Effects of Amlodipine on Sympathetic Nerve Traffic and Baroreflex Control of Circulation in Heart Failure

Guido Grassi, Domenico Spaziani, Gino Seravalle, Giovanni Bertinieri, Raffaella Dell’Oro, Cesare Cuspidi, Giuseppe Mancia

Abstract—Short-acting calcium antagonists exert a sympathoexcitation that in heart failure further enhances an already elevated sympathetic activity. Whether this is also the case for long-acting formulations is not yet established, despite the prognostic importance of sympathetic activation in heart failure. It is also undetermined whether in this condition long-acting calcium antagonists favorably affect a mechanism potentially responsible for the sympathetic activation, i.e., the baroreflex impairment. In 28 heart failure patients (NYHA functional class II) under conventional treatment we measured plasma norepinephrine and efferent postganglionic muscle sympathetic nerve activity (microneurography) at rest and during arterial baroreceptor stimulation and deactivation induced by stepwise intravenous infusions of phenylephrine and nitroprusside, respectively. Measurements were performed at baseline and after 8 weeks of daily oral amlodipine administration (10 mg/d, 14 patients) or before and after an 8-week period without calcium antagonist administration (14 patients). Amlodipine caused a small and insignificant blood pressure reduction. Heart rate, left ventricular ejection fraction, and plasma renin and aldosterone concentrations were not affected. This was the case also for plasma norepinephrine (from 2.43 ±0.41 to 2.50±0.34 nmol/L, mean±SEM), muscle sympathetic nerve activity (from 54.4±5.9 to 51.0±4.3 bursts/min), and arterial baroreflex responses. No change in the above-mentioned variables was seen in the control group. Thus, in mild heart failure amlodipine treatment does not adversely affect sympathetic activity and baroreflex control of the heart and sympathetic tone. This implies that in this condition long-acting calcium antagonists can be administered without untoward neurohumoral effects anytime conventional treatment needs to be complemented by drugs causing additional vasodilatation. (Hypertension. 1999;33:671-675.)

Key Words: nervous system, sympathetic n nervous system, autonomic n baroreceptors n calcium antagonists n heart failure

Calcium antagonists have been regarded as harmful in the treatment of congestive heart failure (CHF).1–3 Recent studies, however, have somewhat modified this widely held opinion because of the evidence that, if longer-acting dihydropyridines are used, patients’ hemodynamics, clinic status, and mortality rate can be either improved or left unaffected.4,5 Mortality of patients with CHF is related to, among other factors, the sympathetic activation typical of this condition,6 which is the reason for the belief that drugs to be used in CHF patients should avoid any further increase and possibly reduce sympathetic influences on the heart and peripheral circulation.7 Whether this can be the case for long-acting dihydropyridines has not been established, however, because (1) short-acting dihydropyridines have been shown to increase sympathetic activity in hypertension6,9 and CHF10,11 and (2) previous reports on long-acting dihydropyridines have been based on norepinephrine (NE) values,11,12 i.e., on values that vary in CHF also as function of changes in peripheral blood flow and tissue clearance of this adrenergic neurotransmitter.13

In the present study, we have quantified sympathetic activity in patients with CHF before and after the daily addition of amlodipine to the existing treatment. The quantification was obtained not only through NE but also through direct assessment of muscle sympathetic nerve activity (MSNA) by microneurography. Baroreflex modulation of MSNA was also quantified because in CHF, impairment and recovery of this reflex parallel (and perhaps cause) the sympathetic activation and inactivation seen before and after drug treatment, respectively.14,15 To the best of our knowledge, this is the first study to evaluate via microneurography the effects of long-term amlodipine treatment on sympathetic activity and reflex sympathetic cardiovascular control in CHF.

Methods

Subjects

Our study was performed in 28 male patients under long-term drug treatment for a CHF caused either by coronary heart disease (n=18) or by idiopathic dilated cardiomyopathy (n=10). Patients were...
Amlodipine and Sympathetic Nerve Traffic in Heart Failure

Protocol and Data Analysis

All patients were hospitalized 4 days before the first study to perform it under standardized conditions. They were taken to the laboratory in the morning after a light breakfast, put in the supine position, subjected to the echocardiographic examination, and fitted with the intravenous cannulas and the various measuring devices. After a 30-minute interval, a blood sample was withdrawn, and BP was then measured 3 times by the mercury sphygmomanometer, and the 3 values were averaged. BP, HR, CVP, and MSNA were measured continuously during (1) an initial 10-minute baseline condition, (2) the stepwise-infusion of 1 vasoactive drug, (3) a second 10-minute baseline condition, and (4) the stepwise-infusion of the second vasoactive drug. Phenylephrine was infused first in half of the patients and nitroprusside was infused first in the remaining half. The patients were then discharged from the hospital and asked either to keep their drug treatment unchanged (control group) or to add to the ongoing therapeutic schedule of amlodipine at the single daily dose of 10 mg. In both instances, no dietary and lifestyle changes were advised. After 2 months (during which the patients were visited twice in the outpatient clinic), they were hospitalized again for 4 days to be restudied according to the protocol adopted for the first study. Adherence to treatment was verified by pill counting. The second study was performed about 4 hours after the assumption of the last dose of amlodipine.

Data were calculated by a single investigator unaware of the patients’ belonging to either treatment group. Values from individual subjects were averaged for the groups with and without amlodipine treatment and expressed as means±SEM. The statistical significance of the differences in mean values was assessed by ANOVA. The 2-tailed t test for paired observations was used to locate the difference between resting conditions and baroreceptor stimulation or deactivation using Bonferroni’s correction for multiple comparisons. The Spearman analysis was used to correlate changes in different variables. A value of P<0.05 was taken as the level of statistical significance.

Results

Basal Values

The Table shows that amlodipine administration was accompanied by a reduction in sphygmomanometric systolic and diastolic BP values, and finger mean BP that did not occur in all patients and thus fell short of statistical significance. LVEDD, LVEF, PRA, and ALDO were not significantly different before and after receiving the drug, which also did not affect NE or MSNA (Figure 1). Sphygmomanometric BPs were slightly and not significantly less in the second study compared with the first study in control patients, which showed in the 2 circumstances superimposable average CVP, echocardiographic, humoral, and MSNA values (Table and Figure 1).

Baroreflex Responses

Figure 2 shows the results obtained during baroreceptor stimulation and deactivation by infusion of vasoactive drugs. HR and the number of sympathetic bursts/min both were (1) progressively reduced by progressively increasing mean BP via phenylephrine and (2) progressively increased by progressively reducing mean BP via nitroprusside. All responses were superimposable before and after the administration of amlodipine. Baroreflex responses to vasoactive drug infusions were superimposable between the first and second studies also in control patients (Figure 2, right top and central panels). Similar resting and baroreflex values were obtained when data were analyzed separately in heart failures of ischemic and dilated idiopathic nature.

Measurements

Supine blood pressure (BP) was measured by a mercury sphygmomanometer and by a finger photoplethysmographic device (Finapres, Ohmeda 2300) capable of providing accurate and reproducible beat-to-beat systolic and diastolic BP values. In 11 patients, 5 of the amlodipine group and 6 of the control group, central venous pressure (CVP) was measured by a catheter placed in the right atrium from an antecubital vein of the right arm and connected with a transducer (model P23XL; Gould Instruments) positioned at the mid-chest level. Heart rate (HR) was continuously monitored by a cardiotachometer triggered by the R wave of an ECG lead. Left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) were obtained by standard B- and M-mode echocardiography. NE concentration was measured by high-performance liquid chromatography, and plasma renin activity (PRA) and plasma aldosterone (ALDO) concentrations were measured by radioimmunoassay. The measurements were obtained from a blood sample drawn from a cannula placed in an antecubital vein of the arm contralateral to that used for finger BP measurements.

Multunit recording of MSNA was obtained through a tungsten microelectrode inserted into the right or left peroneal nerve, as previously described in detail. In baseline conditions, MSNA was quantified as burst frequency over time (bursts/min) and as number of bursts corrected for HR values (bursts/100 heart beats), ie, by parameters that our group and others have shown to be highly reproducible on both a short- and a long-term basis. The number of sympathetic bursts/min was also used to quantify sympathometric activity during 3 stepwise intravenous infusions of phenylephrine (doses: 0.4, 0.8, and 1.1 μg·kg⁻¹·min⁻¹) and nitroprusside (doses: 0.4, 0.8, and 1.2 μg·kg⁻¹·min⁻¹) to obtain a progressive baroreceptor stimulation and deactivation, respectively. Both infusions were maintained for 15 minutes, with each incremental step lasting 5 minutes. The drug initially infused was followed by the second one after a 45-minute recovery period. Mean BP, MSNA, and HR were averaged for 10 minutes under baseline conditions before infusion and for the 5 minutes of each step, with the baroreceptor responses estimated by calculating changes in MSNA burst frequency and in HR associated with changes in mean BP.

In 14 patients (8 with coronary heart disease and 6 with dilated cardiomyopathy; age, 53.7±6 years, mean±SEM) amlodipine was added to their long-term treatment (see below). In the remaining 14 patients (9 with coronary heart disease and 5 with dilated cardiomyopathy; age, 59.1±2.9 years) current treatment was left unchanged to allow us to use them as controls. Patients were addressed to the amlodipine or control group on a sequential basis, ie, when 1 patient was assigned to 1 treatment group, the next patient fitting the inclusion criteria was assigned to the other treatment group. Long-term treatment consisted of oral furosemide (20 to 40 mg daily), and angiotensin-converting enzyme (ACE) inhibitors (enalapril, 10 mg daily) was part of the long-term drug assumption schedule in 15 patients (7 in the amlodipine and 8 in the control groups), their use in the remaining ones having been stopped for the occurrence of cough or hypotension. Digoxin (0.125 mg/d) was administered in 5 patients (3 in the amlodipine and 2 in the control groups). All patients included in the study were normotensive and in sinus rhythm. Body mass index was 25.8±3.6 kg·m⁻². The ‘echocardiographic’ cardiothoracic ratio was 0.45±0.06, and the ‘echocardiographic’ left ventricular end diameter was 55±5 mm. The study protocol was approved by the Institutional Ethics Committee. All patients gave their written consent to participate after being informed of the study nature and purpose.

In 11 patients, 5 of the amlodipine group and 6 of the control group, central venous pressure (CVP) was measured by a catheter placed in the right atrium from an antecubital vein of the right arm and connected with a transducer (model P23XL; Gould Instruments) positioned at the mid-chest level. Heart rate (HR) was continuously monitored by a cardiotachometer triggered by the R wave of an ECG lead. Left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) were obtained by standard B- and M-mode echocardiography. NE concentration was measured by high-performance liquid chromatography, and plasma renin activity (PRA) and plasma aldosterone (ALDO) concentrations were measured by radioimmunoassay. The measurements were obtained from a blood sample drawn from a cannula placed in an antecubital vein of the arm contralateral to that used for finger BP measurements.

Multunit recording of MSNA was obtained through a tungsten microelectrode inserted into the right or left peroneal nerve, as previously described in detail. In baseline conditions, MSNA was quantified as burst frequency over time (bursts/min) and as number of bursts corrected for HR values (bursts/100 heart beats), ie, by parameters that our group and others have shown to be highly reproducible on both a short- and a long-term basis. The number of sympathetic bursts/min was also used to quantify sympathometric activity during 3 stepwise intravenous infusions of phenylephrine (doses: 0.4, 0.8, and 1.1 μg·kg⁻¹·min⁻¹) and nitroprusside (doses: 0.4, 0.8, and 1.2 μg·kg⁻¹·min⁻¹) to obtain a progressive baroreceptor stimulation and deactivation, respectively. Both infusions were maintained for 15 minutes, with each incremental step lasting 5 minutes. The drug initially infused was followed by the second one after a 45-minute recovery period. Mean BP, MSNA, and HR were averaged for 10 minutes under baseline conditions before infusion and for the 5 minutes of each step, with the baroreceptor responses estimated by calculating changes in MSNA burst frequency and in HR associated with changes in mean BP.

Data were calculated by a single investigator unaware of the patients’ belonging to either treatment group. Values from individual subjects were averaged for the groups with and without amlodipine treatment and expressed as means±SEM. The statistical significance of the differences in mean values was assessed by ANOVA. The 2-tailed t test for paired observations was used to locate the difference between resting conditions and baroreceptor stimulation or deactivation using Bonferroni’s correction for multiple comparisons. The Spearman analysis was used to correlate changes in different variables. A value of P<0.05 was taken as the level of statistical significance.
The progressive increase and decrease in mean BP caused by phenylephrine and nitroprusside infusions were accompanied by CVP increases and reductions, respectively. The changes were small, only significant from the second step of the vasoactive drug infused, and similar at baseline and after 8 weeks in the control and amlodipine groups (Figure 2, bottom panels).

Discussion
In our patients with mildly symptomatic CHF, the administration of a therapeutic dose of amlodipine for several weeks was associated with (1) no improvement but also no deterioration in cardiac and hemodynamic parameters and (2) no activation of the sympathetic nervous system as assessed either indirectly by NE or directly by quantification of MSNA through microneurography. Because the ability of sympathetic nerve traffic to change in response to an appropriate stimulus was documented in the same patients by vasoactive drug infusion, this provides the first evidence that this long-acting dihydropyridine can be administered in patients with CHF, without aggravating the sympathoactivation typical of this condition.

The ability of amlodipine to be sympathetically neutral in CHF represents an advantage over short-acting dihydropyridines and other vasodilators, the administration of which leads to an additional increase in sympathetic cardiovascular drive of CHF patients.10,11 In this context, however, the drug’s effect remains different from that of CHF treatments such as digitalis, which lowers MSNA when given acutely,23 and NE, when given on a different from that of CHF treatments such as digitalis, which lowers MSNA when given acutely,23 and NE, when given on a long-term basis.24 It also remains different from treatment with an ACE inhibitor, which markedly reduces NE and MSNA and other vasodilators, the administration of which leads to an additional increase in sympathetic cardiovascular drive of CHF patients.10,11 In this context, however, the drug’s effect remains different from that of CHF treatments such as digitalis, which lowers MSNA when given acutely,23 and NE, when given on a long-term basis.24 It also remains different from treatment with an ACE inhibitor, which markedly reduces NE and MSNA when administered in patients with mild CHF for a period of time identical to that adopted for amlodipine administration in the present study.15 Whether this difference persists over longer treatment time spans and includes patients with more severe CHF remains to be determined.

Our study shows that the sympathoinhibitory and sympathoexcitatory responses to vasoactive drug-induced baroreceptor stimulation and deactivation are also unaffected by amlodipine. This marks a further difference with the ACE inhibitor treatment, which in CHF improves the baroreflex ability to restrain sympathetic nerve firing.15 Whether this dissimilarity is responsible for the concomitant difference in the effects of the 2 treatments on sympathetic tone remains to be determined, also considering that other factors not explored in the present study (ie, other reflexes, central factors, renin-angiotensin system, insulin sensitivity, and other metabolic factors) and probably involved in the neurohumoral profile of untreated and treated CHF patients, may play a role.

Several other results should be mentioned. First, in our patients, the pressor and depressor effects of vasoactive drug infusions triggered some alterations in CVP, possibly altering cardiac receptor activity.16 However, the changes were (1) inconsistent at doses of vasoactive drugs that already caused clear-cut reflex alterations in sympathetic activity and (2) small at all vasoactive drug doses used. Thus, although a contribution of cardiac receptors cannot be excluded, the reflex sympathetic responses largely depended on arterial baroreceptors both before and during amlodipine administration. Second, because in humans sympathetic nerve traffic can only be measured from superficial nerves, whether the sympathoexcitatory responses to vasoactive drug-induced baroreceptor stimulation and deactivation are also unaffected by amlodipine. This marks a further difference with the ACE inhibitor treatment, which in CHF improves the baroreflex ability to restrain sympathetic nerve firing.15 Whether this dissimilarity is responsible for the concomitant difference in the effects of the 2 treatments on sympathetic tone remains to be determined, also considering that other factors not explored in the present study (ie, other reflexes, central factors, renin-angiotensin system, insulin sensitivity, and other metabolic factors) and probably involved in the neurohumoral profile of untreated and treated CHF patients, may play a role.

Several other results should be mentioned. First, in our patients, the pressor and depressor effects of vasoactive drug infusions triggered some alterations in CVP, possibly altering cardiac receptor activity.16 However, the changes were (1) inconsistent at doses of vasoactive drugs that already caused clear-cut reflex alterations in sympathetic activity and (2) small at all vasoactive drug doses used. Thus, although a contribution of cardiac receptors cannot be excluded, the reflex sympathetic responses largely depended on arterial baroreceptors both before and during amlodipine administration. Second, because in humans sympathetic nerve traffic can only be measured from superficial nerves, whether the sympathoexcitatory responses to vasoactive drug-induced baroreceptor stimulation and deactivation are also unaffected by amlodipine. This marks a further difference with the ACE inhibitor treatment, which in CHF improves the baroreflex ability to restrain sympathetic nerve firing.15 Whether this dissimilarity is responsible for the concomitant difference in the effects of the 2 treatments on sympathetic tone remains to be determined, also considering that other factors not explored in the present study (ie, other reflexes, central factors, renin-angiotensin system, insulin sensitivity, and other metabolic factors) and probably involved in the neurohumoral profile of untreated and treated CHF patients, may play a role.

Several other results should be mentioned. First, in our patients, the pressor and depressor effects of vasoactive drug infusions triggered some alterations in CVP, possibly altering cardiac receptor activity.16 However, the changes were (1) inconsistent at doses of vasoactive drugs that already caused clear-cut reflex alterations in sympathetic activity and (2) small at all vasoactive drug doses used. Thus, although a contribution of cardiac receptors cannot be excluded, the reflex sympathetic responses largely depended on arterial baroreceptors both before and during amlodipine administration. Second, because in humans sympathetic nerve traffic can only be measured from superficial nerves, whether the sympathoexcitatory responses to vasoactive drug-induced baroreceptor stimulation and deactivation are also unaffected by amlodipine. This marks a further difference with the ACE inhibitor treatment, which in CHF improves the baroreflex ability to restrain sympathetic nerve firing.15 Whether this dissimilarity is responsible for the concomitant difference in the effects of the 2 treatments on sympathetic tone remains to be determined, also considering that other factors not explored in the present study (ie, other reflexes, central factors, renin-angiotensin system, insulin sensitivity, and other metabolic factors) and probably involved in the neurohumoral profile of untreated and treated CHF patients, may play a role.
a vasodilator does indeed have heterogeneous effects on sympathetic activity in different vascular districts. However, Goldsmith has recently shown that in patients with CHF, amlodipine does not alter a global marker of sympathetic activity such as NE spillover, which is in line with our finding that in CHF subjects, this drug did not cause any alteration in NE. Furthermore, amlodipine did not cause any alteration in HR, ie, a marker of sympathetic modulation of the sinus node. This suggests that neither muscle activity nor visceral sympathetic activity throughout the body was affected by amlodipine treatment. Finally, in our patients, administration of amlodipine was not accompanied by the increase in PRA and ALDO described with the administration of other dihydropyridines both in hypertensives and in patients with CHF. This may be related to the concomitant lack of sympathetic activation because the renin-angiotensin system and the sympathetic nervous system reinforce each other, ie, although a sympathetic activation directly or indirectly stimulates renin secretion from juxtaglomerular cells, the resultant increased production of angiotensin II stimulates, through central and peripheral mechanisms, sympathetic cardiac and vascular effects.

Our study has some potential limitations but also a clinical implication. One limitation is that when no change from a given intervention is found, the possibility may exist that the study did not have sufficient statistical power. However, the sympathetic and baroreflex data before and after amlodipine administration did not show any trend toward a possible change. Furthermore, previous studies have been able to detect sympathetic and baroreflex changes by various interventions when the study size was smaller than the present one, in which a total of 56 microneurographic recordings was obtained. Finally, the absence of any effect of amlodipine on sympathetic nerve firing was clear not only by between-subject but also by within-subject comparisons, ie, under a condition in which microneurographic data are highly reproducible on a short- and a long-term basis. It is therefore unlikely that a statistical shortcoming was responsible for our results. A second limitation is that the study could not be designed to have administration of placebo in the control group. However, administration of placebo has not shown to be associated with changes in sympathetic nerve...
traffic and baroreflex responses in several experimental settings, which makes it unlikely that lack of placebo administration in the control group affected our conclusion. A third limitation is that, because our patients had a mildly symptomatic CHF and a modest impairment of left ventricular function, our conclusion cannot be safely extrapolated to more severe CHF conditions in which the relationship between amiodipine and sympathetic cardiovascular influences may well be different. However, CHF is far more common in its mild than in its severe form, which gives our findings clinical relevance.

The clinical implication is that in CHF, amiodipine and other long-acting dihydropyridines are probably less suitable drugs than ACE-inhibitors, which lower sympathetic activity and enhance baroreflex control of autonomic cardiovascular influences. It should be emphasized, however, that the finding that amiodipine did not increase sympathetic nerve traffic, worsen the baroreflex, or both may also be seen under a more favorable light because it suggests that long-acting dihydropyridines can be used with no adverse neurohumoral consequences anytime traditional treatment of CHF (e.g., diuretics, digitalis, or ACE-inhibitors) needs to be complemented by drugs with a vasodilator effect. This may apply to the condition of CHF and hypertension, whereas any extrapolation of this kind to patients with CHF and angina pectoris should be made with caution, without further direct investigation.

References

Effects of Amlodipine on Sympathetic Nerve Traffic and Baroreflex Control of Circulation in Heart Failure

Guido Grassi, Domenico Spaziani, Gino Seravalle, Giovanni Bertinieri, Raffaella Dell'Oro, Cesare Cuspidi and Giuseppe Mancia

*Hypertension*. 1999;33:671-675
doi: 10.1161/01.HYP.33.2.671

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/33/2/671

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org//subscriptions/