Pharmacological Therapy Adherence: A Poorly Explored Benefit of Cardiac Rehabilitation

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Abstract

**Background:** Participation in cardiac rehabilitation programs (CRP) or supervised exercise programs (SEP) is strongly recommended in the secondary prevention of coronary artery disease (CAD). To optimize the therapy outcome there should be high adherence to drug therapy (ADT).

**Objective:** To analyze adherence to drug therapy in supervised exercise program participants.

**Methods:** Data from 191 patients (74% men) aged between 35 and 92 years (mean age 71±10.0) regularly attending SEP in a private clinic in Rio de Janeiro, RJ. Information on ADT was sourced from structured interviews conducted by the doctors responsible for the SEP sessions. Demographic and clinical data, as well as information about SEP attendance, were extracted from electronic medical records.

**Results:** 92% of patients reported correct use of medications/dosages prescribed by their doctors in the week preceding the interview, while 8% admitted having partially failed; 66% knew their medications/dosage by heart. There were no differences between patients adhering and partially adhering to the drug therapy regarding sex — women 96% and men 91% (p= 0.25) — or age -> 65, 92% and <65 years, 92% (p=0.96). Patients with a medical background were able to list more accurately the medications/dosage compared to those without a medical background (86% vs. 61%; p<0.01).

**Conclusion:** Regular participants of SEP conducted in a private clinic showed a high rate of ADT. This may be related to medical assessment completed just before starting the exercise sessions. Whatever the reason, the high ADT appears to be an additional and important benefit of regularly attending the SEP, which had not have its clinical and epidemiological potential properly explored.

**Keywords:** Exercise; Cardiovascular diseases; Drug utilization

Introduction

A few decades ago, participation in cardiac rehabilitation programs (CRP) or supervised exercise (SEP) programs has been recommended as an important part in the secondary prevention of coronary artery disease (CAD)¹³. As pointed out in a recent editorial, CRP and SEP have been shown to be beneficial not only in CAD, but also in at least 20 other abnormal conditions or cardiovascular diseases⁴. Although there is substantial evidence of many physiological, psychological, clinical and epidemiological benefits from participating in CRP or SEP⁵⁶, a little explored aspect is that patients who regularly attend these programs can more accurately follow the medications prescribed by their doctors, that is, they can present greater adherence to the drug treatment (ADT).

According to the World Health Organization, one of the definitions of adherence is an individual taking medication, following the diet and making lifestyle changes, following the recommendations of a health professional⁷. Depending on the clinical logic,
many studies have shown that adherence to these recommendations may represent increased survival, reduced ischemia events and lower health costs in selected populations of patients with heart diseases\textsuperscript{8-10}. Despite scientific evidence of the benefits of this attitude, it is known that in everyday clinical practice there is considerable difficulty in getting the patient to adhere to this set of actions\textsuperscript{11-13}.

In the context of CRP and SEP, the issue of adherence has been the subject of several studies, including some recent ones\textsuperscript{14,15}. It was possible to identify that obesity, characterized by body mass index, negatively influenced adherence to participation in SEP\textsuperscript{16}, while the distance from home to the SEP site did not appear to be a determining factor for adherence to participation\textsuperscript{17}. A survey conducted on PubMed in mid-2015 identified more than 20,000 articles specifically referring to ADT, which shows the importance and the interest of health professionals\textsuperscript{18}.

Despite the extensive literature on adherence to treatment and ADT, there seems to be a gap in the knowledge about the role of participation in SEP on ADT. It can be assumed that patients who are adherent to a SEP also present high ADT and this may represent an additional benefit that is yet little explored regarding the participation in CRP or SEP.

The aim of this study was to analyze the ADT of patients regularly attending a SEP in a private clinic in Rio de Janeiro, RJ. ADT rates were compared with patients stratified by sex, age, and medical education and the time they have been attending the SEP.

Methods

Prospective study including the analysis of data from 196 adult patients who attended a SEP from April 22 to May 29, 2015 in a private clinic located in the south of the city of Rio de Janeiro, RJ. The patients going to the clinic are usually referred to a SEP by their doctors, who work in private centers, and nearly all of them are white and of a high socioeconomic status. The last information is corroborated by their ability to pay a monthly fee that is, on average, higher than a minimum wage in the period, although 31 of them seek (and eventually succeed) partial or total reimbursement from their private health insurance.

Before starting the SEP, patients underwent an initial assessment: medical history, physical examination, electrocardiogram and rest spirometry, 4-second exercise testing\textsuperscript{19}, cardiopulmonary exercise testing\textsuperscript{20} and comprehensive kinanthropometric assessment with flexibility\textsuperscript{21} and muscular power\textsuperscript{22} exercises.

Of 196 participants, all those who attended at least one SEP session during the study period and who agreed to participate were included in the study. Five patients we were excluded from the analysis for one of the following reasons: a) clinically diagnosed dementia; b) did not use any drug regularly and c) could not be interviewed.

All patients signed an Informed Consent Form according to Resolution CNS 466/12. This study has been approved by the Research Ethics Committee of the institution under no. 218/10.

The participants could freely choose the time to attend the exercise sessions because the SEP runs from Monday to Saturday for many hours. While the weekly attendance prescribed varied from one to six sessions per week, depending on the clinical recommendation and the patient’s availability, the average attendance to the SEP was three times a week.

The SEP sessions were individually prescribed and included aerobic, muscle strengthening and flexibility exercises. For certain patients, according to clinical characteristics, inspiratory muscle training, manual isometric training, motor coordination and balance exercises were also performed. The session was supervised in person by a multidisciplinary team led a physician qualified in Exercise and Sport Medicine and included trainers, physiotherapists and nursing technicians. The patient/staff ratio was always smaller than or equal to 3/1.

Before the session, the patients were briefly evaluated by the physician, where weight, blood pressure and heart rate (HR) were measured and recorded\textsuperscript{23}; when individually prescribed or necessary, single lead digital electrocardiogram scan was taken, and oxygen saturation,
blood glucose and peak expiratory flow, were determined before the doctor prescribed the aerobic exercises.

To obtain ADT data, individualized and structured interview was conducted — three questions with three or four response options (Chart 1) - by one of the five doctors supervising the SEP sessions and familiar with the patients. These doctors were previously instructed by the study investigators on how to conduct the interview and how to record the patients’ responses in an encoded form. Drug names (or trade names) and their dosages were checked against the information available on electronic medical records and, for any inconsistencies, the drug therapy effectively in force was carefully checked. The answers to questions about ADT were analyzed for all patients and separately according to five criteria: sex, age — older or younger than 65, whether or not they had any medical background, presence or absence of CAD and length of stay in the SEP — less than four months and more than one year.

In order to obtain clinical and physiological benefits that could corroborate the information obtained on ADT, HR and systolic and diastolic blood pressure at rest were measured immediately before the exercise session in a sitting position, as previously described above. Data from all sessions attended by patients with or without ADT the week before and on the day of the interview were analyzed. For adhering and partially adhering patients, the typical variability (coefficient of variation) found in the same type of patients was compared.

Statistical analysis

The frequencies of response options and clinical characteristics were properly calculated and their distributions were compared using the chi-square test. Other comparisons were made by Student’s t test or Mann-Whitney test depending on the nature of distribution of the variable concerned. For statistical analysis, the software Prism 6.0 (GraphPad, USA) was used, adopting a 5% significance level.

Results

Of the 196 participants who were enrolled in the SEP from April to May 2015, 191 participants responded to the interview. Of the total of participants, one patient was excluded due to clinically diagnosed dementia, one was excluded for not using any medications and the other three patients were not interviewed.
The patients interviewed were mostly male (74% of the total), aged 71±10, about 35-92 years old and most of them were aged 70-80 (36%). Regarding the time of participation in the SEP, 75% (n=144) participated for more than 12 months, 21% (n=42) of which participated for more than 10 years and only 12% (n=23) had joined up to three months before the interview. The main clinical characteristics and the drug groups regularly used by 191 patients, separated according to ADT, are shown in Table 1. With the sole exception of the rate of patients using diuretics (p<0.03), all other comparisons among adhering and partially adhering patients did not present any statistically significant differences.

### Table 1
Major clinical and pharmacological therapy aspects of 191 SEP patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adhering patients (n = 176)</th>
<th>Partially adhering/adhering patients (n = 15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main clinical aspects</strong></td>
<td>n</td>
<td>% *</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>121</td>
<td>68.8</td>
<td>p=0.71</td>
</tr>
<tr>
<td>Systemic arterial hypertension</td>
<td>101</td>
<td>57.4</td>
<td>p=0.42</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32</td>
<td>18.2</td>
<td>p=0.25</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>123</td>
<td>69.9</td>
<td>p=0.15</td>
</tr>
<tr>
<td>History of coronary angioplasty</td>
<td>76</td>
<td>43.1</td>
<td>p=0.20</td>
</tr>
<tr>
<td>Coronary artery bypass grafting surgery</td>
<td>45</td>
<td>25.5</td>
<td>p=0.51</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>16</td>
<td>9.0</td>
<td>p=0.58</td>
</tr>
<tr>
<td><strong>Pharmacological therapy - Main groups</strong></td>
<td>n</td>
<td>% *</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>120</td>
<td>68.2</td>
<td>P=0.67</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>143</td>
<td>81.3</td>
<td>P=0.60</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>136</td>
<td>77.3</td>
<td>P=0.80</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>44</td>
<td>25.0</td>
<td>P=0.32</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>98</td>
<td>55.7</td>
<td>P=0.74</td>
</tr>
<tr>
<td>Diuretics</td>
<td>59</td>
<td>33.5</td>
<td>P=0.03</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>56</td>
<td>31.8</td>
<td>P=0.90</td>
</tr>
<tr>
<td>Other antiarrhythmic drugs</td>
<td>15</td>
<td>8.5</td>
<td>P=0.52</td>
</tr>
<tr>
<td><strong>Number of medications</strong></td>
<td>n</td>
<td>% *</td>
<td></td>
</tr>
<tr>
<td>Up to 4 hours</td>
<td>111</td>
<td>63.1</td>
<td>P=0.45</td>
</tr>
<tr>
<td>More than 4</td>
<td>65</td>
<td>36.9</td>
<td>P=0.45</td>
</tr>
</tbody>
</table>

* % of patients with the conditions or drugs for the specific group – adhering or partially adhering
SEP – Supervised Exercise Program; NS – non-significant; S – significant to 5% probability; ACEI/ARB – angiotensin-converting enzyme inhibitor/angiotensin receptor blocker

On the first question of the interview on ADT, 176 patients (92%) reported that they had continuously and correctly taken all medications in the week preceding the question, 8% failed at least once and no patient reported to have failed to take all prescribed medications. Regarding the question about the name of medications, the dosage and the number of times per day (posology), 66% were able to list all of these items
correctly, 14% did not get only one medication right, 14% were able to list only a few of them and 7% did not know the name and dosage of any medications that would be presumably prescribed by their doctors. Regarding the question of what they did to remember the medications and their dosages, 57% said they used only their memory, 31% wrote them down in a “little box” with “everything organized not to forget” or similar methods, 8% needed the assistance of a caregiver or a family member to remember and only 4% would regularly review the prescription or a list for guidance (Table 2).

By analyzing clinical and demographic data, it was found that there was no difference between men and women regarding ADT, with values of 91% and 96%, respectively (p=0.25). There was no difference in relation to the age group younger and older than 65, with identical percentages of 92% (p=0.96). The presence of CAD did not influence ADT, with values of 92% and 93% (p=0.71), respectively, among those with and without this clinical condition.

Comparing patients with longer participation in the SEP with those who had joined just a few months before, some differences were identified. Those who had more than 12 months of SEP tended to know how to list all medications/dosages more accurately (69%) compared to those who had less time (52%) without, however, reaching statistical significance (p=0.08). Another characteristic observed was that 60% of those registered for over 12 months used their own memory to remember the medications vs. 48% of those who were there less than four months (p=0.10). The participants who had been attending the SEP for longer were more independent; only 4% of them relied on relatives or caregivers to take medications, while among those with less than four months, 17% relied on someone else (p<0.03). On the other hand, there was no difference regarding the period of time attending the SEP in relation to ADT (p=0.08).

Finally, as the last criterion, patients were separately analyzed for medical background. Of the 191 SEP patients studied, 37 had medical background and had ADT exactly identical to the other 144 (p=0.35). However, the proportion of participants with medical background who listed all medications was 86% compared to the other 61% (p<0.01) (Table 3).
The results of the coefficient of variation of systolic blood pressure (SBP) of adhering and non-adhering patients on the days preceding the interview was 4.62% and 6.47%, respectively (p<0.02). The HR coefficient of variation was similar among adhering and partially adhering patients: 3.80% and 4.43%, respectively (p=0.22).

**Discussion**

CRP has been a frequent target of studies around the world with more than 2,800 articles published in the last 10 years on PubMed, mentioning the term “cardiac rehabilitation” in the title or abstract. Previous studies have shown that patients who were enrolled in a CRP had greater control of smoking and cholesterol. It also reduces cardiovascular mortality by 26% and the recurrence of hospitalizations.

Some studies have suggested that low adherence to CRP may be more related to hospital readmissions, regular use of antidepressants, obesity, physical inactivity and older age. On the other hand, there are reports that patients adhering to CRP present greater adherence to other forms of secondary prevention, for example, adopting healthier eating habits, which occurred in 72% of patients analyzed by Griffo et al. It seems that the longer the patient stays in the CRP, the greater their knowledge about the disease, which is consistent with our findings, in which those participating for more than 12 months could list the medications more accurately, were more independent and dependent only on their memory to take medications, making ADT a habit.

Some important studies on ADT were published a few decades ago. Since then, the issue has become the subject of several articles in various scientific journals. It is known that ADT is essential to reduce chronic disease outcomes such as systemic arterial hypertension (SAH) and diabetes mellitus. In the outpatient setting, the percentage of ADT is low, which tends to worsen when associated with other factors, such as the amount of drugs, duration of treatment of chronic diseases and/or low education level.

In the search for wider knowledge on the subject, this study examined patients from a CRP of a private clinic in the south of Rio de Janeiro specializing in Exercise and Sport Medicine, evaluating the profile of a population used to doing exercises, while focusing on the context of ADT.

Something that made it difficult to search ADT and consequently to conduct this study was the lack of a gold standard to analyze this variable. Ideally, this should be done using direct methods including drug count and monitoring or qualified supervision of intake, supported by searching for drug metabolite in body fluids — blood and urine.

These methods are obviously extremely costly and complex and prone to errors, and do not apply to outpatients. An indirect form of analysis is using simple questionnaires, which are mainly validated in the context of SAH, not covering the complexity of the patients of this study, though. As the medical staff of the clinic consists of five professionals only, instead of applying a questionnaire, we chose to conduct an interview adapted to the reality, in which the doctor, familiar with the patients, asked the questions following a pre-structured sequence and a target format of encoding of responses, thereby ensuring uniformity in the responses. The interviews were applied for six weeks, including 191 (97%) patients out of 196 who were attending the CRP in the period.

It is worth noting the very specific nature of the study participants, mostly male and 88% of which had been going to the clinic for more than 16 weeks. Regarding the clinical characteristics, it was found that most patients were hypertensive and/or had coronary artery disease requiring conservative treatment or patients who had been gone through coronary artery bypass grafting surgery. In this sample, there was a high rate of patients fully adhering to medications/dosages (92%), which is consistent with what has been observed with respect to other forms of adherence compared to patients regularly involved in CRP.

It is worth noting that the high ADT found in the study is far superior than other research studies. Recent examples of attempts to expand the ADT were using text messages to remind the patient to take medications, reaching a maximum ADT of 68%, and the pharmacist’s intervention, increasing ADT to 80%.

The results found here have probably been influenced by the presence of a multidisciplinary team that was available to resolve doubts during the exercise sessions. Moreover, as part of the pre-session routine evaluation, patients were routinely asked about the use of medications and about symptoms since the last session. Another aspect that is most likely to be relevant is that the sample...
consists of individuals belonging to a higher socioeconomic status and high level of education, regularly practicing exercises as part of promotion of their health.

Another interesting point was the possibility of indirectly checking the reliability of responses to the interview. As a reference, we used a previous study with a very similar population, which revealed the expected variation of HR and blood pressure at rest and pre-session, in SEP patients \cite{23}. Although exercise influences the control of SBP and HR, it was found, in this study, a smaller variation of SBP levels \((p=0.02)\) and a smaller variation trend in HR \((p=0.22)\) in adhering patients compared to those partially adhering to the drug therapy. These findings are quite logical and expected in this indirect attempt to validate the responses given by patients in interviews and compare very well with those obtained in another study \cite{23}.

Although in other studies the number of medications prescribed may have negatively interfered in ADT \cite{32,33}, participants who were using less than and more than four cardiology drugs were compared, where no statistical significance was found between the groups \((p=0.45)\). This finding is likely to have been influenced by a high ADT index. The high ADT found was not influenced by demographic or clinical characteristics. Considering the five criteria studied, there were no differences in ADT for any of them — sex, age, presence or absence of CAD, presence or absence of medical background and time spent in the SEP — with differences only in those with medical background as to the form of “controlling” that ADT, or being able to list the medications using their own memory or through other methods.

This objectively points out to the fact that regularly attending a private SEP helps the patient adhere to the drug therapy, regardless of their medical condition, polypharmacy, age or sex, as opposed to what was found in a literature review study \cite{37}. Besides, it is true that after a serious cardiac event, the patient is more prone to changing lifestyle \cite{39}. Such change can be made by quitting smoking, joining a CRP and through increased ADT, which are considered priorities in the secondary prevention of CAD \cite{39}.

It seems appropriate to emphasize the need for an approach that is more focused on the patient than on the disease, improving doctor-patient communication \cite{38} for a better ADT. The need to use medications, their effects, potential consequences of poor adherence and the benefits of simple changes that can help reduce the risk of cardiovascular events should be explained. In this context, the doctors responsible for the SEP sessions can play an important and collaborative role with the patients’ doctors.

This study has some limitations. The first one is the lack of comparison of ADT rates among patients attending and not attending SEP, with similar clinical and demographic conditions. It is possible to speculate that patients participating in a SEP have higher levels of commitment and involvement with their clinical condition and with the therapeutic approach prescribed by their doctors, thus favoring a higher ADT. However, the experience in the practice of clinical cardiology is rich enough in terms of examples that allow considering an ADT result greater than 90% as exceptionally positive and favorable even without the possibility of demonstrating that fact against a formal control group. It would be interesting to try, in a future study, comparing patients of a selected group of doctors, with homogeneous clinical and demographic profiles, with and without participation in SEP, as for ADT.

Another important limitation are the peculiarities of the patients studied, such as mostly males, mostly white and high socioeconomic level, varied clinical profile and, in most cases, attending SEP for many months, which greatly hinders and limits the possibility of generalizing our results to all types of CRP or SEP.

In short, the practical message for clinical cardiologists is that regular and prolonged participation in a SEP with in-person and effective supervision of a doctor seems to contribute for the patient to present an ADT higher than 90\%. It is not possible to affirm whether other SEP formats, with or without such medical supervision or in other settings or conditions, would generate so high and appropriate ADT results. Indeed, other studies are needed to test these assumptions.

Finally, we can state that, considering the SEP characteristics as it was performed and controlled, generating a high ADT in patients may be included as one more benefit of regular and prolonged participation in CRP or SEP. It is thus possible that some clinical and
epidemiological benefits of regular participation in CRP or SEP can be related to a proportionally higher rate of ADT prescribed by the doctor. This is another positive factor that can contribute to an increasingly frequent and early referral of patients with heart disease to CRP or SEP.

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Potential Conflicts of Interest
Fabio Akio Nishijuka declares that this study has no relevant conflicts of interests. Claudio Gil Soares de Araújo is a business partner of a medical service company in Exercise and Sports Medicine.

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