Study of Coronary Sinus Flow Reserve Through Transesophageal Doppler Echocardiography in Normal Subjects

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Objective - *To evaluate the Coronary Flow Reserve in the Coronary Sinus through transesophageal Doppler echocardiography in normal subjects.*

Methods - *We obtained technically adequate flow samples for analysis in 10 healthy volunteers (37±8 years, 5 men) with no history of heart or systemic disease and with mean left ventricular mass index by transthoracic echocardiography of 87±18 g/m². Coronary sinus flow velocity was recorded within the coronary sinus with the patient in a resting condition and during intravenous adenosine infusion at a dose of 140 µg/kg/min for 4 minutes. Recording of coronary sinus blood flow was possible in all cases with measurement of peak systolic, diastolic, and retrograde velocities (PSV, PDV, and PRV, cm/sec), mean systolic and diastolic velocities (MSV and MDV, cm/sec), and systolic and diastolic velocity time integral (VTI S and VTI D, cm/sec).*

Results - *The coronary flow reserve was calculated as the ratio between the blood flow in the basal state and the maximum measured hyperemic blood flow with adenosine infusion. Results are shown as mean and standard deviations. (CFR = PSV + PDV – PRV/basal PSV): 1st min = 2.2±0.21; 2nd min = 3±0.3; 3rd min = 3.4±0.37; 4th min = 3.6±0.33.*

Conclusion - *Although coronary sinus flow had significantly increased in the first minute, higher velocities were seen at third and fourth minutes, indicating that these should be the best times to study coronary sinus flow with intravenous adenosine in continuous infusion.*

Keywords: transesophageal Doppler echocardiography, coronary sinus, coronary reserve

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The capacity to increase coronary blood flow in response to an appropriate stimulus was determined by coronary flow reserve (CFR) or vasodilatating coronary reserve [1]. The most important methods for studying CFR are expansive and invasive, requiring time and appropriate laboratory equipment [2-4]. The main techniques used are flow measurement with intracoronary Doppler, positron emission tomography, and measuring coronary sinus flow by dilution term [5]. In the last few years, several authors have shown the possibility of velocity monitoring of coronary sinus flow (CSF) and CFR by transesophageal 2-dimensional Doppler echocardiography [6,7].

Transesophageal Doppler echocardiography (TEE) is a semi-invasive procedure, with a low rate of complications, which evaluates CSF in real time with good reproducibility, and allows the monitoring of flow before and after the administration of a vasodilator drug [8], providing important information about CFR [9].

CSF by TEE can be monitored within a distance of 1 to 1.5 cm, from the ostium with adequate alignment between the ultrasound beam and the coronary sinus (CS), where achieving adequate flow would be possible in more than 90% of cases [6].

This method is useful for evaluating coronary flow (CF) in cases of specific lesion in the left anterior descending coronary artery [10] or in situations with alterations in coronary circulation, as well as micro-circulation [9,10], being of great applicability in evaluating patients with myocardial ischemia [11]. As far as drugs used to evaluate coronary vasodilator capacity, adenosine and dipyridamole are Known to be effective for intravenous application. Adenosine induces quick and massive vasodilatation mainly mediated by A1 and A2 purinergic receptors, previously called P1 purinergic receptor subtype [12,13], and may provoke depression of the sinoatrial and atrioventricular nodes, being dose-dependent, and diminution of arterial blood pressure [14,15]. Dipyridamole and adenosine have been used to evaluate CFR; both drugs produce comparable increases in the total and

regional coronary flow. However, adenosine has fewer deleterious effects on cardiac electrophysiological properties [16]. Adenosine does not produce significant changes in ST segment, QT interval, myocardial creatine phosphate level or lactate level [17]. Adenosine has a short half-life and can be used in bolus or in continuous infusion with few side effects [12,17]. The effect of dipyridamole is slower and indirect, causing an increase in endogenous adenosine levels [18]. Recently, Kozàkovà et al [19] observed a more prominent vasodilator response with continuous adenosine infusion, while the response to dipyridamole is dose-dependent, which may lead to an underestimation of the vasodilator response in patients with obstructive disease of the coronary sinus [14].

The present study proposes an evaluation of the coronary blood flow reserve by transesophageal Doppler echocardiography examining coronary sinus flow velocity in the basal state and after intravenous adenosine in continuous infusion.

Methods

In the period from February through August 1997, we obtained technically adequate transesophageal Doppler flow samples for analysis of coronary sinus flow reserve in 10 healthy volunteers (mean age 37±8 years, 5 men) with no history of heart or systemic disease and with mean left ventricular mass index analyzed by transthoracic echocardiography of 87 g/m^2±18.

Coronary stenosis was supposedly excluded after a non-invasive investigation (clinical history, blood samples, basal electrocardiogram, normal treadmill test, normal effort thallium stress test, transthoracic and transesophageal Doppler echocardiography).

All subjects were requested to abstain from xanthine-containing, food and drinks for at least 30 hours before the examination.

This study was approved by the Scientific Commission and Ethics Committee of the Heart Institute of the University of São Paulo (USP, Brazil) and the University of Zürich (Switzerland). Subjects were included after giving informed consent.

The control group was screened at the intensive care unit. During the study, a Dixtal monitor (Dixtal Biomedical Ind. & co. Ltd., São Paulo, Brazil) continuously monitored blood pressure by non-invasive means with pulse oximetry and 3-lead electrocardiography. A 12-lead electrocardiogram was recorded in the basal state and at the end of every minute of vasodilator drug infusion. Injectable adenosine was provided by a laboratory (Wyeth Lab., Paris, France) and infused with an OT-601 Pump (JMS Co., Ltd. Hiroshima, Japan) in a continuous solution for 4 minutes while the examination was recorded on videocassette tapes (Panasonic VCR) for later analysis.

A 3-liter/minute nasal catheter with oxygen and peripheral intravenous punching with a number 18G intravascular catheter was introduced into the right antecubital vein for administration of a vasodilator drug by continuous infusion. Blood pressure was assessed in the contralateral arm to that receiving adenosine at the end of every minute.

A transthoracic Doppler echocardiography with a 2.5 MHz transducer was performed before the semi-invasive procedure in all subjects.

After application of topical anesthesia of the oropharynx with xylocaine spray, the subject was placed on the left side, lightly sedated with intravenous midazolan in a dose of 0.15 to 0.20 mg/kg. The transducer was lubricated with lidocaine gel and with flexing of the subject's head, a transesophageal 5 MHz monoplane or biplane probe ATL 6000 and 4 Plus (Ultramark ® 6 and 4 plus; Advanced Technology Laboratories, Inc.; Bothell, WA, U.S.A.) was introduced into the upper esophagus. The Doppler flow samples in the coronary sinus were obtained through the transversal and longitudinal plan approximately 30 to 40 cm from the incisors, with a light retroflexion of the transducer (fig. 1).

Investigation of flow velocity in the coronary sinus – The pulsed Doppler sample was positioned in the coronary sinus within a distance of 10 to 15 mm from the ostium and at an angle between the Doppler beam and the long spindle of the coronary sinus of less than 30 degrees. Flow velocity was recorded during 06 consecutive cardiac cycles in prolonged expiration in the basal state and during adenosine infusion. The diameter of the coronary sinus was measured in the basal state and after administration of the vasodilator drug. Intravenous adenosine was infused at a dose of 140 µg/kg/min, for 4 minutes, with recording of the flow velocity at the end of every minute. Anterograde systolic maximum velocity, anterograde diastolic maximum velocity, retrograde maximum velocity, systolic and diastolic velocity time integral (VTI S and VTI D, cm/sec) were analyzed. The coronary flow reserve was calculated as the relation between coronary sinus flow in the basal state and in a state of maximum vasodilatation (CFR = PSV + PDV – PRV/basal PSV).

Primarily, all the variables were analyzed descriptively. For the continuos variables, this analysis was made through observation of minimum and maximum values, and

Fig. 1 - "Zoomed" 2-D image of the coronary sinus, from which the samples of flow were obtained. CS- coronary sinus; RA- right atrium; TV- tricuspid valve; RV- right ventricle.

through calculation of averages and standard deviation. For the classificatory variables, the absolute and relative frequencies were calculated.

To check the group behavior regarding the conditions studied, the Profile Analysis Technique [20] was used, which consists of the adjustment of a multi-varied linear model, by which the following hypotheses were tested: H01: The average response profile is parallel to the abscissa axis, ie, the evaluation condition factor has no effect. When H01 was rejected, the interest contrasts were tested.

In testing the above hypotheses, the Wilks' test was used, with approximation of the F statistic.

The comparisons between the averages of flow velocities in the control group were made through the nonpaired Student t- test [21] and the level used was p<0.001. The significance level used for the tests was 5%.

Results

The semi-invasive interventions occurred with no incidents in any subjects. Their recovery evolved in a stable manner without any clinical occurrences. No significant changes in left ventricular end-diastolic and systolic diameter and ejection fraction were encountered with adenosine.

During adenosine infusion we did not observe any side effects in the control group. In the beginning of the examination, a light increase occurred in heart rate and blood pressure. Two minutes later, blood pressure and heart rate were back to normal. At that moment, we began the adenosine infusion.

Adequate samples of flow velocity in the CS were obtained in 10 subjects of the control group (100%) (fig. 2).

From the morphological point of view, 2 distinct Doppler sample curves in the CS were obtained, a biphasic curve with systolic predominant component that occurred in 8 out of 10 subjects (80%) and a diastolic predominant component in 2 remaining subjects (20%).

Through quantitative analyses, flow samples in the control group were investigated as were the peak systolic
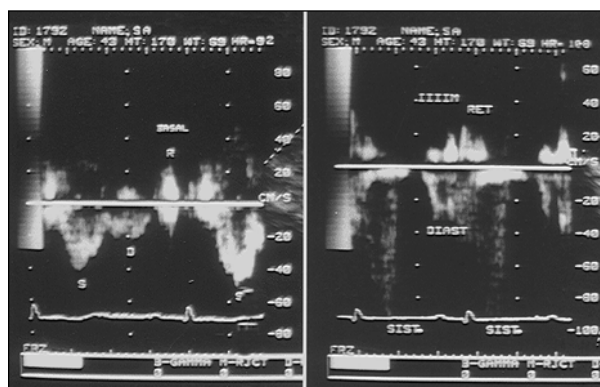
Fig. 2 - Normal biphasic Doppler flow pattern recording in coronary sinus characterized by systolic and diastolic anterograde flow as well as a short period of end-diastolic retrograde flow. Coronary sinus flow in the basal state and at third minute during adenosine infusion. S- systolic flow; D- diastolic flow; R- retrograde flow.

velocity, peak diastolic velocity, mean systolic velocity, mean diastolic velocity, and systolic and diastolic velocity time-integral (VTI S and VTI D. cm/s). A short diastolic retrograde peak flow was observed in the CS in all subjects. The coronary flow velocity, variables (PDV, MDV, VTI D, PSV, MSV, VTI S) and coronary flow reserve, increased in all subjects during adenosine infusion (tab. I).

Analyses of heart rate and blood pressure during adenosine infusion - We believe that no interference with heart rate and mean blood pressure occurred in CSFR; however, a light increase in the heart rate and a decrease in blood pressure were observed during adenosine infusion.

Coronary flow reserve in normal subjects - Coronary sinus flow reserve had significantly increased during the first minutes. Higher velocities were seen at the third and fourth minutes, indicating that these should be the best times to study coronary sinus flow with intravenous adenosine during continuous infusion.

Results are shown as mean and standard deviations (2.2±0.21 1°min, 3.0±0.30 2°min, 3.4±0.37 3°min, 3.6±0.33 4° min) (fig. 3).

	PSV	PDV	PRV	MSV	MDV	VTIS	VTID	HR	SBP	DBP
Rest	39.3	25.3	23.2	33.3	21.3	7.2	4.3	77	123	78
	± 7.8	± 3.6	±4.8	± 5.9	± 3.9	±1.6	±1.4	± 14	± 12	± 17
Aden	68.6	46.7	25.7	53.5	37.3	14.9	9.5	82	115	76
1min	± 18.4	± 17.3	± 4.1	± 15.2	± 18.5	± 6.7	± 2.8	± 23	± 16	± 15
Aden	88.7	58.7	28.4	66.3	44.9	16.8	13.8	95	115	72
2min	± 20.4	± 8.9	± 4.3	± 21.4	± 11.3	± 7.2	± 6.5	± 16	± 24	± 17
Aden	106.8	59.8	32	73.7	45.8	21.7	14.4	94	112	73
3min	± 22.3	± 15.4	± 7.5	± 24.3	± 12.1	± 8.1	± 7.3	± 16	± 16	± 19
Aden	111.4	66.45	35.4	82.8	52.1	23.8	15.6	90	110	70
4min	± 19.2	± 19.3	± 8.2	± 13.2	± 15.3	± 6.4	± 6.4	± 17	± 16	± 11

Table I - Study of coronary sinus flow reserve through transesophageal Doppler echocardiography in normal subjects.

Results are shows as mean and standard deviations

Rest- basal state; PSV- peak systolic velocity; PDV- peak diastolic velocity; PRV- peak retrograde velocity; MSV- mean systolic velocity; MDV- mean diastolic velocity; VTIS - systolic velocity-time integral; VTI D- diastolic velocity-time integral; HR- heart rate; SBP- systolic blood pressure; DBP- diastolic blood pressure; Aden- adenosine.
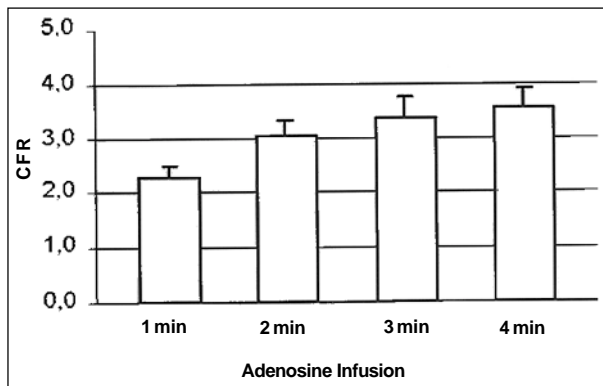
Fig. 3 - Coronary flow reserve (CFR) in coronary sinus in normal subjects.

Discussion

In the last 2 decades, a surprising development has taken place in transesophageal Doppler echocardiography (TEE), making it possible to measure blood flow velocity (BFV) in the coronary arteries and coronary sinus. In addition, the infusion of intravenous vasodilator drugs is now possible during the examination, making it possible to increase the BFV, allowing comparisons between flows during the basal state and flow during maximum dilatation.

TEE with adenosine infusion constitutes a new semi-invasive method that permits the determination of CFR through blood flow samples in normal subjects and in a variety of cardiac diseases [6,19,22] making the comparis with other methods already used as described in the introduction [4,23].

Determination of CFR is an established method for assessing information about coronary artery stenosis [24] and has been used to evaluate normal subjects and results of PTCA [25] and, we propose through this investigation, to evaluate healthy volunteers to compare subsequently with results obtained in patients after PTCA and bypass surgery.

To evaluate CFR, we chose adenosine because it is an effective drug with few side effects when compared with other drugs. In 1991, Illiceto et al [8] described for the first time the calculation of CFR by TEE recordings of CFV in the LAD in patients without and in patients with coronary artery disease. The CFR in the control group without coronary disease was 3.2 ± 1.0, and in patients with significant stenosis of the LAD it was 1.5 ± 1.5.

In the same year, Kern et al [17] investigated CFR with adenosine infusion in a dose of 50, 100 and 150 μg/kg and measured CFV in the basal state and the hyperemic response for 3 minutes in patients without coronary disease and observed an increase in the flow velocity with the maximal dose infused and CFR was 2.94 ± 1.5.

In 1995, Redberg et al [26] reported the possibility of flow monitoring in the LAD in approximately 70% to 80% of cases. Tsutsui et al [27] demonstrated CFR during adenosine infusion in the LAD in a control group of healthy volunteers and observed similar results –to those of previous studies. When CFR is > 2, no critical LAD stenosis exists [28].

Doppler flow sample measurements in the CS during intravenous dipyridamole were obtained for assessment of CSF reserve comparing patients without cardiac disease and patients with idiopathic dilated cardiomyopathy [6].

In Siostrzonek et al [6] control group, 9 patients with suspected cerebral embolism but without cardiac disease had a CFR of 3.4 ± 2, and a CFR value of 1.8 was the reference used to compare patients without cardiac disease and patients with dilated cardiomyopathy. In that study, a significant increase in CSF > 95% was observed in the control group as was an increase in CSF and CFR only in 3 of 9 patients with dilated cardiomyopathy.

In 1997, Mundigler et al [7] evaluated the CFR in 2 different groups of patients. Fourteen neurosurgical patients without cardiac disease composed their control group, and 2 distinct samples were considered for their studies in CS. When CFR was calculated through anterograde flow velocity-time integral, the value was 2.59 ± 0.74, and when calculated through anterograde maximum flow velocity, the CFR was 1.76 ± 0.52. In some studies [6,7,22] the CFR values by TEE in the coronary sinus were significantly reduced in patients with idiopathic dilated cardiomyopathy, syndrome X, and significant LAD stenosis when compared with other groups without cardiac disease.

In the present study, Doppler flow samples monitoring in real time beat-to-beat in the CS were feasible in all subjects, and CFR was calculated as the ratio between blood flow in the basal state and the maximum measured hyperemic blood flow with adenosine infusion.

Retrograde peak flow was present in all subjects and was included in the calculation of CFR in the CS (CFR = PSV + PDV - PRV/PSV). The evaluation of flow velocity and CFR in our control group was superior to the ones described so far because our control group was formed of young healthy volunteers without neurological and cardiac disease, and from the first minutes of adenosine infusion, we observed CFR > 2. May be that is the reason why we found CFR more homogenous during the entire study protocol.

Our original study shows the potential reliability of the TEE method before and after intravenous adenosine infusion in normal subjects with supposedly normal left ventricular function. The measurement technique of CFR in the coronary sinus of the present study is the first one described. Technically, the achievement of samples in the coronary sinus was easier to obtain in spite of some interference with the Doppler signal.

Despite the fact that the TEE method had been studied by several authors who demonstrated its efficiency, limitations do exist: 1) Our control group was formed by young, healthy volunteers, and we evaluated a small group; however, the analyzed group had uniform pattern flow samples; 2) The coronary sinus flow measurement was sometimes difficult due to the heart and breathing movements of the subjects mainly because of intolerance to the examination. 3) Subjects, who are lightly sedated, sometimes could not cooperate in an adequate way during the examination; 4) In several homogenous cardiac cycles, CSFV had varia-

tions dependent on the breathing cycles, which modified the position of the transducer and changed the patterns of the flow samples.

Therefore, it is important to consider the position of the transducer to obtain samples as close as possible to the expected average.

New data about the subjects condition will be possible through subsequent studies, suggesting a routine application of the method due to low risk and low cost, and be-

cause TEE with adenosine infusion is rapid, safe, and effective.

Conclusion - In our Doppler echocardiography study we demonstrate that coronary sinus flow velocity and coronary flow reserve increased during intravenous adenosine infusion in the coronary sinus in normal subjects and that the systolic variables (PSV, MSV and VTI S) were superior to the diastolic (PDV, MVD and VTI D) ones.

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