VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2010, Vol. 17, No. 6, pp. 612–618

ISSN 1897–5593

Effect of L-arginine or L-citrulline oral supplementation on blood pressure and right ventricular function in heart failure patients with preserved ejection fraction

Juan José Orozco-Gutiérrez[1], Lilia Castillo-Martínez[1, 2], Arturo Orea-Tejeda[1, 2], Oscar Vázquez-Díaz[1], Adrián Valdespino-Trejo[1], René Narváez-David[2], Candace Keirns-Davis[3], Olín Carrasco-Ortiz[1], Adolfo Navarro-Navarro[1], Rocío Sánchez-Santillán[1]

[1]Heart Failure Clinic, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico
[2]Cardiology Department, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico
[3]Massachusetts General Hospital, Boston, MA, USA

Abstract

Background: *The effect of L-arginine and L-citrulline on blood pressure and right ventricular function in heart failure patients with preserved ejection fraction (HFpEF) is unknown. We have therefore evaluated, in a randomized clinical trial, the effect of these aminoacids in chronic outstanding and stable patients with HFpEF.*

Methods and results: *All patients underwent an echocardiogram and radioisotopic ventriculography rest/exercise, and were randomized in a consecutive manner to the L-arginine group (n = 15; 8 g/day); and the citrulline malate group (n = 15; 3 g/day). The duration of follow-up was two months. The principal echocardiographic finding was a statistically significant decrease in pulmonary artery pressure in the L-arginine (56.3 ± 10* vs *44 ± 16.5 mm Hg, p < 0.05) and the citrulline (56.67 ± 7.96* vs *47.67 ± 8.59 mm Hg, p < 0.05) groups. Duration on treadmill and right ventricular ejection fraction post exercise increased, while diastolic and systolic artery pressure decreased significantly in both groups. There were no other statistically significant differences between the groups.*

Conclusions: *Administration of L-arginine and citrulline to patients with HFpEF improved right ventricular function by increasing right ventricular ejection fraction, and probably decreasing systolic pulmonary artery pressure.* (Cardiol J 2010; 17, 6: 612–618)

Key words: L-arginine, citrulline, heart failure, blood pressure, right ventricle

Introduction

Heart failure (HF) is a clinical syndrome of considerable morbidity and mortality. The physiopathology of HF results from the interaction of multiple deleterious mechanisms that include ventricular remodeling, over-activation of the neurohormonal system and cytokines as well as endothelial dysfunction. Endothelial dysfunction is one of the primary factors in a number of other patho-

Address for correspondence: Dr. Arturo Orea-Tejeda, Heart Failure Clinic Director Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Providencia 1218-A Int. 402, Colonia del Valle Delegación Benito Juárez 03100, Mexico, D.F. Mexico, tel./fax: (5255) 55 13 93 84, e-mail: artorea@yahoo.com.mx

Received: 20.02.2010 Accepted: 11.05.2010

logical conditions often seen in these patients such as systemic hypertension, diabetes mellitus, and atherosclerosis [1].

Left ventricular ejection fraction (LVEF) is preserved in 30 to 50% of HF cases [2], but their prognosis is as poor as those with depressed systolic function. Systemic hypertension, coronary artery disease and senility are the commonest causes of this type of dysfunction. Chronic systemic hypertension augments wall stress and induces parallel hypertrophy of the sarcomeres, which increases wall thickness. Muscular hypertrophy and increase in the thickness of the collagen matrix prevents progressive dilatation and maintains stable wall stress, but it also diminishes distensibility [3].

Pulmonary arterial hypertension (PAH) has recently been identified in heart failure patients with preserved ejection fraction (HFpEF) [4]. The prevalence reaches 83% [5] and persists after correcting for pulmonary capillary wedge pressure. This suggests that apart from post-capillary pulmonary venous congestion, a pre-capillary component contributes to higher pulmonary artery pressure in patients with preserved ejection fraction and is an important factor in an adverse prognosis [5].

Rector et al. [6] demonstrated in HF patients (LVEF 18 ± 5%) that administration of oral L-arginine (5.6 to 12.6 g/d.) over the course of six weeks significantly improves limb blood flow during exercise and arterial compliance; they also found that circulating levels of endothelin were reduced by L-arginine. Plasma endothelin has a strong relationship with mean pulmonary vascular resistance. In another study, patients with HF (LVEF 19 ± 9%) were supplemented with 8 g/day L-arginine. After four weeks, the authors found an 8.8% improvement in acetylcholine-mediated vasodilation of the radial artery [7].

L-arginine is a basic, semi-essential amino acid formed from citrulline and ornithine that participates as an intermediary compound in the urea cycle. It is also the precursor for the endogenous synthesis of nitric oxide (NO) due to the activity of nitric oxide synthase (NOS), which releases L-citrulline as a byproduct [8].

L-citrulline is an alpha amino acid that is metabolized in the vascular endothelium, renal and other cells to L-arginine. Oral L-citrulline increases the blood concentration of L-arginine more effectively than oral L-arginine itself, because it undergoes neither intestinal nor hepatic metabolism. Since it is not a substrate for arginase, it does not induce the expression or activate the enzyme. This makes citrulline a promising treatment in cardiovascular disease involving L-arginine deficiency, bioavailability of NO and endothelial dysfunction. Increases in peak L-arginine concentrations of 227% from basal levels four hours after administration were obtained when L-citrulline was given at a dose of 3.8 g/m body surface area. The same dose of L-arginine increased circulating levels by only 90% [9, 10].

L-arginine is the sole substrate for NOS and thus is essential for NO production. It is estimated that the average diet is borderline in arginine content, and circulating levels can be reduced by administration of arginine-deficient protein [11, 12], by pregnancy [13–17], aging, or stress [18].

The administration of arginine and citrulline may play a fundamental role in patients in heart failure by preventing endothelial dysfunction. However, no study has focused on patients in heart failure with preserved ejection fraction and right ventricular dysfunction. Likewise, to our knowledge, the clinical outcome of oral administration of L-arginine and L-citrulline on patients with HFpEF has not been reported.

The aim of the present study was to evaluate the effects of oral supplementation with L-arginine or L-citrulline malate on arterial pressure and right ventricular function in patients with HFpEF.

Methods

Study population

This controlled clinical study included ambulatory patients who came to the Heart Failure Clinic of the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" between January and December 2008. Patients were recruited if they were men or non-pregnant women more than 18 years of age with a confirmed diagnosis of heart failure with preserved ejection fraction, stable and in New York Heart Association functional classes I to III. Candidates were excluded if they presented with lung disease, ischemia treatable by revascularization, myocardial infarction, unstable angina or a history of myocardial revascularization (percutaneous transluminal coronary angioplasty or aorto-coronary by-pass grafts), cerebrovascular events during the previous three months, dysfunctional prosthetic heart valve, obstructive or non-obstructive cardiomyopathy, uncorrected congenital heart disease, active myocarditis, history of resuscitation from sudden death, or severe arrhythmias.

Heart failure was established by characteristic signs and symptoms as well as echocardiographic and radioisotopic ventriculography findings. Preserved

ejection fraction was defined by LVEF ≥ 45%, fractional shortening ≥ 28%, left atrial diameter > 45 mm, ventricular septal thickness > 12 mm, posterior wall thickness > 12 mm, and characteristic pattern of transmitral Doppler flow (slow, inverted, pseudonormal or restrictive) [19]. Right ventricular dysfunction was defined as ejection fraction ≤ 35% measured by radioisotopic ventriculography [20, 21].

All patients were on standard HF therapy (diuretics, ACE inhibitors, angiotensin II antagonists, aldosterone receptor blockers, beta-adrenergic receptor blockers and digitalis (in patients with atrial fibrillation).

After baseline measurements, patients were randomly assigned to one of the following groups: 1) oral L-arginine supplementation (n = 15) who received 8 g per day of L-arginine powder split into two doses of 4 g; or 2) oral L-citrulline (n = 15) who received 3 g per day of L-citrulline malate powder in two doses of 1.5 g. Randomization was performed using a sequential series of numbered sealed envelopes containing computer-generated random assignments. A copy of the randomization sequence was kept in a locked cabinet away from the study personnel. Randomization envelopes were opened by a third party who informed the patients. Patients, investigators, and study personnel were blinded to the treatment group allocation. Study products were packaged identically and indistinguishable from one another.

Supplements were provided as weighed daily amounts to be taken as a drink mixed with juice or water throughout the day, during the two-month treatment period. Compliance was evaluated using the supplement consumption records kept daily by patients, and by collecting the empty containers.

The study was approved by the institutional Ethics Committee of Biomedical Research in Humans of the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", and all participants gave written informed consent.

Measurements

All participants underwent multi-stage exercise testing according the modified Bruce protocol to obtain functional capacity (METs), blood pressure and heart rate at rest and after exercise. Heart rate, systolic and diastolic blood pressures were recorded by cuff when the subject was standing immediately before testing and during the last minute of the last exercise stage. Subjects exercised until reaching an age-specific target heart rate or developing symptoms necessitating termination of the test or high blood pressure.

Right ventricular function was evaluated by radioisotopic ventriculography. The procedure was performed at rest in the supine position using an *in vivo* red blood cell labeling with 99mTc by standard methods [22]. The patients were to have fasted for four hours prior to the study and refrained from caffeine for 24 hours. They were injected with 40 mg of stannous pyrophosphate in 1.5 mL saline. Ten minutes later, the patients were positioned on the bed of the camera with the detector in the right anterior oblique position. A rapid bolus of 20 mCi technetium-99m pertechnetate was given intravenously as the list mode acquisition was initiated. Following the first pass study, and after time for equilibration in the blood volume, a standard gated cardiac blood pool study was acquired in the left anterior oblique (LAO) and left lateral projections. The R to R interval was divided into 16 frames not greater than 0.04 s in length. Multi-gated acquisition was recorded for 900 s in a 64 x 64 matrix. Quantification was performed on the LAO view. Processing and measurements were made according to the Nuclear Cardiology Society recommendations.

Systolic pulmonary artery pressure (SPAP) was measured by evaluation of maximal velocity of tricuspid regurgitation (TR) according to European guidelines for the diagnosis and treatment of pulmonary hypertension (PH), considering echocardiographic diagnosis of PH 'likely' when TR is > 3.4 m/s (or SPAP > 50 mm Hg) and 'possible' when TR is between 2.9–3.4 m/s (or SPAP is between 35–40 m Hg, with or without additional echocardiographic signs, or when TR is ≤ 2.8 m/s (or ≤ SPAP is ≤ 36 mm Hg) with additional variables suggestive of PH (right ventricular hypertrophy or dilation) [23].

The cardiologist who performed the echocardiograms and radioventriculography did not have access to patients' information.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as absolute and relative frequency. For comparisons between the groups χ^2 or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables were used. To compare the changes from baseline to two months, the Wilcoxon signed rank test was used. A p value of < 0.05 was considered statistically significant. All analyses were performed using a commercially available package (SPSS for Windows, version 10.0, SPSS Inc., Chicago, Illinois, USA).

Table 1. Baseline clinical characteristics of the study population.

Variables	Arginine group (n = 15)	Citrulline group (n = 15)
Age (years)	63 ± 14	66 ± 10
Female	7 (46.7%)	6 (40%)
Male	8 (53.3%)	9 (60%)
NYHA:		
I	8 (53%)	4 (26%)
II	6 (40%)	11 (73%)
III	1 (6%)	0 (0%)
Ischemic heart disease	6 (40%)	7 (46%)
Diabetes mellitus	8 (53%)	8 (53%)
Obesity	8 (53%)	9 (60%)
Dyslipidemia	4 (27%)	5 (33%)
Systemic hypertension	14 (93%)	13 (87%)
Hypothyroidism	4 (27%)	6 (40%)
Atrial fibrillation	3 (20%)	3 (20%)
Pulmonary arterial hypertension	10 (71%)	13 (87%)
ACEI	2 (13%)	6 (40%)
ARA	12 (80%)	9 (60%)
Aspirin	6 (40%)	5 (33%)
Thiazide diuretic	6 (40%)	3 (20%)
Loop diuretic	4 (27%)	5 (33%)
Nitrates	2 (13%)	4 (26.7%)
Spironolactone	13 (87%)	10 (66.7%)
Betablockers	12 (80%)	12 (80%)
Digitalis	5 (33%)	3 (20%)

Data is presented as mean ± standard deviation or n (%); ACEI — angiotensin converting enzyme inhibitor; ARA — angiotensin receptor antagonist

Results

Of the 30 patients included in the study, three were eliminated. In the arginine group; one patient presented with gastrointestinal distress and another was hospitalized for non-cardiovascular causes. One patient in the citrulline group underwent surgery for a non-cardiovascular cause. Other than the patients with gastrointestinal symptoms, no adverse effects were observed.

The baseline characteristics of the study groups are shown in Table 1. Non-significant differences were observed among the groups. In both groups, there were patients using digitalis because they have atrial fibrillation. Basal echocardiography and radioisotopic ventriculography results also revealed no significant differences.

After two months of follow-up, the principal echocardiographic finding was a statistically significant decrease in systolic pulmonary artery pressure in both groups (Table 2).

Also, duration on the treadmill and right ventricular ejection fraction during the stress increased significantly in the arginine and citrulline groups. Furthermore, in the citrulline group there was a significative increase in right ventricular ejection fraction after the stress test (Table 2).

Both systolic and diastolic blood pressure decreased significantly in the two groups, but the decrease in systolic blood pressure was greater in the arginine group but was not statistically significant (Fig. 1).

Discussion

The present controlled clinical study is one of the first to report an improvement in pulmonary artery pressure and right ventricular ejection fraction after two months of oral supplementation with L-arginine or citrulline in patients with HFpEF and right ventricular dysfunction. This outcome is noteworthy because HFpEF and pulmonary arterial hypertension frequently co-exist. Apart from increased post-capillary pulmonary pressure, there is an additional pre-capillary pulmonary factor in which the tone and/or pulmonary vascular remodeling can contribute to increased pulmonary artery pressure.

Table 2. Echocardiographic and ventriculographic results of study groups at baseline and after two months.

Variables	Baseline		Two-month follow-up	
	Arginine group (n = 13)	Citrulline group (n = 14)	Arginine group (n = 13)	Citrulline group (n = 14)
Echocardiogram				
LVSD [mm]	31 ± 5.5	30 ± 5	29 ± 6	29 ± 5
RVDD [mm]	41 ± 7	42 ± 6	38 ± 6	40 ± 7
SPAP [mm Hg]	56 ± 10	57 ± 8	44 ± 16*	48 ± 9*
Radioisotopic ventriculography				
Duration on treadmill [min]	7 ± 6	6 ± 3	8 ± 4*	6 ± 3*
LVEF (%): resting *vs* stress	33 ± 14 *vs* 37 ± 14	41 ± 14 *vs* 37 ± 14	38 ± 12 *vs* 38 ± 13	39 ± 16 *vs* 39 ± 17
RVEF (%): resting *vs* stress	25 ± 9 *vs* 26 ± 12	28 ± 13 *vs* 26 ± 11	26 ± 9 *vs* 34 ± 15*	27 ± 7 *vs* 33 ± 15*

*Denotes $p < 0.05$ *vs* baseline; data is presented as mean ± standard deviation; LVSD — left ventricular systolic diameter; RVDD — right ventricular diastolic diameter; SPAP — systolic pulmonary artery pressure; LVEF — left ventricular ejection fraction; RVEF — right ventricular ejection fraction

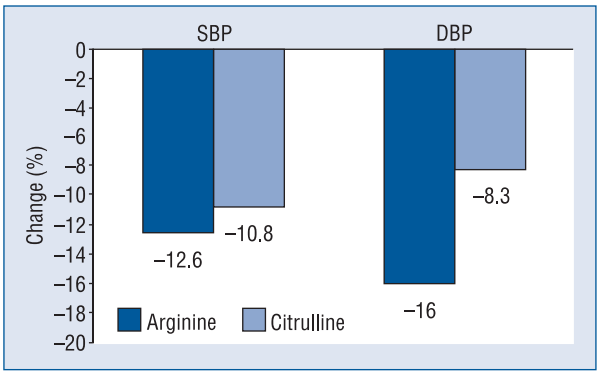

Figure 1. Percentage change in blood pressure in study groups after two-month follow-up; SBP — systolic blood pressure; DBP — diastolic blood pressure.

Lam et al. [5] recently suggested that the severity of the pulmonary arterial hypertension could serve to identify patients with HFpEF with excellent diagnostic accuracy. In these cases, use of amino acid precursors to NO could be a therapeutic option.

Systolic pulmonary artery pressure was measured by evaluation of maximal velocity of tricuspid regurgitation. This technique is widely validated, but its precision is debatable [23]. It is known that using indirect measurements of SPAP by echocardiography means that it is not possible to assess total pulmonary resistance, and therefore whether the decrease of pulmonary artery pressure is due to a decline in precapillary resistance or to a decrease of pulmonary capillary wedge pressure (PCWP). This is a parameter used to quantify left ventricular filling pressures and help to discriminate between PH and pulmonary venous hypertension (i.e. secondary to left ventricular disease; the cut-off used is 15 mm) [24].

Patients with PH typically have Doppler mitral inflow patterns of impaired relaxation (grade I diastolic dysfunction), with normal E' waves on DTI and E/E' septal ratios < 10, despite high SPAP. In contrast, patients with high SPAP secondary to elevated atrial pressures and left-heart disease tend to have pulsed-wave Doppler mitral inflow patterns of grade II or III, with increased E/E' ratios [23]. At the moment, there is no conclusive data that supports the use of usual indexes for monitoring clinical evolution or treatment response in patents with PH. But, SPAP can frequently be estimated using the TR method. However, it is very important to consider the contribution of left ventricular end-diastolic pressures in the pulmonary hemodynamics of a specific patient, because left-heart disease is probably the most frequent cause of pulmonary hypertension. In these cases, mild to moderate increases in pulmonary pressure and pulmonary wedge pressure are found, and PVR is generally normal [23].

The impact of arginine treatment on the pulmonary hemodynamics of adults with pulmonary vascular disease has been mixed [25, 26]. However, chronic arginine supplementation could improve lung circulation in patients with pulmonary arterial hypertension. Short-term administration of L-arginine (500 mg/kg infused over 30 min) in ten subjects with PAH resulted in a reduction in pulmonary artery pressure [25]. Infusion of L-arginine has

also resulted in markedly increased plasma levels of L-arginine as well as a rise in plasma L-citrulline. The peak plasma level of L-citrulline had a significant correlation with reduction in pulmonary artery pressure, possibly because of vasodilatation mediated by NOS metabolism of exogenous L-arginine and increased NO production.

Arginine deficiency has been shown to accompany persistent PH of the newborn (PPHN) [27], and acute L-arginine infusion (500 mg/kg over 30 min) of infants with PPHN was associated with a rise in PaO_2 over the five hour period following infusion [28]. Other studies demonstrated that chronic administration of L-arginine ameliorated chronic PH and vascular remodeling induced in rats by either chronic hypoxia or monocrotaline injection [29].

Consistent with other studies [30, 31] we observed a statistically significant decrease in systemic blood pressure and systolic pulmonary artery pressure with oral arginine and citrulline.

A study published by Nagaya et al. [32] suggests that oral supplementation with L-arginine has beneficial effects on hemodynamic values and exercise capacity in patients with PAH. Acute hemodynamic responses to oral L-arginine (0.5 g/10 kg b.w. weight) compared to placebo were examined in 19 patients with PAH. Cardiopulmonary exercise tests were performed to measure peak oxygen consumption and the ventilatory response to carbon dioxide production before and after one week of treatment with L-arginine (1.5 g/10 kg b.w. per day) or placebo. Oral supplementation with L-citrulline significantly increased plasma L-arginine, which indicated enhanced NO production.

As Rector et al. [6] demonstrated, limb blood flow during exercise and arterial compliance was associated with circulating levels of endothelin and was reduced by L-arginine. Plasma endothelin has a strong relationship with mean pulmonary vascular resistance and it could be a rational hypothesis to explain our findings in the pulmonary pressure reduction. In our cases, the fact that neither NO nor endothelin were measured means a limitation to our preliminary results. However, their dynamic effect on pulmonary vessels have been sufficiently described by other groups and can explain our findings [6, 7].

Most of our patients were on angiotensin receptor antagonist treatment. As we have been informed by Koifman et al. [33], this, in combination with arginine, serves to improve the flow mediated vasodilatation decreasing afterload and increase nitric oxide urinary excretion. These effects had been observed even in cardiac transplant recipients [34].

Until now, when one spoke of HFpEF, it was necessary to take into account that the values were taken at rest. When patients with HFpEF were subjected to stress (as we demonstrated with the radioisotopic ventriculography) [35], both ventricular ejection fractions tended to diminish, or at best remain the same. This condition has a direct impact on the functionality of the patients, leading to progressive decrease in their tolerance of daily activities. Thus, lowering systemic and pulmonary artery pressure, by improving the afterload of both ventricles, will lead to increased right ventricular ejection fraction. The greatest effect will be seen after physical exertion and will be evident as a decrease in right ventricular diastolic diameter. Even right ventricular systolic function improved, it could increase left ventricle end-diastolic-volume, but reduction of systemic blood pressure as was observed, allows preserve the LVEF. Whether right ventricular output increase results in pulmonary congestion, it was not observed as could be demonstrated with better exercise tolerance, probably as consequence of a decrease in systemic systolic and diastolic blood pressure.

It is also noteworthy that improvement in systolic arterial pressure and right ventricular function was similar in both treatment groups, but L-citrulline was better tolerated and required a lower dose. Consequently, especially in HFpEF patients with PAH and concomitant right ventricular failure, the use of L-arginine or L-citrulline could be an adjunct to conventional therapy. In addition, in patients with higher right ventricular diastolic diameter and pulmonary artery systolic pressure with smaller left chamber diameters (left ventricular and atrial end-diastolic diameters), it is frequent to find elevated troponin levels that are associated with worse prognosis [36].

Finally, conventional heart failure treatment was not different during the intervention, and the observed changes should be explained by aminoacids supplementation, although a control group was not included.

This study has several limitations: the number of patients studied was small, the intervention period was short and it is probable that a longer follow-up would show changes in variables such as left ventricular diastolic diameter and ejection fraction. Finally, the lack of direct quantification of pulmonary pressures is a drawback. However, the findings of this study support continued investigation into the effect of L-arginine and L-citrulline on right ventricular function, systemic arterial pressure and systolic pulmonary artery pressure in heart failure patients with preserved ejection fraction. More studies are

required to evaluate the effects observed on a larger number of patients for a longer period.

Acknowledgements

We wish to express our gratitude to Pronat Laboratories for their support and generosity and especially to Ing. Sergio Becerril and Lic. Francisco López for donating the aminoacids that made this study possible.

The authors do not report any conflict of interest regarding this work.

References

1. Bauersachs J, Widder JD. Endothelial dysfunction in heart failure. Pharmacol Rep, 2008; 60: 119–126.
2. Anguita M, Ojeda S. Diagnóstico y tratamiento de la insuficiencia cardiaca diastólica. Rev Esp Cardiol, 2004; 57: 570–575.
3. Aurigemma G, Gaasch W. Diastolic heart failure. New Eng J Med, 2004; 351: 1097–1105.
4. Shapiro B, Nishimura R, McGoon M, Redfield M. Diagnostic dilemmas: diastolic heart failure causing pulmonary hypertension, pulmonary hypertension causing diastolic dysfunction. Adv Pulmon Hypertens, 2006; 5: 13–20.
5. Lam C, Roger V, Rodeheffer R, Borlaug B, Enders F, Redfield M. Pulmonary hypertension in heart failure with preserved ejection fraction. A community-based study. J Am Coll Cardiol, 2009; 53: 1119–1126.
6. Rector TS, Bank AJ, Mullen KA et al. Randomized, double-blind, placebo-controlled study of supplemental oral L-arginine in patients with heart failure. Circulation, 1996; 93: 2135–2141.
7. Böger RH, Bode-Böger SM. The clinical pharmacology of L-arginine. Annu Rev Pharmacol Toxicol, 2001; 41: 79–99.
8. Hambrecht R, Hilbrich L, Erbs S et al. Correction of endothelial dysfunction in chronic heart failure: Additional effects of exercise training and oral L-arginine supplementation. J Am Coll Cardiol, 2000; 35: 706–713.
9. Romero MJ, Platt DH, Caldwell RB, Caldwell RW. Therapeutic use of citrulline in cardiovascular disease. Cardiovasc Drug Rev, 2006; 24: 275–290.
10. Kaye DM, Parnell MM, Ahlers BA. Reduced myocardial and systemic L-arginine uptake in heart failure. Circ Res, 2002; 91: 1198–1203.
11. Visek WJ. Arginine needs physiological state and usual diets: A reevaluation. J Nutr, 1986; 116: 36–46.
12. Zieve L. Conditional deficiencies of ornithine or arginine. J Am Coll Nutr, 1986; 5: 167–176.
13. Raij L, Cofee K, Guerra J, Holmes D. Glomerular thrombosis in pregnancy: Role of the L-arginine-nitric oxide pathway. Kidney Int, 1994; 45: 775–781.
14. Kashyap ML, Sivasamboo R, Sothy SP, Cheah JS, Gartside PS. Carbohydrate and lipid metabolism during human labor: Free fatty acids, glucose, insulin, and lactic acid metabolism during normal and oxytocin-induced labor for postmaturity. Metabolism, 1976; 25: 865–875.
15. Kerr GR. The free amino acids of serum during development of Macaca mulatta: II. During pregnancy and fetal life. Pediatr Res, 1968; 2: 493–500.
16. Ogburn PL Jr, Johnson SB, Williams PP, Holman RT. Levels of free fatty acids and arachidonic acid in pregnancy and labor. J Lab Clin Med, 1980; 95: 943–949.
17. Whaley WH, Zuspan FP, Nelson GH, Ahlquist RP. Alterations of plasma free fatty acids and glucose during labor. Am J Obstet Gynecol, 1967; 97: 875–880.
18. Milakofsky L, Harris N, Vogel WH. Effects of repeated stress on plasma arginine levels in young and old rats. Physiol Behav, 1993; 54: 725–728.
19. Arnold JM, Massie BM, Baker DWet al. HFSA 2006 Comprehensive HF Practice Guideline. J Card Fail, 2006; 12: e1–e122.
20. Voelkel NF, Quaife RA, Leinwand LA et al. Right ventricular function and failure. Report of a National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. Circulation, 2006; 114: 1183–1891.
21. Setaro JF, Cleman MW, Remetz MS. The right ventricle in disorders causing pulmonary venous hypertension. Cardiol Clin, 1992; 10: 165–183.
22. Corbett JR, Akinboboye OO, Bacharach SL et al. Equilibrium radionuclide angiocardiography. J Nucl Card, 2006; 13: e56–e79.
23. Galie N, Hoeper MM, Humbert M et al. Guidelines for diagnosis and treatment of pulmonary hypertension. The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Resp J, 2009; 34: 1219–1263.
24. Galie N, Torbicki A, Barst R et al. Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology (ESC). Guidelines on diagnosis and treatment of pulmonary arterial hypertension. Eur Heart J, 2004; 25: 2243–2278.
25. Mehta S, Steart DJ, Langleben D, Levy RD. Short-term pulmonary vasodilation with L-arginine in pulmonary hypertension. Circulation, 1995; 92: 1539–1545.
26. Suradacki A, Zmudka K, Bieron K, Kostka-Trabka E, Dubiel JS, Gryglewski RJ. Lack of beneficial effects of L-arginine infusion in primary pulmonary hypertension. Wien Klin Wochenschr, 1994; 106: 521–526.
27. Vosatka RJ, Kashyap S, Trifiletti RR. Arginine deficiency accompanies persistent pulmonary hypertension of the newborn. Biol Neonate, 1994; 66: 65–70.
28. McCaffrey MJ, Bose CL, Reiter PD, Stiles AD. Effect of L-arginine infusion on infants with persistent pulmonary hypertension of the newborn. Biol Neonate, 1995; 67: 240–243.
29. Mitani Y, Maruyama K, Sakurai M. Prolonged administration of L-arginine ameliorates chronic pulmonary hypertension and pulmonary vascular remodeling in rats. Circulation, 1997; 96: 689–697.
30. Perticone F, Ceravolo R, Pujia A et al. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation, 2001; 104: 191–196.
31. Smith HA, Canter JA, Christian KG et al. Nitric oxide precursors and congenital heart surgery: A randomized controlled trial of oral citrulline. J Thorac Cardiovasc Surg, 2006; 132: 58–65.
32. Nagaya N, Uematsu M, Oya H et al. Short-term oral administration of L-arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. Am J Respir Crit Care Med, 2001; 163: 887–891.
33. Koifman B, Topilski I, Megidish R et al. Endothelial cell function, and hemodynamic variables in patients with heart failure secondary to coronary heart disease. Am J Cardiol, 2006; 98: 172–177.
34. Lim DS, Mooradian SJ, Goldberg CS et al. Effect of oral L-arginine on oxidant stress, endothelial dysfunction, and systemic arterial pressure in young cardiac transplant recipients. Am J Cardiol, 2004; 94: 828–831.
35. Silva-Tinoco R, Castillo-Martínez L, Orea-Tejeda A et al. Effect of left ventricular dysfunction on right ventricle ejection fraction during exercise in heart failure patients: Implications in functional capacity and blood pressure response. Cardiol J, 2009; 16: 127–132.
36. Orea-Tejeda A, Sánchez-González R, Castillo-Martínez L et al. Troponin elevation and its association with renal dysfunction, clinical findings in heart failure patients. Cardiol J, 2010; 17: 42–48.