Case Report

Effect of Pravastatin as an Adjunctive Therapeutic for Mitral Insufficiency with Hyperlipidemia in a Dog

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Pravastatin (PS) has been found to increase left ventricle (LV) expansion capacity and decrease LV constriction and left atrial pressure in healthy dogs. To date, there are no available reports on the effects of PS in dogs with hypercholesterolemia with chronic heart failure (CHF). This case report demonstrates a successful long-term treatment plan using PS in a dog suffering from mitral insufficiency with hyperlipidemia. A 12-year-old, castrated male Chihuahua dog had mitral insufficiency with hyperlipidemia. The dog presented with symptoms of chronic coughing. PS was orally administered (1 mg/kg, SID) in addition to general treatment for mitral insufficiency. The follow-up period was 375 days. PS administration decreased the heart rate (HR), vertebral heart size (VHS), and N-terminal probrain natriuretic peptide (NT-proBNP) concentration of the dog. In addition, PS administration also improved chronic cardiac failure induced by mitral insufficiency and hyperlipidemia. This report suggests that PS can be useful as an adjunctive therapeutic for dogs with hypercholesterolemia with mitral insufficiency.

1. Introduction

Statins are 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors that reduce blood cholesterol levels by inhibiting the HMG-CoA reductase in the mevalonic acid pathway [1]. In addition, this group of medications has been shown to have multifaceted effects, including anti-myocardial hypertrophy, anti-inflammatory effects, and antioxidant activity [1]. Statins activate the PI3 kinase-Akt pathway by inhibiting the mevalonate pathway. Statins also activate endothelial nitric oxide synthase (eNOS), followed by an increase in nitric oxide (NO) production [1, 2]. Pravastatin (PS), a statin medication, has been reported to prevent cardiomyocyte cell death via an increase in NO release, a decrease in myocyte endothelin-1 production, and an increase in protein kinase Akt activation [3]. Moreover, statins have been described to modulate both the neurohormonal activation and the autonomic nervous system by activating eNOS and increasing NO production [1]. For example, it has been shown that elevated cholesterol levels are associated with the overexpression of angiotensin II type 1 receptors [4] and that statins decrease the levels of these receptors, thus resulting in both decreased angiotensin II-mediated vasoconstriction and enhanced response to angiotensin receptor blockers [5–7]. Furthermore, simvastatin has been reported to normalize sympathetic outflow and reflex regulation in rabbits with chronic heart failure (CHF) [8]. Therefore, these drugs may be useful for the treatment of CHF with hypercholesterolemia in dogs. In a previous study, we have reported that PS increases left ventricle (LV) expansion capacity and decreases LV constriction and left atrial pressure in healthy dogs [9]. Consequently, we suggested that PS may be effective in improving heart failure with LV diastolic dysfunction or elevated left atrial pressure in dogs. To date, no reports are available on the effects of PS in dogs with hypercholesterolemia with CHF. This case report demonstrates a successful long-term treatment plan using PS in a dog suffering from mitral insufficiency with hyperlipidemia.
2. Case Presentation

A 12-year-old, castrated male Chihuahua dog weighing 4.2 kg was referred to the hospital with a diagnosis of chronic coughing. The medical history of the dog included tracheal collapse. Physical examinations revealed a grade III murmur and cough. Respiration rate was 20 breaths/min. The dog was coughing. The medical history of the dog included tracheal debris that was gradually increasing in size. Consequently, the administration of alacepril (1.5 mg/kg, SID) and a low-fat meal were initially prescribed. The subsequent treatment was continued for a period of two months. However, cardiomegaly continued to progress, whereas the frequency of coughing was not reduced. Moreover, hyperlipidemia was not improved. Abdominal ultrasonography revealed biliary tract obstruction. Cough disappeared one week after PS administration. In this case, however, LV fractional shortening (FS) and LV ejection fraction (EF) decreased after PS administration, which could be improved with the prognosis.

Furthermore, the radiographic vertebral heart size (VHS) decreased after PS administration. In addition, blood biochemical tests revealed that the total cholesterol, triglyceride, and N-terminal probrain natriuretic peptide (NT-proBNP) concentrations were significantly decreased from Day 11 to Day 211 (Table 1). An increase in creatine kinase value was not observed throughout the administration period. Additional hematologic and biochemical findings indicating renal or hepatic failures and adverse effects were not observed up to 375 days after PS administration (Table 1).

Table 1: Hematological, serum biochemical, and cardiac biomarker parameters after pravastatin administration.

| Variables                        | Reference Range | 0 | 11 | 30 | 45 | 65 | 96 | 121 | 150 | 211 | 283 | 375 |
|----------------------------------|-----------------|---|----|----|----|----|----|-----|-----|-----|-----|-----|
| White blood cells (×10³/mm³)     | 6–17            | 12.0 | 10.1 | 11.1 | 10.7 | 8.7 | 9.1 | 10.6 | 9.4 | 11.2 |
| Red blood cells (×10³/mm³)       | 550–850         | 652 | 656 | 723 | 758 | 645 | 718 | 676 | 695 | 686 |
| Packed cell volume (%)           | 37–55           | 45.1 | 45.1 | 49.9 | 51.6 | 44.3 | 49.9 | 46.4 | 47.3 | 47.0 |
| Alanine aminotransferase (U/L)   | 10–100          | 59 | 102 | 109 | 112 | 118 | 123 | 105 | 92 | 98 |
| Aspartate aminotransferase (U/L) | 0–50            | 22 | 25 | 27 | 28 | 24 | 30 | 29 | 28 | 30 |
| Alkaline phosphatase (U/L)       | 23–212          | 443 | 297 | 319 | 361 | 330 | 367 | 303 | 244 | 242 |
| Blood urea nitrogen (mg/dL)      | 7–27            | 14.3 | 16.3 | 17.2 | 13.4 | 17.7 | 19.9 | 17.2 | 14.4 | 18.2 |
| Creatinine (mg/dL)               | 0.5–1.8         | 0.6 | 0.8 | 0.8 | 0.8 | 0.6 | 0.6 | 0.7 | 0.8 | 0.7 |
| Triglyceride (mg/dL)             | 17–79           | 577 | 396 | 180 | 178 | 424 | 402 | 209 | 205 | 263 | 162 | 294 |
| Total cholesterol (mg/dL)        | 111–320         | 360 | 281 | 274 | 273 | 279 | 295 | 295 | 317 | 256 | 253 | 239 |
| Creatine kinase (U/L)            | 10–200          | 60 | 75 | 69 | 75 | 98 | 75 | 63 | 70 | 79 | 75 | 166 |
| Serum N-terminal probrain natriuretic peptide (pmol/L) | <900 | 2449 | 1352 | 1117 | 1402 | 1305 | 1209 | 1020 | 1058 | 988 | 2704 | 2146 |

3. Discussion

In dogs with mitral insufficiency, increased HR, LA/Ao ratio and serum NT-proBNP concentration, and pulmonary hypertension (PH) can be considered negative prognostic factors [10, 11]. However, our case study reveals that HR apparently decreased after PS administration. This may be due to the PS-induced inhibition of the sympathetic nerve activity via blocking angiotensin II-mediated activity [1]. In addition, VHS, LA/Ao ratio, sPA, and serum NT-proBNP concentration decreased after PS administration, which could be improved with the prognosis.

Furthermore, we identified that both SV and CO decreased on Days 30 and 45 after PS administration but thereafter increased and maintained well. No substantial changes in the maximum systolic mitral regurgitation velocity (MRmax) were identified after PS administration. The maximum systolic tricuspid regurgitation velocity (TRmax) and systolic pulmonary arterial pressure (sPA), calculated using the modified Bernoulli equation (4 x TRmax² + 10), both decreased after PS administration (Table 2). The peak velocity of early diastolic mitral annular motion (Em)/peak velocity of diastolic mitral annular motion (Am) ratio increased during PS administration compared with preadministration. E/Em decreased on Days 34 and 65 after PS administration but increased after Day 96, and a higher value was then observed (Table 2).
Table 2: Echocardiographic and circulation variables after pravastatin administration.

| Variables                                | 0   | 11  | 30  | 45  | 65  | 96  | 121 | 150 | 211 | 283 | 375 |
|------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Body weight (kg)                         | 4.3 | 4.4 | 4.3 | 4.3 | 4.3 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 |
| Radiographic vertebrae heart size (VHS) | 11.0| 10.5| 10.3| 10.3| 10.0| 10.0| 10.5| 10.0| 9.8 | 10.5| 10.5|
| Heart rate (beats/min)                   | 150 | 139 | 132 | 107 | 132 | 130 | 119 | 110 | 114 | 131| 131 |
| Systolic blood pressure (SBP; mmHg)      | 126 | 168 | 154 | 148 | 148 | 160 | 178 | 164 | 156 | 153 | 154|
| Diastolic blood pressure (DBP; mmHg)     | 68  | 83  | 91  | 73  | 90  | 105 | 99  | 107 | 100 | 93  | 84  |
| Mean blood pressure (MAP; mmHg)          | 87  | 100 | 109 | 100 | 105 | 135 | 120 | 135 | 121 | 122 | 104 |
| Left atrium (LA; mm)                     | 19.5| 15.9| 16.3| 16.4| 16.2| 17.2| 16.9| 16.2| 16.2| 13.3| 14.1|
| Right atrium (RA; mm)                    | 13  | 12.3| 12.3| 12.5| 11.5| 11.9| 13  | 11  | 13  | 10.2| 11.4|
| Aorta (Ao mm)                            | 11.2| 11.1| 11.5| 11.7| 12.1| 12.6| 12.4| 12.6| 12.5| 11.3| 12.4|
| LA/Ao                                    | 1.74| 1.43| 1.42| 1.40| 1.34| 1.37| 1.36| 1.29| 1.29| 1.18| 1.14|
| RA/Ao                                    | 1.16| 1.11| 1.06| 1.06| 0.95| 0.94| 1.04| 0.87| 1.04| 0.9  |0.91 |
| LV fractional shortening (FS; %)         | 57  | 43  | 52  | 47  | 47  | 51  | 43  | 47  | 45  | 43  | 43  |
| LV ejection fraction (EF; %)             | 88  | 76  | 84  | 80  | 80  | 84  | 75  | 80  | 78  | 76  | 76  |
| End-systolic left ventricular inner dimension (LVIDs; mm) | 12.7| 16.4| 13  | 15.1| 14  | 13.2| 15.8| 14.9| 15.7| 16.6| 17  |
| End-diastolic left ventricular inner dimension (LVIDd; mm) | 29.6| 28.7| 26.8| 28.7| 26.3| 26.8| 27.4| 28.1| 29.6| 29.4| 30.1|
| Normalized end-diastolic left ventricular inner dimension (LVIDdN) | 1.90| 1.85| 1.74| 1.86| 1.71| 1.75| 1.84| 1.84| 1.94| 1.92| 1.97|
| Pulmonary valve flow velocity (m/s)      | 0.78| 0.78| 1.00| 0.89| 1.09| 0.89| 1.01| 0.89| 1.03| 0.80| 0.89|
| Peak velocity of early diastolic transmitral flow wave (E; cm/s) | 76.5| 97.0| 78.0| 93.6| 75.2| 84.0| 72.0| 91.9| 83.1| 90.6| 84.1|
| Peak velocity of late transmitral flow wave (A; cm/s) | 94.3| 70.2| 62.3| 66.3| 71.1| 58.7| 61.5| 61.7| 69.6| 60.4| 65.7|
| E/A                                      | 0.81| 1.38| 1.25| 1.41| 1.06| 1.43| 1.17| 1.49| 1.19| 1.5  |1.28 |
| Deceleration time of early diastolic transmitral flow (DTE; ms) | 108 | 80  | 104 | 108 | 136 | 136 | 104 | 92  | 104 | 120 | 120 |
| Stroke volume (SV; mL)                   | 5.1 | 5.2 | 3.8 | 3.6 | 5.0  | 7.2  | 4.7  | 4.3 | 4.9 | 6.1  |6.1  |
| Aortic ejection flow velocity (AEV; m/s) | 0.73| 0.86| 0.99| 0.88| 0.83 | 0.91 | 0.76 | 0.84| 1.26| 0.80 |0.84|
| Cardiac output (CO; L/min)               | 0.668| 0.680| 0.381| 0.339| 0.544| 0.694| 0.484| 0.633| 0.494| 0.522| 0.497|
| Peak velocity of aortic valve regurgitation (AR; cm/s) | 1.29| 216 | 104 | 275 | 245 | 214 | 147 | 256 | 241 | 260 | 265|
| Maximum systolic mitral regurgitation velocity (MRmax; m/s) | 5.76| 6.10| 5.98| 5.86| 5.32| 5.63| 5.40| 5.64| 5.70| 5.25| 5.54|
| Maximum tricuspid regurgitation velocity (TRmax; m/s) | 3.20| 2.97| 2.17| 2.73| 2.88| 2.83| 2.63| 2.67| 2.67| 2.60| 2.23|
| Systolic pulmonary arterial pressure (sPA; mmHg) | 51.0| 45.3| 28.8| 39.8| 43.2| 42.0| 37.7| 38.5| 38.5| 37.0| 29.9|
| Left ventricular Tei index               | 0.49| 0.49| 0.55| 0.38| 0.32 | 0.77 | 0.70 | 0.51 | 0.29 |0.53 | 0.40|
| Right ventricular Tei index             | 0.13| 0.30| 0.18| 0.22| 0.37 | 0.40 | 0.23 | 0.33 | 0.30 |0.66 | 0.55|
| Peak velocity of early diastolic mitral annular motion (Em; cm/s) | 6.7 | 8.4 | 6.5 | 10.2| 9.1  | 6.7  | 6.5  | 7.1  | 4.9  | 5.8  |7.4  |
| Peak velocity of diastolic mitral annular motion (Am; cm/s) | 11.5| 13.1| 7.7 | 11.6| 10.8 | 9.6  | 9.2  | 8.5  | 7.4  | 9.7  | 11  |
| Em/Am                                   | 0.58| 0.64| 0.84| 0.88| 0.84 | 0.70 | 0.70 | 0.83 | 0.65 | 0.60 |0.67 |
| E/Em                                    | 11.5| 11.5| 12.1| 9.2 | 8.2  | 12.6 | 11.0 | 12.9 | 16.9 | 16.1 |9.5  |
| Tricuspid annular plane systolic excursion (TAPSE; mm) | 12.1| 13.0| 12.4| 13.2| 11.4 | 12.5 | 11.9 | 11.7 | 11.0 |10.2 |
which could be attributed to the decrease in HR after PS administration.

Furthermore, MRmax did not markedly change from the baseline value. In contrast, both TRmax and sPA decreased after PS administration, which may be caused by the pulmonary artery dilation from the inhibitory effect of statins on Rho kinase [12]. In addition, because the decreased eNOS expression [12] and increased endothelin-1 expression [13] have been identified as causes of PH, both PS-induced eNOS activation [2] and decreased ET-1 expression [3] may be involved in sPA reduction. E/Em temporarily decreased after PS administration, thus suggesting that PS administration decreases left atrial pressure reduction. Finally, the decrease in serum NT-proBNP observed after the administration of PS may be associated with the reduction of cardiac load facilitated by the stain-induced inhibition of angiotensin II type 1 receptor expression and vascular contraction by angiotensin II [1].

In this case, coughing was apparently improved after PS administration. This may be due to cardiac load reduction as evidenced by the decrease in VHS and LA/Ao ratio after PS administration. In contrast, statins are known to have anti-inflammatory effects by acting on several pathways or factors, such as cholesterol biosynthesis pathway, Ras and Rho kinase, nuclear factor-xB and activator protein-1-mediated proinflammatory pathways, and peroxisome proliferator-activated receptor and Kruppel-like factor-2 [14]. Therefore, coughing improvement following PS administration may be due to the multifaceted effects of statins, including cardiac load reduction and anti-inflammatory effects.

In conclusion, PS administration in addition to the general treatment for mitral insufficiency with hyperlipidemia in a dog was found to decrease tachycardia and left atrial pressure and also improved hyperlipidemia and PH without reducing blood pressure. Moreover, the clinical symptoms of chronic cardiac failure were also improved. Therefore, PS administration may be effective as an adjunctive therapy in improving cardiac function and lipid metabolism in dogs with both mitral insufficiency and hyperlipidemia.

**Abbreviations**

| Symbol | Definition                        |
|--------|----------------------------------|
| A:     | Peak velocity of late transmitral flow |
| Ao:    | Aorta                            |
| Am:    | Peak velocity of diastolic mitral annular motion |
| CHF:   | Chronic heart failure            |
| CO:    | Cardiac output                   |
| DT_E:  | Deceleration time of early diastolic transmitral flow |
| E:     | Ejection velocity of early diastolic transmitral flow |
| EF:    | Ejection fraction                |
| Em:    | Peak velocity of early diastolic mitral annular motion |
| eNOS:  | Endothelial nitric oxide synthase |
| FS:    | Fractional shortening            |
| HMG-CoA: | 3-Hydroxy-3-methyl-glutaryl-CoA          |
| HR:    | Heart rate                        |
| LA:    | Left atrium                       |
| LV:    | Left ventricle                    |
| MRmax: | Maximum systolic mitral regurgitation velocity |
| NO:    | Nitric oxide                      |
| NT-proBNP: | N-terminal probrain natriuretic peptide |
| PH:    | Pulmonary hypertension            |
| PS:    | Pravastatin                       |
| sPA:   | Systolic pulmonary arterial pressure |
| SV:    | Stroke volume                     |
| TRmax: | Maximum systolic tricuspid regurgitation velocity |
| VHS:   | Vertebral heart size.             |

**Data Availability**

The clinical data used to support the findings of this case are included within the text and in tables.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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**References**

[1] K. Ramasubbu, J. Estep, D. L. White, A. Deswal, and D. L. Mann, ”Experimental and clinical basis for the use of statins in patients with ischemic and nonischemic cardiomyopathy,” *Journal of the American College of Cardiology*, vol. 51, no. 4, pp. 415–426, 2008.

[2] Y. Rikitake and J. K. Liao, ”Rho GTPases, statins, and nitric oxide,” *Circulation Research*, vol. 97, no. 12, pp. 1232–1235, 2005.

[3] S. Verma, V. Rao, R. D. Weisel et al., ”Novel cardioprotective effects of pravastatin in human ventricular cardiomyocytes subjected to hypoxia and reoxygenation: beneficial effects of statins independent of endothelial cell,” *Journal of Surgical Research*, vol. 119, no. 1, pp. 66–71, 2004.

[4] K. Strehlow, S. Wassmann, M. Böhm, and G. Nickenig, ”Angiotensin AT1 receptor over-expression in hypercholesterolaemia,” *Annals of Medicine*, vol. 32, no. 6, pp. 386–389, 2000.

[5] G. Nickenig, A. T. Baumer, Y. Temur, D. Kebben, F. Jockenhovel, and M. Böhm, ”Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men,” *Circulation*, vol. 100, no. 21, pp. 2131–2134, 1999.

[6] M. Horiuchi, T. X. Cui, Z. Li, J. M. Li, H. Nakagami, and M. Iwai, ”Fluvastatin enhances the inhibitory effects of a selective angiotensin II type 1 receptor blocker, valsartan, on vascular neointimal formation,” *Circulation*, vol. 107, no. 1, pp. 106–112, 2003.

[7] P. van der Harst, L. J. Wagenaar, H. Buikema et al., ”Effect of intensive versus moderate lipid lowering on endothelial function and vascular responsiveness to angiotensin II in stable coronary artery disease,” *The American Journal of Cardiology*, vol. 96, no. 10, pp. 1361–1364, 2005.
[8] R. U. Pliquett, K. G. Cornish, J. D. Peuler, and I. H. Zucker, “Simvastatin normalizes autonomic neural control in experimental heart failure,” *Circulation*, vol. 107, no. 19, pp. 2493–2498, 2003.

[9] S. Arita, N. Arita, and Y. Hikasa, “Effect of pravastatin on echocardiographic circulation parameters in dogs,” *The Journal of Veterinary Medical Science*, vol. 76, no. 4, pp. 481–489, 2014.

[10] M. Borgarelli, P. Savarino, S. Crosara et al., “Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease,” *Journal of Veterinary Internal Medicine*, vol. 22, no. 1, pp. 120–128, 2008.

[11] W. Moonarmart, A. Boswood, V. Luis Fuentes, D. Brodbelt, K. Souttar, and J. Elliott, “N-terminal pro B-type natriuretic peptide and left ventricular diameter independently predict mortality in dogs with mitral valve disease,” *The Journal of Small Animal Practice*, vol. 51, no. 2, pp. 84–96, 2010.

[12] A. Giaid and D. Saleh, “Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension,” *The New England Journal of Medicine*, vol. 333, no. 4, pp. 214–221, 1995.

[13] A. Giaid, M. Yanagisawa, D. Langleben et al., “Expression of endothelin-1 in the lungs of patients with pulmonary hypertension,” *The New England Journal of Medicine*, vol. 328, no. 24, pp. 1732–1739, 1993.

[14] M. K. Jain and P. M. Ridker, “Anti-inflammatory effects of statins: clinical evidence and basic mechanisms,” *Nature Reviews Drug Discovery*, vol. 4, no. 12, pp. 977–987, 2005.