Patients with diastolic heart failure account for about a half of the whole heart failure patients. Although their prognoses are comparable to those of systolic heart failure patients, most therapeutic agents which are currently used for heart failure patients are agents, which have been clinically tested for systolic heart failure patients with lowered LVEF. There is no medicament, which has an effect to relieve diastolic functional failure and which has been proven to improve the prognoses of diastolic heart failure patients.

[0009]

For the acute exacerbation phase of diastolic heart failure patients, a diuretic agent or a venodilatory vasodilator is used, as in the case of systolic heart failure patients. However, when such a medicament is administered to a patient with diastolic heart failure, there are problems in that the cardiac output and the blood pressure tend to decrease, or the patient is repeatedly hospitalized due to the higher frequency of recurrence in comparison with a systolic heart failure patient.

Further, it is said that most of the patients, who were diagnosed with systolic heart failure, actually suffer from left ventricular diastolic ~~functional disorder~~dysfunction.

[0010]

Among the existing medicaments used for the treatment in the acute phase, there is no medicament which selectively relieves left ventricular diastolic ~~functional disorder~~dysfunction, and there are patients with symptoms of lung congestion or dyspnea, which are not relieved, or which need a long time to be improved. Thus, a new therapeutic agent is desired.

As described above, at this point, there is no effective therapeutic method for diastolic heart failure or left ventricular diastolic ~~functional disorder~~dysfunction, and thus the development of a new therapeutic means is urgently needed.

[0011]

On the other hand, 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a prodrug thereof, or a cyclodextrin clathrate thereof is a selective agonist for EP4, which is a receptor subtype of prostaglandin E2, and is reported to be effective for immune diseases (autoimmune diseases such as amyotrophic lateral sclerosis, multiple sclerosis, Sjogren's syndrome, chronic rheumatoid arthritis and systemic lupus erythematosus, rejection after organ transplantation, and the like), asthma,

Patent Document 5: JP-A-2001-233792
Patent Document 6: WO2002/016311

Summary of the Invention
Problems that the Invention is to Solve
[0015]

Diastolic heart failure is a disease caused by diastolic ~~functional disorder~~ dysfunction of a heart, in particular of a left ventricle. Since there is currently no medicament showing an effect to improve left ventricular diastolic function itself, there is no effective medical therapy, which can preferentially treat diastolic heart failure so far.

For diastolic heart failure patients in the acute exacerbation phase, a diuretic agent or a vasodilator is sometimes prescribed with the purpose of relieving the symptoms of lung congestion and dyspnea. However, left ventricular diastolic ~~functional disorder~~ dysfunction itself, which is the cause of the pathology thereof, is not cured, and the recurrence cannot be prevented.
[0016]

Namely, an object of present invention is to provide a medicament, which improves diastolic function of a left ventricle itself without depending on the diuretic effect or vasodilation effect; controls the pathological condition of diastolic heart failure or left ventricular diastolic ~~functional disorder~~dysfunction; and prevents the recurrence, and can prevent dyspnea and death due to this pathological condition.

Means for Solving the Problems
[0017]

EP4 agonists are generally predicted to relieve the congestion state of heart failure patients since EP4 agonists have a vasodilation effect and an effect to relieve renal dysfunction. However, these effects are the same as those of the existing vasodilators, and thus diastolic heart failure or left ventricular diastolic ~~functional disorder~~ dysfunction is not relieved. Accordingly, when an EP4 agonist is administered to a patient with diastolic heart failure, there is a possibility that the agonist only causes the similar problems as those of a diuretic agent or a vasodilator, for example the decrease in the cardiac output, the decrease in the blood pressure, or the frequent recurrence.
[0018]

As a result of extensive studies, the inventors of the present invention found that, among the compounds known as EP4 agonists, 4-[(2-{(2R)-2-

[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid (sometimes abbreviated to a compound A below) improves diastolic function of a left ventricle by directly acting on a heart, and can effectively treat particularly diastolic functional failure/diastolic ~~functional disorder~~ dysfunction among heart failure types, and thus the inventors completed present invention.

[0019]

Namely, present invention is as follows.

1. An agent for improving left ventricular diastolic function, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

2. The agent according to the above 1, which is an agent for treating heart failure and/or relieving a symptom.

3. The agent according to the above 2, wherein the heart failure is acute heart failure or chronic heart failure.

4. The agent according to the above 2 or 3, wherein the heart failure is diastolic heart failure.

5. The agent according to the above 2, wherein the symptom is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

6. The agent according to the above 1 to 5, which further has an effect to improve left ventricular systolic function.

7. The agent according to the above 6, which is an agent for treating systolic heart failure and/or relieving a symptom.

8. The agent according to the above 7, wherein the symptom is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

9. An agent for improving the survival rate of heart failure, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

10. An agent for improving left ventricular distensibility, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

11. An agent for preventing myocardial fibrillization, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-

29. An agent for reducing the dose of an existing agent for treating heart failure, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or cyclodextrin thereof.
30. An agent for reducing the side effect of an existing agent for treating heart failure, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or cyclodextrin thereof.

Effects of the Invention
[0020]

Since 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid (the compound A), a salt thereof, a solvate thereof or a prodrug thereof, or a cyclodextrin clathrate thereof (sometimes abbreviated to "the compound used for the agent of present invention" below) has an effect to relieve diastolic ~~functional disorder~~ dysfunction of a left ventricle by directly acting on a heart in addition to a vasodilation effect, it is effective particularly for diastolic heart failure among acute and chronic heart failure, and can relieve lung congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema, hepatomegaly and/or the like more effectively than the existing vasodilators. Further, left ventricular diastolic function is generally impaired also in systolic heart failure, and the existing diuretic agents/vasodilators cannot relieve left ventricular diastolic ~~functional disorder~~dysfunction. Accordingly, it is expected that the compound used for the agent of present invention has better efficacy also for systolic heart failure in comparison with the existing diuretic agents/vasodilators.

Brief Description of the Drawings
[0021]

[Figure 1] Figure 1 shows the intensity balance of the left ventricular relaxation effects and the left ventricular contraction effects of the compound A and milrinone, which is an existing agent for treating heart failure, in an acute heart failure model.

[Figure 2] Figure 2 shows the influences of the compound A and milrinone on the survival rate in a chronic heart failure model.

[Figure 3] Figure 3 shows the influences of the compound A and milrinone on the left ventricular diastolic wall strain (DWS) index in a chronic heart failure model.

Mode for Carrying Out the Invention

[0022]

The compound used for the agent of present invention improves diastolic function of a left ventricle, and can relieve the state, in which diastolic function of a left ventricle is impaired, namely left ventricular diastolic functional failure (which is sometimes called just diastolic functional failure).

In this specification, heart failure includes heart failure in the acute phase or in the chronic phase, namely acute heart failure or chronic heart failure. The definition of acute heart failure sometimes includes chronic heart failure in the acute exacerbation phase. Further, heart failure is sometimes called congestive heart failure.

[0023]

Regarding heart failure, the functional disorders of a heart and the pathological conditions caused by the disorders are shown in Table 1 below. Diastolic heart failure (heart failure in diastole) is heart failure, in which only diastolic function of a left ventricle is impaired, but systolic function is normal or only slightly deteriorated. On the other hand, in systolic heart failure (heart failure in systole), both systolic function and diastolic function of a left ventricle are impaired. Diastolic heart failure and systolic heart failure are sometimes called diastolic failure and systolic failure, respectively. Further, the state, in which left ventricular diastolic function is impaired, is called left ventricular diastolic ~~functional disorder~~dysfunction, left ventricular diastolic functional failure, left ventricular diastolic disorder or left ventricular diastolic failure; and the state, in which systolic function is impaired, is also called left ventricular systolic ~~functional disorder~~dysfunction, left ventricular systolic functional failure, left ventricular systolic disorder or left ventricular systolic failure.

[0024]

for the agent of present invention is administered repetitively to a mammal (a human, a dog, a rat or the like) in which heart failure has been already developed, in comparison with the case without the administration. The prevention of the myocardial fibrillization leads to the prevention of the deterioration of the distensibility of a left ventricle (namely, passive diastolic disorder of a left ventricle) and thus left ventricular diastolic ~~functional disorder~~ dysfunction is relieved.

[0038]

Furthermore, as described above, in a patient with diastolic heart failure, the ventricle cannot dilate sufficiently during diastole and a sufficient blood volume cannot be pumped, due to the ventricular wall thickening and the myocardial fibrillization. Since the compound used for the agent of present invention prevents the myocardial fibrillization and prevents the deterioration of the distensibility in a left ventricle, the compound can be used as an agent for improving the cardiac output. It is possible to easily measure and decide whether the compound used for the agent of present invention has improved the cardiac output, by using an invasive, noninvasive or low-invasive device for monitoring the cardiac output.

[0039]

In order to use the compound used for the agent of present invention with the above purpose, the compound used for the agent of present invention can be generally administered systemically or topically in the form of oral or parenteral administration after appropriately formulating the compound. As the parenteral administration, intravenous administration, intramuscular administration, subcutaneous administration, percutaneous administration and the like are mentioned. The administration path of the compound used for the agent of present invention may be any method as long as it is a method enabling the intravital administration of an effective amount thereof, and for example, oral administration or administration by injection, or administration as a patch is preferable.

[0040]

Although the dose depends on the age, the weight, the symptom, the therapeutic effect, the administration method, the administration period and the like, the administration is generally oral and once to several times a day wherein an amount per each time is 0.1 ng to 1 mg per adult, parenteral and once to several times a day wherein an amount per each time is 0.1 ng to 1 mg per adult, or intravenous and continuous for 1 hour to 24 hours a day. For example, when the compound used for the agent of present invention is orally

Claims

[Claim 1]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for treating heart failure and/or relieving a symptom.

[Claim 2]

The use according to claim 1, wherein the heart failure is acute heart failure or chronic heart failure.

[Claim 3]

The use according to claim 1, wherein the heart failure is diastolic heart failure.

[Claim 4]

The use according to any one of claims 1 to 3, wherein the symptom is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

[Claim 5]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for treating heart failure, which changes Peak positive dP/dt and Peak negative dP/dt of a mammal having a pathological condition of heart failure, wherein the change ratio of the Peak negative dP/dt calculated from the values before and after the administration of the agent is larger than the change ratio of the Peak positive dP/dt.

[Claim 6]

The use according to claim 5, which is use for treating diastolic heart failure and/or relieving a symptom.

[Claim 7]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate

thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for improving the survival rate of heart failure.

[Claim 8]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for improving cardiac output.

[Claim 9]

A medicine for treating heart failure, which is produced by combining 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof, with one or more compounds selected from an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, a β-blocker, a digitalis preparation, a diuretic agent, a natriuretic peptide, a vasodilator, a phosphodiesterase III inhibitor and/or an aldosterone antagonist.

[Claim 10]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for treating heart failure in which diastolic function is impaired.

[Claim 11]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for reducing the dose of an existing agent for treating heart failure.

[Claim 12]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for reducing the side effect of an existing agent for treating heart failure.

[Claim 13]

The use according to claim 11 or 12, wherein the existing agent is one or more compounds selected from an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, a β-blocker, a digitalis preparation, a diuretic agent, a natriuretic peptide, a vasodilator, a phosphodiesterase III inhibitor and/or an aldosterone antagonist.

[Claim 14]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for preventing heart failure associated with hypertension from occurring.

[Claim 15]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for improving left ventricular diastolic function.

[Claim 16]

The use according to claim 15, which is use for treating heart failure and/or relieving a symptom.

[Claim 17]

The use according to claim 16, wherein the heart failure is acute heart failure or chronic heart failure.

[Claim 18]

The use according to claim 16, wherein the heart failure is diastolic heart failure.

[Claim 19]

The use according to claim 16, wherein the symptom is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

[Claim 20]

The use according to claim 15, which is use for further improving left ventricular systolic function.

[Claim 21]

The use according to claim 20, which is use for treating systolic heart failure and/or relieving a symptom.

[Claim 22]

The use according to claim 21, wherein the symptom is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

[Claim 23]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for improving left ventricular distensibility.

[Claim 24]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for preventing myocardial fibrillization.

[Claim 25]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for selectively improving left ventricular diastolic function, which selectively improves left ventricular diastolic function in comparison with left ventricular systolic function.

[Claim 26]

The use according to claim 25, which is use for treating diastolic heart failure and/or relieving a symptom.

[Claim 27]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent treating and/or improving diastolic functional failure.

[Claim 28]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent treating and/or improving diastolic functional disorder.

[Claim 29]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent treating diastolic heart failure and/or relieving a symptom.

Patients with diastolic heart failure account for about a half of the whole heart failure patients. Although their prognoses are comparable to those of systolic heart failure patients, most therapeutic agents which are currently used for heart failure patients are agents, which have been clinically tested for systolic heart failure patients with lowered LVEF. There is no medicament, which has an effect to relieve diastolic functional failure and which has been proven to improve the prognoses of diastolic heart failure patients.

[0009]

For the acute exacerbation phase of diastolic heart failure patients, a diuretic agent or a venodilatory vasodilator is used, as in the case of systolic heart failure patients. However, when such a medicament is administered to a patient with diastolic heart failure, there are problems in that the cardiac output and the blood pressure tend to decrease, or the patient is repeatedly hospitalized due to the higher frequency of recurrence in comparison with a systolic heart failure patient.

Further, it is said that most of the patients, who were diagnosed with systolic heart failure, actually suffer from left ventricular diastolic dysfunction.

[0010]

Among the existing medicaments used for the treatment in the acute phase, there is no medicament which selectively relieves left ventricular diastolic dysfunction, and there are patients with symptoms of lung congestion or dyspnea, which are not relieved, or which need a long time to be improved. Thus, a new therapeutic agent is desired.

As described above, at this point, there is no effective therapeutic method for diastolic heart failure or left ventricular diastolic dysfunction, and thus the development of a new therapeutic means is urgently needed.

[0011]

On the other hand, 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a prodrug thereof, or a cyclodextrin clathrate thereof is a selective agonist for EP4, which is a receptor subtype of prostaglandin E2, and is reported to be effective for immune diseases (autoimmune diseases such as amyotrophic lateral sclerosis, multiple sclerosis, Sjogren's syndrome, chronic rheumatoid arthritis and systemic lupus erythematosus, rejection after organ transplantation, and the like), asthma,

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Summary of the Invention
Problems that the Invention is to Solve
[0015]

Diastolic heart failure is a disease caused by diastolic dysfunction of a heart, in particular of a left ventricle. Since there is currently no medicament showing an effect to improve left ventricular diastolic function itself, there is no effective medical therapy, which can preferentially treat diastolic heart failure so far.

For diastolic heart failure patients in the acute exacerbation phase, a diuretic agent or a vasodilator is sometimes prescribed with the purpose of relieving the symptoms of lung congestion and dyspnea. However, left ventricular diastolic dysfunction itself, which is the cause of the pathology thereof, is not cured, and the recurrence cannot be prevented.
[0016]

Namely, an object of present invention is to provide a medicament, which improves diastolic function of a left ventricle itself without depending on the diuretic effect or vasodilation effect; controls the pathological condition of diastolic heart failure or left ventricular diastolic dysfunction; and prevents the recurrence, and can prevent dyspnea and death due to this pathological condition.

Means for Solving the Problems
[0017]

EP4 agonists are generally predicted to relieve the congestion state of heart failure patients since EP4 agonists have a vasodilation effect and an effect to relieve renal dysfunction. However, these effects are the same as those of the existing vasodilators, and thus diastolic heart failure or left ventricular diastolic dysfunction is not relieved. Accordingly, when an EP4 agonist is administered to a patient with diastolic heart failure, there is a possibility that the agonist only causes the similar problems as those of a diuretic agent or a vasodilator, for example the decrease in the cardiac output, the decrease in the blood pressure, or the frequent recurrence.
[0018]

As a result of extensive studies, the inventors of the present invention found that, among the compounds known as EP4 agonists, 4-[(2-{(2R)-2-

[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid (sometimes abbreviated to a compound A below) improves diastolic function of a left ventricle by directly acting on a heart, and can effectively treat particularly diastolic functional failure/diastolic dysfunction among heart failure types, and thus the inventors completed present invention.

[0019]

Namely, present invention is as follows.

1. An agent for improving left ventricular diastolic function, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

2. The agent according to the above 1, which is an agent for treating heart failure and/or relieving a symptom.

3. The agent according to the above 2, wherein the heart failure is acute heart failure or chronic heart failure.

4. The agent according to the above 2 or 3, wherein the heart failure is diastolic heart failure.

5. The agent according to the above 2, wherein the symptom is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

6. The agent according to the above 1 to 5, which further has an effect to improve left ventricular systolic function.

7. The agent according to the above 6, which is an agent for treating systolic heart failure and/or relieving a symptom.

8. The agent according to the above 7, wherein the symptom is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

9. An agent for improving the survival rate of heart failure, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

10. An agent for improving left ventricular distensibility, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

11. An agent for preventing myocardial fibrillization, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-

29. An agent for reducing the dose of an existing agent for treating heart failure, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or cyclodextrin thereof.
30. An agent for reducing the side effect of an existing agent for treating heart failure, which comprises 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or cyclodextrin thereof.

Effects of the Invention

[0020]

Since 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid (the compound A), a salt thereof, a solvate thereof or a prodrug thereof, or a cyclodextrin clathrate thereof (sometimes abbreviated to "the compound used for the agent of present invention" below) has an effect to relieve diastolic dysfunction of a left ventricle by directly acting on a heart in addition to a vasodilation effect, it is effective particularly for diastolic heart failure among acute and chronic heart failure, and can relieve lung congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema, hepatomegaly and/or the like more effectively than the existing vasodilators. Further, left ventricular diastolic function is generally impaired also in systolic heart failure, and the existing diuretic agents/vasodilators cannot relieve left ventricular diastolic dysfunction. Accordingly, it is expected that the compound used for the agent of present invention has better efficacy also for systolic heart failure in comparison with the existing diuretic agents/vasodilators.

Brief Description of the Drawings

[0021]

[Figure 1] Figure 1 shows the intensity balance of the left ventricular relaxation effects and the left ventricular contraction effects of the compound A and milrinone, which is an existing agent for treating heart failure, in an acute heart failure model.

[Figure 2] Figure 2 shows the influences of the compound A and milrinone on the survival rate in a chronic heart failure model.

[Figure 3] Figure 3 shows the influences of the compound A and milrinone on the left ventricular diastolic wall strain (DWS) index in a chronic heart failure model.

Mode for Carrying Out the Invention

[0022]

The compound used for the agent of present invention improves diastolic function of a left ventricle, and can relieve the state, in which diastolic function of a left ventricle is impaired, namely left ventricular diastolic functional failure (which is sometimes called just diastolic functional failure).

In this specification, heart failure includes heart failure in the acute phase or in the chronic phase, namely acute heart failure or chronic heart failure. The definition of acute heart failure sometimes includes chronic heart failure in the acute exacerbation phase. Further, heart failure is sometimes called congestive heart failure.

[0023]

Regarding heart failure, the functional disorders of a heart and the pathological conditions caused by the disorders are shown in Table 1 below. Diastolic heart failure (heart failure in diastole) is heart failure, in which only diastolic function of a left ventricle is impaired, but systolic function is normal or only slightly deteriorated. On the other hand, in systolic heart failure (heart failure in systole), both systolic function and diastolic function of a left ventricle are impaired. Diastolic heart failure and systolic heart failure are sometimes called diastolic failure and systolic failure, respectively. Further, the state, in which left ventricular diastolic function is impaired, is called left ventricular diastolic dysfunction, left ventricular diastolic functional failure, left ventricular diastolic disorder or left ventricular diastolic failure; and the state, in which systolic function is impaired, is also called left ventricular systolic dysfunction, left ventricular systolic functional failure, left ventricular systolic disorder or left ventricular systolic failure.

[0024]

for the agent of present invention is administered repetitively to a mammal (a human, a dog, a rat or the like) in which heart failure has been already developed, in comparison with the case without the administration. The prevention of the myocardial fibrillization leads to the prevention of the deterioration of the distensibility of a left ventricle (namely, passive diastolic disorder of a left ventricle) and thus left ventricular diastolic dysfunction is relieved.

[0038]

Furthermore, as described above, in a patient with diastolic heart failure, the ventricle cannot dilate sufficiently during diastole and a sufficient blood volume cannot be pumped, due to the ventricular wall thickening and the myocardial fibrillization. Since the compound used for the agent of present invention prevents the myocardial fibrillization and prevents the deterioration of the distensibility in a left ventricle, the compound can be used as an agent for improving the cardiac output. It is possible to easily measure and decide whether the compound used for the agent of present invention has improved the cardiac output, by using an invasive, noninvasive or low-invasive device for monitoring the cardiac output.

[0039]

In order to use the compound used for the agent of present invention with the above purpose, the compound used for the agent of present invention can be generally administered systemically or topically in the form of oral or parenteral administration after appropriately formulating the compound. As the parenteral administration, intravenous administration, intramuscular administration, subcutaneous administration, percutaneous administration and the like are mentioned. The administration path of the compound used for the agent of present invention may be any method as long as it is a method enabling the intravital administration of an effective amount thereof, and for example, oral administration or administration by injection, or administration as a patch is preferable.

[0040]

Although the dose depends on the age, the weight, the symptom, the therapeutic effect, the administration method, the administration period and the like, the administration is generally oral and once to several times a day wherein an amount per each time is 0.1 ng to 1 mg per adult, parenteral and once to several times a day wherein an amount per each time is 0.1 ng to 1 mg per adult, or intravenous and continuous for 1 hour to 24 hours a day. For example, when the compound used for the agent of present invention is orally

Claims

[Claim 1]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for treating heart failure and/or relieving a symptom associated with heart failure.

[Claim 2]

The use according to claim 1, wherein the heart failure is acute heart failure or chronic heart failure.

[Claim 3]

The use according to claim 1, wherein the heart failure is diastolic heart failure.

[Claim 4]

The use according to claim 1, wherein the heart failure is systolic heart failure.

[Claim 5]

The use according to any one of claims 1 to 4, wherein the symptom associated with heart failure is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

[Claim 6]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for improving the survival rate of heart failure.

[Claim 7]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for improving cardiac output.

[Claim 8]

A medicine for treating heart failure, which is produced by combining 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a

cyclodextrin clathrate thereof, with one or more compounds selected from an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, a β-blocker, a digitalis preparation, a diuretic agent, a natriuretic peptide, a vasodilator, a phosphodiesterase III inhibitor and/or an aldosterone antagonist.

[Claim 9]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for treating heart failure in which diastolic function is impaired.

[Claim 10]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for preventing heart failure associated with hypertension from occurring.

[Claim 11]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for improving left ventricular diastolic dysfunction.

[Claim 12]

The use according to claim 11, wherein the use is for treating heart failure and/or relieving a symptom associated with heart failure.

[Claim 13]

The use according to claim 12, wherein the heart failure is acute heart failure or chronic heart failure.

[Claim 14]

The use according to claim 12, wherein the heart failure is diastolic heart failure.

[Claim 15]

The use according to claim 12, wherein the symptom associated with heart failure is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

[Claim 16]

The use according to claim 11, which is use for further improving left ventricular systolic function.

[Claim 17]

The use according to claim 16, which is use for treating systolic heart failure and/or relieving a symptom associated with heart failure.

[Claim 18]

The use according to claim 17, wherein the symptom is congestion, dyspnea, shortness of breath, malaise, decrease in urine volume, limb edema and/or hepatomegaly.

[Claim 19]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for improving the deterioration of left ventricular distensibility.

[Claim 20]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for preventing myocardial fibrillization.

[Claim 21]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent for selectively improving left ventricular diastolic function, which selectively improves left ventricular diastolic function in comparison with left ventricular systolic function.

[Claim 22]

The use according to claim 21, which is use for treating diastolic heart failure and/or relieving a symptom associated with heart failure.

[Claim 23]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a

cyclodextrin clathrate thereof for the manufacture of an agent treating and/or improving left ventricular diastolic functional failure.

[Claim 24]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent treating and/or improving left ventricular diastolic dysfunction.

[Claim 25]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent treating diastolic heart failure and/or relieving a symptom associated with heart failure.

[Claim 26]

Use of 4-[(2-{(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoic acid, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for the manufacture of an agent treating and/or relieving dyspnea associated with heart failure.