CHAPTER III: METHODOLOGY

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3.1 Study Design

I) Study Design

It was a Single Blinded Randomized Controlled Trial. The protocol of proposed work was submitted to the Manipal University and consequently Institutional Ethical Committee (IEC) of two proposed centers; Kasturba Hospital in India and Golsar Hospital in Iran approved the study. Ethical clearance was obtained from both centers to conduct the study.

II) Study Centers

This study was conducted at two centers during 3 time intervals:

- Center I; India: Kasturba Hospital; Manipal:  
  Period I: April 2008 to May 2009  
  Period II: March 2010 to November 2010.

- Center II; Iran: Golsar Hospital; Rasht: From July 2009 to February 2010

Eligible patients who met inclusion criteria and given written informed consent and agreed to participate in the study were randomly assigned to Hospital-based, or Home-based or Control group by means of block randomization with block size of six. The cardiologists who evaluated the primary outcome variables of (LVEF & Functional capacity) were masked to the patients’ assignment.

Pilot study: A pilot study was performed on 10 subject in order to establish a uniform way of prescribing exercise intensity in Home-based group. In addition, an educational program by means of a flyer was produced and translated to local languages to deliver to the patients and teach the patient.(Appendix V)

III) Sample Size

Sample size was decided based on Quality Of Life; SF-36 outcome. The sample size calculation was done based on following formula: 103
\[ n = \frac{2[Z(\frac{\alpha}{m}) + Z(\beta)]\sigma^2}{d^2} \]

Where \( n \) is the number of subjects per each group, \( m \) is the number of groups. Since there were 3 groups of intervention in the present study, keeping the \( \alpha=0.05 \), we used Bonferoni adjustment for \( Z\alpha \) and we kept \( Z(\frac{\alpha}{3}) \) in the formula. While keeping the power of study at 90\%, corresponding \( Z_{\alpha/3} \) and \( Z\beta \) are substituted. \( (d) \) is the standard deviation of the variable which we used results of previous studies in the same center and same type of patients (Milton, Maiya, et al, 2008)\(^{104}\) and compared with the results of our pilot study which both were comparable. According to our pilot study on 10 subjects we had found almost similar SD of 9. And \( \sigma \) is the acceptable clinical difference of the variable which was decided based on the previous studies\(^{24, 104}\) and clinical experts. We considered at 6.6 scores improvement in the outcome as previous study in the same population.\(^{104}\) Therefore:

\[ Z_{\alpha/3} = 2.12, \]
\[ Z_\beta = 1.28 \]
\[ d = 6.6, \]
\[ \sigma = 9 \]

\[ n = \frac{2[Z(\frac{\alpha}{3}) + Z(\beta)]^2 \sigma^2}{d^2} = 43.62 \approx 44 \]

The sample needed for 3 groups will be 132. Considering a 25 % drop out rate,

The needed sample size for total study calculated:

\[ N = \frac{N_1}{1-AR} = \frac{132}{1-0.25} = 176 \]

Thus, a total of 180 (60 per group) subjects were enrolled to the study and randomly allocated to 3 groups of Hospital, Home-based or control group.
3.2 Subjects

After approval from institution and University research cell, post-coronary event patients (Acute Coronary Syndrome) who treated surgically (CABG or PTCA) or conservatively from mentioned centers were screened for eligibility. Recruited patients who met the inclusion criteria and given written informed consent enrolled in the study. A total of 180 subjects treated surgically or conservatively were enrolled in the study and were allocated into either experimental group (Hospital versus Home-based group) or Control group by means of block randomization with block size of 6.

3.3 Inclusion criteria

- Diagnosed CAD – post-coronary-event patients (Acute coronary syndrome at first episode) with maximum of one month post discharge at the time of entry to cardiac rehabilitation; treated surgically or conservatively, and stratified as low and moderate risk
- Age 35 to 75 years

3.4 Exclusion criteria

- High risk group (based on AACVPR-99 guidelines)[Appendix I]
- Systemic, orthopedics and/or neurological problems restricting participation in aerobic exercises program.
- Patients who are contraindicated for stress testing and exercise training.
- Patients not willing to participate

3.5 Outcomes

- Quality of Life –SF-36 v2
- Left Ventricular Ejection Fraction – Transthoracic Echocardiography
- Functional Capacity – Symptom limited Bruce Protocol
- Skinfold measurements, BMI & Waist circumference
3.6 Instruments

- **Training Treadmill** (In center I: STAYFIT – SF i6 MTM, In center II: H/P/Cosmos Mercury Med 4) – Figure 3.1
- **Exercise Test Machine** (In center I: Quinton TM-65, In Center II: MEDSET- Medizintechnik) – Figure 3.6&7
- **Echocardiography machine**: (In center I: General Electric-Vivide 3, In center II, Mylab-60) - Figure 3.4&5
- **SF-36 V2** health-related QOL questionnaire (Appendix II)
- Skinfold Caliper- Figure 3.8
- 3 lead ECG Monitor (In center I: L&T Medical-7147, In Center II: ECG Monitoring was provided by treadmill) – Figure 3.2
- BP Apparatus - Figure 3.1
- Weighing Scale
- Measuring tape
- RPE Scoring system (Appendix III)

![Figure 3.1. A. ECG Monitor (L& T Medical- 7147), B. BP Apparatus, C. Training Treadmill (Center I: StayFit i6 MTM )](image-url)
Figure 3.2. ECG Monitor – L&T Medical 7147

Figure 3.3. Training treadmill (Center II: H/P Cosmos Mercury Med 4)

Figure 3.4. Echo Cardiography Machine (Center II: Mylab 60)  
Figure 3.5. Echo Cardiography Machine (Center I: General Electrics Vivide 3)
Figure 3.6. Exercise Test Machine: (Center II: MEDSET- Medizintechnik)

Figure 3.7. Exercise Test Machine: (Center I: Quinton TM-65)

Figure 3.8. Skinfold Caliper
3.7 Procedure

I) Ethical Clearance

Complete proposal of the work was submitted to the Institutional Ethical committee (IEC) of both centers. IEC of both centers approved the proposal to conduct the study. (Appendix XII)

II) Screening & Randomization of patients

The research scholar visited both centers at different time intervals as mentioned in section 3.1. Low and moderate risk CAD patients (Acute Coronary Syndrome) treated surgically or conservatively were screened for inclusion criteria. Complete information about the study was explained to patients and eligible patients after giving written informed consent (Appendix IV) underwent symptom-limited exercise test for risk stratification (AACVPR-99) as well as evaluation of functional capacity at baseline. Then, enrolled patients were assigned to one of three groups; Hospital-based CR, Home-based CR or Control group by means of block randomization.

Random numbers generated by using “Stat. Direct.” Software using block size of 6. Thus, 10 blocks were selected randomly to allocate 180 subjects into 3 groups.

Flowchart of the study according to the CONSORT guidelines is presented. (Figure 3.9)
III) Baseline Data Collection

Base line data included the primary outcomes (Quality of Life in terms of SF-36 V2, Functional Capacity in terms of Symptom-limited Bruce exercise test, and Left Ventricular Ejection Fraction by means of transthoracic echocardiogram) as well as demographic information (eg. Age, gender, living arrangements, highest level of education completed, socioeconomic status, and employment status), medical history (including history of myocardial infarction) and risk factors profile (including dyslipidemia, smoking status and diabetes) height, weight, and waist circumference were recorded. The primary out comes
like base line MET level, ejection fraction, and quality of life by SF-36 questionnaire were taken before the commencement of the study intervention.

### IV) Study Intervention: Exercise-based CR

The ACSM guidelines were used for principle of exercise prescription for both experimental groups. The exercise prescriptions were based on peak HR obtained during the symptom limited graded exercise tolerance test by using Bruce protocol. Karvonen Formula was used to calculate target heart range for the intensity of exercise for both experimental groups. In addition, Rating of Perceived Exertion (RPE) also was explained as subjective criteria for intensity of exercise.

All subjects recruited were given orientation to the program. A session of informal health education about their condition and disease were given by the physiotherapists to the patients and to their family members. Risk factors modifications advice according to the risk factors each patient, life style modification, and smoking cessation advice were given prior to the start of rehabilitation program to study groups. Awareness about cardiac rehabilitation, exercise program, adherence to the program and its benefits which they undergo were given to both Hospital and Home-based groups. Both experimental groups underwent 12 weeks Cardiac Rehabilitation either in the form of Hospital-based or Home-based program.

### A) Group IA. Hospital-based Group

The Hospital-based group underwent structured, supervised exercise training program for a period of three months. The program led directly by qualified physiotherapist; research scholar. The exercise program consisted of following components according to ACSM-2006 guidelines

- **Warm up**: 5-10 minutes (Breathing exercise, stretching exercise and walking on treadmill)
• **Training:**

  - **Mode:** Graded Aerobic training on treadmill
  
  - **Intensity:** 40-70% of HRmax (graded intensity) using Karvonen Formula:

    **Karvonen Formula:** \( \text{THRR} = [(\text{HRmax} - \text{RHR}) \times (40\%-70\%)] + \text{RHR} \)

    Where THRR: Target Heart Rate Range
    
    HRmax: Maximum HR achieved on exercise test
    
    RHR: Resting Heart Rate

    *Even though VO2max is a gold standard in prescribing exercise intensity, due to higher cost, it is not practiced regularly. We used more practical way of “Karvonen Formula” to prescribe exercise intensity. According to direct correlation of Rating of Perceived Exertion (RPE) with VO2max, we also explained about RPE while prescribing exercise intensity.*

  - **Duration:** 20-40 minutes

• **Cool down:** 5-10 minutes (active recovery)

• **Frequency:** at least 3 days/week

**Exercise intensity progression**

Throughout the 12 weeks of training, as patients became more conditioned to the exercise program, progression of the exercise intensity was done as needed. As the RPE falls with improving fitness the intensity of exercise was increased at 5 to 10 percent of the maximum heart rate and by maintaining RPE of 11 to 14 throughout the 12 weeks of duration. For the first four weeks we kept exercise training within the duration of 15 to 20 min. and from 5th to 8th week increased to 20 to 30 minutes, and the final 9th to 12th week duration was increased to 30 to 40 minutes. (Figure 3.10)
### B) Group IB. Home based Group

Exercise component of cardiac rehabilitation program for Home-based group was an individualized program of aerobic exercises; preferably brisk walking. Initial session of exercise prescription and training was given in the department under supervision and direction of qualified physiotherapist; research scholar. Then the program protocol was given to the patient to continue at home for 12 weeks. Patients also were given training in palpating the pulse and calculating the heart rate, and to rate the Borg’s Rating of Perceived Exertion (RPE) of 11 to 14. The exercise program consisted of following components for Home-based group: (According to ACSM guidelines-2006)$^{94}$

- **Warm up**: 5-10 minutes including Breathing exercise, stretching exercise and gentle active exercise to larger muscle groups like lower limb and trunk muscles

- **Training**:
  - **Mode of Exercise**: Brisk walking was the preferred mode of exercise.
  - **Intensity**: 40-70 % of HRmax (graded intensity) using Karvonen Formula:

![Figure 3.10. Progression of exercise in Hospital-based CR based on Intensity & time during 12 weeks](image)
Karvonen Formula: \[ \text{THRR} = [(\text{HR}_{\text{max}} - \text{RHR}) \times (40\%-70\%)] + \text{RHR} \]

Where THRR: Target Heart Rate Range

HRmax: Maximum HR achieved on exercise test

RHR: Resting Heart Rate

*Even though VO\textsubscript{2}max is a gold standard in prescribing exercise intensity, due to higher cost, it is not practiced regularly. We used more practical way of “Karvonen Formula” to prescribe exercise intensity. According to direct correlation of Rating of Perceived Exertion (RPE) with VO\textsubscript{2}max, we also explained about RPE while prescribing exercise intensity.

- **Duration:** 20-40 minutes

- **Cool down:** 5-10 minutes (active recovery) including stretching exercises and gentle active exercise or walking with slow pace.

**Frequency:** at least 3 days per week

In Home-based group in order to maximize the uniformity of exercise with Hospital-based group, exercise intensity was calculated based on Karvonen formula in terms of THRR. Since teaching the patient to control the HR while doing exercise at home practically is difficult, an alternative method have been used by converting the THRR into speed of walk. In this group, after determining safe HR zone, initial session carried out in the center to achieve the THRR of the individual patient and corresponding achieved speed was recorded as guidance for patient. Instruction to patient was given in terms of a particular distance to cover in particular time duration to achieve the calculated speed.

According to direct correlation of RPE with VO\textsubscript{2}max, in the present study, for ease of patients, we also explained about RPE while prescribing exercise intensity.
**Exercise intensity progression**

As patients became more conditioned to the exercise program, progression of the exercise intensity was done as needed. As the RPE falls with improving fitness the intensity of exercise was increased at 5 to 10 percent of the maximum heart rate and by maintaining RPE of 11 to 14 throughout the 12 weeks of duration. For the first four weeks they did exercise training within the duration of 15 to 20 min and from 5\textsuperscript{th} to 8\textsuperscript{th} week increased to 20 to 30 minutes, and the final 9\textsuperscript{th} to 12\textsuperscript{th} week duration was increased to 30 to 40 minutes. (Figure 3.11)

![Diagram showing exercise intensity progression](image)

**Figure 3.11.** Progression of exercise in Home-based CR during 12 weeks.

Home-based group patients were received a Exercise log book for recording the exercise they performed, and regularly contacted by phone every two weeks to find out how they adhere to the program and advice or necessary changes in their program and to monitor the progress. Also research scholar called each patient to come to the center once in a month in order to increase intensity of exercise and convert it to new speed of walk for better understanding of patient. Subjects also advised to contact the research scholar if any advice or help needed. They were given detailed awareness of signs and symptoms to be monitored while doing exercise program, do and don’t and the criteria for the
termination of exercise were well explained to them. (As discussed in section “Termination criteria for exercise”)

C) **Group II: Control Group**

Subjects in control group underwent baseline assessment of all outcomes as discussed for study group. These patients were instructed to follow the management advised by their physician. No modification in their routine normal activities was done and not received advice for any formal exercise training program.

V) **Monitoring**

Subjective ratings and symptoms provide useful clinical information.\(^{105}\) Rating of Perceived Exertion (RPE) and symptomatic complaints such as degree of chest pain, angina, burning sensation discomfort, and dyspnea were collected from the patients routinely.\(^{105}\)

- **Rating of Perceived Exertion (RPE):** RPE (appendix III) provides a subjective means of monitoring exercise intensity. HR-VO\(_2\) relationship can be evaluated further in relation to individuals RPE which is helpful in monitoring the exercise intensity. This method is appropriate for setting exercise intensity in persons with low fitness, cardiac patients and those who are under medication that affect HR response to exercise; taking into account personal fitness level, environmental conditions and general fatigue level. Light to moderate intensity (RPE of 11 to 14) is suitable for cardiac patients.\(^{105}\)

It is important to use standardized instruction to reduce problems of misinterpretation of RPE. The following instruction is recommended by ACSM guidelines was used:\(^{105}\)

> “During the exercise we want you to pay close attention to how hard you feel the exercise work rate is. This feeling should reflect your total amount of exertion and fatigue, combining all sensations and feeling of physical stress,
effort and fatigue. Do not concern yourself with any one factor such as leg pain, shortness of breath or exercise intensity, but try to concern on your total inner feeling of exertion. Try not to underestimate or overestimate your feeling of exertion. Be as accurate as you can.”

- **PULSE & HR:** HR can be evaluated using several methods. Radial pulse involves feeling the pulse by placing 1\textsuperscript{st} and 2\textsuperscript{nd} fingers over radial artery near the thumb side of wrist. The pulse is typically counted for 15 seconds and multiplied by 4 to determine HR/min.

- **ANGINA and DYSPNEA:** subjectively rated according to angina rating scale:\textsuperscript{105}
  1. Mild; barely noticeable
  2. Moderate; bothersome
  3. Moderately severe; very uncomfortable
  4. Most severe; never experienced

**VI) Indications for termination of exercise**

Detailed awareness of signs and symptoms to be monitored while doing exercise program and subjective symptoms and criteria for the termination of exercise were well explained to the subjects; as follows:

- **DYSPNEA and ANGINA:** according to the rating system mentioned above in case of reaching a rating of 3, or a degree of chest discomfort would cause patient to stop the activity.

- **SIGNS OF POOR PERFUSION:** including: light headedness, confusion, ataxia, pallor, cyanosis, cold and clammy skin.

It was explained to the patients; in case of feeling any of these symptoms to stop the exercise and check the HR as explained for them and contact other family members or therapist if needed.
VII) Medical Treatment

In both centers, the medical treatment of cardiologist approach was according to standard guidelines from AHA/ACC guidelines and all the three groups were treated medically as per the same guidelines.106

VIII) Re-assessment

After 12 weeks, all subjects underwent post-intervention re-evaluation of primary outcomes including SF-36 questionnaire to assess the quality of life, Functional Capacity, and Left Ventricular Ejection Fraction as well as secondary outcomes as described earlier.

3.8 Data Analysis

We used “Stat.Direct” software for random table generation. Data analysis was done by using SPSS v17 software package. Level of significance set at P≤0.05 with Confidence Interval of 95% while keeping power of study at 90%. Our primary outcome; SF-36 however is a categorical data, but since it is calculated based on the scoring system with a wide range of 0 to 100, therefore we used parametric test for analysis. Other main outcomes including LVEF, Functional capacity and secondary data are a continuous variable and we used parametric test. Baseline comparison of means was done by one way ANOVA to find out the between group differences. Since we had only two levels of measurements, Pre-post difference was calculated and converted to percentage by formula:

\[
\% \text{ of change} = \left( \frac{Post - Pre}{Pre} \right) \times 100
\]

Mean of this percentage of change of all outcomes including LVEF, MET level and SF-36 main Scores and all subdomains were compared within & between groups by one way ANOVA.107