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ORIGINAL ARTICLE

Pharmacological Stress Echocardiography with Low Dose Dobutamine Associated to Isometric Exercise and Early Atropine – Report of an Experience with the New Protocol*

*Ecocardiografía bajo Estrés Farmacológico con Dobutamina con Baja Dosis Asociada a Ejercicio Isométrico y Atropina Precoz – Relato de la Experiencia con Nuevo Protocolo**

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SUMMARY

Introduction: The pharmacological stress echocardiography with dobutamine(PSE-Db) provides satisfactory safety profile, however serious adverse events may occur predominantly derived from clinical condition. PSE-Db has a higher incidence of complications than physical stress, which leads to the supposition that the lower the dose of dobutamine used the lower the risk. **Objective:** To report our experience with PSE-Db new protocol using low-dose dobutamine, associated with isometric exercise and atropine early. **Methods:** We selected 156 patients referred for evaluation of ischemia, which showed no changes in basal contractility or significant valvular heart disease, divided into two groups, GrFem, 76 females patients with a mean age of 59 (+ -14) and GrMasc, 80 males patients aged 54 (+ -13) years. **Results:** In all patients, the maximum dose of dobutamine was used 5mcg/Kg/minutein 5 patients (3.2%); 10mcg/Kg/minute in 83 patients (53.2%); 15mcg/Kg/minute in 62 patients (39.7%) and 20mcg/Kg/minute in 6 patients (3.9%). It was not necessary to use doses of 30 and 40mcg/kg/minute, and 96.1% of patients met the criteria interrupt dose 15mcg/kg/min or less. Atropine was not used in 30 patients (39.5%) ofGrFem; and 8 patients (10%) of GrMasc. In 2 patients using beta-blockers, the test was ineffective due to very low increase of cardiac frequency. **Conclusions:** The implementation of the PSE-Db associated with early isometric exercise and simultaneous administration of atropine, achieved the objectives of the exam, with reduction in the dose of dobutamine compared to the usual protocols, and with no significant complications.

Descriptors: Echocardiography, Stress; Exercise; Dobutamine; Atropine

RESUMEN

Introducción: La ecocardiografía bajo estrés farmacológico con dobutamina (EEF-Db) ofrece perfil de seguridad satisfactorio; sin embargo, eventos adversos serios pueden ocurrir, predominantemente, derivados de la condición clínica. EEF-Db presenta mayor incidencia de complicaciones de que el estrés físico, el cual lleva a suponer que cuanto menor la dosis de dobutamina utilizada menor el riesgo. **Objetivo:** Relatar la experiencia en EEDbt con nuevo protocolo. **Método:** Exámenes de EEDbt fueron realizados con protocolo diferenciado por la administración de dobutamina, en baja dosis, asociada, precozmente a ejercicio isométrico continuo y atropina. Fueron seleccionados 156 pacientes (pac) referidos para evaluación de isquemia, con visibilidad miocárdica adecuada, que no presentaban, en condiciones basales, altera-

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ciones de la contractilidad ni valvulopatías significativas y divididos en 2 grupos. GrFem, 76 pac del sexo femenino, con edad promedio de 59 (+-14) años y GrMasc, 80 pac del sexo masculino, con edad de 54(+ -13)años. **Resultados:** En el total de pacientes, la dosis máxima de dobutamina utilizada fue 5mcg/Kg/minuto en 5pac(3,2%); 10mcg/Kg/minuto en 83pac(53,2%); 15mcg/Kg/minuto en 62 pac (3 9.7%) y 20mcg/Kg/minuto en 6 pac (3,9%). No fue necesaria la utilización de las dosis de 30 y 40mcg/kg/minuto, siendo que 96,1% de los pac alcanzaron los criterios de interrupción con dosis igual o inferior a 15mcg/kg/min. No fue adicionada atropina en 30 pac (39,5%) de GrFem; y en 8 pac (10%) de GrMasc. En 2 pac, la prueba fue ineficaz por respuesta cronotrópica, acentuadamente baja por el uso de betabloqueador. **Conclusiones:** La realización del EEDbt con nuevo protocolo, permitió alcanzar los objetivos del examen, con baja dosis de dobutamina y con complicaciones poco expresivas.

Descritores: Ecocardiografía bajo Estrés, Ejercicio, Dobutamina, Atropina

Introduction

Pharmacological stress echocardiography (PEE) is a diagnostic method which has gained valued over time, being widely used in echocardiography laboratories.

It is especially indicated to detect myocardial ischemia. It is also indicated for risk stratification purposes in patients with chronic coronariopathy after myocardial infarction or in patients who are candidate for vascular surgery; myocardial viability assessment and contractile reserve in ventricular dysfunction; and also in valve diseases when there is doubt as to the hemodynamic effect, although in these cases physical stress is preferred[1-3].

Physical exercise as stressing agent, whether on a bicycle or ergometric treadmill, has been poorly used in Brazil, and it is reduced to a small number of centers, although it is a more physiological technique with lower incidence of intercurrences when compared to the pharmacological stress. Some patients have limitations for physical exercises and, in such cases, the pharmacological stress is an option.

Different drugs can be used as stressing agent. In our field, dobutamine and dipyridamole are the most used ones, both with similar accuracy. Dipyridamole é contraindicated to respiratory compromised patients as it can potentially cause bronchospasms, having its effect neutralized by the use of xanthines, such as aminophylline. On the other hand, dobutamine, due to its adrenergic effect, potentializes the onset of arrhythmias, and its use is limited in patients with such condition. Nevertheless, dobutamine is chosen for the assessment of myocardial viability at low doses[4-8]. Both substances are complementary, and their selection is based on the objectives of the exam and on patient's characteristics[5]. Not less important is the experience of the medical team that also determines which drug will be used.

The main echocardiography limitation is the fact it depends on a favorable acoustic window for visualization of all myocardial segments, which restricts its use in a reduced number of patients. This limitation is compensated by the use of ultrasonic contrast agents, currently not available in our field for clinical use.

The most used protocol for PEE with dobutamine (PEE-Db) is administering the drug at progressive doses, starting at 5 mcg/kg/min and escalated to 10, 20, 30 and 40 mcg/kg/min. When the sub maximum frequency is not achieved with the full dose of dobutamine, atropine is added, starting at 0.25 mg every minute up to a maximum of 1 mg[9] (Figure 1).

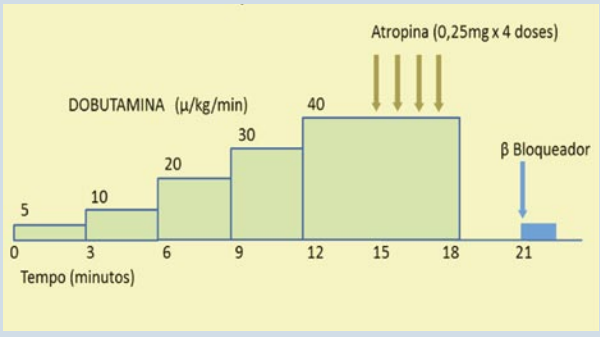

Figure 1: Classical Dobutamine-Atropine Protocol.

Atropine increases the sensibility of dobutamine tests during coronary disease diagnosis in patients using beta-blocker and in patients with single artery lesion[10].

In most centers, there is a trend to use atropine early, as of the 20 mcg/kg/min dobutamine dose (Figure 2).

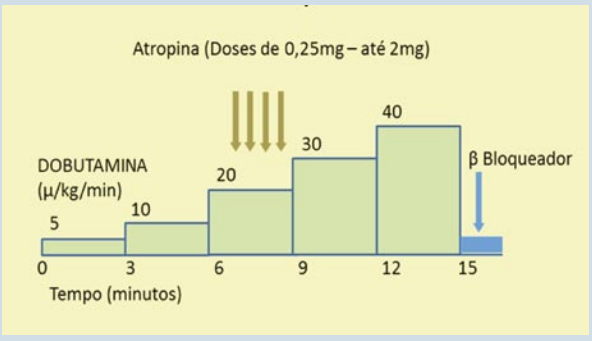

Figure 2: Protocol Dobutomina-Atropine Precose

In this protocol, at the peak of the stress, intravenous metoprolol is administered which, in addition to quickly reducing the heart rate, increases the sensibility for ischemia detection, as described by Mathias, et al6.

San Román et al.[7] proposed an accelerated protocol for low risk patients, starting at 20 mcg/kg/min during 3 minutes and increasing to 40 mcg/kg/min, followed by a single dose of atropine of mg. The protocol was considered to be safe in this group of patients with a complication level similar to the ones of conventional protocols.

In 1993, Mertes et al.[8] used a protocol with a maximum dose of dobutamine 50 mc/kg/min and assessed safety in 1,118 patients. The results showed the dose was safe, with no higher level of complications than the maximum 30 mcg/kg/min dose.

PEE-Db offers a satisfactory safety profile. However, serious adverse events may occur. According to the surveys conducted by the European Association of Echocardiography9, in a total of 64,542 patients subjected to PEE-Db, the following major complications have been reported: ventricular tachycardia – 40 patients; ventricular fibrillation – 10 patients; acute myocardial infarction – 5 patients; extended ischemia – 2 patients; severe arterial hypotension – 8 patients; asystole – 1 patient; and death – 5 patients. According to the American Society of Echocardiography[10], acute myocardial infarction or ventricular fibrillation is estimated to occur in 1 in 2,000 exams, which represents a higher incidence than in the series mentioned before.

In the case of EE-Db, complications may occur during infusion or after it is interrupted[11]. For this reason, it is recommended to observe the patient for a period of 30 to 40 minutes after test completion. In the Holter electrocardiography test, no increased arrhythmia or ischemia was noted after this period[12].

In order to achieve the sub maximum frequency using the conventional protocol, most of the patients require dobutamine administration at higher doses than 30 to 40 mcg/kg/min associated with atropine.

Patients with glaucoma or urinary retention are contraindicated to using atropine. This limits the results of the PEE-Db in such cases when the preconized heart rate is not achieved. The incidence of severe arrhythmias was not associated to the dose used. Arrhythmias are more associated to the degree of ischemia, previous myocardiopathy or baseline arrhythmias[8].

As mentioned before, PEE-Db has a higher incidence of complications than physical stress echocardiography, which allows us to suppose that the lower the dose of dobutamine used, the lower the risk.

Although the level of complications in PEE-Db is low, every measurement taken to reduce its incidence is useful and, in this context, the use of low doses of dobutamine would be desirable.

This paper reports the experience with PEE-Db in the new protocol. The protocol is different due to the administration of dobutamine at low doses, early associated with continuous isometric exercise and atropine.

Method

1) Casuistry

One hundred and fifty six patients were selected for ischemia assessment, with no contraindication for the use of atropine, adequate myocardial visibility and with no baseline contractility changes or significant valve diseases. They were divided into 2 groups, FemGr with 76 female patients aged 59 (+14) years old in average, and MalGr with 80 male patients aged 54 (+3) in average.

2) Protocol

Exams were performed with the patient in left lateral decubitus position. Drugs were administered and pressure was controlled in the right arm. The left arm was free for the purposes of performing the exercise.

Initially, a baseline exam was performed and corresponding images were captured, according to the American Society of Echocardiography criteria10. Subsequently, dobutamine was initiated at 5 mcg/kg/min and maintained for 3 minutes. The dose was increased to 10 mcg/kg/min, followed by an intermediate dose of 15 mcg/kg/min, and followed by doses of 20, 30 and 40 mcg/kg/min, with 3-minute intervals. As of 10 mcg/kg/min, isometric exercise was initiated and maintained until the end of the stress period. Increased rate increase response was noted during the first two minutes of exercise. Upon low chronotropic response in the third minute, atropine was initiated at 0.5 mg per minute until 2 mg.

It was noted that upon administration of dobutamine 15 mc/kg/min, subsequently, the patient was administered the second dose of atropine, which was repeated at one-minute intervals until the forth dose, which was still administered in the same dobutamine infusion step (Figure 3).

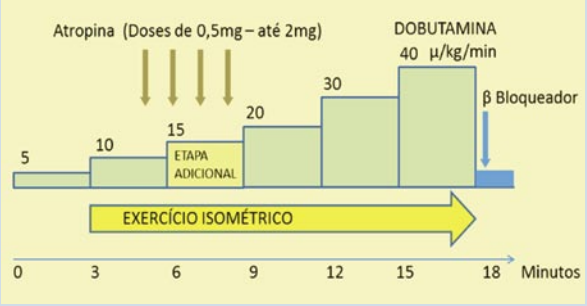

Figure 3: New Protocol: Dobutamine – Isometric Exercise Early Atropine

Isometric exercise included squeezing a rubber ball with one hand (like the ones used in physiotherapy treatments). The diameter of the ball ranged from 5 to 7 cm. Before that, the patient was given the chance to choose from different balls with three increasing levels of resistance the one which best adapted to his/her characteristics and strength. During the test, the isometric exercise was continuous and at maximum intensity, with small intervals in case of muscle fatigue.

In some cases, when the conditions of the patient so permitted, a second ball for the right hand was used as additional stimulus. Stress was interrupted when the sub maximum heart rate was achieved. Signs of ischemia, significant arrhythmia s or marked increased in blood pressure could be detected. At the peak of stress, metoprolol was administered intravenously at 5 mg.

This paper, in addition to assessing contractility, mapped out the flow in colors, measuring intracavity gradients with continuous Doppler.

Results

In the total of patients, the maximum dobutamine dose used was 5 mcg/kg/min in 5 patients (3.2%); 10 mcg/kg/min in 83 patients (53.2%); 15 mcg/kg/min in 62 patients (39.7%) and 20 mcg/kg/min in 6 patients (3.9%). Doses higher than 30 and 40 mcg/kg/min were not necessary, with 96.1% of the patients met the interruption criteria with dose equal or lower than 15 mcg/kg/min (Table 1).

Table 1

Doses de dobutamina:	GrFem (76pac)		GrMasc (80pac)	
	N°pac.	%	N°pac	%
5mcg/Kg/minuto	5	6,6		
10mcg/Kg/minuto	45	59	38	47,5
15mcg/Kg/minuto	24	31,6	38	47,5
20mcg/Kg/minuto	2	2,6	4	5

Atropine was used in the FemGr in 46 patients (60.5%), 30 patients (39.5%) did not need to use it because they met the interruption criteria with dobutamine associated to the isometric exercise only. Atropine was used in the MalGr in 72 patients (90%), 8 patients (10%) did not need to use it.

In 1 patient of each group the test was ineffective due to markedly low chronotropic response due to the use of beta-blocker, although with a full dose of atropine. For this reason, tests were interrupted at dobutamine 20 mcg/kg/min. Hyper-reactive blood pressure was

noted in 12 patients, which determined stress interruption in 1 case. No patients showed decrease in blood pressure. Significant intraventricular gradient was detected in 15 patients (9.6%), 7 patients from the FemGr and 8 patients from the MalGr.

Stress was interrupted due to frequent ventricular arrhythmia in 4 patients. There were no cases of sustained ventricular tachycardia or ventricular fibrillation (Table 2).

Table 2

RESULTS	GrFem(76pac)	GrMasc(80pac)
	N° pac.	N° pac.
No ischemia	58	59
Ineffective	1	1
Ischemic due to regional wall motion abnormalities	10	7
Ischemic at ECG with no regional wall motion abnormalities	4	11
Interrupted due to hyper-reactive blood pressure	0	1
Interrupted due to arrhythmia	3	1
Total	76	80
Gradient detection intraventricular peak from 35 to 55 mmHg	7	8

Discussion

Dobutamine increases heart rate by stimulating Alpha 1, Beta 1 and Beta 2 adrenergic receptors, increasing oxygen consumption. Blood pressure increase is lower than the one caused by the exercise, and it may cause hypotension.

Sympathetic stimulation also increased contractility. Hyperdynamic condition induced in this manner may cause the onset of intracavity gradients in the left ventricle, as described by Camarozano et al[13]. These authors found significant gradients with dobutamine doses higher than 20 mcg/kg/min, progressive and proportional to the amount administered to the patient.

This paper detected intracavity gradients in 7 patients of the FemGr and 8 patients of the MalGr, the maximum dobutamine dose was 20 mcg/kg/min. Peak instantaneous gradients ranged from 35 mmHg to 55 mmHg in these patients. The clinical significance of these gradients is not certain[13].

Physical exercises may be characterized in two different ways: dynamic or isotonic exercises, with muscle contraction followed by joint movement; and static or isometric exercises, with muscle contraction with no joint movement.

The isometric exercise, as used in this paper, increases heart rate, and maintains or even reduces systolic volume, with little increased cardiac output. On the other hand, there is a significant increase in peripheral vascular resistance, and this increases blood pressure. Continuous muscle contraction during maximum intensity isometric exercise reduces arterial flow in the contracted muscle, with consequent accumulation of metabolites, chemoreceptors stimulation, and significant increase in sympathetic activity[14].

The magnitude of sympathetic stimulation during isometric exercises depends on the intensity of the exercise, its duration and the volume of muscle mass involved. To all this, we can add muscle adaptation to strain, which will be inversely proportional to sympathetic stimulus. This means that the less the muscle adapts, the higher the adrenergic stimulation will be.

In this study, the exercise was performed by the left forearm muscle. Although the muscle mass involved is not large, in most of the patients, adaptation to the exercise of this muscle mass is low, especially because it is the left arm, used less by a predominantly right-handed population, and because the population under study usually has a high incidence of sedentarism.

Low muscle adaptation to the exercise is very important for obtaining the right sympathetic stimulation

and the consequent need for a smaller dose of dobutamine and atropine. Reinforcing the statement made, female patients needed a smaller dose of dobutamine to meet the objectives of the test as they had less muscle adaptation than male patients. Additionally, in the female group, 40% of the patients met the interruption criteria without using atropine, while in the male group, the percentage of no atropine was 8%. The fact the female group is slightly older than the male group and, consequently, has a lower sub maximum rate contributes to these findings.

It is necessary to highlight that for the exercise to be efficient, it must be employed at maximum intensity, continuously and with the least possible number interruptions to alleviate fatigue. This allows maximum sympathetic stimulus due to the accumulation of metabolites in the muscle being used, which is perceived by the patient as muscle fatigue.

The adrenergic effect of the isometric exercise is potentialized by the parasympathetic blocking caused by atropine and the consequent sympathetic release. Atropine pharmacological effect is quickly decreased, and it is necessary to repeat administration every minute as per the protocol.

However, in this paper, in one patient in each group, the test was not effective due to markedly low chronotropic response due to the use of beta-blocker, although the full dose of atropine had been administered. In these two cases, tests were interrupted at dobutamine 20 mcg/kg/min as we understood higher doses would increase risks with no significant heart rate increase.

The combination of sympathetic stimulation produced by the isometric exercise and parasympathetic blocking caused by atropine showed to be effective in reducing total dobutamine dose when compared to traditional protocols. Such fact is clear when we consider that 96.1% of the patients met the interruption criteria with dose equal or lower than 15 mcg/kg/min of dobutamine, and only 3.9% of the patients used 20 mcg/kg/min. Doses higher than 30 and 40 mcg/kg/min were not used, except in the two cases mentioned above.

Sunyao et al.[15] used isometric exercise during EE-Db as of dobutamine 20 mc/kg/min. However, the exercise was at low intensity and limited to 4-minute duration. There was no concomitant atropine administration, which, when necessary, was administered late, after the 40 mc/kg/min dose of dobutamine.

In 2008, San Román, et al.[7] proposed a faster dobutamine protocol, starting at 20 mcg/kg/min for 3 minutes and increasing to 40 mcg/kg/min, followed by a single dose of 1 mg atropine. The protocol was restricted to low risk patients, and it was considered safe in these conditions, with complication level similar to the one of traditional protocols.

In 1993, Mertes, et al.[8] used a protocol that indicated a maximum dobutamine dose of 50 mc/kg/min, and they assessed safety in 1,118 patients with different pathology profiles, including history of myocardial revascularization or previous infarction. It is necessary to highlight these patients maintained their usual medications. 639 patients were taking antianginal drugs, including variable combinations of beta-blocker with sustained-release nitrates and calcium channel antagonists. Medication maintenance certainly had a protection effect, reducing complications. The most important arrhythmias were non-sustained ventricular tachycardia in 40 patients (3.5%). Only one patient required pharmacological intervention. All episodes happened at high doses of dobutamine, the average was 38 + 7 mcg/kg/min. Results were considered safe by the authors.

The low doses of dobutamine used in the proposed protocol raise expectation of a smaller number of complications, although the lack of a control group and the small number of patients do not allow for a definite conclusion.

Publications presenting a similar protocol to the protocol proposed were not found in the literature. Thus, to the best of our knowledge, this is the first publication using EE-Db early associated to isometric exercise and concomitant administration of atropine.

Study Limitations

The relatively small number of patients does not allow for definite conclusions. It is important to note the test based on the proposed protocol is feasible, but less sympathetic mimetic stimulation by dobutamine was not defined to be associated to less test sensibility, as no coronary angiography was performed. As to the incidence of complications, it is not possible to compare to other protocols from other papers because the number of patients is small, the sample is selected (patients

with global or segment ventricular dysfunction were not included) and, also, there is no control group with usual protocol. This paper shall be considered as initial experience requiring the inclusion of a larger number of exams.

Conclusions

EE-Db early associated to isometric exercise and concomitant administration of atropine allowed for the achievement of exam objectives with low doses of dobutamine when compared to usual protocols, with low incidence of complications.

References

1. Douglas PS, Khandheria B, StainbackRF, Weissman NJ, Peterson ED, et al. Appropriateness criteria for stress echocardiography J Am Coll Cardiol. 2008;**51**(11):1127-47.
2. Neskovic A, OtasevicP.Stress-echocardiography in idiopathic dilated cardiomyopathy: instructions for use.Cardiovasc Ultrasound. 2005;**3**(10):3.
3. Agricola E, Oppizzi M, Pisani M, Margonato A. Stress echocardiography in heart failure. Cardiovasc Ultrasound 2004;2011;**2**(19):11.
4. Camici PG, SanjayPrasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. Circulation. 2008;**117**(1):103-14.
5. Picano E, Molinaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. Cardiovasc Ultrasound. 2008;**6**(19):30.
6. Mathias W, Tsutsui JM, Andrade JL, Kowatsch I, Lemos PA, Leal SM, et al.Value of rapid beta-blocker injection at peak dobutamine-atropine stress echocardiography for detection of coronary artery disease. J Am Coll Cardiol. 2003;**41**(9):1583–9.
7. San Román JA, Sanz-Ruiz R, , Ramón Ortega JR, Pérez-Paredes M, Jesús Rollán MJ, Muñoz AC, et al. Safety and predictors of complications with a new accelerated dobutaminestress echocardiography protocol. J Am Soc Echocardiogr. 2008;**21**(1):53-7.
8. Mertes H, Sawada SG, Ryan T, Segar DS, Kovacs R, Feigenbaum H. Symptoms, adverse effects, and complications associated with dobutamine stress Echocardiography. Experience in 1118 patients. Circulation.1993;**88**(1):15-9.
9. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Stress echocardiography expert consensus statement. European Association of Echocardiography (EAE) Eur J Echocardiogr. 2008; **9**(4):415-37.
10. Pellikka P, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. Recommendations for performance, interpretation, and application of stress echocardiography - American Society of Echocardiography. J Am Soc Echocardiogr. 2007;**20**(9):1021-41.
11. Geleijnse ML, Boudewijn J, Krenning BJ, Nemes A, Van-Dalen BM, Osama I.I. Incidence, pathophysiology, and treatment of complications during dobutamine-atropine stress echocardiography. Circulation. 2010;**121**(15):1756-67.
12. Chauvel C, Cohen A, Khireddine M. Safety of dobutamine stress echocardiography. A 24 h Hotter monitoring study Eur Heart J. 1996;**17**(12):1898-901.
13. Camarozano A, Weitzel LH, Bastos D, Vieira AM, Sahate A, Cedenilla M, et al. Analise dos gradientes intraventricular e aórtico ao ecocardiograma de estresse com dobutamina: correlação entre hiperdinamia miocárdica e complicações. Rev Bras Ecocardiogr. 2006; **3**(2):21-7.
14. Brum PC, Forjaz CLM, Tinucci T, Negrão CL. Adaptações agudas e crônicas do exercício físicono sistema cardiovascular. Rev paul Educ Fis. 2004;**18**(n.especial):21-31.
15. Yao SS, Moldenhauer S, Sherrid MV. Isometric handgrip exercise during dobutamine-atropine stress echocardiography increases heart rate acceleration and decreases study duration and dobutamine and atropine dosage. Clin Cardiol. 2003;**26**(5):238-42.