Transseptal approach for mitral valve replacement

To the Director

Borracci et al. study (1) shows the evolution of other of the available techniques for the mitral valve approach. In 1958, Effler basically described two accesses: through the fossa ovalis passing by the right atrium and through the posterior interatrial sulcus. (2) The second approach is technically easier, so nowadays, widely used. However, transseptal technique allows a broader view of the valve, which is preferred in case of small atriums, reoperations or ventricular hypertrophy, although it has the disadvantage of being technically more demanding. Several authors, since Dubost, (3) have used this technique. Most of the studies are retrospective and/or no randomized and heterogeneous in their populations and surgical techniques (both thorax and mitral valve approach), this makes difficult the comparison between the different studies. In Borraci et al. study transseptal approach technique was used in 62 patients undergoing mitral valve replacement and the objective was to assess technical difficulties and complications associated with the technique. From the point of view of the technique itself, there were no complications and delays in clamp times (52.5 ± 11.5 min), despite being more demanding. Mortality at 60 days was of 8.1% (5 patients) which can be related to 6.5 % (4 patients) of sepsis due to endocarditis; 18 patients (29% of the sample) had atrial fibrillation (AF) in the preoperative period, which 83.3% recovered high sinus or nodal rhythm in the postoperative period (although no remote evolution is reported). Of those patients with no preoperative AF there are no reports of how many of them had new AF after the surgery. A total of 9.7% of the patients had union rhythm in the immediate postoperative, 4.8% needed a definite pacemaker due to AV block or persistent nodal rhythm. In the study made by Nienaber in 2006 (4) with 531 patients (comparison of left atrial approach vs. transseptal), 35% to 39% (p=ns) had new AF; about 4.2% and 8.7% (p=ns) new union rhythm and 5.1% to 10.5% (p=0.02) needed definite pacemakers.

Borracci et al. study reaffirms that this approach is safe and has arrhythmic alterations similar to other techniques. As most of the studies, it contains a small number of patients, lack of control group and long-term follow-ups (they use the published bibliography), all this encourages the thorough study of the described technique.

Blas Mancini, M.D.

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Authors' reply

We thank Dr. Mancini's comments regarding the advantages and disadvantages of transseptal approach for mitral valve. For many years we used the usual technique over the interatrial sulcus, but in small atriums and reoperations it was difficult to observe and manipulate the anterior mitral hemi-ring. The finding and use of this new approach solved all the visual and technical difficulties we had, so nowadays we use it as a routine. We try to make a minimal incision on the right atrium and at the top of the left atrium we try to maintain the coronary branch that goes through it until the sinus node, in order to reduce the rate of nodal rhythms and blocks. This way of access allows us to associate the tricuspid annuloplasty and the intrasurgical ablation technique of atrial fibrillation, given the easy exposure of the pulmonary veins and the endocardium of the right atrium. As we have already mentioned, although the atriotomy and the atriography need more surgical time, it is compensated with a faster implantation, given a best exposure of the mitral ring. Particularly and from the technical point of view, we should be careful in not carrying the top atrial incision behind the aorta, which would difficult the closure.

Dr. Raúl A. Borracci[MTSAC], by the authors

Psychosocial stress and low resilience. A risk factor for hypertension

To the Director

The objective of Costa de Robert et al. (1) in their study was to determine if low resilience (LR) in those persons with psychosocial stress (PS) is a factor that is associated with hypertension. A total of 53 persons were studied, some of them hypertensive but with no antihypertensive treatment, to whom some tests to assess psychosocial stress and degree of resilience were performed. This enabled to divide the sample into four groups (G), according to whether they had or not PS and if they also had normal or low resilience. To determine if LR in those persons with PS is an associated factor (risk factor) with hypertension, it was necessary to compare what percentage of hypertensive had PS+LR and how many of those non hypertensive had it. The different percentages compared among the groups had marked if PS+LR factor was associated with hypertension or if it was equal in those non hypertensive. I believe this analysis, was not done (Table 3). Contrariwise, it was analyzed if each of the groups (with no PS+NR, with no PS+LR, with PS+LR and with PS+LR) was more associated

than other with hypertension (Table 1). In this analysis there is a confusing element, "waist circumference" (p=0.05), that could affect the conclusions. For example, if we compare the number of patients with an increase in their "perimeter waist" among the groups with LR vs. NR, independently of PS there we would find p=0.001, that is to say that an increased "waist circumference" is more frequent in those with LR than in those with NR (67%, 20/30 vs. 22%, 5/23, chi²=10.5), element that could act confusing.

In table 1, when percentages of hypertensive are compared, we have that:

G1	G2	G3	G4
With no PS+ NR	With no PS + LR	With PS + NR	With PS + LR
23% (3/13)	80% (4/5)	80% (8/10)	92% (23/25)

We can observe that there is a clear difference between G1 and groups 2 to 4 (chi²= 20.7, 3 gl., p=0.0001) and no difference between G4 ant the rest, as authors stated. From the statistical comparison comes up that in groups 2, 3 and 4 there are more hypertensive than in G1:

	Fisher's method "p-values" (Values per cell < 5)
G1 vs. G2	0.047
G1 vs. G3	0.012
G1 vs. G4	< 0.001

And that there are no statistical differences among G2, G3 and G4, leaving aside beta error. These results may indicate that in those patients with PS (independently of the resilience level) and in those with LR (whether they had or not PS) there would have more hypertensive patients. So, without taking into account the small size of the sample, those persons with PS or LR should be more associated with hypertension. The same happens when comparing SAP and DAP (Table 1). By Bonferroni we conclude that there were differences between G1 and groups 3 and 4; but taking into account these results the conclusion should have been that, those patients with PS, whether they had or not LR, are associated with higher arterial pressure in those with no PS, regardless the level of resilience.

Although this topic is very interesting, the analysis and conclusions of the study should be different of the ones suggested by the authors.

Dr. Raúl A. Borracci[MTSAC]

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Authors' reply

We thank the interest in our work; but however we should clarify certain statements.

Based in the objective of the study which was to determine if low resilience (LR) in persons with chronic psychosocial stress (PS) is a risk factor for hypertension, the percentage of individuals with PS+LR between hypertensive and normotensive was compared, as well as the potential confusing elements. The results showed that the percentage of individuals with PS+LR and the levels of creatinine in plasma were higher in hypertensive than in normotensive. Based on these results, a logistic regression model adjusted by age, sex and plasma creatinine levels was used. The result was: the coefficient for PS joined to LR was of 2.39 with a standard error of 0.90 and p<0.01. The odds ratio was of 10.9 with confidence intervals of 95%, lower of 1.8 and upper of 65.2. For that reason, we consider that not only the analysis considered by Dr.Borracci was made, but, also, having included other variables in a logistic regression model, the potential confusing elements could be controlled. Based on these results the conclusions of this study were obtained.

Regarding the second oobservation made by the reader, we can say that in the study the potential confusing elements as age, sex, education, cardiovascular disease history, nicotinism, consumption of alcoholic beverages and body mass index (BMI), were analyzed and none of them showed significant differences among the groups. It is interesting to emphasize that the BMI did not show differences among the groups, so obese or overweight individuals were balanced in the groups.

Regarding the percentage of hypertensive, the reader has made an error saying that the percentage of hypertensive was of 80% (4 of 5 patients) in G2, when actually it was of 23% (1 of 5 patients) (Table 1). Based on these considerations, the following analysis is incorrect.

Anyway, we should emphasize that it is a preliminary observational study, with a small sample, essentially when the four groups are analyzed. As a consequence, some differences have no statistical significance. This is a shortcoming. Later studies with a greater sample size would confirm o refute this preliminar analysis.

Dra. Sara Costa de Robert[MTSAC]**,**
Dr. Pedro Forcada, Dra. Patricia Carrizo

Is amiodarone the panacea in Chagas disease?

"There is a tendency in scientific investigation to overestimate the value of facts over the value of ideas".
Dr. Mauricio Rosenbaum

To the Director

Amiodarone is used for cardiac arrhythmias in Chagas disease since many years.

Dr. Julio Urbina from Venezuela describes its antiparasitic action when blocking ergosterol synthesis and disrupting Ca^{2+} hemostasis in Trypanosoma cruzi, potentiated when combined with posaconazole, an antifungal that acting in a synergic way inhibits

ergosterol biosynthesis. In the last 20 years, several studies have demonstrated that Trypanosoma cruzi, as well as most of the pathogenic fungi and yeasts, need specific sterols in order to maintain its ability to reproduce.

Amiodarone inhibits proliferation both extracellular epimastigote and intracellular amastigotes cultivated in vitro, in lower concentration than those obtained in the tissues with therapeutic doses of the drug.

In Argentine, itraconazole is available in tablets of 100 mg.

Although in Chile, itraconazole is used since several years alone or combined with allopurinol with favourable clinical outcomes; its action is attributed on a sensitive T cruzi strain.

A recent study published in the journal Chemotherapy, Dr. Paniz Mondolfi, in New York, United States, uses amiodarone in doses of 800 mg daily and itraconazole 100 mg daily for 6 months, showing as anti-rTc24 (PGR24-his) lytic antibodies and complement-mediated lysis (CML), whose levels are used to determine the presence of active parasites. At 2 months, a decrease of lytic antibodies, with the disappearance of these antibodies 6 months before finishing the treatment, with no alteration of the conventional antibodies (ELISA and IIF) is seen.

T cruzi causes organic damage. The first randomized multicenter study with benznidazole (BENEFIT) is being carried out. It would be useful in chronic Chagas, although the undesirable effects related to its mechanism of action limit its use. It acts by reaction of its nitro-reduced derivatives with macromolecules with DNA-RNA, proteins and possibly unsaturated lipids. A better clinical evolution is observed in those treated patients.

Sudden death is the most common type of death within chagasic outpatient population and although it is associated with cardiac compromise, in many cases it occurs in asymptomatic patients with no electrocardiographic alterations.

Amiodarone is an interesting alternative in patients with cardiopathy, waiting for more convincing clinical outcomes.

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Could cold pressor test predict the appearance of cardiovascular events in patients with non proven coronary disease?

To the Director

Dr. Pautasso's group (1) has worked in this investigation and the work that originates this letter shows the results of a commendable dedication to a subject matter of academic and welfare interest.

Oxidative stress and endothelial dysfunction are important factors in the development of atherosclerosis, and this is the common pathophysiology via for most of the cardiovascular risk factors, included hypertension, diabetes mellitus, dislipidemia and nicotinism (smoking).

Endothelial dysfunction and oxidative stress result in ischemic heart disease, myocardial infarction and, as a consequence of this, impairment of ventricular function with heart failure.

Studies that demonstrated the association of endothelial dysfunction with incidence of coronary events in the population with bad response of the coronary arteries assessed with acetylcholine and cold pressor test have been published. (2-4)

The usefulness of myocardial perfusion with cold pressor test to evaluate endothelial dysfunction in asymptomatic patients with unknown coronary disease and its evolution controlled by perfusion test has already been studied by our team. (5, 6)

In comparison with other published studies as Masoli et al. (5) and Traverso et al in a follow-up of the "PARADIGMA" Register population (6), Pautasso et al. study shows a high number of patients, a longer average follow-up, includes diabetics and the objective was to establish the incidence of coronary events in patients with positive cold pressor test, that in previous studies it was not a defined objective.

The high prevalence of positive cold pressor test of 32.4% (even compared with those studies including diabetics) was surprising. The association of positive test

with male and high body mass index is described; the latter should be related to a high incidence of diabetes that should be also investigated.

Regarding the predictive value for cardiovascular events, the only two independent variables were diabetes and positive cold pressor test, with unstable angina as the most frequent event which required a revascularization method.

When the result of the test is positive it implies four times more likely to suffer an event than with negative result, so there is a subgroup of patients that would have a lethargic evolution according to their cold pressor test response.

It is not possible to establish comparisons with studies published in our media. For example, the population of the follow-up of the "PARADIGMA" Register has a lower mean age (52 ± 5 years), the prevalence of coronary risk factor is similar, but there are two significant differences: in the "PARADIGMA" Register, diabetics were excluded and the prevalence of the cold pressor test was significantly lower (18.3%). In this sense, the population of Pautasso et al. study is similar to the one in Schachinger's work. (4)

We should emphasize that the endpoints at 12 months of the "PARADIGMA" Register (6) were positivism in the follow-up of the perfusion test with effort and not the direct association with cardiovascular events.

As authors expressed, the lower prevalence of positive cold pressor test in diabetics is surprising, as they were excluded from other studies considering them patients' carriers of pathology equivalent to cardiovascular disease due to their risk. The follow-up was not as longer as the one done in Schachinger's work, (4) that was of 6.7 years.

Other points to take into account: 1) clinical risk stratification when entering the study was not performed, in order to make a comparison with other studies and 2) during the follow-up they did not have the results of a new perfusion test with effort in order to assess which were positive, which may change the risk in this subgroup of patients.

Once more, we should emphasize Pautasso et al. work which gives us (local) data about a subgroup of patients with greater risk of events, in a population considered of low risk, which may enable us to adopt changes in primary prevention.

Drs. Daniel Cragnolino[MTSAC], Roberto Agüero

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Authors' reply

We thank Drs. Daniel Cragnolino and Roberto Agüero comments in their letter related to our work.

The prevalence of the cold pressor test in our population was of 32.4%, while in the "PARADIGMA" Register was significantly lower (18.3%). Maybe, this difference is due to a higher average age in our population. Although in "PARADIGMA" study diabetic patients were excluded, they did not show, at least in this group, a positive prevalence of cold pressor test statistically different of those of non diabetic patients. However, diabetic patients had a higher body mass index than the ones in non diabetic, as Drs. Cragnolino and Agüero expressed.

In Schächinger et al. study, (2) whose population was similar in age and prevalence of coronary risk factors to the population in the "PARADIGMA" Register, the sympathetic activation produced by the cold pressor test caused vasoconstriction in 64% of the population, twice as much as the one observed in our work. In both studies diabetic patients were taken into account and the most frequent event was unstable angina that required some myocardial revascularization procedure. However, predictor variables for cardiovascular events at long-term was the cold pressor test in both populations as well as diabetes for our group, while hypertension was the other independent of events variable in Schächinger's work.

On the contrary, in Suwaidi et al. study, (3), of 157 patients receiving intracoronary acetylcholine, 27% (42 patients) had severe vasoconstriction coming from the endothelium, a similar proportion to our population. It is probable that those patients with positive result in the cold pressor test belong to our group. (4-6) In the follow-up at 28 months there were no cardiovascular events in individuals with or with no mild endothelial dysfunction. We have also confirmed the same that is to say that those patients with negative cold pressor test did not have events up to 30 months. We also coincide with Suwaidi et al. that the most frequent events were those procedures of myocardial revascularization.

We also coincide with Drs. Cragnolino and Agüero regarding the importance of stratifying patients when entering in order to compare with other studies. We could not do it because these patients were referred to our nuclear medicine center by their general practitioner and although we asked for previous studies in order to make the medical history, not all of them had the necessary data to perform the corresponding stratification.

We think that cold pressor test could help identifying those individuals with low ischemic risk, whom during their evolution could present some cardiovascular events.

Maybe we need a greater number of works and patients in order to establish for certain the usefulness of this study as a predictor of cardiovascular events.

Drs. José E. Pautasso[MTSAC] and Martín Koretzky

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Antioxidant role of vitamin E in the atherogenesis induced by hyperfibrinogenemia

To the Director

Llorens et al. (1) study shows in a model of atherogenesis induced by hyperfibrinogenemia in rats that vitamin E used in doses equivalent to 400 mg/d would reverse oxidative stress and the alteration of endothelial function due to its antioxidant effect and this conduct should be indicated as primary prevention in subclinic atherosclerosis.

The use of synthetic antioxidants for atherosclerosis prevention and its clinical sequelaes is a recurrent idea, but few studies showed its usefulness, since they did not show neutral and even harmful results (HOPE, WHI, HATS, GISSI-Prevenzione, etc studies).

The work shows difficulties when explaining the protective role of vitamin E, although mentioning general mechanisms. Vitamin E is a humoral factor carried by lipoproteins and even if it can decrease LDL oxidative capacity, it would show lower effectiveness to reverse oxidative stress considering that this is an intraendothelial phenomenon. (2)

Following the methodological aspects, the assessment of endothelial function and oxidative stress has shortcomings. To evaluate the action of nitric oxide (NO) it is necessary to determine its bioavailability, which depends on the synthesis, the action and the metabolism. The NO is synthesized in an equimolar way with L-citrulline, from L-arginine due to the action of the NO synthase isoforms'. In an in vitro study it would be correct to measure L-citrulline as an index of NO production, but as there are other sources of L-citrulline, the effectiveness of its determination in vitro as an index of NO production is low, so it would mean that all the L-citrulline of plasma comes from the action of NO synthase on L-arginine.

Regarding the determination of nitrites and nitrates by Griess reaction, it is an indirect way of determine NO status, and even more indirect of oxidative stress. For the latter the determination in plasma or urine of the TBARS superoxide anion, 8-isoprostanes, and antioxidant defense (SOD, catalase, GSH/GSSG) is used. (3)

Regarding endothelial activation, cGMP is the mediator of NO vasodilators effects'. (4) Some NO effects' are independent of cGMP; so it is not correct to say that it is the mediator of its physiological effects. The functions of endothelial barrier are not related to NO vasodilators effects', so they are not mediated by cGMP.

On the other hand, given that TNF-α is a proinflammatory cytokine, in those models of atherosclerosis other markers of endothelial activation as ICAM, VCAM, E-selectin and von Willebrand factor are used, (5) therefore TNF-α measurement would not be enough to indicate the existence of endothelial activation.

Finally, although the rat is not a good model of atherogenesis, the use of hyperfibrinogenemia model and the method by administration of adrenaline to induce it sounds attractive.

Drs. Gerardo Elikir, Vicente Lahera, Lucas Masnatta
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Authors' reply

It is true that the results regarding antioxidants effectiveness are controversial, so we decided to study in an experimental model the morphofunctional substrate of free radicals, which is the mitochondria with and with no aggregates of exogenous antioxidants, to understand the mechanism of action of the drug and its probable

benefits.

Those patients included in HOPE study had to have previous cardiovascular events or proven risk factors and also they must be receiving ramipril, as the proposal was for secondary prevention. (1)

WHI study was not focused strictly on the prevention of heart disease, but also on breast and colorectal cancer and postmenopausal women fractures'. The main objective of the study was cardiovascular disease with events (non fatal AMI and death due to FCE) and invasive breast cancer as primary adverse factor. (2)

Those patients included by Brown et al. in HATS study had coronary heart disease, that is to say that the proposal was as secondary prevention.

GISSI-Prevenzione was a multicenter, randomized, open study in which a follow-up of 11.324 survivors of myocardial infarction patients (of more than 3 months) for 3.5 years (October 1993-September 1995) was made, but with the administration of fish oil in order to assess the effect of omega 3. In the group of the follow-up it was made concomitantly with antihypertensive and lipid-lowering therapy. (3)

There are other studies such as CHAOS, SPACE, ASAP, PPP and other where positive results for the use of exogenous antioxidants are observed but for primary prevention and not associated with statins, since these inhibit the effect of vitamin E molecule. (4)

In order to measure the reactive oxygen species, direct and indirect methods are used; in our study we use the indirect one (NO) and we control SOD values, enzyme that catalyzes the conversion of superoxide in hydrogen peroxide and allows knowing the total oxidative state, results that are impossible to present in a same manuscript. (5)

Endothelial activation should be distinguished from dysfunction; to mark the "activation" biochemically TNF-α is used and for dysfunction those mentioned by the doctors Elikir, Lahera and Masnatta.

Drs. Mónica Moyá, Candelaria Llorens, María del Carmen Baez

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Anomalous origin of the left coronary in the pulmonary artery: corrective surgery outcomes'

I commend Dr. Lugones et al. (1) for the excellent analysis and experience in the treatment of the anomalous origin of the left coronary artery from the pulmonary artery.

The anomalous origin of the left coronary artery from the pulmonary artery is the most usual cause of myocardial ischemia and infarction in paediatrics population; with no treatment it has a mortality of > 90% within the first years of life. It is usually presented as an isolated lesion and it has an incidence of 0.25% to 0.5% of live births (1 out of 300.000 of live births in the United States). (2) Coronary perfusion is maintained from the pulmonary artery during neonatal period as a result of high pulmonary vascular resistance (PVR), and as the PVR decreases there is an inverse flow from the aorta artery with short circuit from left to right. This "diastolic steal" of coronary flow leads to left ventricle myocardial ischemia, with dependence on the development of collateral circulation from the dilated right coronary artery.

Although the anomalous origin of the left coronary is a rare lesion, a "high index of suspicion" in any infant with total myocardial dysfunction is required, and it should be the first differential diagnosis together with dilated cardiomyopathy.

Coronary angiography is not used as a routine now, as the diagnosis can be done with colour Doppler echocardiogram with a sensitivity of 100% and a specificity of 91%. Other non-invasive diagnostic methods to take into account are multislice tomography and nuclear magnetic resonance.

Surgical treatment is the gold standard in the therapy for the anomalous origin of the left coronary and the desired outcome is the restoration of a double coronary circulation, which have changed the natural history of this congenital cardiopathy. Surgical correction should include not only the coronary problem but another endpoint of left ventricle ischemic insult, as the degree of mitral regurgitation.

The authors have used the direct reimplantation of the left coronary artery inside the aorta in more than 90%; this technique obtained more popularity after the development of the arterial switch and it is the one we adopt as a routine regardless the place of origin of the left coronary in the pulmonary artery.

We recommend avoiding deep hypothermia and circulatory arrest, performing a quick surgery with cardiopulmonary bypass to normothermia or mild hypothermia and decreasing aortic clamping time, which enables a faster gradual myocardial recovery of the hibernating myocardium with no need of circulatory support. (3)

The treatment of mitral regurgitation as a result of left ventricle ischemia is controversial and it should be

conservative, allowing the recovery of LV function and with that the improvement of mitral regurgitation. Only those patients showing irreversible ischemic damage resulted in fibrosis and/or calcification of papillary muscles with severe mitral regurgitation should be treated with mitral plastic at the moment of coronary reimplantation. (4)

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Cardiac myxomas: clinical presentation, surgical outcomes and long-term prognosis

To the Director

We are pleased every time we find in the medical literature an article related to cardiac tumors, as they are not so frequent, but with the development of new diagnostic techniques they are communicated more frequently every day.

We find very interesting the results published by Dr. Enzo L. Gonzalez et al. in their journal (1) and we join to the congratulations issued by Dr. Augusto Torino and Dr. Ricardo León.

There are few scientific papers published in Latin America that show a long-term follow-up of groups of patients undergoing surgical treatment due to cardiac myxoma diagnosis. Recently, in a study made by our group (2) we show our experience regarding this topic in 23 years of work, which although having less causes than the ones presented by Dr. Gonzalez and his group, shows similar results regarding the average age in which this entity appears and its predominance in female. Regarding the most frequent location of myxomas, we conclude that the majority are located at the level of the left atrium, attached with base in the interatrial septum; which corresponds to its embryological origin. (3) Due to this fact, the wide removal of the base is recommended in order to avoid tumor recurrences and the use of autologous or bovine pericardial patch as a way of correcting septal defect created as the myxoma exeresis, (4) as Gonzalez et al. outline in their study, as well as the electrofulguration of the affected area in cases where the removal is difficult.

Despite these surgical options, several patients with tumor recurrence at short and long-term are described; they would not only be related to an inadequate surgical technique or with a difficult myxoma removal due to its location, but in many cases it is associated with patients with genetic predisposition; appearing simultaneously with other entities as the aforementioned Carney complex. (3, 5)

Finally, and regarding the decision of surgical moment and the type of surgery according to the level of urgency, we consider important the particular assessment of each patient according to the symptomatology and once diagnosed the cardiac myxoma (despite its magnitude and location) it is very important to perform an early surgery, due to the high possibility of severe complications in these patients, that can cause important sequelaes, and also death.

We thank Dr. Enzo L. Gonzalez et al. for sharing with us their experience in this type of surgery, which encourages us to continue developing our study.

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