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POSITION STATEMENT OF THE MALDIVIAN MEDICAL ASSOCIATION

POSITION STATEMENT FOR USE OF ENHANCED EXTERNAL COUNTERPULSATION (EECP) FOR CHRONIC STABLE ANGINA OR CONGESTIVE HEART FAILURE

Section: Medicine
Policy No: 02/08
Approved Date: 27 March 2008



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POSITION STATEMENT OF MALDIVIAN MEDICAL ASSOCIATION

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Topic: Enhanced External Counterpulsation (EECP) for Chronic Stable Angina or Congestive Heart Failure

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AIDE MEMOIRE

MMA POSITION STATEMENT PURPOSE

The purpose of the MMA position statements is to promote evidence based cost-effective and safe health care for the people of the Maldives by:

- Educating doctors regarding optimal methods of diagnosis and treatment, by providing the latest information available on specific topics.
- Ensuring the availability of evidence based specialized health care by advising the government, its agencies and the public regarding issues which have the potential to affect health care and delivery and to minimize harm to patients.
- Actively supporting doctors in their individual and group efforts to achieve these goals.

The purpose of this position statement is to provide the position of MMA on the use of EECP. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care and comply with evidence based best practices in Medicine when providing medical care to the Maldivian population.

This Position statement has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and the Maldivian government approval status for EECP.



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Description

Enhanced external counterpulsation (EECP) is based on the concept of counterpulsation and consists of 3 pairs of pneumatic cuffs placed around the lower extremities at the calves, lower thighs, and upper thighs. An electrocardiographic trigger is used to sequentially inflate the cuffs, starting at the calves, during onset of diastole and simultaneously deflate all cuffs before onset of systole. A standard course of EECP therapy consists of 35 one-hour sessions during a 7-week period. The mechanism by which EECP improves anginal symptoms is poorly understood but may involve nonspecific placebo effects and various hemodynamic factors. Hemodynamically, EECP acts like intra-aortic balloon counterpulsation by augmenting diastolic blood flow in multiple vascular beds, including the coronary arteries, and by reducing cardiac afterload (22). Endothelial function has been shown to improve after a course of EECP therapy (23). In addition, EECP therapy has been associated with the release of growth factors, such as vascular endothelial growth factor (VEGF) that promotes the formation of collaterals in the coronary circulation (24). Finally, EECP therapy may result in a “training effect” by decreasing peripheral vascular resistance in the same manner as physical exercise (15).

MMA POLICY

INDICATIONS for EECP

Individuals who have disabling, chronic, stable angina, (defined as Class III or Class IV angina by the New York Heart Association* or equivalent) AND fully meet the criteria detailed in Section I and Section II are candidates in whom EECP may be considered as medically necessary.

SECTION I

Candidates for EECP are individuals REFRACTIVE to optimal medical therapy AND not readily amenable to surgical interventions such as percutaneous transluminal coronary angioplasty (PTCA) or cardiac bypass surgery (CABG). Unsuitability to better options of PTCA or CABG could be due to any of the following:

1. Their condition is inoperable; or
2. They are at high risk of operative complications or postoperative failure; or
3. Their coronary anatomy is not readily amenable to such procedures; or
4. They have comorbid states which create excessive risk.

SECTION II

The patient does not have any of the following CONTRAINDICATIONS to therapy:



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1. Cardiac catheterization within 2 weeks (may cause bleeding at the femoral puncture site); or
2. Arrhythmias such as atrial fibrillation, atrial flutter, ventricular tachycardia, and frequent premature ventricular beats (might interfere with the device's triggering mechanism); or
3. Aortic insufficiency (regurgitation might prevent diastolic augmentation); or
4. Peripheral vascular disease and/or phlebitis (increased risk of thromboembolus); or
5. Deep vein thrombosis, varicosities and stasis ulcers; or
6. Severe hypertension, greater than 180/110 mmHg, (treatment could produce diastolic blood pressure above acceptable limits); or
7. Bleeding diatheses, Coumadin (warfarin) therapy with PT greater than 15 seconds and/or INR greater than 2.0 (cuffs could cause bleeding in legs); or
8. Pregnant women and women of childbearing potential who do not employ a reliable contraceptive method (possible danger to the fetus).

SECTION III

A single course of treatment consists of a total of 35-36 hours of EECP; treatment is administered for one to two hours daily, 5 days a week, for approximately 3½ to 7 weeks.

REPEAT COURSE

A repeat course of therapy is considered medically necessary in those individuals with chronic stable angina who have objectively demonstrated a response to EECP. This would include those patients who demonstrate one or more of the following:

1. Early improvement in radionuclide stress perfusion imaging compared to a pre-EECP baseline; or
2. Reduction in antianginal medication use; or
3. Improvement in exercise tolerance.

*New York Heart Association (NYHA) definitions:

Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.

Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.



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SECTION IV

Investigational and Not Medically Necessary:

EECP is considered investigational and not medically necessary for the treatment of all conditions not addressed above, including, but not limited to, congestive heart failure (CHF).

SCIENTIFIC BACKGROUND

Treatment of Chronic Stable Angina

1. TEC ASSESSMENT

This MMA policy is based on a 1999 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment on EECP for chronic stable angina which was updated with 2002 and 2005 TEC Assessments. All three concluded the EVIDENCE WAS INSUFFICIENT to determine whether EECP improved the net health outcome or is as beneficial as any established alternatives in patients with chronic stable angina.

In particular, the 2005 TEC Assessment (2) offered the following observations and conclusions regarding EECP for the treatment of chronic stable angina:

- There is INSUFFICIENT EVIDENCE to draw conclusions about the benefits of EECP.
- The results of the single randomized, controlled trial, the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) MUST BE INTERPRETED WITH CAUTION IN VIEW OF THE HIGH SUBJECT DROPOUT RATE AND UNCERTAINTY REGARDING THE CLINICAL SIGNIFICANCE OF THE REPORTED IMPROVEMENT IN PHYSIOLOGIC MEASURES, especially when intent-to-treat analysis is applied. (3,4)

The MUST-EECP trial applied a randomized, controlled, double-blinded protocol that compared active treatment to placebo (inactive counterpulsation sham treatment) among 139 patients with Canadian Cardiovascular Society (CCS) Classification Scales class I-III chronic, stable angina. (3) The CCS classification scales are a functional assessment tool based on the level of exertion that elicits symptoms. Four outcomes were examined:

1. Self-reported frequency of angina, analyzed two ways
2. Self-reported use of on-demand nitroglycerin
3. Exercise duration tolerance testing



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4. Time to exercise-induced ischemia (defined as time to depression of \geq 1mm in the ST segment on electrocardiogram)

All patients underwent the same 35-hour protocol, followed by an exercise tolerance test within one week of completion of therapy. FOLLOW-UP BEYOND THE TREATMENT PERIOD WAS NOT CONDUCTED.

Intention-to-treat analyses were reported for the angina count and nitroglycerin usage outcomes only. There was a statistically significant difference ($p=0.01$) between groups in the change in time to \geq 1 mm ST segment depression. Patients in the EECp group had an average difference of 37 seconds longer time to ST segment depression compared to the sham-treated group. There was no significant difference between treatment groups in the change in exercise duration from baseline to the post-treatment period ($p<0.31$). In addition, there were no statistically significant differences between groups with respect to angina counts ($p<0.09$) or nitroglycerin use ($p>0.1$).

In addition to a number of procedural restrictions found in the design, implementation, and reporting of this study, the RESULTS THEMSELVES ARE OF QUESTIONABLE SIGNIFICANCE clinically. Of the four relevant endpoints, only the time to ST segment depression was statistically different in the EECp group compared to the sham-treated group. The clinical significance of a 37-second improvement in time to ST segment depression is unknown. Given that it occurred while the other three endpoints were statistically unchanged with therapy, the difference does not suggest a marked improvement clinically. THAT BOTH GROUPS SHOWED INCREASED EXERCISE DURATION SUGGESTS A DEGREE OF PLACEBO EFFECT; exercise duration possesses a motivational component that time to S-T segment depression does not. Although the MUST-EECP results are consistent with observational studies, and despite respectable effort in conducting the study, the randomized controlled trial DOES NOT PROVIDE CONVINCING EVIDENCE SUPPORTING THE EFFICACY OF EECp.

Arora and colleagues published a 12-month follow-up study to the MUST-EECP trial. (4) However, ONLY 71 (54%) OF THE ORIGINAL 139 SUBJECTS WERE INCLUDED IN THE STUDY. Subjects treated with EECp reported greater improvement in several quality of life scales. Nevertheless, BECAUSE OF DATA LIMITATIONS, THESE FINDINGS COULD NOT BE CORRELATED WITH TREATMENT RESPONSES REPORTED IN THE FIRST STUDY. The findings are further imperfect by the SMALL SAMPLE SIZE AND POTENTIALLY BIASED SAMPLE OF THE ORIGINAL SUBJECT POOL.

- COMPARATIVE STUDIES OF EECp DO NOT ADDRESS THE HARD OUTCOMES OF CARDIAC DEATH OR RECURRENT CARDIAC EVENTS such as myocardial infarction and revascularization



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procedures.(5,6)

- Several case series and registry-based studies have reported the outcomes of large numbers of patients treated in a number of different institutions. There are several problems with this kind of evidence. These studies, while contributing to the body of knowledge of EECP, do little to address the efficacy or durability of EECP treatment. **THE LACK OF COMPARISON GROUPS MAKES IT IMPOSSIBLE TO RULE OUT EITHER PLACEBO-EFFECT OR SPONTANEOUS RECOVERY AMONG PATIENTS WITH MILDER DISEASE.** Furthermore, it is not known what proportion of patients initially starting EECP treatments is actually included in the final analyses.

Two-year clinical results from registry data were reported by Soran and colleagues in 2006 (7); however, as noted in the 2005 TEC Assessment, **THE LACK OF A COMPARISON GROUP PRECLUDES THE ABILITY TO REACH SCIENTIFIC CONCLUSIONS FROM THIS DATA.**

A 2002 practice guideline published jointly by the American College of Cardiology and the American Heart Association concurred with the above TEC Assessment, stating, “...ADDITIONAL CLINICAL TRIAL DATA ARE NECESSARY BEFORE THIS TECHNOLOGY CAN BE RECOMMENDED DEFINITELY.” (8)

In 2006, two prospective cohort studies (N=55 and N= 61) with one year outcomes found enhanced CCS classification as the main outcome, which persisted for one year in 79% and 78% of patients in the respective studies.(9,10) Both studies had higher rates of treatment completion and follow-up than the previously reported (registry) studies of long-term outcomes. These studies address the need for data regarding treatment durability, but their **SINGLE-ARM DESIGN DOES NOT ALLOW INFERENCES WITH REFERENCE TO IMPROVEMENT IN NET HEALTH OUTCOMES.**

Although one trial involving a sham-controlled arm supports the use of EECP therapy, further larger-scale sham-controlled studies regarding the effectiveness of EECP therapy and its mechanisms of action need to be conducted.(26) Enhanced external counterpulsation therapy is US FDA approved and is recommended by the American Heart Association as a potential therapy for **REFRACTORY ANGINA** under approved circumstances. It has a class IIb indication (usefulness/efficacy is less well established).(8)

An updated search of the MEDLINE database through March 16, 2008 failed to identify any new data which alter the above conclusions on the use of EECP in refractory angina, which MMA endorses as a valid assessment of scientific data.



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Treatment of Congestive Heart Failure

In June 2002, Vasomedical received US FDA clearance to market the EECP Therapy System Model for the treatment of congestive heart failure. This expanded US FDA approval was granted through the 510(k) process and was based on the outcomes reported in multicenter, single center and registry-based clinical investigations. The 510(k) summary states that objective measures such as peak oxygen consumption, exercise duration, and pre-load adjusted maximal left ventricular power are improved following EECP therapy, as well as subjective measures of patient response to therapy, such as quality of life and functional ability measures. (11) However, it should be emphasized that NO CLINICAL DETAILS OF THESE STUDIES ARE PROVIDED IN THE US FDA SUMMARY, AND THESE STUDIES ARE NOT CONTROLLED TRIALS.

The 2005 TEC Assessment (2) included congestive heart failure in the analysis and concluded THE EVIDENCE SUPPORTING THE ROLE OF EECP AS AN EFFECTIVE TREATMENT FOR HEART FAILURE IS LACKING IN BOTH QUANTITY AND QUALITY.

The TEC Assessment further offered the following observations:

- There were few published controlled trials weigh against EECP to usual treatment. The TEC Assessment did evaluate data from the PEECH trial (Prospective Evaluation of EECP in Congestive Heart Failure). Final results of the PEECH trial were published in 2006, (13). This randomized, multicenter study compared EECP to usual care in 187 optimally medically managed patients with NYHA functional class II/III heart failure of ischemic or idiopathic etiology, with ejection fraction $\leq 35\%$. THE RESULTS OF THE PEECH TRIAL, FOUND STATISTICALLY IMPROVED, BUT MODEST, CHANGES IN EXERCISE DURATION, AND IMPROVED FUNCTIONAL CLASSIFICATION BUT NOT IN QUALITY OF LIFE OR PEAK OXYGEN UPTAKE. (12)
- Three studies from the international EECP Patient Registry (IEPR) of patients with angina and concomitant heart failure showed the feasibility of using EECP for the treatment of heart failure. (14-16) Without a doubt, the main reason of these studies was to justify studying EECP for this indication. With the exception of major adverse cardiac outcomes, THE IEPR REGISTRY OUTCOMES ARE PERTINENT TO ANGINA RATHER THAN TYPICAL HEART FAILURE OUTCOMES; THUS, THESE RESULTS CONTRIBUTE LITTLE TO THE BODY OF EVIDENCE ON EECP AS A TREATMENT OF HEART FAILURE.
- A single-arm study by Soran and colleagues (17) indicated that patients responded with some restitution, but the LACK OF A COMPARISON ARM PRECLUDED INFERENCES ABOUT THE TRUE EFFECTS OF THERAPY.



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- Treatment durability for either angina or heart failure has not been addressed with long-term studies. Therefore, THE EVIDENCE WAS INSUFFICIENT TO DETERMINE WHETHER EECp IMPROVES THE NET HEALTH OUTCOME OR IS AS BENEFICIAL AS ANY ESTABLISHED ALTERNATIVES IN PATIENTS WITH CHRONIC STABLE HEART FAILURE.

MUST EECp STUDY

STUDY DESIGN

MUST-EECP study (multicenter study of enhanced external counterpulsation), is the foremost and ONLY multicentre, prospective, randomised, blinded, placebo (sham) controlled trial on the subject. In this trial, conducted in seven centres, 139 outpatients with angina, documented coronary artery disease, and positive exercise treadmill test were randomly assigned to receive 35 hours of active (n = 72 patients) or inactive (n = 67 patients) counterpulsation over a period of four to seven weeks. Fifty nine patients in the active and 65 in the inactive group completed the study.

STUDY OUTCOME

The outcome was measured in terms of exercise duration, time to ≥ 1 mm ST segment depression, average daily anginal attacks, and glyceryl trinitrate use. Patients undergoing active counterpulsation had a significant increase in time to ≥ 1 mm ST segment depression and a decrease in anginal episodes, but there was no significant improvement in the duration of exercise or glyceryl trinitrate usage.

ADVERSE EVENTS

More patients in the active counterpulsation group of MUST-EECP study experienced adverse events (55% v 26%, $p < 0.001$), including device related adverse experiences (leg pain, back pain, skin abrasion, bruising, blistering, oedema, paraesthesia). Leg discomfort was the most frequent device related adverse effect. The non-device related adverse events were minor and generally tolerated.

LIMITATIONS

1. **Small trial:-** The MUST-EECP was a SMALL TRIAL considering the prevalence and subjective nature of the anginal symptoms and,



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therefore, was NOT POWERFUL ENOUGH TO RECOMMEND EECP FOR ROUTINE USE IN PATIENTS WITH ANGINA PECTORIS.

- 2. Cautious patient selection process:-** Furthermore, THE PATIENT SELECTION FOR THE TRIAL WAS VERY CAUTIOUS as is evident from the long list of exclusion criteria, which further limit the use of this technique on a wide scale. The exclusions were: myocardial infarction or coronary artery bypass graft in the preceding three months; cardiac catheterisation in the preceding two weeks; unstable angina; overt congestive heart failure or left ventricular ejection fraction < 30%; significant valve disease; blood pressure > 180/100 mm Hg; permanent pacemaker or implantable defibrillator; non-bypassed left main stenosis > 50%; severe symptomatic peripheral vascular disease; varicosities; deep vein thrombosis, phlebitis or stasis ulcer; bleeding diathesis or warfarin use with international normalised ratio of prothrombin time > 2.0; atrial fibrillation or frequent ventricular premature beats that would interfere with EECP triggering; baseline ECG abnormalities that would interfere with interpretation of exercise ECG; pregnancy or childbearing potential in women; and subjects unable to undergo treadmill testing.
- 3. Lack of important data:-** Another shortcoming of the MUST-EECP trial is LACK OF DATA ON THE RATE–PRESSURE PRODUCT AT THE TIME OF 1 MM ST SEGMENT DEPRESSION BEFORE AND AFTER TREATMENT.

FOLLOW UP

Follow up analysis of patients in the MUST-EECP trial at one year showed greater improvement in the health related quality of life measures (perform activities of daily living, ability to work, bodily pain, confidence in health, energy, ability to engage in social activities with family and friends, anxiety and depression, and quality of life issues from the effects of angina on health and functioning) in the active treatment group.

HOWEVER IT WAS NOT REPORTED WHETHER THE DECREASE IN ANGINAL EPISODE REPORTED AT THE END OF 4–7 WEEKS OF ACTIVE TREATMENT WITH COUNTERPULSATION PERSISTED AT ONE YEAR.(3) ALSO, IT WAS NOT REPORTED WHETHER THE DECREASE IN ANGINA DURING THE ACTIVE TREATMENT PERIOD WAS CORRELATED WITH THE IMPROVED HEALTH



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RELATED QUALITY OF LIFE MEASURES AT ONE YEAR.

AHA / ACC POSITION

A 2005 practice guideline published jointly by the American College of Cardiology and the American Heart Association on the use of EECp were in accord with the above TEC Assessment, stating, “UNTIL MORE DATA ARE AVAILABLE, ROUTINE USE OF THIS THERAPY CANNOT BE RECOMMENDED FOR THE MANAGEMENT OF PATIENTS WITH SYMPTOMATIC REDUCED LVEF.” (18)

ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina , mentions EECp as an alternative Therapy for Chronic Stable Angina IN PATIENTS REFRACTORY TO MEDICAL THERAPY WHO ARE NOT CANDIDATES FOR PERCUTANEOUS INTERVENTION OR REVASCULARIZATION, in class II b with the level of evidence: B. (19). There was no change in this stand by ACC or AHA in their 2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the Management of Patients With Chronic Stable Angina(20).

ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction mentions the EECp as a less extensively studied therapy for this group of patients (21).



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MMA CONCLUDES

EECP use should be LIMITED to patients with debilitating (functional class III and IV) refractory angina who are not candidates for revascularization, are symptomatic despite taking maximal anti-anginal pharmacotherapy, and have no contraindications to EECP use. EECP is considered investigational and not medically necessary for the treatment of all conditions not addressed above.

Even though data indicate an improvement in angina in selected patients undergoing EECP, the role of EECP in the treatment algorithm of angina pectoris has not yet been well defined. Large scale trials and long term data are needed to incorporate this technique into the standard treatment recommendations for angina pectoris.

MMA endorses the stand taken by the AHA and ACC that until more data are available, routine use of this therapy cannot be recommended for the management of patients with symptomatic reduced LVEF.

MMA concluded this position after an updated search of the MEDLINE database through March 16, 2008 failed to identify any new data concerning EECP as a reliable treatment of heart failure or angina except for those mentioned in the final conclusions of this report.



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