Iodine-123-Metaiodobenzylguanidine SPECT of Regional Cardiac Adrenergic Denervation in Brugada Syndrome

Denis Agostini, Patrice Scanu, Philippe Loiselet, Gérard Babatasi, Yves Darlas, Gilles Grollier, Jean Claude Potier and Gérard Bouvard

Service de Médecine Nucléaire, Service de Cardiologie and Service de Chirurgie Cardio-Thoracique, CHU Côte de Nacre, Caen, France

We present the case of 44-yr-old man who presented syncope with ventricular tachycardia in the setting of Brugada syndrome. In addition to the electrocardiographic evidence of the syndrome and the absence of apparent structural heart disease, clear defects of myocardial neuronal metaiodobenzylguanidine (MIBG) uptake on MIBG SPECT imaging also were found in inferior, apical and septal walls. Thallium-201 SPECT distribution was homogeneous along the left ventricle. Thus, cardiac MIBG scintigraphy provides information about left ventricular dysinnervation in a patient with Brugada syndrome, enhancing the clinical utility of myocardial MIBG SPECT imaging in life-threatening ventricular arrhythmias.

Key Words: Brugada syndrome; cardiac innervation; iodine-123-metaiodobenzylguanidine; SPECT

J Nucl Med 1998; 39:1129–1132

Brugada and Brugada (*1*) have recently described a syndrome including ventricular fibrillation coupled to right bundle branch block with left axis deviation and a prolonged His-ventricular delay (HV) interval and persistent ventricular repolarization (ST) segment elevation in three right precordial leads, with or without T-wave inversion on the electrocardiogram (ECG).

Regional sympathetic denervation may play a role in the genesis of arrhythmias; tissue deprived of its nerve supply responds in an exaggerated fashion to certain agents, a phenomenon called denervation supersensitivity (*2*). Metaiodobenzylguanidine (MIBG) is an analog of guanethidine that is taken up by the adrenergic nerve endings and appears to share common uptake and storage mechanisms with norepinephrine (*3,4*). When labeled with ^{123}I, MIBG allows evaluation of myocardial adrenergic uptake in humans (*5*). Assessment of cardiac adrenergic innervation using ^{123}I-MIBG is clinically useful in various heart diseases (*6,7*). We report on a patient with Brugada syndrome in whom regional cardiac adrenergic denervation was detected using ^{123}I-MIBG SPECT imaging.

CASE REPORT

A 44-yr-old man was referred to us because of syncope due to an episode of polymorphic ventricular tachycardia. Physical examination and chest radiograph were normal. Twelve-lead ECG showed a sinus rhythm with an incomplete right bundle branch block and a persistent ST segment elevation with T-wave inversion from leads V1 to V2 (Fig. 1). Programmed stimulation induced nonsustained polymorphic ventricular tachycardia. Infusion of flecainide acetate induced ST segment elevation, which is additional ECG evidence of Brugada syndrome (Fig. 2). A normal HV interval was found on the electrophysiologic study. The results of right and left ventricular catheterizations were normal. Right and left epicardial coronary arteries were free of lesions. The results of endomyocardial biopsies of the right ventricle were normal. Radionuclide left ventricle ejection fraction was normal (67%). Dipyridamole-resting ^{201}Tl SPECT distributions were homogeneous along the left ventricle (imaging obtained after injection of 111 MBq ^{201}Tl at the end of pharmacological stress and 4 hr later), excluding reversible ischemic disease of the coronary arteries. Three days later, the patient had planar and SPECT MIBG imaging. The heart-to-mediastinum ratio activity of MIBG was 226% (i.e., in the normal range of our laboratory, 230% ± 30%) (*8,9*). MIBG SPECT imaging showed defects in inferior, apical and septal myocardial walls (Fig. 3).

The patient was discharged with the diagnosis of Brugada syndrome. He received an automatic cardiac implantable defibrillator. At this writing, the patient is alive with no recurrence 6 mo after his first arrhythmia.

INDICATION FOR MIBG SPECT IMAGING

The pharmacological precursor, MIBG sulfate, was obtained commercially (CIS Biointernational, Gif sur Yvette, France). The radiochemical purity of the radioisotope was guaranteed to exceed 99.8% by the manufacturer at the time of delivery. Thin-layer chromatography demonstrated that the radiopharmaceutical purity of each dose exceeded 90%.

All sympathomimetic medicines that could interfere with the uptake of MIBG were discontinued for at least five half-lives before the procedure. The patient was pretreated with 30 drops of Lugol's solution in a cup of water 2 days before and 4 days after administration of the radiopharmaceutical. About 296 MBq ^{123}I-MIBG was administrated intravenously at noon. Scans were performed 4 hr later for SPECT [180° rotation (32 views × 60 sec, beginning at 45° right anterior oblique projection)] and planar cardiac evaluations to allow clearance of extraneuronal MIBG uptake. A one-headed gamma camera (Elscint Apex-415, Haifa, Israel) equipped with low-energy, all-purpose, large-field-of-view, parallel-hole collimators, was used. The data were reconstructed by filtered backprojection; images were acquired through a dedicated nuclear medicine computer (Elscint). Energy discrimination was provided by a 20% window centered on the 159-keV photopeak of ^{123}I.

Oblique tomographic slices in the short, vertical long and horizontal long axes were computed and displayed. Areas of sympathetic denervation were defined as regions that demonstrated reduced MIBG uptake of >50%. Reduced uptake was shown in inferior, apical and septal walls (Fig. 3). Uptake was different from the usual homogeneous MIBG uptake seen in normal subjects. The patient did not have diabetes mellitus or renal or liver disease that could affect MIBG uptake or metabolism.

The cardiac tomographic protocol applied for thallium imag-

Received Apr. 23, 1997; revision accepted Oct. 13, 1997.

For correspondence or reprints contact: Denis Agostini, MD, Service de Médecine Nucléaire, CHU Côte de Nacre, Caen 14000, France.

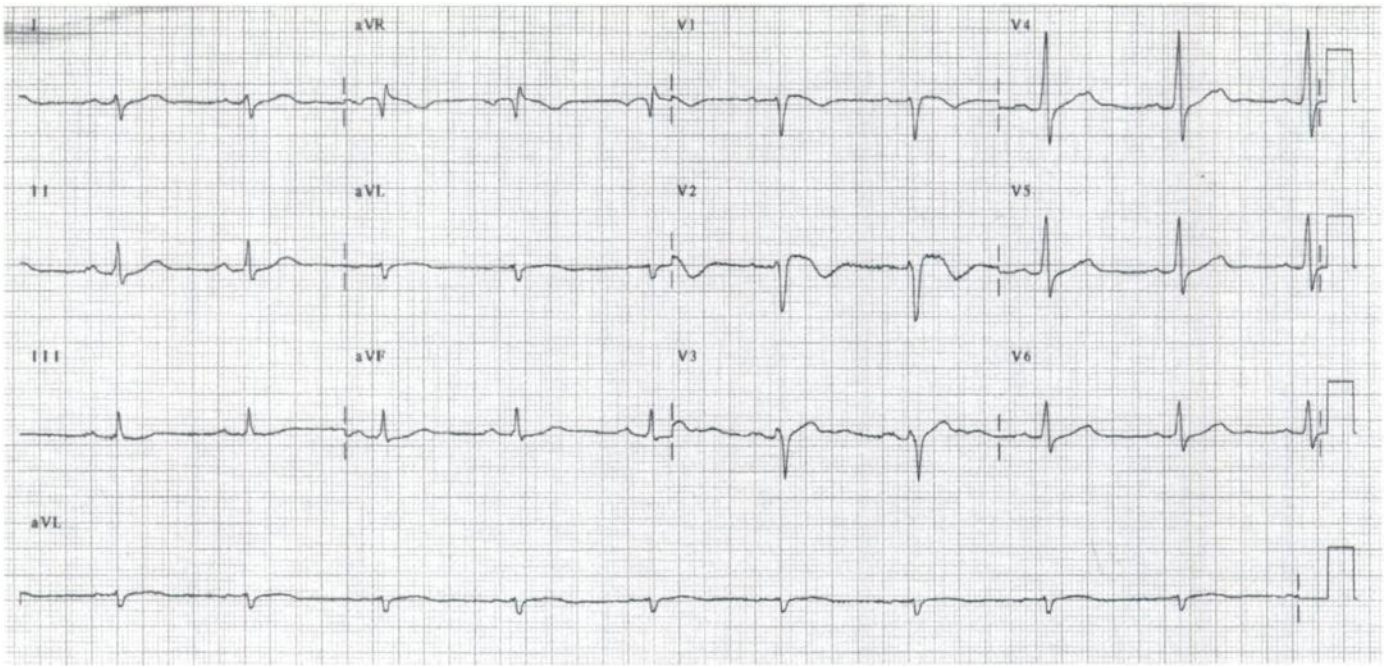

FIGURE 1. Electrocardiogram from patient during sinus rhythm. High take-off ST segment elevation with T-wave inversion (leads V1 and V2).

ing was similar to that used for MIBG SPECT, except for the energy discrimination centered on the 69-keV photopeak of ^{201}Tl.

DISCUSSION

This report shows a relationship between adrenergic denervation and Brugada syndrome in humans without apparent structural heart disease. Life-threatening ventricular arrhythmias usually occur in patients with arrhythmogenic right ventricular dysplasia (ARVD). Some of these patients have cardiac sympathetic denervation, which can be assessed by ^{123}I-MIBG SPECT (*10*). Our patient had no evidence of right ventricular dysfunction in echocardiography, ventriculography and endomyocardial biopsies. The cause of adrenergic denervation in this patient is unknown. Lekalis et al. (*11*) showed similar denervation by using MIBG SPECT in a patient with ventricular fibrillation without structural heart disease.

Myocardial scintigraphy with MIBG reflects the status of myocardial sympathetic innervation, and MIBG uptake correlates significantly with myocardial norepinephrine concentration (*2*). Our patient showed abnormal MIBG uptake in inferior, apical and septal walls, indicating that myocardial areas were deprived of their adrenergic nerve supply. Pharmacological stress-resting thallium imaging was homogeneous, indicating normal coronary perfusion. The global uptake of MIBG was not

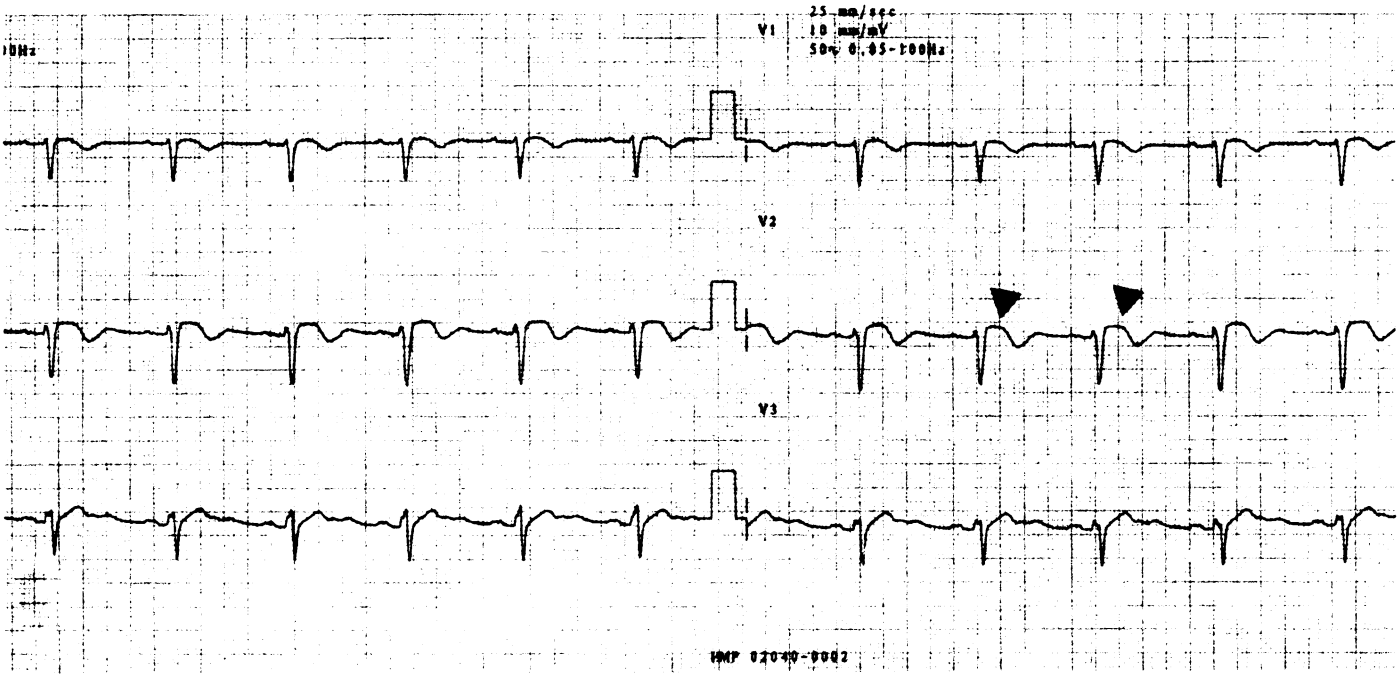

FIGURE 2. Electrocardiogram focused on V1, V2 and V3 leads from patient during sinus rhythm. ST segment elevation was augmented by infusion of flecainide acetate on lead V2 (arrowheads).

FIGURE 3. Iodine-123-MIBG images in the horizontal long axis (HLA), short axis (SA) and vertical long axis (VLA) in a normal volunteer and in the patient with Brugada syndrome. There is a normal distribution of ^{123}I-MIBG in the normal volunteer (upper), whereas, in the patient, ^{123}I-MIBG demonstrates a reduced tracer uptake in the basal posteroapical and septal areas of the left ventricle (middle). The corresponding ^{201}Tl images of the patient (lower) show a normal perfusion in the areas of the demonstrated sympathetic denervation.

significantly decreased, whereas the extent and magnitude of MIBG defect seen on the tomographic imaging seemed to be important. However, Manrique et al. (*9*) and Wichter et al. (*10*) recently reported the same results regarding the regional cardiac adrenergic abnormalities with normal global MIBG uptake. MIBG SPECT is more sensitive than planar MIBG imaging in detecting moderate or mild adrenergic abnormalities. It is known from experimental data that abnormalities of the sympathetic innervation of the myocardium may predispose a patient to arrhythmias (*2*). Denervation supersensitivity makes the heart more vulnerable to electrical induction of ventricular arrhythmias, and this vulnerability is significantly attenuated by beta-blockers. Our patient developed a nonsustained polymorphic ventricular tachycardia during infusion of isoproterenol.

The defect of cardiac MIBG uptake may result from several causes. In normal subjects, regional MIBG uptake may be nonhomogeneous and apparently lower in the septum and the inferoposterior wall than in the anterior or lateral walls, as reported previously (*12*).

Several mechanisms have been proposed for the heterogeneous MIBG distribution. Physiologic variation in sympathetic innervation demonstrated that the anterior wall has predominantly sympathetic afferent innervation (*13*). In contrast, a recent study by Minisi et al. (*14*) indicated that sympathetic afferent nerves were distributed equally to the inferoposterior and anterior walls in dogs. However, our series of normal volunteers showed homogeneous uptake of MIBG in myocardial walls compared with that in patients with ARVD (*9*). Estorch et al. (*15*) showed that global uptake of MIBG related to age and that myocardial MIBG uptake decreased in patients over 60 yr of age. The range of MIBG uptake in the patients under 60 yr of age reported by Estorch et al. (*15*) was 195% ± 25%.

High uptake of MIBG in the liver might cause artifacts in reconstruction SPECT (*4,12*). In our patient, we noted a high uptake of MIBG in the hepatic area, but the defect in the lateral wall cannot be explained by this mechanism alone.

Mirozumi et al. (*16*) suggested that the heterogeneous MIBG distribution in the left ventricle is caused by the depressor reflex mediated by the parasympathetic nerve fibers predominantly located in the inferoposterior wall. Heterogeneous MIBG distribution is probably a physiological phenomenon, not an artifact.

In heart failure (*6,7*), competitive uptake of ^{123}I-MIBG with circulating catecholamines in the heart is a possible mechanism of decrease in adrenergic storage. Our patient had no symptoms of heart failure and no left ventricular dysfunction. Therefore, our scintigraphic results probably showed regional cardiac adrenergic abnormalities in Brugada syndrome as described in ARVD (*9,10*). However, Miyazaki et al. (*17*) did not find MIBG abnormalities in three of four patients with Brugada syndrome, but they did not explain the MIBG imaging protocol or the results of the MIBG scan for the fourth patient. Moreover, they found heart variability, suggesting that autonomic dysfunction was not a primary process in Brugada syndrome.

Others causes of nonvisualization of the heart may be drugs that interfere with the uptake of ^{123}I-MIBG in the heart, such as reserpine, labetalol and tricyclic antidepressants (*3,4*). Our patient had no medications that might have interfered with MIBG uptake.

The heart-to-mediastinum ratio activity may be a helpful tool in cardiomyopathy (*7*) and in pheochromocytoma (*8*). In contrast, we suggested that heart-to-mediastinum MIBG uptake is not a useful parameter in patients with arrhythmias. Our patient had a heart-to-mediastinum ratio activity within the normal range (i.e., 230% ± 30%) (*8,9*).

The defects in regional cardiac MIBG uptake might be a potential indicator of impairment of cardiac neuronal catechol-

amine metabolism and might be a clinical aid for diagnosing arrhythmias and determining follow-up treatment.

CONCLUSION

At present, the usefulness of cardiac ^{123}I-MIBG scintigraphy in evaluating patients with Brugada syndrome is uncertain. A large number of patients and long-term follow-up studies are required to address the impact of MIBG SPECT imaging in assessing regional cardiac neuronal function and in determining the denervation and reinnervation of the myocardium.

ACKNOWLEDGMENTS

We thank Mrs. Françoise Dronne and the technical staff from the Department of Nuclear Medicine, CHU Côte de Nacre, Caen, France for valuable assistance.

REFERENCES

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. *J Am Coll Cardiol* 1992;20:1391–1396.
2. Zipes DP. Influence of myocardial ischemia and infarction on autonomic innervation of heart. *Circulation* 1990;82:1095–1105.
3. Wieland DM, Brown LE, Les Rogers W, et al. Myocardial imaging with radioiodinated norepinephrine storage analog. *J Nucl Med* 1981;22:22–31.
4. Kline RC, Swanson DP, Wieland DM, Thrall JH, Cross MD, Pitt B. Myocardial imaging in man with I-123 metaiobenzylguanidine. *J Nucl Med* 1981;24:1194–1196.
5. Sisson JC, Wieland DM, Sherman P, Mangner MC, Tobes MC, Jacques S. Metaiodobenzylguanidine as an index of adrenergic nervous system integrity and function. *J Nucl Med* 1987;28:1620–1624.
6. Schofer J, Spelman R, Schubert A, Weber K, Schluter M. Iodine-123 metaiobenzylguanidine scintigraphy: a noninvasive method to demonstrate myocardial adrenergic nervous system dysintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1988;12:1252–1258.
7. Merlet P, Valette H, Dubois Randé JL, et al. Prognosis value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med* 1992;33:471–477.
8. Agostini D, Scanu P, Babatasi GY, et al. Pheochromocytoma with catecholamine-induced impairment of cardiac neuronal function. *Am Heart J* 1995;130:1128–1230.
9. Manrique A, Loiselet P, Scanu P, et al. Assessment of ^{123}I-MIBG SPECT defects with circumferential profile analysis in arrhythmogenic right ventricular dysplasia. *J Nucl Cardiol* 1997;4(suppl 32):26.2.
10. Wichter T, Hindricks G, Lerch H, et al. Regional myocardial sympathetic dysinnervation in arrhythmogenic right ventricular cardiomyopathy An analysis using ^{123}I-meta-iodobenzylguanidine scintigraphy. *Circulation* 1994;89:667–683.
11. Lekalis J, Antoniou A, Prassopoulos V, Kostamis P, Moulopoulos S. Regional adrenergic denervation in ventricular fibrillation without apparent heart disease. *Am Heart J* 1994;127:951–953.
12. Gill JS, Hunter GJ, Gane G, Camm AJ. Heterogeneity of the human myocardial sympathetic innervation: in vivo demonstration by iodine-123-metaiodobenzylguanidine scintigraphy. *Am Heart J* 1993;126:390–398.
13. Geis WP, Kaye MP. Distribution of sympathetic fibers in the left ventricular epicardial plexus of the dog. *Circ Res* 1968;23:165–170.
14. Minisi AJ, Thames MD. Distribution of the left ventricular sympathetic afferent demonstrated by reflex responses to transmural myocardial ischemia and to intracoronary and epicardial bradykinin. *Circulation* 1993;87:240–246.
15. Estorch M, Carrio I, Berna L, et al. Myocardial iodine-labeled metaiodobenzylguanidine 123 uptake relates to age. *J Nucl Cardiol* 1995;2:126–132.
16. Mirozumi T, Kusuoka H, Fukuchi K, et al. Myocardial iodine-123-metaiodobenzylguanidine images and autonomic nerve activity in normal subjects. *J Nucl Med* 1997;38:49–52.
17. Miyazaki T, Mitamura H, Miyoshi S, et al. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol* 1996;27:1061–1070.

Effect of Metabolic Substrate on BMIPP Metabolism in Canine Myocardium

Ryuji Nohara, Ryohei Hosokawa, Taku Hirai, Kazumi Okuda, Motonari Ogino, Yasuhisa Fujibayashi, Masatoshi Fujita and Shigetake Sasayama

Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto, Japan

The lipid tracer 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) is clinically useful, and its basic metabolism is being analyzed. Because the pharmacokinetics of this lipid tracer may be affected by blood concentrations of fatty acid or glucose, this study evaluated the effects of excess levels of lipid or glucose on BMIPP uptake and metabolism. **Methods:** A technique using an open-chest dog model was used. Blood sampling was performed from the left anterior descending coronary artery and great cardiac vein after an injection of ^{123}I-BMIPP either with a glucose infusion (n = 6) or a lipid infusion (n = 5). High performance liquid chromatography and double-tracer kinetic analyses clarified the extraction, retention, backdiffusion and further metabolism of BMIPP. These results were compared with data from control dogs (n = 6). **Results:** In this experiment, a 10-fold increase over the normal lipid blood concentration and twofold increase over the normal blood glucose concentration were evaluated with either intralipid or glucose infusion, respectively. In the lipid infusion studies, the extraction significantly decreased compared with the control values (74% ± 12% to 58% ± 8%; $p < 0.05$), and the washout increased from 50% ± 13% to 68% ± 16% ($p < 0.05$). The BMIPP backdiffusion increased ($p < 0.05$), and the levels of the further metabolites decreased ($p < 0.05$), while the retention level remained constant (normal, 89% ± 9%; lipid infusion, 91% ± 3%; ns). In the glucose infusion studies, the BMIPP extraction, retention and washout showed no statistical differences compared to controls; however, these parameters showed the same tendencies as those in the lipid infusion group. In addition, the BMIPP backdiffusion increased significantly (control, 25.1% ± 8%; glucose infusion, 48.7% ± 25.6%; $p < 0.05$) as it did after the lipid infusion. **Conclusion:** BMIPP metabolism and uptake are affected by excess concentrations of lipid and glucose in the blood. However, the retention of BMIPP was not affected by either type of infusion. The BMIPP backdiffusion and the further metabolite comprising 10% of the tracer extracted were affected both by the lipid and glucose infusions. These results indicate that an excess fat concentration and glucose affect BMIPP uptake, especially the extraction of BMIPP and BMIPP backdiffusion.

Key Words: iodine-123-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid; lipid metabolism; triglyceride pool; glucose

J Nucl Med 1998; 39:1132–1137

As an important tracer of lipid metabolism (*1*), 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) has methyl group introduced into the beta-position and shows a good cardiac image different from that shown by myocardial perfusion (*2,3*). We have already shown that BMIPP uptake is related to the adenosine triphosphate (ATP) contents (*4*) and that both extraction and retention are closely related to the mitochondrial function, which was evaluated using etomoxir (*5*), a carnitine shuttle inhibitor. We also showed that ischemia strongly affects

Received May 13, 1997; revision accepted Oct. 15, 1997.

For correspondence or reprints contact: Ryuji Nohara, MD, Graduate School of Medicine, Department of Cardiovascular Medicine, Kyoto University, 54 Kawaracho, Shogoin, Sakyo-ku, Kyoto 606 Japan.