill	Post-elective heart surgery incl 17 CABG, 5 aortic valve replacement	Hemodynamic stability	No i.v. fluid boluses; no diuretics within 1 hour of onset of study interval, no changes in medications for 15 minutes, no changes in ventilator treatment
Young 1993 93159934	Prospective	Location: UK Setting: ICU Mean age: ND % Male: ND Enrolled: 19	Hemodynamics Critically ill	Clinically septic patients incl 5 perforated viscus, 4 pulmonary infection, 4 sepsis post-trauma	Microbiological evidence of sepsis or positive blood culture	Alteration in therapy

Evidence Table 1. Comparison Studies: Part I

Author, Year UI	Design	Demographics	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Zacek 1999 20032610	Prospective, cross sectional	Location: Czech Setting: ICU Mean age: ND % Male: ND Enrolled: 28	Hemodynamics Critically ill	Adults undergoing elective cardiac surgery: 19 CABG, 4 aorta valve replacements	PAC inserted prior to anesthesia or during surgery	Cardiac pacing, motor disturbance, low quality TEB signal
Zubarev 1999 99300756	Prospective	Location: Russia Setting: critical care Mean age: ND % Male: ND Enrolled: 11	Hemodynamics Critically ill	AMI complicated by acute left ventricular failure	ND	ND

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Antonicelli 1991 91368949	Stroke volume	No model detail. 4 electrodes: 2 around neck, one at xiphisternal joint, one at abdomen. Sinusoidal AC 4maRMS/100 KHz passed thru thorax. Kubicek modified equation.	Pulsed Doppler echocardiography with bi-dimensional transducer at 2.5 MHz.		
Atallah 1995 95398907	Cardiac index	NCCOM-3 (BoMed Mfrs, Irvine CA): 8-spot electrode array situated according to manufacturer's instructions	Thermodilution: Values were the mean of 3 injections of 10ml 5% dextrose at room temp.		
Balestra 1992 92103922	Cardiac output	NCCOM-3 Revision 4 (BoMed Mfrs, Irvine CA): 2.5 mA 60kHz. Kubicek modified by Sramek-Bernstein	Thermodilution: balloon-tipped pulmonary artery flow-directed catheter (Baxter Edwards 131-7F): Injection 10mL iced isotonic saline boluses.	Electrode position explicitly evaluated on healthy volunteers only. 10 critically ill patients TD vs. external electrodes	10 critically ill patients TD vs. internal electrodes
Barin 2000 20214491	Cardiac output	RheoCardioMonitor (Rheo-Graphic PTE, Singapore): 6 single spot electrodes: 2 at appendix level, 2 on the neck, one on left knee, one in middle forehead. 2mA RMS AC current 100kHz. Kubicek equation.	Thermodilution: 7F balloon-tipped pulmonary artery flow-directed catheter (Baxter Edwards 131-7F): 5 injections 10mL iced isotonic saline boluses.		
Barry 1997 11056698	Cardiac index	NCCOM 3, BoMed, Cheshire UK--8 spot electrodes placed at root of neck and chest wall. 2.5mA rms, 70 kHz.	Thermodilution: Modified PAC (Model 746H8F, Baxter Healthcare)		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Belardinelli 1996 96259436	Cardiac output, stroke volume	NCCOM-3 Series R7S (BoMed Mfrs, Irvine CA): 2.5 mA 70kHz. Sramek-Bernstein	Thermodilution: 7Fr Swan Ganz catheter (Baxter Edwards 131-7F): Bolus Injection 20mL 4C dextrose.	Direct Fick: 3 blood samples obtained from pulmonary and left brachial arteries--arteriovenous oxygen difference calculated as average value.	
Bogaard 1997 98075787	Cardiac output, stroke volume	IPG-104 Minilab, RJL Systems, Detroit, Equip Medkey, Gouda Holland). Constant sinusoidal AC 0.8mA , 60 kHz introduced thru one spot electrode on forehead, 4 electrodes at lower abdomen. 2 prs in mid-axillary lines at base of neck and at xiphoid level of sternum detect voltage change. Kubicek equation	Indirect Fick (equilibrium CO-2 rebreathing method)		
Bowling 1993 94007883	Ejection fraction	NCCOM-3 Series R7 (BoMed Mfrs, Irvine CA): 2.5 mA 70kHz. 8 impedance-quality gel electrodes place on neck and and thorax. Sramek-Bernstein	Radionuclide ventriculography		
Castor 1994 94153663	Cardiac output	NCCOM-3 R7 (BoMed Mfrs, Irvine CA). 2 pairs of electrodes 5 cm apart at neck & lower thoracic aperture at level of xiphoid .Current 2.5mA RMS, 70 kHz. Sramek-Bernstein equation.	Thermodilution: ice-cold 5% glucose 10mL. Standard method used by Baxter.	Doppler echo-cardiography (Quantascope-Vital Science, Denver) placed at suprasternal notch.	

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Clancy 1991 91341839	cardiac output	NCCOM.3R.7 connected to Zenith laptop #184 Model 2WL-184-2. 2 electrodes on each side of neck, 2 at thorax. Low amplitude 2.5 mA current, 70 kHz. Sramek-Bernstein.	Thermodilution: 7FSwan-Ganz catheter, Baxter Edwards Labs)		
Critchley 1996 96338592	Cardiac output	NCCOM3-R7. Sramek-Bernstein equation	Thermodilution: 7.5F PAC (BioSensor Intl, Singapore) inserted through jugular vein. 10ml cold 0.9% saline injected 1-3 sec. Determination by Sirecust 1261 monitor (Siemens Medical) .		
Critchley 2000 20399480	CO, lung fluid content	NCCOM-3R-7 connected to Zenith laptop #184 Model 2WL-184-2. 2 electrodes on each side of neck, 2 at thorax (total of 8 lateral spot elecrtrodes). Srameck-Bernstein.	Thermodilution: 7FSwan-Ganz catheter calculated with Sirecust 961/1261 monitor.		
Demeter 1993 94032793	Cardiac output	Minnesota Impedance Cardiograph Model 304B (Surcom, Minneapolis) connected to computer Model 2400S (Gould, Cleveland). 4 electrode tapes applied at chest and neck. Constant current 4mA, 100kHz. 3 baseline signals averaged for 3 separate positions. Kubicek equation.	Thermodilution: Catheter (Baxter Edwards) measured by computer 9520A). 5 CO obtained of iced saline in 3 positions.		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Doering 1995 96019885	Cardiac index	NCCOM-3 (BoMed Mfrs, Irvine CA). Revision 7 software. 8 electrodes placed at thorax and neck.	Thermodilution: Marquette Electronics, Chicago. Manual injection 10mL 5% dextrose.		
Drazner 2002 21947433	Cardiac output, cardiac index	BioZ--patches on right side of neck placed posterior to ear lobe to avoid interference with venous access, and patchs on left placed equal distance anterior to lobe. Chest leads placed according to manufacturer. Measurements obtained either on 10 or 30 beat averaging.	Thermodilution n=50: right sided cardiac catheter-ization using balloon-tipped flotation catheter.Output obtained by average of 3-5 independent values.	Fick (subset N=28). Oxygen consumption obtained by Sensor-Medics Corp Delta Trac Metabolic Monitor (Yorba LInda CA).	
Genoni 1998 98373881	Cardiac output	NCCOM-3 R7 (BoMed Mfrs, Irvine CA): Value of CO obtained as average of 12 beats--5 measurements at 1 min intervals, and 2 extremes discarded.	Thermodilution: 7.5 Fr PA catheter (Baxter Edwards) measured by computer 9520A). Infusion of iced 10mL sodium chloride injected 3 times.		
Hirschl 2000 20346676	Cardiac index	Impedance cardiograph (Cardioscreen, Messtechnik, Ilmenau German)--4 pairs electrodes placed according to Bernstein. Calculation by Sramek-Bernstein.	Thermodilution: 7Fr Swan Ganz catheter (Baxter Edwards) inserted via central subclavian or jugular vein. Injection of 10mL ice cold dextrose.		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Horstmann 1993 94328978	Cardiac output	Tetrapolar impedance (Diefenbach, Kardio-Dynagraph). No details provided.	Thermodilution: Schwarze-Picker IVH4. 7F catheter, injections of 10mL iced saline, connected to CO computer		
Jewkes 1991 92118578	Stroke volume, cardiac output	NCCOM-3 (BoMed Mfrs, Irvine CA) using spot electrode array. 2.5mA, 70 kHz current. Sramek-Bernstein equation..	Thermodilution: 10ml ice cold saline at end-expiration, calculated by COM-1 computer. Measurements taken as average of 3 consec-utive readings.	Studied different electrode types and placements in 4 normal volunteers in first phase of study	Second phase involved 16 ICU patients.
Kerkkamp 1999 99300751	Left ventricular systolic function, systolic time ratio,	NCCOM-3 R7 (BoMed Mfrs, Irvine CA). 10 electrodes placed according to mfr's specifications.	Echocardiography Toshiba Sonolayers SSH 140A		
Kindermann 1997 98023345	Stroke volume	CARDIOmed 30 and CARDIOwin system, Homburg/ Saar, Germany): at beginning of each series, LVET determined by fingertip opto-plethysmography. SV was estimated using Kubicek.	Pulsed Doppler echocardiography, according to Ritter. Programming of AV delay done either by short 30 ms postponing mitral valve closure until end-diastolic filling is abruptly terminated at onset of LV contraction, or 250ms shortening time interval from ventricular pacing to mitral valve closure.		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Kizakevich 1993 94032797	Systolic ejection dynamics	Not described. Tetrapolar band electrodes placed around neck and below xiphoid process. Kubicek equation	Doppler echo-cardiography		
Marik 1997	Cardiac output	IQ (Renaissance Technologies, Newton PA)	Thermodilution	Ventricular angiography	
Mattar 1991 92036473	Systolic time intervals, diastolic time intervals	NCCOM3-R7. 2.5 mA at 70 kHz. Kubicek's equation	Radionuclide ventricular angiography	Bios nuclear stethoscope	Mobile gamma-ray measuring probe
Mehlsen 1991 92119899	Cardiac output	Minnesota Impedance Cardiograph (Surcom, Minneapolis) --tetrapolar circular lead system, 4mA, 1200kHz. Kubicek equation.	Thermodilution: Swan-Ganz catheter (model 93A-131-7F, Edwards Labs)--bolus injections of 10ml 0C isotonic solution. CO calculated by Model 95120 computer, Edwards Labs.	Indicator dilution technique: Itracath inserted into right cubital vein, advanced to right atrium. Catheter inserted into right brachial artery. I131-labelled human serum albumin (185 kBq, Kjeller, Norway) injected.	
Ng 1993 94907300	Cardiac output, stroke volume	NCCOM-3 R7 (BoMed Mfrs, Irvine CA). 8 electodes at root of neck and lower chest at xiphisternum. Sramek-Bernstein equation.	Theromodilution: Swan-Ganz catheter 93A-83L (Baxter, Holland) and CO computer (Marquette Electronics, Milwaukee)		
Perrino 1994 94220628	Cardiac output	NCCOM-3 R7 (BoMed Mfrs, Irvine CA) using spot electrode array. 2.5mA, 70 kHz current. Compatible software: Cardiodynamic Data Processing.	Thermodilution: room temp injectate obtained at end-expiration by calibrated computer (SpaceLabs, Redmond WA).		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Pickett 1992 92264297	Cardiac output	HDC, Mesa AZ Sramek equation and Kubicek equation.	Theromodilution: 10 ml injection iced 5% dextrose calculated with Edwards' model 9520A computer		
Raaijmakers 1998a 99079379	Cardiac output	Homemade cardiograph, 9 spot electrode array, sinusoidal current 1mA, 64kHZ, both equations	Thermodilution: Pulmonary artery catheter (Baxter-Edwards) 10 ml saline bolus at room temperature		
Raaijmakers 1998b 99214718	Cardiac output, Extravascular lung water	9 spot electrode array. 1mA at 64 kHz. Korsten cross-section equation.	Double indicator dilution technique (COLD)		
Sageman 1993 93339081	Cardiac output	NCCOM-3 R7 (BoMed Mfrs, Irvine CA). Sramek-Bernstein equation.	Theromodilution: 5 ml injections of iced 5% dextrose calculated with HP 78534C computer		
Sageman 2002 21843329	Cardiac index	BioZ 1.52, CardioDynamics, San Diego). Measurements of SV averaged over 16-30 beats.	Thermodilution: not described		
Shoemaker 2001 21393819	Cardiac output, cardiac index	"Improved device" (Wantagh, Bristol PA): redesigned software increased signal/noise ratio. 4mA, 100 kHz AC. (Wang X et al)	Thermodilution: Not otherwise described		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Shoemaker 2000 21021875	Cardiac index	"Improved device" (Wantagh, Bristol PA): redesigned software increased signal/noise ratio. (Wang X et al)	Thermodilution: 7F balloon-tipped pulmonary artery flow-directed catheter (Baxter Edwards)		
Shoemaker 1998 99087206	Cardiac index	Same as above	Same as above		
Shoemaker 1994 95079738	Cardiac index	Same as above	Same as above		
Spiess 2001 11687996	Cardiac index	BioZ system: no further details	Thermodilution: internal jugular cannulation by 7.5F introducer, PAC (Baxter Edwards Model #831-HF75 or 139 H7.5		
Summers 2001 21233995	Ejection fraction by Weissler and Capan methods	Sorba Medical Systems--not described	Echocardiography		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Thangathurai 1997 97331660	Cardiac output	Model IG101(Renaissance Technologies, Newton PA:) array of 11 prewired hydrogen elect-rodes--2 injecting electrodes at lateral aspect of lower thorax at level of xiphisternal junc-tion. 4 sensing electrodes placed 5cm inside area, 3 leads across precordium and shoulder. 4 mA 100 Khz current. Author's equation.	Thermodilution: 10ml saline injectates at room temp made at end-expiration.		
Thomas AN 1991 92129741	Cardiac output	NCCOM-3 R6 using 8 Medicotest VL-00-S electrodes, and 2 positioned on chest.	Thermodilution: 10 ml 5% dextrose at temp of 4C-10C. Determination by CO computer 9520A, Edwards.		
Thomas SH 1992 93152372 (Trial 1)	Cardiac output, stroke volume	NCCOM-3 R7 (BoMed Mfrs, Irvine CA). 10 electrodes at root of neck & at xiphisternum. Current 2.5mA RMS, 70 kHz. Sramek-Bernstein equation.	Thermodilution: bolus injection of 20ml 4°C 5% dextrose into right atrium via flow-directed balloon catheter (Kimal Scientific Products, Uxbridge)		
Thomas SH 1992 93152372 (Trial 2)	Cardiac index, stroke volume index, LVET	NCCOM-3 R7 (BoMed Mfrs, Irvine CA). 10 electrodes at root of neck & at xiphisternum. Current 2.5mA RMS, 70 kHz. Sramek-Bernstein equation.	Thermodilution: bolus injection of 20ml 4°C 5% dextrose into right atrium via flow-directed balloon catheter (Kimal Scientific Products, Uxbridge)		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Van der Meer 1999 99161702	Mitral valve regurgitation	IPG-104 Minilab (RJL Systems, Detroit, & Sanofi Sante, Holland) 4 prs electrodes, current 0.8mA, 50 kHz.. Sramek-Bernstein equation.	Doppler echo-cardiography (HP Sonos 1000, Andover MA)		
Van der Meer 1999 99151080	LVEF	IPG-104 Minilab, RJL Systems, Detroit, Sanofi Sante, Massluis Holland). 4 electrodes applied according to Bernstein: Constant sinusoidal AC 0.8mA , 50 kHz.	Dobutamine stress echocardiography		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Van der Meer 1997 97385315	Cardiac output	IPG-104 Minilab, RJL Systems, Detroit, Equip Medical, MassluisHolland). Constant sinusoidal AC 0.8mA , 50 kHz introduced thru one spot eletrode on forehead, 4 electrodes at lower abdomen. 2 prs in mid-axillary lines at base of neck and at xiphoid level of sternum detect voltage change. Sramek-Bernstein-equation.	Thermodilution: PAC inserted into jugular, 10 ml 0,9% saline at temp of 5C. Determination by CO computer 9520A, Edwards.		
Woltjer 1996b 97166939	Stroke volume	System described in van der Meer above and: 9 spot electrode configuration used--5 electrodes applied (1 to forehead, 4 in semicircular manner low on abdomen, 2 in mid-axillary lines, 2 in mid-clavicular lines). Constant sinusoidal AC 0.8 mA, 60 kHz. Both Kubicek and Sramek-Bernstein equations compared.	See van der Meer above		
Woltjer 1996a 97034589	Stroke volume				

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Van der Meer 1996 97081838	Cardiac output	IPG-104 Minilab, RJL Systems, Detroit, Equip Medical, Massluis Holland). Constant sinusoidal AC 0.8 mA , 50 kHz introduced thru one spot electrode on forehead, 4 electrodes at lower abdomen. 2 prs in mid-axillary lines at base of neck and at xiphoid level of sternum detect voltage change. Kubicek equation	Thermodilution: 7Fr Swan Ganz catheter (Baxter Edwards) inserted via central subclavian or jugular vein. Injection of 10mL 5C dextrose randomly chosen, repeated 4 times and averaged.		
Van der Meer 1996 96310167	LVEF	IPG-104 Minilab, RJL Systems, Detroit, Equip Medical, Massluis Holland). 4 electrodes applied according to Bernstein: Constant sinusoidal AC 0.8 mA, 50 kHz. 4 separate equations used, adopted from Capan and Judy, 2 newly developed.	Radionuclide ventriculography		
Velmahos 1998 98347548	Cardiac index	Wang's new prototype TEB: 11 noninvasive disposable prewired hydrogen electrodes-- 2 placed at side of neck, 2 at lateral aspect of lower thorax, 4 placed 5cm inside the area defined by electrodes. 3 ECG leads placed across precordium and left shoulder. 4mA, 100 kHz AC.	Thermodilution: 7Fr PAC (Baxter Edwards)--3-5 measurements, averaged.		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Weiss 1995 96071685 (stable patients)	Cardiac output	NCCOM-3 R7 (BoMed Mfrs, Irvine CA) using spot electrode array. 2.5mA, 70 kHz current.	Thermodilution: Swan-Ganz catheter attached to American Edwards 9520A computer. Readings done using 3-5 injections of 10ml 5% dextrose at room temp.		
Weiss 1995 96071685 (unstable patients)	Cardiac output	NCCOM-3 R7 (BoMed Mfrs, Irvine CA) using spot electrode array. 2.5mA, 70 kHz current.	Thermodilution: Swan-Ganz catheter attached to Nihon Kohden BSM-8500A. Readings done using 3-5 injections of 10ml 5% dextrose at room temp.		
Woltjer 1997 97468636	Stroke volume, PCWP	IPG-104 Minilab, RJL Systems, Detroit, Equip MediKey, Gouda,Holland). 9 electrodes applied constant sinusoidal AC 0.8 mA, 50 kHz. Kubicek equation.	Thermodilution: 7F single lumen balloon tipped catheter (Arrow International, Reading PA) by injection of 10ml 0.9% saline solution at 5C.		
Woo 1992 91302095	Cardiac output	NCCOM-3 (BoMed Mfrs, Irvine CA) attached to electrodes (MediTrace, Graphic Controls Corp, Buffalo) Sramek-Bernstein equation.	Thermodilution calculated based on 3 injections at end expiration (5-8C, 10 ml each, 1 min apart).		
Wong KL 1996 97238198	Cardiac output	NCCOM-3 R7 (BoMed Mfrs, Irvine CA) 8 spot electrodes placed according to BoMed's instructions. CO measurement averaged from 16 successive artifact-free heartbeats.	Thermodilution: average of 3 vaules using CO computer (M1012A HP, Boeblinger Germany), 5 ml boluses of 5% dextrose solution at 4C. Sramek-Bernstein.		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
World 1996 96318217 (Trial 1)	Cardiac output	NCCOM-R7 (Kimal Scientific Products) Procedure not described.	Thermodilution: PAC (Baxter Healthcare) with iced 5% dextrose injectate.		
World 1996 96318217 (Trial 2)	Cardiac output	NCCOM-R7 (Kimal Scientific Products) Procedure not described.	Doppler probe (Abbott Labs) passed orally into esophagus.		
Yakimets 1995 95347996 (Trial 1)	Cardiac index, stroke volume	NCCOM-3 R7 (BoMed Mfrs, Irvine CA) using spot electrode array. 2.5mA, 70 kHz current. Compatible software: Cardiodynamic Data Processing. Sramek-Bernstein.	Fick method at rest and during supine exercise on bicyle ergometer (Ergomed #740L, Siemens Ltd, Langdon Germany). CO determined from oxygen uptake, oxygen consumption, arterial oxygen content, or mixed venous oxygen uptake measured by Quinton Q-Plex metabolic cart.		
Yakimets 1995 95347996 (Trial 2)	Cardiac index, stroke volume, cardiac output	NCCOM-3 R7 (BoMed Mfrs, Irvine CA) using spot electrode array. 2.5mA, 70 kHz current. Compatible software: Cardiodynamic Data Processing. Sramek-Bernstein.	Thermodilution 3 injections of 10ml room temp 5% dextrose injected into tight atrium through proximal lumen of PAC (nF, American Edwards).		

Evidence Table 1. Comparison Studies: Part II

Author, Year UI	Parameters Tested	Bioimpedance System, Procedure, Equation	Comparison 1 and Procedure	Comparison 2 and Procedure	Comparison 3 and Procedure
Young 1993 93159934	Cardiac index	NCCOM-3 R6 (BoMed Mfrs, Irvine CA. 8 electrodes placed on neck and thorax, 2 electrodes placed on right sternal border, over the apex beat, according to manufacturer's instructions.	Thermodilution performed using COM-1 computer. Temps less than 10C, injections made manually during expiration. Average of 3 measurements.		
Zacek 1999 20032610	Cardiac output	Hotman AH/HHC (Hemo Sapiens, Irvine CA)--8 solid gel electrodes applied on skin at neck and thorax. Sramek-Bernstein.	Thermodilution--value of CI was average of 4 consecutive injections of saline solution at room temp. Marquette Electronics software was used.		
Zubarev 1999 99300756	LVEA, LVET, DTI	Bioimpedance polyrheocardiography system with "tetrapolar electrode location." 1 injection band electrode at neck and 1 at thorax. 2 sensing band electrodes at neck and 2 at xyphoid. Kubicek equation modified by Gunderov using human thorax as a frustum of a cone, not cylinder.	Thermodilution-- No elaboration provided		

Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Antonicelli 1991 91368949	RM=56 (14) r=0.95 D=-0.73ml, SD=8.46 ml Also provides separate SM data for each visit with 14 measurements in each visit and r=0.96, 0.95, 0.96, 0.94 respectively)	Correlation excellent.	No	Yes	No	Yes
Atallah 1995 95398907	RM=86 (5) No r given D=TD-TEB=-0.69 L/min.m^2 SD=0.66	TEB is unreliable in CO measurement and cannot replace or be interchanged with TD.	Yes	No	No	Yes
Balestra 1992 92103922	SM=10 r^2=0.55 (external electrodes) [r^2=0.98 (internal electrodes) – not pertinent for the report] D=TEB-TD=1.99 L/min SD=2.20 (external electrodes) [D=TEB-TD=-0.05 L/min SD=0.26 (internal electrodes)]	Values comparable but not identical to TD--discrepancy probably caused by position of the electrodes. Method is accurate and could be a good alternative to TD.	Yes	Yes	Yes	No
Barin 2000 20214491	RM=142 (47) r^2=0.74 D=TEB-TD=-0.18 L/min SD=0.78 Subgroup data provided for men and women and for first 20 and last 27 patients	TEB performs best when cardiac rhythm is normal. Presence of BBB and AF can cause errors in determining Q point, preceding peak ejection period, and may lead to inaccuracies of EF but not CO. Premature ventricular contractions are hemodynamically less effective and result in small signals.	Yes	Yes	Yes	Yes

Four criteria that specifically relate to the scope of this report were used to assess the methodological quality of the studies. The following yes/no questions were developed and applied. Does the study provide:

1. A description of the apparatus/device to measure bioimpedance (including manufacturer and model)?
2. The equation used to calculate impedance measurements?
3. A description of the patients in the study, with clear inclusion and exclusion criteria?
4. A description of the medical and/or surgical condition and the indication for use of impedance cardiography monitoring in the patients enrolled?

Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Barry 1997 11056698	RM=239 (7) r^2=0.01 D=TEB-TD=-0.16 L/min-m^2 SD=1.16	TEB shows poor agreement with thermodilution and cannot be recommended for CO monitoring in this situation.	Yes	Yes	Yes	Yes

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2. The equation used to calculate impedance measurements?
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4. A description of the medical and/or surgical condition and the indication for use of impedance cardiography monitoring in the patients enrolled?

Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Belardinelli 1996 96259436	TD Group A (ischemic cardiac myopathy): RM=45 (15) r=0.94 (Rest) RM=180 (15) r=0.90 (exercise) Group B: RM=30 (10) r=0.90 (rest) RM=120 (10) r=0.90 (exercise) Fick Group A (ischemic cardiac myopathy): RM=45 (15) r=0.85 (rest) RM=180 (15) r=0.93 (exercise) Group B: RM=30 (10) r=0.95 (rest) RM=120 (10) R=0.89 (exercise) Detailed D are provided in table III in the paper	TEB is an accurate and reproducible technique for measuring CO, SV--no significant differences were found among devices. In critically ill patients, there was moderate agreement, and drug-induced changes in SV were accurately detected.	Yes	Yes	Yes	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Bogaard 1997 98075787	RM=81 (14) r=0.79 (SV), r=0.92 (CO) for TEB -Hct D=0.55ml, SD=12.4 ml for TEB-Hct (SV) D=0.01 L/mm SD=1.28 for TEB-ct (CO) Also provides data for differently corrected TEB, e.g. r=0.73 (SV), r=0.89 (CO) for TEB-135, or TEB-150. See table A for more details on different D calculations	The validity of TEB for measuring SV, CO during submaximal exercise seems acceptable. "Addition of non-invasive hemodynamic measurements might prove to be of much benefit…The improvement in validity using an Hct-based blood resistivity is small."	Yes	Yes	yes	Yes
Bowling 1993 94007883	SM=20 r=0.74 D=(TD-TEB)=-8.9% SD=7.15%	TEB should not be used in place of radionuclide ventriculography.	Yes	Yes	Yes	No

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4. A description of the medical and/or surgical condition and the indication for use of impedance cardiography monitoring in the patients enrolled?

Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Castor 1994 94153663	RM=131 (10) during controlled IPPV ventilation No r given D=TEB-TD=1.4% SD=16.2% RM=56 (10) during apnea No r given D=TEB-TD=-2.2% SD=11.2% RM=152 (10) during spontaneous breathing in ICU No r given D=TEB-TD=-2.1% SD=11.0%	Simultaneous measures of TEB/DU lead to prolonged disturbance of impedance signal. Metallic DU transducer absorbs current between 2 inner sensing electrodes, reducing dZ/dtmax signal, thus calculation results in decreased CO values. (The investigator was unaware of the measurements.) 2 major problems of TEB: correct signal processing of critical parameters, and the empirically derived equations. Compared with TD, TEB overestimates CO in normal range during spontaneous ventilation and IPPV, also in low flow conditions. TEB seems to underestimate CO during IPPV and sepsis. Other limitations: aortic regurgitation, tachyarrhythmias, open-heart surgery, extreme obesity. Other sources of errors: incorrect electrode placement.	Yes	Yes	No	Yes
Clancy 1991 91341839	RM=51 (17) r=0.91 D=TEB-TD=0.23L/min SD=0.56	TEB: less expensive, has no associated patient risk (whereas TD is associated with cardiac arrythmia, pneumorthorax, infection), easier to use, produces continuous data profile, allowing earlier intervention.. Constraints include: obese body habitus, cervical collars, diaphoretic skin, electrocautery, motion artifacts, open thoraces. Other clinical limitations: cardiac arrhythmias, valvular insufficiency, ventricular arrhythmias, HBP, CHF.	Yes	No	No	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Critchley 1996 96338592	RM=157(8) r=0.60 D [logarithmic]=lnTD=lnTEB=0.14 SD=0.66 Note that values are in log scale for the estimation of bias.	Technology appears to be too inaccurate to provide useful intra-operative monitor for abdominal surgery, resulting from factors related to surgery that alter VEPT and hence the calibration of TEB. When operating conditions remain stable, instruments perform to a high degree of repeatibility.	Yes	Yes	Yes	Yes
Critchley 2000 20399480	SM=24 r=0.39 D=TD-TEB=1.49 L/min SD=4.16 Also gives correlations between effect and Zo (=0.83)	All newer generations of TEB still use basic method of calculating CO as BoMed even the electronics and signal processing is now improved. Lung injury leads to BoMed significantly underestimating CO which is related to excessive lung fluid which effectively shortcircuits impedance changes.	Yes	Yes	Yes	Yes
Demeter 1993 94032793	SM=10 supine 1 position r=0.97 (TEB-Hct), [0.99 (TEB-135), 0.99 (TEB-150)] SM=10 45° position r=0.90 (TEB-Hct), [0.82 (TEB-135), 0.82 (TEB-150)] SM=10 supine 2 position r=0.84 (TEB-Hct), [0.74 (TEB-135), 0.74 (TEB-150)]	TEB correlates highly to TD, recommended for open heart recovery patients.	Yes	Yes	Yes	Yes

Four criteria that specifically relate to the scope of this report were used to assess the methodological quality of the studies. The following yes/no questions were developed and applied. Does the study provide:

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2. The equation used to calculate impedance measurements?
3. A description of the patients in the study, with clear inclusion and exclusion criteria?
4. A description of the medical and/or surgical condition and the indication for use of impedance cardiography monitoring in the patients enrolled?

Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Doering 1995 96019885	SM=34 ICU admission r^2=0.23 D=TEB-TD=0.21 SD=0.53 (L/min.m^2) SM=34 Normothermia r^2=0.08 D=TEB-TD=0.02 SD=0.72 (L/min.m^2) SM=34 Postextubation r^2=0.05 D=TEB-TD=0.04 SD=0.86 (L/min.m^2) SM=34 24h ICU r^2=0.21 D=TEB-TD=0.18 SD=0.76 (L/min.m^2)	Do not use immediately after cardiac surgery: agreement between methods is poor. Use of this device as trending is inappropriate at this time. Mean TEB values exceeded TD consistently, difference reflecting low post-op level of blood flow. One patient's abnormal chest morphology precluded TEB measurement.	Yes	Yes	Yes	Yes

Four criteria that specifically relate to the scope of this report were used to assess the methodological quality of the studies. The following yes/no questions were developed and applied. Does the study provide:

1. A description of the apparatus/device to measure bioimpedance (including manufacturer and model)?
2. The equation used to calculate impedance measurements?
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4. A description of the medical and/or surgical condition and the indication for use of impedance cardiography monitoring in the patients enrolled?

Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Quality Criteria: Equation	Quality Criteria: Population	Quality Criteria: Condition
Drazner 2002 21947433	TD SM=50 r=0.76 (CO) r=0.64 (CI) D=TEB-TD=0.03 L/min SD=1.1 (CO) D=TEB-TD=0.01 L/min m^2 SD=0.6 (CI) Fick SM=28 r=0.73 (CO) r=0.61 (CI) D=TEB-Fick=0.74 L/min SD=1.1 (CO) D=TEB-Fick=0.4 L/min m^2 SD=0.6 (CI)	BioZ measures were significantly correlated, suggesting the modality may have clinical utility in heart failure.	Yes	No	Yes	Yes
Genoni 1998 98373881	RM=60 (10) r^2=0.14 D=TD-TEB=1.81 L/min SD=2.14 Subgroup data for ZEEP and PEEP also given	TEB is not an accurate and reproducible method for determining CO, independently from the application of PEEP. From a subsequent letter: TEB provided non-uniform positive results; previous studies were uncontrolled and those prospective studies that had good design and examined large populations had heterogeneous categories of patients, thus leading to inconclusive results; few efforts have been spent in improving knowledge of technical problems of the technique.	Yes	Yes	Yes	Yes

Four criteria that specifically relate to the scope of this report were used to assess the methodological quality of the studies. The following yes/no questions were developed and applied. Does the study provide:

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Quality Criteria: Equation	Quality Criteria: Population	Quality Criteria: Condition
Hirschl 2000 20346676	RM=175 (29) No r given, but IPD given D=TD-TEB=0.61 L/min.m^2 SD=0.74	TEB is not a general substitute for TD--CO cannot be accurately assessed in a considerable percentage of critically ill patients. Heart valve dysfunction, pleural effusion, positive end-expiratory pressure are conditions associated with low accuracy and reliability, and these increase with age of the patient. In elderly, atherosclerotic changes reduce Windkessel effect of aorta and lead to reduction of the changes in TEB.	Yes	Yes	Yes	Yes
Horstmann 1993 94328978	SM=35 at rest r=-0.006 RM=unknown (35) 4 measurements per patient (?) at exercise r=0.45	TEB is not a reliable technique to measure absolute values of CO at rest. During exercise, large scatter limits the method to the measurement of relative change in CO in larger groups--heart rate alone is a better indicator of increase of CO than TEB.	No	Yes	Yes	Yes
Jewkes 1991 92118578	RM=160 (16) r=0.72 (CO), r=0.83 (SV) D=TD-TEB=-0.86 L/min SD=0.88 (CO) D=TD-TEB=-13 mL SD=11.1 (SV)	Main source of observer error in TEB relates to placement of electrodes and electrode type which can change skin-electrode interface which can affect dynamic component of the signal. Alterations in electrode position alter Z values which are proportional to L according to the Sramek-Bernstein formula. TEB overestimates at low and underestimates at high values of CO.	Yes	Yes	No	No
Kerkkamp 1999 99300751	Data provided on systolic time ratio, index of contractility, acceleration index, Heather index – no data on SV, CO, or CI	TEB: noninvasive, simple to use, especially in situations where sequential monitoring is required.	Yes	Yes	No	No

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Kindermann 1997 98023345	No direct data on CO, SV, or CI. Aimed for optimization of AV delay. For AV delay optimal, r=0.655 in ATP and r=0.529 in AVP based on 53 and 49 patients, respectively	SV is not very precise for TEB	Yes	Yes	Yes	No
Kizakevich 1993 94032797	Tables 2 and 4 provide correlation data on several parameters of systolic event timing and systolic ejection indices, but no data on SV, CO, or CI.	Users of dZ/dt timing features for determining aortic valvular events might consider alternative impedance features to improve ejection time accuracy.	No	No	Yes	Yes
Marik 1997	SM=24 TD r=0.08 (CO) D=(TEB-TD)=0.06 SD=0.06 (estimated from plot) VA r=0.02 (EF) D=((TEB-VA)=1% SD=17%	Poor agreement between CO, EF, LVEDV. TEB produces unreliable and misleading data which lead to inappropriate clinical interventions	Yes	Yes	Yes	Yes
Mattar 1991 92036473	SM=17 r^2=0.48 against angiography or nuclear stethoscope (no separate data).	TEB is usually correlated with TD.	Yes	Yes	Yes	Yes

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Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Quality Criteria: Equation	Quality Criteria: Population	Quality Criteria: Condition
Mehlsen 1991 92119899	RM=58 (on unstated number of both healthy subjects and ill patients) Contrast is against either TD or isotope dilution (n=28, n=30 respectively) No r given but IPD given D=TEB-(TD or ID)=0.23 L/min SD=1.13	TEB is reliable and useful, highly recommended for hemo-dynamic effects of physiological and pharmacological interventions but not for quantitative studies of central blood volume. Systematic difference found between absolute values of CO measured by TEB and dilution techniques (TEB overestimated low values and underestimated high values) but close correlation between changes.	Yes	Yes	No	No
Ng 1993 94907300	SM = 27 (duplicate means) r=0.87 (CO) r=0.86 (SV) D=TH-TEB=1.4 L/min (CO) SD=1.4 D=TH-TEB=14 ml (SV) SD=13.4 ml	Difficulties in obtaining signals caused by interference due to poor skin contact, abnormally high ECG T-wave, motion artifacts due to ventilation or vibration of the air mattress. Reproducibility is better since it is hand-free and avoids intra-observer variation. TEB underestimates CO because it detects only pulsatile impedance signals during systole. TEB cannot be considered sufficiently accurate for routine use in intensive care patients.	Yes	No	Yes	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Perrino 1994 94220628	RM=451 (43) [excludes 7 patients with inadequate signals] r=0.84 D=TEB-TD=-0.41 L/min SD=1.0 Also gives data on correlation of changes in CO	TEB is a simple to use, continuous monitor of CO, Considerable progress has been made but clinically significant errors are revealed, e.g. in obese or arrhythmic patients, and interference of electrical noises. The validity of TEB in patients with CAD and impaired ventricular function has yet to be established. Reassessment of the technology is warranted.	Yes	Yes	Yes	No
Pickett 1992 92264297	RM=201 (43) r=0.75, r=0.86 when using SM with means of multiples D=TD-TEB=0.125 L/min SD=1.03	TEB is essentially equivalent in accuracy and reproducibility within defined limits.	Yes	Yes	Yes	Yes
Raaijmakers 1998a 99079379	RM=30 (13) r=0.42 (SB equation), r=0.75 (Kubicek equation) D=TD-TEB=2.4 L/min SD=2.8 (SB) or 1.8L/min SD=2.0 (K)	Kubicek equation is superior to Sramek-Bernstein. Accuracy needs further improvement to become a useful clinical tool.	Yes	Yes	Yes	Yes
Raaijmakers 1998b 99214718	RM=29 (13) r=-0.24 (extravascular lung fluid)	Using bioimpedance to estimate pulmonary edema yields different results for cardiogenic and non-cardiogenic edema	Yes	Yes	Yes	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Sageman 1993 93339081	SM=50 r^2=0.24 D=TD-TEB=-0.33 L/min SD=3.14 Also subgroup data for ventilated, non-ventilated, tube thoracotomies, obese, IBW) given in Table 1	Degree of correlation and agreement is poor. Use of TEB as substitute for TD in measuring cardiac output in post-aortocoronary bypass patients cannot be recommended. The presence of certain equipment may contribute to distortion of thorax electric field. Bandage may prohibit correct postioning of throrax electrodes. Alterations in cutaneous blood flow may have an impact.	Yes	Yes	Yes	Yes
Sageman 2002 21843329	RM=216(20) r^2=0.86 D=TD-TEB=0.07L/min.m^2 SD=0.20 (Also gives data for correlation of changes over time: r=0.95)	Improvements have substantially increased precision and reliability.TEB is equivalent to TD-derived cardiac index in post-op cardiac surgery patients. TEB requires adherence of chest and neck electrodes--if patients have oily skin or are diaphoretic, electrodes may become dislodged. Measurement familiarity with the equipment is required for accurate data retrieval.	Yes	Yes	Yes	Yes
Shoemaker 2001 21393819	SM?=151 r=0.91 D=-0.30L/min.m2 SD=1.1	Advantages include technical convenience and continuous display of data allowing calculation of amount of deficit or excess of each variable. Easy, cheap, fast, safe, sensitive. It also provides an approach to an organized coherent therapeutic plan based on physiologic criteria for the emergency patient proceeding from ER. Linear discriminant function predicted outcome correctly in 95% of survivors, 62% of nonsurvivors in early period after admission.	Yes	Yes	Yes	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Shoemaker 2000 21021875	RM=311 (45) r=0.78 D=TEB-TD=-0.16 L/min.m^2 SD=0.95	Noninvasive monitoring is easier, quicker, more convenient. Real time hemodynamic monitoring in ED provides early warning of outcome and may be used to guide therapy.	Yes	Yes	Yes	Yes
Shoemaker 1998 99087206	RM=2192 (680) r=0.85 D=TEB-TD=-0.124 L/min.m^2 SD=0.75 Subgroups per setting provided ED subgroup RM=990 r=0.83, D=-0.058 L/min.m^2 SD=0.78 OR subgroup RM=407 r=0.88, D=-0.027 L/min.m^2 SD=0.46 ICU subgroup RM=795 r=0.85, D=-0.17 L/min.m^2 SD=0.68	TEB can be acceptable alternative where noninvasive monitoring is not available.	Yes	Yes	Yes	Yes
Shoemaker 1994 95079738	RM=842 (68) r=0.86 D=TEB-TD=-0.013 L/min (no range or SD noted)	Unsatisfactory measurements can be caused by clinical conditions such as pleural effusion, severe pulmonary edema, chest tubes, other conditions where electrolyte solutions would allow the electrical signal to bypass normal thoracic structures. Bioimpedance underestimates corresponding TD estimations in clinical conditions where very high cardiac output values are associated with tachycardia and cardiac dysrhythmias.	Yes	Yes	Yes	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Spiess 2001 11687996	RM=182(47) r=0.71 D=TEB-TD=-0.28 L/min.m^2 SD=0.67 Also subgroup data are given for each of 4 timepoints, e.g. for time point 1 r=0.87, time point 2 r=0.73, time point 3 r=0.73, time point 4 r=0.56	BioZ generally agrees with TD: in fact it is more accurate and unaffected by cardiopulmonary bypass. The only time point when there was less accuracy was at end of surgery immediately before transport t ICU--stainless steel wires used to approximate the sternum may have altered current flow in the chest. Abnormal waveforms can easily be observed on BioZ's display screen.	Yes	Yes	Yes	Yes
Summers 2001 21233995	SM=15 only EF correlations r=0.89 by Weissler method, r=0.89 by Capan method No SV, CO, or CI data.	Lack of familiarity with the device, difficulties in recording and matching electrical and mechanical events of LV, and an uncertainty of its inherent accuracy has prevented widespread use among practicing physicians. Simple and inexpensive technology that could potentially be used effectively.	No	No	Yes	Yes
Thangathurai 1997 97331660	RM=256 (23) r=0.89 D=TEB-TD=0.1 L/min SD=1.0 Also subgroup data by original software, revised software, esophagectomy patients	Easier, faster, safer than TD. Generally accurate and reliable and can be clinically useful in patients undergoing non-cardiac surgical procedures.	Yes	Yes	Yes	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Thomas AN 1991 92129741	RM=101 (28) No r given, but IPD given D is provided broken in two subgroups Subgroup of <12 hours RM=46 (28) D=TEB-TD=-1.08 L/min SD=0.96 Subgroup of 12-24 hours RM=55 (28) D=TEB-TD=0.09 L/min SD=0.54	TEB is not consistently reliable in intensive care. Poor technique can weaken agreement between comparative measurements--if a single electrode becomes displaced, NCCOM3 produces unacceptably low CO values without recognizing that the wave form is abnormal.	Yes	No	No	Yes
Thomas SH 1992 93152372 (Trial 1)	Subgroup ICU SM=15 No r given D=8.1 ml (SV) SD=13.02 ml D=0.55 L/min (CO) SD=0.28	Calculation of SV remains controversial because of questionable assumptions used in Kubicek's equations. Notwithstanding such reservations, we found acceptable agreement in patients with CV disease.	Yes	Yes	Yes	Yes
Thomas SH 1992 93152372 (Trial 2)	Subgroup CAD SM=34 r=0.65 (SVI), r=0.25 (CI) Must revisit paper	Calculation of SV remains controversial because of questionable assumptions used in Kubicek's equations. Notwithstanding such reservations, we found acceptable agreement in patients with CV disease.	Yes	Yes	Yes	Yes
Van der Meer 1999 99161702	SM=26 r=0.85 D=TEB-Echo=0.20 L/min SD=0.74 Also subgroup data for presence and absence of valve pathology	Both measurements are influenced by aortic valve pathology. TEB is capable of reliable estimation of SV even in MVR.	Yes	Yes	Yes	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Van der Meer 1999 99151080	No SV, CO, CI data. Correlation of wall motion score with Heather index (r=-0.78) and between WMS and RZ time (r=0.75)	TEB might be a valuable method for peri- and post-op monitoring.	Yes	Yes	Yes	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Van der Meer 1997 97385315	SM=37 r=0.60 D=TEB-TD=0.06 L/min SD=1.25 (after 12 obese exclusion, D=TEB-TD=0.99 L/min SD 0.96)	Inaccurate measurements: TEB method should not be routinely used in ICU. Frequency of the current ought to be further investigated.	Yes	Yes	Yes	Yes
Woltjer 1996b 97166939	Kubicek equation with modified semi-circular electrode array: r=0.90 mean difference (2sd) 0.5 (17.1 ml) using Sramek Bernstein:for lateral spot electrode array: r=0.0.64; -2.7 (29.3 ml) (abstract appears to incorrectly report; this result given in Table 2	Sramek-Bernstein equation was valid only with the lateral spot electrode array for calculating stroke volume, and the Kubicek equation worked well only with the modified semi-circular spot electrode array. They found a higher correlation coefficient to thermodiluation with the Kubicek equation/modified MSC electrode configuration compared to the Sramek-Bernstein/lateral spot electrode configuration.				
Woltjer 1996a 97034589	Kubicek equation: r=0.90 mean difference (2sd) 2.0 (17.7 ml) using Kubicek's equation for normal weight patients and r=0.80; -2.7 (14.4ml) for obese patients. Sramek and Bernstein: correlation and mean difference +/- 2 standard deviations was r=0.63, -0.8(30.8 ml) and r=0.43, -7.7(26.2) for obese patients.	Weight affects calculation of stroke volume with Sramek Bernstein's equation; weight correction factor does not adequately adjust. Kubicek not seriously biased by weight; appears more accurate than Sramek Bernstein .				

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Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Van der Meer 1996 96310167	SM=24 R=0.75 D=TEB-TD=-0.24 L/min SD 12.4% (LVEF)	Noninvasive estimation of LVEF is possible. We found fair correlation when incorporating LVET and heart rate in the equation. Whether the equation is accurate enough to measure LVEF in patients with cardiac pathology must be investigated.	Yes	Yes	Yes	Yes
Van der Meer 1996 97081838	SM=21 r=0.83 with SB equation lateral spot D=TEB-TD=0.15 L/min SD=0.96 Table 3 provides also r and D values for different equations and electrode configurations (8 sets)	There is no difference between reliabilities of Sramek-Bernstein and Kubicek's adjusted formulas if they are used with correct electrode positioning. These formulas should be abandoned, at least in this specific set of patients.	Yes	Yes	Yes	Yes
Velmahos 1998 98347548	RM=50 (17) r^2=0.68 No D given, but IPD given	Limitations: low signal to noise ratios from pleural effusions, chest tubes, pulmonary edema, severe CHF, severe pneumonia. Identifying and correcting circulatory deficits early may result in improved outcomes.	Yes	Yes	Yes	Yes
Weiss 1995 96071685 (stable patients)	RM=51 (15) r=0.69 D=TEB-TD=0.231 L/min SD=2.19	Presence of valvular disease contraindicates TEB monitor. Severity of condition does not affect accuracy of TEB. Wide range in inter-subject bias variability limits value of TEB at assessing absolute values.	Yes	Yes	Yes	Yes
Weiss 1995 96071685 (unstable patients)	RM=49 (13) r=0.81 D=TEB-TD=0.02 L/min SD=2.33 Also subgroup data given according to cardiac output	Best overall agreement between 2 methods. Severity of condition does not affect accuracy of TEB.	Yes	Yes	Yes	Yes

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Woltjer 1997 97468636	SM=24 r=0.69 (SV) D=TEB-TD=0.1 ml SD=22.8 ml Excluding 5 patients with aortic valve disorder, r=0.87. Also good correlation (r=0.92) for the O/C ratio.	Results showed moderate overall correlation between TD and TEB, and no significant difference. When data of patients with aortic valvular disorder were excluded, correlation is considerably improved. TEB can predict PCWP and measure SV over wide range of clinically relevant values.	Yes	Yes	Yes	Yes
Woo 1991 91302095	RM=80 (44) r=0.51 D not provided, but separate data are given for subgroups with <0.5 or >0.5 L/min difference (biased split, cannot use in summary calculations).	TEB did not reliable provide CO estimations sufficiently similar to TD. Variables such as height, weight, mitral or tricuspid regurgitation, dyspnea had significant correlation with skin impedance results. Nurses must be aware that TEB may not be dependable replacement for appropriately functioning PAC in critically ill patients with severe heart failure and ischemic or idiopathic dilated cardiomyopathy. TEB cannot be recommended.	Yes	Yes	Yes	Yes
Wong KL 1996 97238198	RM=128 (18) r=0.86 D=TEB-TD=-0.66 L/min SD=0.915	Good correlation obtained. Common problems influence CO: intra- and extra-cardiac shunts, valvular heart disease, alteration in hematocrit, electrocautery, mechanical ventilation and during low CO rate. Further studies are needed.	Yes	No	Yes	Yes
World 1996 96318217 (Trial 1)	SM=21 No r given but IPD given D=TEB-TD=-0.14 L/min SD=0.8 L/min	In patients principally with sepsis, TEB provides CO estimate at least as acceptable as TD but does not permit rapid assessment of large numbers of injured patients.	Yes	No	No	

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
World 1996 96318217 (Trial 2)	SM=50 No r given but IPD given D=TEB-esoph Doppler=0.48 L/min Also given subgroup data in orthopedic vs. other patients	There is more variability between TEB and Doppler than expected. Doppler has the advantage of rapidity, especially in the event of injured soldiers on arrival to a field hospital.	Yes	No	No	Yes
Yakimets 1995 95347996 (Trial 1)	SM=17 at rest r=0.684 (CO) 0.62 (CI) 0.76 (SV) D=TEB-Fick=-1.05 L/min SD=1.53 (CO) D=TEB-Fick=-0.555 L/min.m^2 SD=0.78 (CI) D=TEB-Fick=-13.47 mL SD=20.92 ml (SV) SM=17 at exercise r=0.219 (CO) 0.26 (CI) 0.43 (SV) D=TEB-Fick=-1.505 L/min SD=2.24 (CO) D=TEB-Fick=-0.745 L/min. m^2 SD=1.12 (CI) D=TEB-Fick=-16.67 ml SD=24.27 ml (SV)	TEB underestimated CO in comparison to Fick. The mean difference became greater during exercise. There is consensus that valvular disease affects accuracy of TEB and its readings should be questioned with these subjects. Gender affects stability of measurements of TEB. TEB has difficulty in assessing SV in subjects with low voltage R wave of ECG. IT is not recommended that TEB be used as a basis for clinical decision or as a basis for hemodynamic monitoring in the management of patients with heart disease.	Yes	Yes	Yes	Yes

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Evidence Table 1. Comparison Studies: Part III

Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Yakimets 1995 95347996 (Trial 2)	SM=28 set 1 r=0.547 (CO), 0.45 (CI), 0.67 (SV) D=TEB-TD=-0.425 L/min SD=1.325 (CO) D=TEB-TD=-0.180 L/min.m^2 SD=0.702 (CI) D=TEB-TD=-3.192 ml SD=13.967 ml (SV) SM=28 set 2 (2-4 hours after surgery) r=0.505 (CO), 0.400 (CI), 0.737 (SV) D=TEB-TD=-0.358 L/min SD=1.24 (CO) D=TEB-TD=-0.140 L/min.m^2 SD=0.67 (CI) D=TEB=TD=-3.69 ml SD=12.49 (SV)	TEB underestimated CO in comparison to TD in initial set of readings and 2-4 hours later.	Yes	Yes	Yes	Yes
Young 1993 93159934	RM=242 (19) r=0.36 D=TD-TEB=1.69 L/min.m^2 SD=1.24	Poor correlation between CI. TEB overestimated at low cardiac index and markedly underestimated at high cardiac index. It is impossible to replace TD with TEB. TEB is too insensitive for clinical use.	Yes	Yes	Yes	Yes

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Author, Year UI	Results	Author's Conclusions	Quality Criteria: Apparatus	Equation	Population	Condition
Zacek 1999 20032610	RM=128 (28) r=0.26 D=TEB-TD=-0.07 L/min.m^2 SD=1.1 Subgroup of CABG patients also given (r=0.30)	Despite controversial opinions on validity of TEB in clinical settings, there is agreement in defining the areas where TEB is unsuitable for use--sepsis, tachycardia >180/min, extreme obesity or height, excessive patient movement, dilatation of aorta, LBBB. TEB technology encounters distinct problems in open-heart surgery.	Yes	Yes	Yes	Yes
Zubarev 1999 99300756	RM=24 (11) r=0.91 Also gives data on time interval determinations	BPCS had better reproducibility than TD in serial measurements of the same patients.	Yes	Yes	No	No

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Evidence Table 2. Non-comparison Studies: Part I

Shading indicates a methodology that appeared to be TEB, but insufficient description was provided to confirm that the method was definitely TEB.

Author Year UI	Design	Demographics, location, setting	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Arora 2001 11730085	Prospective	Location: Canada Setting: ICU Mean age: 69.2 % Male: 87.5 Enrolled: 16	Angina pectoris	Hemodynamics Critically ill	Proved stenosis >70% in at least 1 major artery. History of MI; development of Q waves for MI or ischemia	ND
Charach 2001 21288902	Prospective	Location: Israel Setting: hospital Mean age: 74 % Male: 50 Enrolled: 30	30 patients with cardiogenic pulmonary edema	Fluid management Critically ill	CHD, valvular heart disease, arterial hypertension, all complicated by CPE	Respiratory failure due to extra-cardiac disease, pacemaker, pulmonary embolism, pleural effusion, prominent extrapulmonary pathology
Conway 1996 96240987	Prospective	Location: Hong Kong Setting: hospital Mean age: 72 % Male: 98 Enrolled: 42	Spinal anesthesia for transurethral prostate or bladder tumor surgery	Hemodynamics Non-critically ill	ND	If NYHA dyspnea class was III or IV; if heart rate was irregular; baseline CVP <0-2 cm H_2O (dehydration)
Critchley 1994 94153689	RCT	Location: Hong Kong Setting: clinic Mean age: 70 % Male: 100 Enrolled: 34	Subarachnoid block for urological surgery	Fluid management Critically ill	ND	Severe cardiac or respiratory disease; abnormal cardiac anatomy; heart rhythm not sinus; meds which have cardiac effect, hemoglobin <10 g/dL

Evidence Table 2. Non-comparison Studies: Part I

Shading indicates a methodology that appeared to be TEB, but insufficient description was provided to confirm that the method was definitely TEB.

Author Year UI	Design	Demographics, location, setting	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Greenberg 2000 12029190	Prospective, time series	Location: USA Setting: clinic Mean age: ND % Male: ND Enrolled: 62	Clinically stable heart failure	Hemodynamics Critically ill	Absence of clinically significant changes in physical signs of heart failure; no changes in prescribed medications	If body surface area estimates exceeded ranges for BioZ algorithm; change in heart failure status; minute ventilations pacemaker; aortic valve incompetence
Haennel 1998 98415680	Prospective	Location: Canada Setting: clinic Mean age: 74 % Male: 70 Enrolled: 10	Dual sensor rate adaptive pacemaker	Pacemaker Non-critically ill	Measured resting ejection fraction >35%, normal serum electrolytes	ND
Jonsson 1995 95407259	Prospective	Location: Denmark Setting: critical care Mean age: 66 % Male: 31 Enrolled: 16	10 aortic aneurysm resection; 5 aortic iiliac prostheses; 1 renal arterial stenosis	Fluid management Critically ill	ND	ND
Kasznicki 1993 93383616	Prospective	Location: Poland Setting: unknown Mean age: 51.7 % Male: 50 Enrolled: 30	Hematological malignancies	Hemodynamics High risk cardiac patients with cancer	ND	ND
Ovsyshcher 1992 93065475	Prospective	Location: USA Setting: clinic Mean age: 65 % Male: 82 Enrolled: 38	Implanted pacemakers	Pacemaker Non-critically ill	ND	ND

Evidence Table 2. Non-comparison Studies: Part I
Shading indicates a methodology that appeared to be TEB, but insufficient description was provided to confirm that the method was definitely TEB.

Author Year UI	Design	Demographics, location, setting	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Ovsyshcher 1993b 93318751	Prospective	Location: USA Setting: clinic Mean age: 65 % Male: 70 Enrolled: 44	Implanted pacemakers:, including 24 DDD, 14 VVI	Pacemaker Non-critically ill	ND	ND
Ovsyshcher 1993a 93171482	Prospective	Location: USA Setting: clinic Mean age: 59 % Male: 64 Enrolled: 11	Implanted bipolar DDD pacemaker	Pacemaker Non-critically ill	ND	ND
Perko 2001 21163459	Prospective	Location: Denmark Setting: hospital Mean age: 66 % Male: 81 Enrolled: 16	Ischemic heart disease, scheduled for cardiac surgery, CABG with CPB and moderate hypothermia	Fluid management Critically ill	ND	ND
Scherhag 1997 97200346	Prospective	Location: Germany Setting: lab Mean age: 67.2 % Male: 56 Enrolled: 50	Suspected CAD	Hemodynamics Critically ill	≥50% stenosis confirmed by angiography	Poor echocardio-graphic image quality, valvular regurgitation, intracardiac shunts, low CO, pregnancy, extreme obesity, severe lung disease

Evidence Table 2. Non-comparison Studies: Part I

Shading indicates a methodology that appeared to be TEB, but insufficient description was provided to confirm that the method was definitely TEB.

Author Year UI	Design	Demographics, location, setting	Clinical condition	Patient population	Inclusion Criteria	Exclusion Criteria
Taler 2002 1201920	Prospective, randomized	Location: USA Setting: hospital Mean age: 66.1 % Male: 48% Enrolled: 117	Chronic resistant hypertension	Chronic hypertension Non-critically ill	Chronic refractory hypertension as defined by P>140/90 mmHg while taking >=2 antihypertensive medications in adequate doses	Unable to return monthly during the trial or identified as noncompliant with medications as the cause of resistant hypertension
Tatevossian 2000 11138876	Prospective,case series	Location: USA Setting: hospital Mean age: % Male: 85% Enrolled: 60	Severe trauma, ARDS	Hemodynamics Critically ill	Hypotension tachycardia estimated blood loss of >=2L	ND
Weinhold 1993 8241224	Prospective	Location: Germany Setting: hospital Mean age: 55.9 % Male: 82% Enrolled: 35	Heart transplant	Myocardial biopsy following heart transplant Critically ill	ND	Pneumothorax, periocardial effusion, aortic insufficiency, catecholamine support, ongoing rejection therapy, acute infection with high body temperature, or septicemia
Zerahn 1999 99394144	Prospective	Location: Denmark Setting: hospital Mean age: 67 % Male: 69 Enrolled: 16	Pleural effusions due to cardiac or malignant diseases – clinically stable	Hemodynamics Critically ill	ND	Pneumothorax

Evidence Table 2. Non-comparison Studies: Part II

Author, Year UI	Parameters Assessed	Bioimpedance System, Procedure, Equation	Author's Conclusion	Quality Criteria			
				Apparatus	Equation	Population	Condition
Arora 2001 11730085	Cardiac output. Stroke volume	BioZ	Known conditions that limit accuracy of BioZ-derived data are septic shock, aortic valve regurgitation, AMI, severe hypertension, tachycardia, patient's height <47in or >91in, weight <66lb or >342lb, patient movement.	Yes	No	Yes	Yes
Charach 2001 21288902	ECW	RS-205 (RS Medical Monitoring, Jerusalem)	RS-205 is suitable for monitoring patients at high risk for developing CPE and for monitoring the efficacy of their clinical management.	Yes	Yes	Yes	Yes
Conway 1996 96240987	Cardiac output	BoMed NCCOM3-R7s	BoMEd measures CO to high degree of repeatability but does not measure CO accurately. When compared with TD [but there is no data], limits of agreement range from acceptable +22% in otherwise healthy patients undergoing neurosurgery to an unacceptable ±50% in critically ill patients.	Yes	No	Yes	Yes
Critchley 1994 94153689	Cardiac output, arterial pressure, central venous pressure	NCCOM3-R7	TEB is valid for following trends in CO and for comparison between different treatments.	Yes	No	Yes	Yes
Greenberg 2000 12029190	Cardiac output	BioZ	BioZ values are reproducible on clinically stable heart failure patients treated in outpatient setting.	Yes	Yes	Yes	Yes
Haennel 1998 98415680	Cardiac output	Minnesota Impedance cardiograph, Model 304A. Sramek-Bernstein equation	Still controversial, TEB method provides simple reliable means of obtaining repeated hemodynamic data during upright exercise.	Yes	Yes	No	No

Four criteria that specifically relate to the scope of this report were used to assess whether there were methodological issues in the two types of studies. For both types of studies the following yes/no questions were developed and applied. Does the study provide:

1. A description of the apparatus/device to measure bioimpedance (including manufacturer and model)?
2. The equation used to calculate impedance measurements?
3. A description of the patients in the study, with clear inclusion and exclusion criteria?
4. A description of the medical and/or surgical condition and the indication for use of impedance cardiography monitoring in the patients enrolled?

Evidence Table 2. Non-comparison Studies: Part II

Author, Year UI	Parameters Assessed	Bioimpedance System, Procedure, Equation	Author's Conclusion	Quality Criteria: Apparatus	Equation	Population	Condition
Jonsson 1995 95407259	Fluid balance	Minnesota Impedance Cardiograph, model 304A	TEB was the only continuously monitored variable that predicted an elevated postoperative fluid balance.	Yes	Yes	No	Yes
Kasznicki 1993 93383616	Stroke Index, cardiac index, heart rate	RM-90/1 K	The authors consider as crucial the monitoring of the cardiovascular system in cancer patients and that it is convenient to use impedance cardiography for this purpose.	Yes	No	Yes	Yes
Ovsyshcher 1992 93065475	Cardiac output	NCCOM-R7 and Pacemate module. Nyboer equation modified by Sramek-Bernstein	The precision of TEB in all pacing modes indicates that detected changes of SV, CO >7% on serial measurements represent true hemodynamic alterations with 95% confidence.	Yes	Yes	No	No
Ovsyshcher 1993b 93318751	Cardiac output	NCCOM-R7, Kubicek equation, modified by Sramek	The precision of this noninvasive method, in conjunction with its ease, makes it well suited for assessing relative effects of acute physiologic or programming changes on CO.	Yes	Yes	No	No
Ovsyshcher 1993a 93171482	Cardiac output	Minnesota Impedance Cardiograph, Model 304B. Nyboar Equation modified by Kubicek	TEB enables easy, highly reproducible, serial, noninvasive assessments of CO of pacemaker patients and can detect clinically significant hemodynamic changes. Hemodynamic findings applied to pacemaker are consistent with data previously obtained using other techniques. Measurements can facilitate optimal programming in pacemaker patients.	Yes	Yes	Yes	No

Four criteria that specifically relate to the scope of this report were used to assess whether there were methodological issues in the two types of studies. For both types of studies the following yes/no questions were developed and applied. Does the study provide:

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4. A description of the medical and/or surgical condition and the indication for use of impedance cardiography monitoring in the patients enrolled?

Evidence Table 2. Non-comparison Studies: Part II

Author, Year UI	Parameters Assessed	Bioimpedance System, Procedure, Equation	Author's Conclusion	Quality Criteria: Apparatus	Equation	Population	Condition
Perko 2001 21163459	Cardiac index, ECW	CDM 3000 Hemodynamic Monitor, CardioDynamics International, San Diego – 62 frequencies 4-1000 kHz	Accuracy of TEB's estimates warrant further investigation. Estimation of actual hydration status cannot be assessed because body impedance values are multifactorial. A small change in distance between electrodes or replacement of electrodes with ones of different impedance can induce essential alterations.	Yes	No	No	Yes
Scherhag 1997 97200346	Cardiac index, stroke volume index	CardioScreen, medic GmbH, Germany. 1 mA current, 100 KHz	Computerized TEB allows cost- and time-effective continuous monitoring during pharmacologic echocardiographic stress testing and provides useful complementary info regarding LVF.	Yes	No	Yes	Yes
Taler 2002 1201920	Stroke volume, cardiac output, cardiac index, systemic vascular resistance	BioZ, Z MARC algorithm	The study findings "argue that measurement of hemodynamic and impedance parameters guide selection of antihypertensive therapy more effectively than clinical judgment alone for patients resistant to empiric therapy."	Yes	No	Yes	Yes
Tatevossian 2000 11138876	Cardiac index	IQ System, Wantagh Inc., Bristol, PA 100-KHz, 4-mA current	"Emergency patients can be monitored with noninvasive techniques early in their hospital course."	Yes	No	Yes	Yes

Four criteria that specifically relate to the scope of this report were used to assess whether there were methodological issues in the two types of studies. For both types of studies the following yes/no questions were developed and applied. Does the study provide:

1. A description of the apparatus/device to measure bioimpedance (including manufacturer and model)?
2. The equation used to calculate impedance measurements?
3. A description of the patients in the study, with clear inclusion and exclusion criteria?
4. A description of the medical and/or surgical condition and the indication for use of impedance cardiography monitoring in the patients enrolled?

Evidence Table 2. Non-comparison Studies: Part II

Author, Year UI	Parameters Assessed	Bioimpedance System, Procedure, Equation	Author's Conclusion	Quality Criteria: Apparatus	Quality Criteria: Equation	Quality Criteria: Population	Quality Criteria: Condition
Weinhold 1993 8241224	Cardiac index, end-diastolic volume index, stroke volume, ejection fraction, acceleration index	NCCOM3-R7 (Osypka GmBH, Germany)	"Besides routinely performed endomyocardial biopsies, the measurement of thoracic electrical bioimpedance represents a noninvasive and ideal monitoring technique for diagnosis of acute heart rejections during outpatient follow-up of heart transplant patient	Yes	No	Yes	Yes
Zerahn 1999 99394144	Stroke volume, cardiac output	BoMed NCCOM-3 2.5 mZ at 70 kHz	Relative increase in baseline impedance was twice as high for cancer patients as for patients with heart failure. There is a close correlation between drying effect of thoracentesis and changes in baseline impedance of the thorax and subsequent improvement in pulmonary airflow, lung volume, lung diffusing capacity.	Yes	Yes	Yes	Yes

Four criteria that specifically relate to the scope of this report were used to assess whether there were methodological issues in the two types of studies. For both types of studies the following yes/no questions were developed and applied. Does the study provide:

1. A description of the apparatus/device to measure bioimpedance (including manufacturer and model)?
2. The equation used to calculate impedance measurements?
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4. A description of the medical and/or surgical condition and the indication for use of impedance cardiography monitoring in the patients enrolled?

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