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***Crataegus oxyacantha* and Heart Failure**

To the Editor:

The statement on "Phytochemicals and Cardiovascular Disease" published in the June 3, 1997, issue of *Circulation*¹ focuses attention on the vast therapeutic possibilities found in plants. One of the 3 groups of substances mentioned, the flavonoids, is found in great abundance in standardized special extracts of Hawthorn leaves with flowers. This extract has been studied extensively in Germany and is currently being used as a treatment modality in NYHA class II heart failure. Clinical studies (double-blind and placebo controlled) have been published in German and other languages^{2,3} along with pharmacological and chemical studies. In a recent article,⁴ 136 patients (NYHA class II heart failure) were randomized (double-blind) to either 160 mg Hawthorn special extract WS 1442 per day or placebo. The difference between the pressure/heart rate product (PHRP) at a 50-W load versus rest was measured before and after treatment, and the change in this parameter was defined as the primary target parameter. The group receiving active medication showed a significant improvement in the PHRP, whereas, in the placebo group, this parameter tended to deteriorate. Other surrogate parameters (patients' subjective assessment of symptoms and quality of life) also improved. The medication was excellently tolerated.

The cardioprotective qualities of Hawthorn extract WS 1442 have been demonstrated by Krzeminski and Chatterjee.⁵ They used the ischemia/reperfusion model in 2 groups of rats, 1 receiving 100 mg · kg⁻¹ · d⁻¹ of the standardized Hawthorn extract WS 1442 orally for 6 days before induction of ischemia and the other serving as a control group. Active treatment effectively protected the animals from reperfusion-induced arrhythmia, mortality, and hypotensive crisis, as observed in the control animals after 7 minutes of coronary occlusion. A better understanding of the pharmacological working principles of WS 1442 is offered by Chatterjee et al.⁶ They fractionated the Hawthorn extract and demonstrated that a subgroup of the flavonoids, namely, the oligomeric procyanidins, possess potent radical scavenging and human neutrophil elastase inhibitory activities. Further research is being carried out with this special Hawthorn extract to investigate its pharmacological properties and its clinical significance, not only in early but also in advanced stages of heart failure and for secondary prevention after myocardial infarction.

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Altered Mitral Flow Pattern in Patients With Hypertrophic Obstructive Cardiomyopathy

To the Editor:

We read with interest the paper of Hamada et al.¹ They used M-mode and Doppler echocardiography in patients with hypertrophic obstructive cardiomyopathy (HOCM) to show that the antiarrhythmic drug cibenzoline, in addition to reducing left ventricular (LV) systolic pressure gradient and LV contractility, also altered the LV diastolic filling profile. Two hours after oral administration of 150 mg of the drug, E-wave velocity increased insignificantly (from 79 to 83 cm/s) and A-wave velocity decreased significantly (from 82 to 55 cm/s), with a significant increase of the E/A ratio (from 1.2 to 2.0).¹ Furthermore, prolongation of isovolumic relaxation time (LV-IVRT) from 73 to 101 ms was noticed. The authors interpreted their findings as the result of a decrease in both left atrial (LA) and LV diastolic pressures.¹ Data on deceleration time of early mitral inflow or on other Doppler indexes of LV filling, such as pulmonary venous flow velocities, were not given, and hemodynamic studies were not performed. Despite these shortcomings and considering the limitations of Doppler echocardiography in these patients,² we would like to offer another possible explanation for the altered mitral flow pattern. The roughly 40% increase of LV-IVRT cannot, in our view, be attributed solely to drug-induced reduction of LV preload in these predominantly asymptomatic or mildly symptomatic patients.¹ LV-IVRT depends on the complex interplay of LA pressure, LV afterload, and LV relaxation. Because of altered ejection dynamics in HOCM,³ LV-IVRT may be an unreliable index and should be interpreted in the context of other indexes of Doppler filling.

It is more likely that cibenzoline in fact caused an impairment of LV relaxation, resulting in longer LV-IVRT and higher early diastolic LV pressures. At lower contractility and thus decreased LV elastic recoil,⁴ the similar E-wave velocities would suggest higher LA pressures in early diastole or, in other words, a similar early transmitral inflow pressure gradient at higher LV early diastolic and LA pressures. The lower atrial velocities under treatment could well be the result of either increased atrial afterload due to elevated LV end-diastolic pressures or drug-induced decreased contractility of the usually enlarged and myopathic left atrium in these patients.⁵ More likely, the combination of both factors led to a roughly 33% reduction of peak atrial velocity,¹ because alteration of LV preload per se usually does not cause such impressive changes in late transmitral flow.^{6,7}

Our interpretation is consistent with the results of a previous study in patients with coronary artery disease and ejection fraction >40%, which showed a significant increase of E-wave velocity after treatment with verapamil. This "enhanced early LV filling" reflected hemodynamically a deterioration of LV systolic function and relaxation.⁸ The findings of another study with DDD pacing in patients with HOCM are similar.⁹

Thus, we believe that the altered mitral flow pattern indicates an elevation rather than a decrease in LV filling pressures in patients with HOCM after treatment with cibenzoline.

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Response

We appreciate the opportunity to respond to the comments that Dr Hahalís et al have made regarding our recent article.¹ In this article, we reported that the class Ia antiarrhythmic drug cibenzoline markedly reduced left ventricular pressure gradient mainly due to a decrease in left ventricular myocardial contractility in patients with hypertrophic obstructive cardiomyopathy (HOCM). In addition, in our study, isovolumic relaxation time (IRT) increased, peak E-wave velocity remained unchanged, peak A-wave velocity decreased, and thus, the E/A ratio increased. We interpreted that these changes might be due to a decrease in both left atrial and ventricular pressures caused by the administration of cibenzoline.

Hahalís et al are concerned about our results in this Doppler echocardiographic study. They state that cibenzoline caused an impairment of left ventricular relaxation, resulting in a longer IRT. Therefore, they interpret that the altered mitral flow pattern indicates an elevation rather than a decrease in left ventricular filling pressure. However, we do not agree with their interpretation.

First, their interpretation is based on the fact that left ventricular elastic recoil decreases at low contractility.² This understanding fits the patients whose systolic dysfunction parallels their diastolic dysfunction. In patients with hypertrophic cardiomyopathy, systolic function is usually supernormal, but diastolic function is markedly disturbed. Thus, patients with hypertrophic cardiomyopathy, especially in HOCM, respond in a paradoxical

manner to a variety of stimuli.³ In fact, Nishimura et al⁴ reported that Doppler mitral flow velocity curves were useful in predicting left ventricular filling pressure in patients with left ventricular systolic dysfunction, but these curves could not be used in patients with hypertrophic cardiomyopathy.

Second, the pattern of mitral flow velocity curve represents the relative pressure gradient between the left ventricle and left atrium during diastole. Thus, an increase in left atrial pressure results in a higher E-velocity, a shorter deceleration time, and a shorter IRT. After the administration of cibenzoline, E-velocity remained unchanged and IRT was significantly prolonged. The deceleration time in 10 patients¹ was also significantly prolonged. Therefore, it is reasonable to interpret that our data may be due to a decrease in left atrial pressure. Gwathmey et al⁵ indicated that intracellular Ca²⁺ overload was closely related to diastolic dysfunction in hypertrophic cardiomyopathy. Experimental studies show that cibenzoline possesses a certain calcium channel-blocking property. The beneficial effect of cibenzoline on the Doppler mitral flow pattern in HOCM may be due to this property.

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Diastolic Suction During Acute Coronary Occlusion

To the Editor:

We congratulate Bell et al on the recent publication of their study¹ that presents evidence indicating a decrease in forces responsible for diastolic suction during an acute occlusion of the left anterior descending coronary artery in dogs. Their experimental preparation is elegant, and we agree with their principal interpretation of their data: the acute loss of regional cardiac contractile function due to myocardial ischemia can result in a decrease in the mechanical generation and storage of elastic forces available to induce ventricular suction during early diastole.

In our view, the authors' introductory remark that "One determinant of filling that may be altered during coronary occlusion but has not previously been studied is the ability of the LV to fill by suction" is an incomplete representation of the literature. In a previous publication,² we described in detail the form of intraventricular pressure gradients found in the normal canine left ventricle during early diastole. In that report, we argued that the pattern of these early diastolic pressure gradients could only be present in a structure that filled by the process of mechanical suction. In a follow-up to that study, we hypothesized that any condition that interferes with regional systolic function might be expected to interfere with the process of diastolic suction and thereby modify the normal pattern of the early diastolic intraventricular pressure gradient. To test this hypothesis,³ we measured the intraventricular pressure gradient in dogs before and after occlusion of the left anterior descending coronary artery and found a strong relationship between the magnitude of the intraventricular pressure gradient and left ventricular systolic function. We concluded that loss of functional myocardium available to store energy during systole and release it during diastole in the form of elastic recoil impairs the process of diastolic suction. Thus, we respectfully suggest that the present work by Bell et al represents evidence complementary to our own, emphasizing again the important link between systolic function and the process of diastolic suction.

In addition, we question the authors' conclusion that because fully relaxed pressure was positive during coronary occlusion, this "resulted in a situation in which a force causing suction was no longer present under operating conditions." To use atmospheric pressure to define the presence or absence of ventricular suction, meticulous care is needed to exclude hydrostatic pressure artifacts in the measurements. In another study,⁴ we demonstrated that inaccuracies of pressure measurement of up to 5 mm Hg may be introduced by certain methods of zeroing micromanometers. Errors of this magnitude may lead to misinterpretation when the presence or absence of ventricular suction is defined in this way. Bell et al do not describe this important aspect of their experimental technique. In addition, by defining and discussing suction only in terms of the presence of subatmospheric pressure, the authors have ignored other plausible arguments that define suction as filling (+dV) in the presence of decreasing pressure (-dP).^{5,6} By that definition, suction is a mechanism that is always operative during the early diastolic filling phase, despite the absence of subatmospheric pressure, even in severely dysfunctional ventricles. This implies that our present notions about the concept of ventricular suction, and thus of equilibrium volume, are incomplete.

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Response

We are pleased to respond to Courtois et al in regard to our article, "Decrease in Forces Responsible for Diastolic Suction During Acute Coronary Occlusion."¹ We are familiar with their elegant work elucidating diastolic intraventricular gradients during coronary occlusion² and cited it originally. It was deleted at the suggestion of a reviewer (with whom we agree) who indicated that intraventricular gradients do not necessarily implicate suction and are not a measure of the force causing suction. In our view and that of others,³ suction represents conversion of potential energy produced during contraction to kinetic energy during filling. An indication that potential energy is present at end systole is a negative transmural pressure after relaxation, ie, the chamber is below equilibrium volume and "under compression" due to stored elastic energy. Our preparation, in which the ventricle relaxes at end-systolic volume without filling, provides a measure of that restoring force. Courtois et al contend that suction always operates during filling regardless of end-systolic volume, offering as proof the presence of intraventricular gradients and the decline in ventricular pressure early during filling. This concept differs from ours because it does not require energy storage at end systole. Although the gradient increases in parallel with restoring forces,⁴ one must be present for inflow to proceed from mitral annulus to apex, regardless of the mechanism of filling. The argument that decreasing ventricular pressure requires an "active" process neglects the fact that with an open mitral valve, the ventricle is part of an open system that includes the left atrium and pulmonary circulation. Pressure and volume changes elsewhere in the system could account for the pressure decline.

The question posed about pressure measurement refers to their article⁵ advocating referencing of pressures to the uppermost level of fluid. This eliminates hydrostatic pressure and results in lower measured pressures than with conventional reference points. Our pressures were referenced to the midpoint of the mitral valve plane, defined by external landmarks. As a practical matter, in our preparation it is impossible to define the position of the uppermost level of fluid within the ventricle because of dynamic motion during each cardiac cycle, which is modified by the various interventions used. Equilibrium volume in dogs of the size we used is ≈ 10 to 20 mL. The hydrostatic pressure in an ellipsoid of this volume with its long axis oriented horizontally is quite small. We therefore opted to use a consistent reference, understanding that this might slightly underestimate restoring forces. Since our design was to compare coronary occlusion to baseline conditions, this approach does not alter our conclusions.

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Chronology of Use of Ticlopidine to Prevent Stent Occlusion

To the Editor:

We read with interest the editorial by Dr Baim, and we wish to provide a chronologically accurate summary with respect to the use of ticlopidine and aspirin after stent implantation. Dr Colombo has greatly contributed to the development of stenting by being the first to demonstrate that use of intravascular ultrasound (IVUS) could eliminate the need for anticoagulation treatment in stented patients.^{2,3} However, it does not seem necessary to attribute the introduction of poststenting treatment with ticlopidine and aspirin to Dr Colombo. Indeed, he does not claim credit for it.

It was Dr Barragan who asserted, as early as 1992, that ticlopidine could prevent stent occlusion.⁴ Pursuant to this, the French registry "Stenting without Coumadin"⁵⁻⁷ was started in December 1992, and all patients included in this registry were treated with ticlopidine and aspirin on the advice of Dr Benvéniste. More than 25 centers participated, and 2900 patients were included between 1992 and 1995. The results demonstrated to the scientific community that the combination of ticlopidine and aspirin, taking into account the molecules currently available, was the treatment of choice for stented patients. These findings were verified in an open, nonrandomized study, the MUST study, monitored by Cardialysis, and eventually validated in a randomized study of ticlopidine and aspirin versus conventional treatment conducted by Schömig et al.⁸ All the French results were published with some delay because of the authors' inexperience in the publication of articles.

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Response

We thank Dr Morice for her comments. As she indicates, the replacement of prophylactic anticoagulation with antiplatelet

therapy in an effort to prevent stent thrombosis was promulgated by several European groups. Indeed, the work of numerous investigators in Italy, France, and Germany led to the widespread replacement of draconian warfarin-based regimens with safer and more effective antiplatelet therapies. Antonio Colombo and colleagues at the Centro Cuore in Milan, Italy,¹ demonstrated that after low-pressure deployment, the majority of stents were underexpanded despite optimal angiographic appearance by IVUS and that suboptimal expansion increased the risk for stent thrombosis.¹ The use of adjunctive high-pressure dilatation allowed these investigators to substitute antiplatelet agents for warfarin. Concomitantly, a multiphase registry that commenced at multiple sites in France evaluated novel regimens for preventing thrombosis, including both low-molecular-weight heparin and ticlopidine.² In the initial phases, patients were treated with aspirin, ticlopidine, and low-molecular-weight heparin. Only in the fifth and final phase did patients receive just aspirin and ticlopidine. The overall incidence of proven or suspected stent thrombosis (1.8%) did not differ significantly among the cohorts treated with aspirin and ticlopidine alone versus aspirin/ticlopidine and low-molecular-weight heparin. The data in this large French registry clearly provided an important link in the chain of evidence suggesting that the incidence of stent thrombosis could be reduced to an acceptably low level with only aspirin and ticlopidine. The finding of these pioneering French and Italian investigators were subsequently corroborated in the randomized German ISAR and the US STARS randomized trials.

It was not our intent to imply primacy of the work of Dr Colombo and colleagues over Dr Morice and her team in making the transition from anticoagulation to antiplatelet-based regimens possible. In a field in which many of the breakthroughs are disseminated before publication, it is frequently difficult to ascertain which individual or groups initially proposed an idea, such as that stents could be safely deployed without any anticoagulation. But we are sure that interventionists and their patients throughout the world should be indebted to these enlightened investigators from France, Italy, and Germany for providing the data that freed us all from the burdens of anticoagulation and its associated complications.

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Effects of Partial Left Ventriculectomy on Cardiac Performance

To the Editor:

We read with great interest the recent article by Gorcsan et al.¹ They report heterogeneous immediate effects of partial left ventriculectomy (PLV) on the slope (E_{es}) of end-systolic pressure-area relations obtained with echocardiographic automated border detection in 8 patients. The average change in E_{es} was from 6.5 ± 3.4 mm Hg/cm² (before PLV) to 4.3 ± 2.5 mm Hg/cm² (immediately after PLV) ($P=NS$). The authors, however, overlooked an error made by the iterative linear regression technique that they used to calculate E_{es} . In the right bottom panel of the Figure, where the decreased E_{es} (1.1 mm Hg/cm²) was demonstrated after PLV, the

end-systolic pressure-area line did not connect the end-systolic points (left upper corner) of each loop but connected early ejection phase (right upper corner) of each loop. This error occurs with the iterative linear regression technique when the x -axis intercept is large and negative ($\approx -64 \text{ cm}^2$ in the example shown). Another uncertainty of their method is the large negative x -axis intercept itself. This unphysiological value implies either insufficient hemodynamic range of data points to draw an end-systolic pressure-area relation line owing to its nonlinear characteristics and/or inadequate methodology to obtain instantaneous LV area. If the pressure-area loops in the left bottom panel ($E_{es}=4.2$ before PLV) and the right bottom panel ($E_{es}=1.1$ after PLV) are superimposed, it seems to us that LV systolic behavior improved remarkably after PLV because the post-PLV loops show higher end-systolic pressures with much smaller end-systolic areas.

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1. Gorcsan J III, Feldman AM, Kormos RL, Mandarino WA, Demetris AJ, Batista RJV. Heterogeneous immediate effects of partial left ventriculectomy on cardiac performance. *Circulation*. 1998;97:839–842.

Response:

We acknowledge and thank Dr Fukamachi and colleagues for their comments regarding our report describing the immediate effects of partial left ventriculectomy (PLV) on cardiac performance in a group of 8 patients with severe heart failure.¹ This study used pressure-area relations by echocardiographic automated border detection as a surrogate for pressure-volume relations to assess ventricular function in a predominately load-independent manner. Estimates of end-systolic elastance (E_{es}) and preload recruitable stroke work demonstrated variable immediate results of PLV. Changes in E_{es} and preload recruitable stroke work were inversely correlated with semiquantitative histological measures of myocardial fibrosis and directly related to degrees of hypertrophy.

Although Fukamachi et al raise some interesting points regarding the analysis of E_{es} from our data, they did not account for the fact that we used cross-sectional area as a surrogate for ventricular volume to estimate ventricular performance. This explains

the negative x -axis intercept values commonly encountered in pressure-area calculations of E_{es} because of the sharply curvilinear area-volume relationship in the low-volume range. Our group has previously validated this identical approach to calculate E_{es} as a predominantly load-insensitive index of contractility in animal models and in humans.^{2,3} Furthermore, 2 major findings support our results independently of the approach used to calculate E_{es} . First, similar results were found in estimates of preload recruitable stroke work that relate the integral of the entire pressure-area loop to end-diastolic area and eliminate the uncertainty of defining end systole.⁴ Second, our measures of alterations in ventricular performance after PLV were correlated significantly with the variability in myocardial fibrosis and hypertrophy by histological measures in these patients. Additional careful study is needed in a larger series of patients to further define the effects of this novel operation on cardiac performance and, more importantly, predict its related impact on patient outcome.

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