Türk Kardiyol Dern Arş 1998; 26: 362-367

Effects of Ionic Versus Non-ionic Contrast Agents on Dispersion of Ventricular Repolarization

Armağan ALTUN, MD, Gültaç ÖZBAY*, MD
*Department of Cardiology, Trakya University, School of Medicine, Edirne, Turkey * Professor of Cardiology, Head Department of Cardiology, Trakya University, School of Medicine, Edirne, Turkey*

İYONİK VE İYONİK OLMAYAN KONTRAST AJANLARIN VENTRİKÜL REPOLARİZASYON DİSPERSİYONU ÜZERİNE ETKİLERİ

ÖZET

İyonik ve iyonik olmayan kontrast ajanlar kardiyovasküler teşhis ve girişimsel işlemlerde kullanılırlar ve genelde iyi tolere edilirler. Bununla birlikte hastaların küçük bir yüzdesinde kontrast ajan enjeksiyonu sonrasında geçici hipotansiyon, bradiaritmi, ventriküler aritmi veya alerjik reaksiyon oluşur. Ventriküler taşiaritmiler tehlikeli olabilir. Yüzeyel EKG'deki QT dispersiyonu, ventrikül repolarizasyon farklılığını gösterir ve bundan dolayı aritmi riski için bu göstergelerden biri sayılabilir. Bu çalışma iyonik (Ioxaglate) ve iyonik olmayan (Iopamidol) kontrast ajanların koroner arter hastaları üzerindeki proaritmik etkilerini araştırmak amacıyla yapıldı.

33 erkek (yaş: 55.2±9.8 yıl) koroner arter hastasına koroner anjiyografi uygulandı. Tüm hastaların sol ventrikülogramları, sağ ve sol koroner arter selektif enjeksiyonundan önce yapıldı. 16 hastaya iyonik (Ioxaglate), 17 hastaya iyonik olmayan (Iopamidol) kontrast ajan verildi. Sol ventrikülogram öncesi ve sonrası tüm hastaların simültane 6 kanal kayıt yapan EKG cihazı ile standart gğüs derivasyonları kaydedildi. EKG kayıtları yüksek hızda (100mm/s) ve yüksek kazançta (20mm/mV) alındı ve daha sonra değerlendirildi. İstatistik analiz için paired student-t testi kullanıldı, tüm sonuçlar ortalama±SD olarak açıklandı.

QTc dispersiyonu (p=0.003), JTc dispersiyonu (p=0.008), TTc dispersiyonu (Tpeak-Tend) (p=0.017), QTdispersiyonu/RR oranı(p=0.0002), JTdispersiyonu/RR oranı(p=0.0015), JTa dispersiyonu/RR oranı (p=0.033) ve TTdispersiyonu/RR oranı(p=0.005) iyonik (Ioxaglate) kontrast ajan grubunda arttı. İyonik olmayan (Iopamidol) kontrast ajan grubunda ise yalnızca TTdispersiyonu/RR oranı (p=0.043) arttı. Ioxaglute olan hastalarda 3'ünde kompleks vefiküler erken vurular, 1'inde nonsustained ventriküler takikardi (VT), Iopramidal alanlardan 2'sinde kompleks ventriküler erken vuru, 1'inde non-sustaired VT oluştu. Sustained VT ya da ventriküler fibrilasyon hiçbir hastada oluşmadı.

Bu veriler iyonik olmayan (Iopamidol) kontrast ajanın, iyonik (Ioxaglate) kontrast ajandan daha az elektrofizyolojik parametreyi olumsuz yönde etkilediğini ve ventrikülerin uyarılabilirliğini arttırabileceğini göstermektedir.

Received: March 5, 1998, accepted June 11, 1998
Corresponding author: Armağan Altun, MD. Denge Yapı Koop D blok D: 8 22030 Edirne-Turkey
Tel::+90 284 212 19 13 Faks:+90 284 235 76 52

Anahtar kelimeler: *Koroner anjiyografi, kontrast ajan, iyonik, iyonik olmayan, QT dispersiyonu*

The number of cardiovascular diagnostic and interventional procedures being performed in cardiac catheterization laboratories in all countries continues to rise steadily. There has been a steady decline in overall morbidity and mortality associated with the procedure [1-2]. Many of the complications and adverse reactions encountered during cardiac catheterization are directly related to the contrast agent [1-5]. Adverse hemodynamic and electrophysiologic effects of contrast agent at cardiovascular diagnostic and interventional procedures are also reduced although a reduction of mortality has not been proven [5-8]. Contrast agents produce a variety of adverse hemodynamic (hypotension) and electrophysiologic (bradyarrhythmias, ventricular tachyarrhythmias, QT prolongation, ST-segment and T waves changes) are due to the osmolality, sodium content, and calcium-chelating properties. Ventricular tachyarrhythmias can be dangerous. QT dispersion refrects variations in repolarization in different regions of myocardium, which presumably represents an the electrophysiological substrate for ventricular tachyarrhythmias [9-15]. QT dispersion may be of value in examing the proarrhythmic effects of drugs [16]. Hovewer no prior studies have examined the effects of ionic versus non-ionic contrast agents on dispersion of ventricular repolarization. Therefore, the purpose of the present study was to determine the effects of ionic (Ioxaglate) versus non-ionic (Iopamidol) contrast agents on regional differences in ventricular repolarization.

MATERIAL and METHODS

The study was of a randomized double-blind design for comparison Ioxaglate meglumine 39.3% and Ioxaglate so-

dium 19.6% (Hexabrix-320), an ionic low osmolar contrast agent and Iopamidol 76% (Iopamiro-370), a non-ionic low osmolar contrast agent used for left ventriculography and selective coronary angiography. Hexabrix-320 has an osmolality of 600 mOsm/kg and a 32% iodine content; these values are 800 mOsm/kg and 37% respectively, for Iopamiro-370. The chief cardiac catheterization laboratory technician selected the contrast agent from commercially available lots a randomized list. The physicians analysing the electrocardiographic data were blinded to the contrast agent. All patients undergoing left ventriculography and selective coronary angiography at the Trakya University, School of Medicine, Cardiology Department were eligible for this study, except those; 1) with unstable angina pectoris on intravenous nitroglycerin therapy; 2) with an acute myocardial infarction receiving streptokinase infusion; 3) undergoing percutaneous transluminal coronary angioplasty; 4)with mitral and/or aortic valve disease; 5)with atrial fibrillation or a permanent pacemaker; 6) with more than 2 extrasystoles/min; 7) with intraventricular conduction defect or WPW syndrome; 8)with taking any antiarrhythmic drugs or drugs known to affect the QT interval; 9)with the serum potassium concentration <3.9 mmol/l; 10)with severe renal and hepatic disease; 11)with contrast agent injection less than one week prior to this study; 12)with a history of sensitivity to contrast agent or iodinecontaining compounds. All patients received diazepam (10 mg) as premedication. Medications for the treatment of angina pectoris were given as prescribed; that is, no dosages were withheld before catheterization. No patient received atropine before or during the procedure. Electrocardiographic leads I and II were monitored continuously during the procedure. Coronary angiography was performed under local anaesthesia via the femoral route, with the aid of an 6Fr Cordis introducer sheath and 6Fr Cordis Judkins catheters. The catheters were connected with devices for both pressure monitoring and the flushing of an isotonic Na-CI-solution with heparin 5 IU/ml. In all patients left ventriculogram preceded the selective injections in the right and left coronary arteries. The left ventriculogram was performed using 6Fr Cordis high flow pigtail catheter; 35 ml contrast agent preheated to 37°C was injected at 13 ml/s. The left ventriculogram in right and left oblique projections were done according to standart methods. On-line digital angiography was available for image enhancement and quantitative programs were used in selected instances. Ejection fraction was determined using routine single or biplane arealength methods. Coronary artery disease was defined as ≥50% luminal diameter narrowing of a major epicardial artery in any projection.

All patients ECG's were recorded with simultaneous 6 channels electrocardiograph from standart chest leads before and after left ventriculogram injections. High speed (100 mm/s) and high gain (20 mm/mV) ECG recordings were taken and analysed later. QT interval was measured manually from the onset of the QRS complex to the end of the T wave, defined visually as the point where the T wave returned to the TP baseline. QTapex(QTa) interval was measured from the onset of the QRS complex to the apex of the T wave, defined as the peak of the T wave and in the case of biphasic T waves the peak of the largest T wave component. JT and JTapex (JTa) intervals were measured from the end of the QRS complex to the end or apex of the T wave, respectively. TT (Tapex-Tend) interval was measured from the apex of the T wave to the end of the T wave. JTa interval reflects the initial part of repolarization, TT interval reflects the terminal portion of ventricular repolarization [17]. Each measurement is given as the mean value of three consecutive beats. Each interval was corrected for the patient's heart rate using Bazzett's (QTc, OTac,....etc). Dispersion of all intervals and dispersion ratios (defined as dispersion divided by cycle length in miliseconds) were calculated [9]. Paired student-t test was used to compare parameters. $P<0.05$ was taken as significant. All results in the text and tables are expressed as mean±1 standard deviation.

RESULTS

Thirty-three male patients were included in the study; 16 received Ioxaglated and 17 Iopamidol. The mean age of the Ioxaglate group was 55.1±9.8 years, while that of the lopamidol-used patients was 55.2±10 years (p=NS) (Table1). There were no significant differences between the two contrast agent groups in the number of patients with significant 1-,2-, or 3 - vessels disease (Table 1). There was no significant differences in the indexes of left ventricular function, such as ejection fraction, left ventricular end-diastolic volume, left ventricular end-diastolic pressure, left ventricular wall motion score index and ORS score (according to modified Selvester-Wagner score system), between the 2 groups (Table 1).

We found TTmean interval, QTc mean interval, QTc dispersion, QTac mean interval, JTc mean interval, JTc dispersion, JTac mean interval, TTc mean interval, TTc dispersion, QTdispersion/RR ratio, JTdispersion/RR ratio, JTa dispersion/RR ratio, and TTdispersion/RR ratio increased in ionic contrast agent (Ioxaglate) group (Table 2). RR interval decreased in ionic conrast agent (Ioxaglate) group (Table 2).

In non-ionic contrast agent (Iopamidol) group; TTmean interval, JTc mean interval, TTc mean interval and TTdispersion/RR ratio increased after left ventriculogram (Table 3). There was no significant difference in other parameters (Table 3).

Couplet/triplet ventricular premature beats (VPB) and nonsustained ventricular tachycardia (VT) (5 to 30 VPBs) occurred in 3 patients and 1 patient used

Table 1. Patients characteristics

	Ionic contrast agent (Ioxaglate) n:16	Non-ionic contrast agent (Iopamidol) n:17	P value
Age (year)	55.1±9.8	55.2±10	NS
No. of coronary arteries with stenosis ≥50% of diameter			
1	10	11	NS
2	4	6	NS
3	2	0	NS
Left ventricular ejection fraction (%)	56±20	62±16	NS
Left ventricular end-diastolic volume (ml)	158±84	128±69	NS
Left ventricular end-diastolic pressure (mmHg)	15±9	16±7	NS
Left ventricular wall motion score index	2.12±1.23	1.81±0.99	NS
QRS score	4.81±4.13	3.5±2.48	NS

Table 2. Mean values of intervals, dispersions and dispersion ratios in ionic contrast agent (Ioxaglate) group

	Before ventriculogram	After ventriculogram	P value
QT mean interval (ms)	407±57	399±39	NS
QT dispersion (ms)	48.1±23.4	58.9±22	NS
QTa mean interval (ms)	324±44	315±36	NS
QTa dispersion (ms)	42.9±20.4	42.3±27.6	NS
JT mean interval (ms)	313±45	305±38	NS
JT dispersion (ms)	47±20.9	57.1±21.4	NS
JTa mean interval (ms)	234±46	222±34	NS
JTa dispersion (ms)	47.9±24.6	45.3±25.5	NS
TTmean interval (ms)	85±16	94±18	**0.038**
TT dispersion (ms)	51.8±22	57.9±15.8	NS
QTc mean interval (ms)	431±46	473±41	**0.0014**
QTc dispersion (ms)	50.6±22.9	70.3±24.7	**0.003**
QTac mean interval (ms)	344±40	373±28	**0.004**
QTac dispersion (ms)	45±20.4	54.1±34.3	NS
JTc mean interval (ms)	332±39	361±35	**0.001**
JTc dispersion (ms)	49.7±20.8	68.7±24	**0.008**
JTac mean interval (ms)	248±43	262±25	**0.04**
JTac dispersion (ms)	45.7±21.6	53.5±30.1	NS
TTc mean interval (ms)	90±16	111±24	**0.002**
TTc dispersion (ms)	54.5±21.8	69.7±20.8	**0.014**
QRS duration (ms)	94±9	97±10	NS
RR interval (ms)	896±150	723±124	**0.0013**
QT dispersion/RR ratio	0.053±0.023	0.083±0.03	**0.0002**
QTa dispersion/RR ratio	0.073±0.147	0.065±0.047	NS
JT dispersion/RR ratio	0.053±0.022	0.081±0.028	**0.0015**
JTa dispersion/RR ratio	0.048±0.022	0.068±0.04	**0.033**
TT dispersion/RR ratio	0.058±0.024	0.084±0.031	**0.005**

Ioxaglate, in 2 patients and I patient used Iopamidol, respectively. Sustained VT or ventricular fibrillation (VF) did not occur. All ventricular arrhythmias developed during injection of contrast media. There was no major complications, such as cerebrovascular accident, embolic episodes, or death.

DISCUSSION

Contrast agent selection is important to cardiologists because the number of cardiovascular diagnostic procedures performed in cardiac catheterization laboratories in all countries continues to rise steadily. Key differences among contrast agents are their tonicity (low-600 to 900 mOsm/kg - versus high - 2000

Table 3. Mean values of intervals, dispersions and dispersion ratios in non-ionic contrast agent (Iopamidol) group.

	Before ventriculogram	After ventriculogram	P value
QT mean interval (ms)	375±33	383±26	NS
QT dispersion (ms)	54.4±21.5	60.2±27.3	NS
QTa mean interval (ms)	307±26	304±26	NS
QTa dispersion (ms)	50±25.4	55.6±25.6	NS
JT mean interval (ms)	280±38	288±27	NS
JT dispersion (ms)	55.2±21.3	60.7±25.8	NS
JTa mean interval (ms)	212±29	205±23	NS
JTa dispersion (ms)	50.8±26.5	57.7±25.8	NS
TTmean interval (ms)	76±15	86±13	**0.007**
TT dispersion (ms)	51.4±20.1	62.2±25.1	NS
QTc mean interval (ms)	414±23	439±26	**0.0007**
QTc dispersion (ms)	60.6±25.1	69±31.9	NS
QTac mean interval (ms)	339±29	348±21	NS
QTac dispersion (ms)	55.6±29.1	63.5±28.6	NS
JTc mean interval (ms)	309±28	330±24	**0.001**
JTc dispersion (ms)	62.1±23.2	70±30	NS
JTac mean interval (ms)	234±28	235±21	NS
JTac dispersion (ms)	53.4±28.6	64.3±27.6	NS
TTc mean interval (ms)	84±13	98±16	**0.002**
TTc dispersion (ms)	57±23.3	70.8±26.9	NS
QRS duration (ms)	93±7	95±5	NS
RR interval (ms)	830±139	766±102	NS
QT dispersion/RR ratio	0.065±0.031	0.081±0.037	NS
QTa dispersion/RR ratio	0.062±0.032	0.073±0.032	NS
JT dispersion/RR ratio	0.068±0.03	0.08±0.036	NS
JTa dispersion/RR ratio	0.062±0.034	0.075±0.031	NS
TT dispersion/RR ratio	0.063±0.027	0.081±0.029	**0.043**

mOsm/kg-osmolality), whether they are ionic or non-ionic, and their cost, averages $5 (high osmolality) to $100 (low osmolality) per 100 ml. All iodinated contrast agents currently in use in cardiovascular diagnostic and interventional procedures exhibit some degree of cardiovascular adverse effects related to the chemical structures of the substances and to the osmolality, viscosity, cation content, and stabilizer content of the solution. Most ionic contrast agent are high osmolality and non-ionic contrast agent of low osmolality. High osmolality ionic contrast agents are associated with several infrequent adverse effects of modest clinical significance including nausea, vomiting and allergic reactions. Bradyarrhythmia, abnormalities in repolarization manifest by ST segment and T wave alterations, depression of ventricular systolic function and lowering of systolic blood pressure occur commonly with ionic contrast agents [18]. Because of their low osmolality and chemotoxicity, non-ionic contrast agents show a reduced risk of cardiohemodynamic adverse effects during coronary angiography, when compared with ionic contrast agents, leading to their strong preference among cardiologists despite their dramatically higher cost [6,8,19-21]. In particular, because the effects of non-ionic contrast agents on ventricular function are less pronounced, their use in "high risk" patients has been advocated. Contrast agents that are ionic but of low osmolality appear to produce adverse effects intermediate between high osmolality ionic contrast and non-ionic contrast agents, but data are limited [18]. An "ideal" contrast agent for cardiovascular diagnostic and interventional procedures should have an osmolality isotonic to blood, a viscosity comparable with blood, and no influence on the electrolyte balance. Deviations from these theoretical requirements may induce characteristic electrophysiologic and cardiohemodynamic changes.

The QT interval reflects the traditional electrocardiographic parameter of the duration of ventricular repolarization. Several studies reported QT interval prolongation produced by ionic contrast agents [6,21-25]. Wisneski et al [21] reported that cardiac injections of Ioxaglate produced significant QT prolongations, whereas similar injections of Iopamidol did not result in any changes in this parameter. Fransson et al [6] found that the QT interval was prolonged after intracoronary injections by Iodixanol and Ioxaglate. Some investigators reported that the reduction in ionized calcium in coronary circulation played a major

role in the prolongation of the QT interval, which may lower the threshold for ventricular tachyarrhythmias [20,22,24,26-28]. The addition of sodium and calcium ions to non-inoic contrast agent has been discussed to reduce the risk of ventricular fibrillation [20,26-28]. It is not clear, however, if this effect is induced by the molecule itself or by the addition of electrolytes.

Interlead variability of QT interval (QT dispersion) on surface ECG reflects regional variations in myocardial repolarization. Increased QT dispersion has been found to be associated with an increased incidence of malignant ventricular arrhythmias and sudden cardiac death [10-15]. QT dispersion provides a potentially simple, cheap, non-invasive method of measuring underlying dispersion recovery of ventricular excitability and should be defined in a way that most accurately reflects this state. Zareba et al [15] showed that increased JT dispersion and prolonged QRS duration were independent factors associated with subsequent arrhythmic cardiac death in ischemic patients. They reperted that, the simultaneus evaluation of the QRS duration, a measurement of ventricular depolarization time, and JT dispersion parameters provided insight into potential mechanisms (delayed depolarization and heterogenous repolarization) that might be associated with arrhythmic cardiac death. TT interval (between the peak and the end of T wave) reflects the terminal part of ventricular repolarization [17]. Therefore TT dispersion reflects inhomogeneity of the terminal part of ventricular repolarization. Neither the initial part of repolarization (JTa) nor conduction abnormalities contribute substantially to TTd. However, no prior studies have examined the effects of ionic (loxaglate) versus non-ionic (lopamidol) contrast agents on QT dispersion. Therefore, the present prospectively designed study aimed to investigate the effect of ionic (loxaglate) versus non-ionic (lopamidol) contrast agents on regional differences in ventricular repolarization in patients with coronary artey disease.

This study shows that left ventriculogram injections of loxaglate are associated with significant increased dispersion of recovery of ventricular excitability (QTc dispersion, JTc dispersion, TTc dispersion, QTdispersion/RR ratio, JTdispersion/RR ratio, JTa dispersion/RR, TTdispersion/RR ratio), while similar injections of lopamidol produce only change in one of these parameters (TTdispersion/RR ratio). Although loxaglate and lopamidol have similar osmolalities, their response of regional heterogeneity of ventricular repolarizatin differs markedly. Osmolality, however, is not the only property affecting the parameters measured, and chemotoxicity may be another factor of importance [3,25,29,30].

Study limitations

A limitation of this study is that the sample was relatively small population of patients who were very carefully studied. Thes was due to in part to patient selection criterias. The ECGs were recorded on a six-chanel recorder (paper speed 100 mm/s, amplifier gain 20 mm/mV) from standart chest leads and read manually according to a strict protocol. Despite the pitfalls of manual analysis, this approach has been accepted as the most accurate for manual measurement of QT intervals. We measured precordial QT intervals because we believe that the unipolar precordial ECGs more accurately reflect local ventricular repolarization times than do the limb leads [10,11,28]. VT/VF occurs in 0.77 to 1.28% of patients undergoing coronary angiography [31]. In our study nonsustained VT occurred in 2 patients (6.06%), sustained VT and VF did not occur. We suggest this higher ratio comes from small study population. We did not evaluate these contrast agents for patients comport after left ventriculogram, such as chest pain, fever, shivers, burning, nausea, vomiting, dyspnoae, allergic, cutaneous. Our impression is that there is less patient discomfort after injections with lopamidol.

Conclusions and clinical implications

This data suggest non-ionic contrast agent (lopamidol) result in significantly fewer effects on electrophysiologic parameters and less increase on ventricular excitability than ionic contrast agent (loxaglate).

Acknowledgment

We express appreciation to Fatih Özçelik, MD, and Turhan Kürüm, MD, for assistance in the cardiac catheterization laboratory.

REFERENCES

1. Gwost J, Stoebe T, Chesler E, Weir EK: Analysis of the complications of cardiac catheterization over nine years. Cath Cardiovasc Diagn 1982; 8: 13-21.

2. Shenadi WH: Contrast media adverse reactions: Occurrence, recurrence and distribution pattern. Radiology 1982; 143: 11-17.

3. Brogan WC, Hillis LD, Lange RA: Contrast agents for cardiac catheterization. Conceptions and misconceptions. Am Heart J 1991; 122: 1129-1133.

4. Bush WH, Swanson DP: Acute reactions to intravascular contrast media. Types, risk factors, recognition, and specific treatment. Am J Radiol 1991; 157: 1153-1157.

5. Lawrence V, Matthai W, Hartmaier S: Comparative safety of high-osmolality and low-osmolality radiographic contrast agents. Report of a multidisciplinary working group. Invest Radiol 1992; 27: 2-8.

6. Fransson SG, Stenport G, Anderson M: Immediate and late adverse reactions in coronary angiography. A comparison between iodixanol and ioxaglate. Acta Radiol 1996; 37: 218-222.

7. Grines CL, Schreiber TL, Savas V, et al: A randomized trial of low osmolar ionic versus nonionic contrast media in patients with myocardial infarction or unstable angina undergoing percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1996; 27: 1381-1386.

8. Lembo NJ, King SB, Roubin GS, Black AJ, Doughas JS: Effects of nonionic versus ionic contrast media on complications of percutaneous transluminal coronary angioplasty. Am J Cardiol 1991; 67: 1046-1050.

9. Altun A, Özbay G: A new method for determination of dispersion of ventricular repolarization. Proceedings of EUROPACE'97, 8th European Symposium on Cardiac Pacing, Monduzzi Editore, S.p.A.- Bologna p:1997; 151-13.

10. Jii JTY, Wyse GD, Gillis AM, Duff HJ, Solyso MA, Mitchell BL: Precordial QT interval dispersion as a marker of torsades de pointes. Circulation 1992; 86: 1376-1382.

11. Yunus A, Gillis AM, Duff HJ, Wyse G, Mitchell LB: Increased precordial QTc dispersion predicts ventricular fibrillation during acute myocardial infarction. Am J Cardiol 1996; 78: 706-708.

12. Goldner B, Brandspiegel HZ, Horwitz L, Jadonath R, Cohen TJ: Utility of QT dispersion combined with signal-averaged electrocardiogram in detecting patients susceptible to ventricular tacharrhythmia. Am J Cardiol 1995; 76: 1192-1194.

13. Fu GS, Meissner A, Simon R: Repolarization and sudden cardiac death in patients with impaired left ventricular function. Eur Heart J 1997; 18: 281-289.

14. Bogun F, Chan K, Harwey M, et al: QL dispersion in nonsustained ventricular tachycardia and coronary artery disease. Am J Cardiol 1996; 77: 256-259.

15. Zereba W, Moss AJ, Le Cessie S: Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease. Am J Cardiol 1994; 74: 550-553.

16. Cui G, Sen L, Sager P, Uppal P, Singh BN: Effects of amiodarone, sematilide, and sotalol on QT dispersion. Am J Cardiol 1994; 74: 896-900.

17. Altun A, Özkan B, Özçelik F, Altun G, Özbay G: Chronic sympathetic activation affects dispersion of ventricular repolarization in syndrome X. Proceedings of EUROPACE'97, 8th European Symposium on Cardiac Pacing, Monduzzi Editore, S.p.A. -Bologna 1997; p:155-158.

18. Moliterno DJ, Topol EJ: Another step toward resolving the constrast controversy. J Am Coll Cardiol 1996; 27: 1387-1389.

19. Katayama H, Yamaguchi K, Kozuka T, Takashima T: Adverse reactions to ionic and nonionic contrast media: A report from the Japanese committee on safety of contrast medial. Radiology 1990; 175: 621-628.

20. Mushick P, Wehrmann D, Schuhmann-Giampieri G, Krause W: Cardiac and hemodynamic tolerability of iodinated contrast media in the anesthetized rat. Invest Radiol 1995; 30: 745-753.

21. Wisneski JA, Gertz EW, Dahlgren M, Muslin A: Comparison of low osmolality ionic (loxaglate) versus nonionic (lopamidol) contrast media in cardiac angiography. Am J Cardiol 1989; 63: 489-495.

22. Caulfield JB, Ziv L, Harthorne JW: Blood calcium levels in the presence of arteriographic contrast material. Circulation 1975; 52: 119-123.

23. Murdock DK, Piao ZE, Euler DE, et al: The use of programmed electrical stimulation to assess the fibrillatory propensity of ionic and nonionic contrast media. Invest Radiol 1985; 20: 579-582.

24. Gertz EW, Wisneski JA, Chiu D, Akin JR, Hu C: Clinical superiority of a new nonionic contrast agent (lopamidol) for cardiac angiography. J Am Coll Cardiol 1985; 5: 250-258.

25. Mitsumori M, Hayakawa K, Soga T: Effects of contrast media on the RR and QT interval during coronary arteriography. Acta Radiol 1991; 32: 120-125.

26. Baath L, Besjakov J, Oksendal A: Sodium-calcium balance in non-ionic contrast media: Effects on the risk of ventricular fibrillation in the isolated rabbit heart. Invest Radiol 1993; 28: 223-227.

27. Vik-Mo H, Danielsen R, Folling M, Kloster Y, Skinningsrud K: Addition of sodium to the nonionic contrast medium iohexol during coronary angiography in man. Acta Radiol 1992; 33: 485-489.

28. Zukerman LS, Friehling TD, Wolf NM, Meister SG, Nahass G, Kowey PR: Effect of calcium-binding additives on ventricular fibrillation and repolarization changes during coronary angiography. J Am Coll Cardiol 1987; 10: 1249-1253.

29. Hanley PC, Holmes DR Jr, Julsrud PR, Smith HC: Use of conventional and newer radiographic contrast agents in cardiac angiography. Prog Cardiovasc Dis 1986; 28: 435-448.

30. Cumberland DC: Low-osmolality contrast medial in cardiac radiology. Invest Radiol 1984; 19 (suppl): S301-S305.

31. Grossman W: Complication of cardiac catheterization: Incidence, causes, and prevention. Grossman W, Baim DS (eds). Cardiac catheterization, angiograhy and intervention. Philadelphia, Lea&Febiger, 1991; p.36.