Results of the multicenter spaniel trial (MUST): taurine- and carnitine-responsive dilated cardiomyopathy in American cocker spaniels with decreased plasma taurine concentration.

Kittleson MD, Keene B, Pion PD, Loyer CG

Abstract
Fourteen American Cocker Spaniels (ACS) with dilated cardiomyopathy (DCM) were studied to determine if individuals of this breed with DCM are systemically taurine- or carnitine-deficient and to determine if they are responsive to taurine and carnitine supplementation. American Cocker Spaniels with DCM were identified using echocardiography, and plasma was analyzed for taurine and carnitine concentrations. Each dog was randomly assigned to receive either taurine and carnitine supplementation or placebos. Echocardiograms and clinical examinations were repeated monthly for 4 months. During this period, the investigators and owners were blinded with respect to the treatment being administered. Each dog was weaned off its cardiovascular drugs (furosemide, digoxin, and an angiotensin converting enzyme inhibitor) if an echocardiographic response was identified. At the 4-month time period, each investigator was asked to decide whether he or she thought his or her patient was receiving placebo or taurine/carnitine, based on presence or absence of clinical and echocardiographic improvement. Unblinding then occurred, and dogs receiving placebos were switched to taurine and carnitine supplementation and followed monthly for 4 additional months. All dogs were reexamined 6 months after starting supplementation; survival time and cause of death were recorded for each dog. Data from 3 dogs were not included because of multiple protocol violations. Each dog had a plasma taurine concentration < 50 nmol/mL (mean +/- SD for the group 15 +/- 17 nmol/mL) at baseline; normal range, 50-180 nmol/mL. The plasma taurine concentration did not exceed 50 nmol/mL at any time in the dogs receiving placebos (n = 5), but increased to 357 +/- 157 nmol/mL (range 140-621 nmol/mL) during taurine and carnitine supplementation (n = 11). Plasma carnitine concentration was within, only slightly below, or slightly above reported limits of normality at baseline (29 +/- 15 mumol/L); did not change during placebo administration; and increased significantly during supplementation (349 +/- 119 mumol/L; n = 11). Echocardiographic variables did not change during placebo administration. During supplementation, left ventricular end-diastolic and end-systolic diameters, and mitral valve E point-to-septal separation decreased significantly in both groups. Shortening fraction increased significantly but not into the normal range. Echocardiographic variables remained improved at 6 months. All dogs were successfully weaned off furosemide, an angiotensin converting enzyme inhibitor, and digoxin once an
echocardiographic response was identified. Nine of the dogs have died since the onset of the study in 1992. One dog died of recurrence of DCM and heart failure 31 months after starting supplementation; six dogs died of noncardiac causes. Two dogs developed degenerative mitral valve disease and died of complications of this disease. Dogs less than 10 years of age lived for 46 +/- 11 months, whereas dogs older than 10 years of age lived for 14 +/- 7 months. Two of the 11 dogs were alive at the time of publication, having survived for 3.5 and 4.5 years, respectively. We conclude that ACS with DCM are taurine-deficient and are responsive to taurine and carnitine supplementation. Whereas myocardial function did not return to normal in most dogs, it did improve enough to allow discontinuation of cardiovascular drug therapy and to maintain a normal quality of life for months to years.

MeSH
Administration, Oral; Analysis of Variance; Animal; Breeding; Cardiomyopathy, Congestive; Carnitine; Dog Diseases; Dogs; Echocardiography; Electrocardiography; Female; Male; Mitral Valve Insufficiency; Myocardium; Single-Blind Method; Support, Non-U.S. Gov't; Taurine

Author Address
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Evaluation of urinary carnitine and taurine excretion in 5 cystinuric dogs with carnitine and taurine deficiency.
Sanderson SL, Osborne CA, Lulich JP, Bartges JW, Pierpont ME, Ogburn PN, Koehler LA, Swanson LL, Bird KA, Ulrich LK

Abstract
Five client owned dogs with cystinuria were diagnosed with carnitine and taurine deficiency while participating in a clinical trial that used dietary management of their urolithiasis. Stored 24-hour urine samples collected from the cystinuric dogs before enrollment in the clinical diet trial were quantitatively evaluated for carnitine and taurine. These results were compared to those obtained from 18 healthy Beagles. Both groups of dogs were fed the same maintenance diet for a minimum of 2 weeks before 24-hour urine collection. The protocol used for 24-hour urine collections was the same for cystinuric dogs and healthy Beagles except that cystinuric dogs were catheterized at baseline, 8 hours, 12 hours, and at the end of the collection, whereas Beagles were catheterized at baseline, 8 hours, and at the end of the collection. Three of 5 dogs with cystinuria had increased renal excretion of carnitine. None of the cystinuric dogs had increased renal excretion of taurine, but cystinuric dogs excreted significantly less (P < .05) taurine in their urine than the healthy Beagles. Carnitinuria has not been recognized previously in either humans or dogs with cystinuria, and it may be 1 risk factor for developing carnitine deficiency. Cystinuric dogs in this study were not taurinuric; however, cystine is a precursor amino acid for taurine synthesis. Therefore, cystinuria may be 1 risk factor for developing taurine deficiency in dogs. We suggest that dogs with cystinuria be monitored for carnitine and taurine deficiency or supplemented with carnitine and taurine.

MeSH
Animal; Carnitine; Case-Control Studies; Cystinuria; Dog Diseases; Dogs; Female; Male; Support, Non-U.S. Gov't; Taurine

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Changes in kinetics of carnitine palmitoyltransferase in liver and skeletal muscle of dogs (Canis familiaris) throughout growth and development.
Lin X, Odle J
J Nutr 2003 Apr 133:1113-9

BROWSE
J Nutr • Volume 133 • Issue 4
VIEW
MEDLINE, full MEDLINE, related records, full text

Abstract
This study was conducted to investigate developmental changes in the kinetics of carnitine palmitoyltransferase (CPT) within hepatic and skeletal muscle tissues of the canine species. Carnitine concentrations, CPT activity and the apparent K(m) for carnitine were measured in tissue homogenates from dogs in six age categories: newborn; 24-h-old; 3-, 6- and 9-wk-old; and adult. Hepatic CPT activity was low at birth, increased by 100% during the suckling period (P < 0.05) and then declined after weaning to adult levels. In contrast, CPT activity in muscle continued to increase with age, reaching adult levels after 9 wk. Congruent with CPT activity, nearly identical concentration profiles of liver and muscle acylcarnitines were observed. The apparent K(m) of hepatic CPT for carnitine also paralleled the increase in CPT activity during the suckling period; however, free and total liver carnitine concentrations declined by 50% during this time (P < 0.05). Beginning at 3 wk of age, the hepatic concentration of free carnitine was at or below the apparent K(m) of CPT for carnitine. A similar relationship existed in muscle of young dogs, but in adults, the free carnitine concentration was markedly increased and exceeded the apparent K(m) by 5-fold. Collectively, we infer that fatty acid oxidation capacity increases rapidly after birth in the canine, after ontogenic increases in CPT activity. Furthermore, based on the relatively low tissue carnitine concentrations when compared with the apparent carnitine K(m) of CPT, we suggest that carnitine may have an important role in the regulation of fatty acid oxidation and that increased dietary carnitine may improve fatty acid oxidative capacity in developing dogs.

MeSH
Animal; Carnitine; Carnitine O-Palmitoyltransferase; Dogs; Female; Kinetics; Liver; Muscle, Skeletal; Pregnancy; Support, Non-U.S. Gov't

Author Address
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Kinetic compartmental analysis of carnitine metabolism in the dog.
Rebouche CJ, Engel AG
Arch Biochem Biophys 1983 Jan 220:60-70

Abstract
This study was undertaken to quantitate the dynamic parameters of carnitine metabolism in the dog. Six mongrel dogs were given intravenous injections of L-[methyl-3H]carnitine and the specific radioactivity of carnitine was followed in plasma and urine for 19-28 days. The data were analyzed by kinetic compartmental analysis. A three-compartment, open-system model [(a) extracellular fluid, (b) cardiac and skeletal muscle, (c) other tissues, particularly liver and kidney] was adopted and kinetic parameters (carnitine flux, pool sizes, kinetic constants) were derived. In four of six dogs the size of the muscle carnitine pool obtained by kinetic compartmental analysis agreed (+/- 5%) with estimates based on measurement of carnitine concentrations in different muscles. In three of six dogs carnitine excretion rates derived from kinetic compartmental analysis agreed (+/- 9%) with experimentally measured values, but in three dogs the rates by kinetic compartmental analysis were significantly higher than the corresponding rates measured directly. Appropriate chromatographic analyses revealed no radioactive metabolites in muscle or urine of any of the dogs. Turnover times for carnitine were (mean +/- SEM): 0.44 +/- 0.05 h for extracellular fluid, 232 +/- 22 h for muscle, and 7.9 +/- 1.1 h for other tissues. The estimated flux of carnitine in muscle was 210 pmol/min/g of tissue. Whole-body turnover time for carnitine was 62.9 +/- 5.6 days (mean +/- SEM). Estimated carnitine biosynthesis ranged from 2.9 to 28 mumol/kg body wt/day. Results of this study indicate that kinetic compartmental analysis may be applicable to study of human carnitine metabolism.

MeSH
Animal; Carnitine; Chromatography; Dogs; Female; Isotope Labeling; Kinetics; Male; Models, Biological; Sex Factors; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.; Tissue Distribution; Tritium
Metabolic and structural abnormalities in dogs with early left ventricular dysfunction induced by incessant tachycardia.

Abstract
OBJECTIVE: To assess morphologic and metabolic abnormalities in dogs with early left ventricular dysfunction (ELVD) induced by rapid right ventricular pacing (RRVP). ANIMALS: 7 Beagles. PROCEDURE: Plasma carnitine concentrations were measured before and after development of ELVD induced by RRVP. At the same times, transvenous endomyocardial biopsy was performed, and specimens were submitted for determination of myocardial carnitine concentrations and histologic, morphometric, and ultrastructural examination. RESULTS: In 4 dogs in which baseline plasma total carnitine concentration was normal, RRVP induced a decrease in myocardial total and free carnitine concentrations and an increase in myocardial esterified carnitine concentration. In 3 dogs in which baseline plasma total carnitine concentration was low, plasma and myocardial carnitine concentrations were unchanged after pacing. Structural changes associated with pacing included perinuclear vacuolization in 3 dogs. Morphometric analyses indicated there was a decrease in myofiber cross-sectional diameter and area following pacing. Electron microscopy revealed changes in myofibrils and mitochondria following pacing. CONCLUSIONS AND CLINICAL RELEVANCE: Results indicated that moderate to severe alterations in myocyte cytoarchitecture are present in dogs with ELVD induced by RRVP and that in dogs with normal plasma carnitine concentrations, myocardial carnitine deficiency may be a biochemical marker of ELVD. Results also indicated that transvenous endomyocardial biopsy can be used to evaluate biochemical and structural myocardial changes in dogs with cardiac disease.

MeSH
Animal; Biopsy; Carnitine; Dog Diseases; Dogs; Histocytochemistry; Male; Microscopy, Electron; Myocardium; Support, Non-U.S. Gov't; Tachycardia; Ventricular Dysfunction, Left
Effects of L-carnitine on tissue levels of free fatty acid, acyl CoA, and acylcarnitine in ischemic heart.
Suzuki Y, Kamikawa T, Kobayashi A, Yamazaki N
Adv Myocardiol 1983 4:549-57

Abstract
In order to evaluate the protective effects of L-carnitine on ischemic myocardium, its effects on tissue levels of free fatty acid (FFA), acyl CoA, acyl carnitine, and adenosine triphosphate (ATP) were studied in ischemic dog hearts. Myocardial ischemia was induced by the ligation of left anterior descending coronary artery for 15 min. L-Carnitine (100 mg/kg) was administered intravenously prior to coronary ligation. In ischemic myocardium, tissue levels of free carnitine and ATP decreased, whereas long-chain acyl carnitine, long-chain acyl CoA, and FFA increased. Pretreatment of L-carnitine prevented the decrease in free carnitine and ATP and the increase in long-chain acyl carnitine and long-chain acyl CoA. A positive correlation was observed between ATP and free carnitine. On the other hand, a negative correlation was observed not only between ATP and the ratio of long-chain acyl CoA to free carnitine but also between ATP and the ratio of long-chain acyl carnitine to free carnitine. These results suggest that L-carnitine has protective effects on ischemic myocardium, probably by preventing the accumulation of long-chain acyl carnitine and long chain acyl CoA.

MeSH
Acyl Coenzyme A; Adenosine Triphosphate; Animal; Carnitine; Constriction; Coronary Disease; Dogs; Fatty Acids, Nonesterified; Heart; Myocardium
Case report: efficacy of oral carnitine therapy for dilated cardiomyopathy in boxer dogs.
Costa ND, Labuc RH

Abstract
This paper investigates the role of carnitine in the etiology and treatment of dilated cardiomyopathy in boxers. Two boxers were diagnosed as having dilated cardiomyopathy on the basis of clinical presentation, chest radiographs, electrocardiography and echocardiography. In one dog, carnitine was administered at 6.0 g (or approximately 250 mg/kg live weight (LW) daily per os, and this dog remained asymptomatic for 4 mo until it presented for anorexia, coughing and weakness. Necropsy and histologic findings were consistent with boxer cardiomyopathy in both dogs. Cardiac carnitine concentration was 567 nmol/g wet weight in the unsupplemented dog, which is below the normal mean +/- SD concentration of 1493 +/- 141 nmol/g wet weight. Low cardiac carnitine concentrations appear to be a consistent finding for dilated cardiomyopathy in boxers. However, in the dog that received carnitine therapy, cardiac carnitine was 2802 nmol/g wet weight, and all tissues assayed in the supplemented dog had higher carnitine concentrations than normal dogs. Elevation of tissue carnitine failed to ameliorate dilated cardiomyopathy in this dog. Oral carnitine supplementation in these therapeutic doses appears not to resolve dilated cardiomyopathy in all boxers.

MeSH
Administration, Oral; Animal; Cardiomyopathy, Congestive; Carnitine; Case Report; Dog Diseases; Dogs; Echocardiography; Electrocardiography; Female; Liver; Male; Muscle, Skeletal; Myocardium; Radiography, Thoracic

Author Address
School of Veterinary Studies, Murdoch University, Australia.
Effects of L-carnitine on ventricular arrhythmias after coronary reperfusion.
Kobayashi A, Suzuki Y, Kamikawa T, Hayashi H, Masumura Y, Nishihara K, Abe M, Yamazaki N
Jpn Circ J 1983 May 47:536-42

Abstract
Effects of L-carnitine on ventricular arrhythmias and myocardial metabolism in a reperfused ischemic myocardium were studied in 35 anesthetized mongrel dogs. The left anterior descending coronary artery was ligated for 40 min and then reperfused for 15 min. L-carnitine (100 mg/kg) was administered intravenously 5 min before the coronary ligation and infused continuously at a rate of 20 mg/kg/min from 5 min before the reperfusion to the end of the experiment. Electrocardiograms were recorded continuously throughout the experiment. Transmural myocardial samples were obtained from both the ischemic and the nonischemic areas after 15 min of reperfusion and used for the determination of ATP, free carnitine, long chain acyl carnitine and long chain acyl CoA. L-carnitine significantly reduced the incidence rate of ventricular fibrillation after reperfusion (from 29% in the controls to 5%, p less than 0.05). ATP in the ischemic myocardium in the L-carnitine group was significantly higher than that in the control group (p less than 0.05). Free carnitine in the control group significantly decreased in the ischemic area as compared with the nonischemic area (p less than 0.01). In L-carnitine group, on the other hand, no difference was observed between them. Long chain acyl CoA in the control group significantly increased in the ischemic area as compared with the nonischemic area (p less than 0.01). In L-carnitine group, on the other hand, no difference was observed between them. Thus, the accumulation of long chain acyl CoA in the ischemic myocardium was reduced by the L-carnitine treatment. These data suggest that L-carnitine has protective effects on ventricular arrhythmias and on metabolic changes after coronary artery reperfusion following coronary artery occlusion.

MeSH
Animal; Arrhythmia; Carnitine; Coronary Disease; Coronary Vessels; Dogs; Ligation; Myocardium; Perfusion; Stereoisomerism
Effects of L-carnitine on action potential or canine papillary muscle impaired by long chain acyl carnitine.
Hayashi H, Suzuki Y, Masumura Y, Kamikawa T, Kobayashi A, Yamazaki N

Abstract
It has been reported that long chain acyl carnitine accumulates in ischemic myocardium, and L-carnitine prevents ventricular arrhythmias as well as the accumulation of long chain acyl carnitine in ischemic and free fatty acid supplemented hearts. The purpose of this study was to observe the electrophysiological effects of long chain acyl carnitine, and to evaluate the protective effect of L-carnitine on the transmembrane action potential impaired by long chain acyl carnitine. Using standard microelectrode techniques, transmembrane action potentials were recorded from isolated canine papillary muscle. Palmitoyl carnitine (0.3 mM and 0.6 mM) decreased the resting membrane potential, action potential amplitude and maximum upstroke velocity of phase 0, and shortened action potential duration and effective refractory period in a concentration-dependent manner. Application of L-carnitine (25 mM) prevented the effect of palmitoyl carnitine (0.3 mM) on the transmembrane action potential. These results suggest that long chain acyl carnitine plays an important role in arrhythmogenesis, and that the effect is prevented by L-carnitine.

MeSH
Action Potentials; Animal; Arrhythmia; Carnitine; Dogs; Fatty Acids, Nonesterified; In Vitro; Palmitoylcarnitine; Papillary Muscles
Short term effects of intra-arterial propionyl-L-carnitine on isolated canine hind-limbs.
Cevese A, Schena F, Poltronieri R, Cerutti G
Cardioscience 1995 Mar 6:59-64

Abstract
Treatment with propionyl-L-carnitine has been shown to increase the walking capacity of patients with peripheral vascular disease, but the mechanisms responsible for the effect are unknown. To study the effects of propionyl-L-carnitine on musculocutaneous vascular beds and the related mechanisms, a preparation of constant-pressure blood-perfused dog hind-limb was used. Since the propionyl-L-carnitine solution had a pH less than 4 the contralateral limb simultaneously received acidified saline. The substances were injected into the perfused arteries in 2 minutes or in 20 minutes, and the cumulative dose of propionyl-L-carnitine was 20 mg/kg for each administration. The preparation was well suited for this study, because there were no major systemic effects of propionyl-L-carnitine, nor signs of cross-circulation between the isolated limbs. Propionyl-L-carnitine increased flow by 130% in 2 minute infusions and by 49% in 20 minute infusions. Acidified saline increased flow by 47% in 2 minute infusions and by 34% in 20 minute infusions. The difference between propionyl-L-carnitine and acidified saline was significant in 2 minute infusions. The 2 minute infusions of propionyl-L-carnitine increased venous PO2 by 34% and PCO2 by 22% while pH decreased by 0.07. The 20 minute infusions of propionyl-L-carnitine increased PO2 by 22% and PCO2 by 24% while pH decreased 0.10 units. Acidified saline increased only venous PO2 in 2 minute infusions (16%). Calculated oxygen consumption of the perfused limbs increased in 2 minute infusions of propionyl-L-carnitine, but not significantly. It was concluded that propionyl-L-carnitine has a direct vasodilator effect in musculocutaneous vascular beds at high doses and probably enhances tissue metabolism.

MeSH
Animal; Blood Circulation; Blood Vessels; Carnitine; Dogs; Female; Hemodynamics; Hindlimb; In Vitro; Infusions, Intra-Arterial; Male; Muscle, Skeletal; Perfusion; Support, Non-U.S. Gov't

Author Address
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Carnitine metabolism during fasting in dogs.
Surgery 1986 Jun 99:684-7

Abstract
During starvation, a series of changes in whole body fuel use occur that result in conservation of fuel, particularly protein. Use of fat stores for ketone production and direct oxidation of fat as a primary fuel are characteristic of starvation. However, the mechanism by which this change develops is unclear. Carnitine is an important compound in the control of fat metabolism, since long-chain free fatty acids must be coupled with it to cross the mitochondrial membrane. This study attempts to define, in the fasting dog model, the interaction between plasma and muscle carnitine, its acyl esters, and the energy substrates available. Eight adult beagle dogs were studied during an 8-day period of starvation. Muscle and plasma were analyzed for free carnitine (FC), acid-soluble fraction, and long-chain esters (LCE), as well as substrate hormone profiles. Total carnitine (TC) and short-chain esters (SCE) were calculated. Muscle was analyzed for carnitine palmitoyl transferase activity (CPT). These measurements were performed on days 3, 5, and 8. There was a significant (p less than 0.05) loss in weight on days 3, 5, and 8. TC and FC increased significantly (p less 0.05) only on day 8; this occurred simultaneously with a significant (p less than 0.05) decrease in CPT. It was preceded by a significant (p less than 0.05) and persistent increase in plasma TC, FC, and LCE that developed on day 3. During starvation there was an increase in plasma carnitine levels before changes in muscle. The increase in muscle carnitine occurred between days 5 and 8 of starvation and seemed to be associated with a fall in CPT. This may be responsible either for or secondary to the decrease in metabolic rate that occurs during prolonged starvation.

MeSH
3-Hydroxybutyric Acid; Animal; Blood Glucose; Blood Urea Nitrogen; Carnitine; Carnitine O-Palmitoyltransferase; Dogs; Fatty Acids, Nonesterified; Glycerol; Hematocrit; Hydroxybutyrates; Insulin; Lipids; Muscles; Starvation; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.; Time Factors; Triglycerides
Effects of L-carnitine on ventricular arrhythmias in dogs with acute myocardial ischemia and a supplement of excess free fatty acids.
Suzuki Y, Kamikawa T, Yamazaki N
Jpn Circ J 1981 May 45:552-9

Abstract
The effects of L-carnitine on ventricular arrhythmias were evaluated in dogs with acute myocardial ischemia and a supplement of excess free fatty acids (FFA). Acute myocardial ischemia was induced by ligation of left anterior descending coronary artery. After 80 minutes of coronary occlusion, high plasma FFA was induced by intravenous injection of heparin 200 μg/kg and Intralipid 5 ml/kg as a bolus. After additional 60 minutes, beating hearts were removed from animals and tissue levels of free carnitine, short and long chain acyl carnitine, FFA and adenosine triphosphate (ATP) were determined. L-carnitine 100 mg/kg was administered intravenously 5 minutes before coronary artery ligation. Electrocardiograms were recorded continuously by a Holter electrocardiographic recorder during the experiment and ventricular arrhythmias were quantified by an arbitrary scoring system. In ischemic and excess FFA supplemented myocardium, free carnitine and ATP decreased, whereas long chain acyl carnitine and FFA increased. And these metabolic changes tended to be reduced by L-carnitine. Pretreatment of L-carnitine also reduced the grade of ventricular arrhythmias induced both by acute myocardial ischemia and by supplemented of excess FFA. These results suggest that the administration of L-carnitine may be beneficial to prevent serious arrhythmias in ischemic heart disease, presumably by restoring the impaired FFA oxidation.

MeSH
Adenosine Triphosphate; Animal; Arrhythmia; Carnitine; Dogs; Fatty Acids, Nonesterified; Myocardial Infarction
[Effects of L-carnitine on the regional function of the stunned myocardium caused by ischemia of short duration]
Hernández Martínez A, Pallarés Carratalá V, Cosín Aguilar J, Andrés Conejos F, Capdevila Carbonell C, Portolés Sanz M
Rev Esp Cardiol 1997 Sep 50:650-7

Abstract
INTRODUCTION AND OBJECTIVES: Myocardial ATP is produced mainly by fatty acid oxidation, a process in which the fatty acid metabolite carrier carnitine is needed to carry the metabolites into the mitochondria. Cardiac ischemia is associated with carnitine depletion. Our objective was to study the functional effect of L-carnitine on myocardium stunned by very brief, repeated ischemias, and to examine its actions in the recovery period. METHODS: The two series studied were the control series (7 dogs) and the carnitine series (7 dogs). L-carnitine was administered to the carnitine series at doses of 250 mg/kg/day starting 7 days before the ischemic protocol and continuing during the follow-up period (10 and 15 days). The ischemic protocol consisted of 20 anterior descending coronary artery occlusions lasting 2 min and with 3 min of reperfusion between occlusions. Global and regional cardiac function parameters were recorded daily. RESULTS: No differences in the global functional (haemodynamic) or ECG of the two series were found, but there were differences in regional myocardial function. The control series segment shortening fraction fell to dyskinesis values during the occlusion periods, then recovered during reperusions. The segment shortening fraction worsened during the stunning period, reaching its maximal impairment on the 5th day, after which it returned to basal values on the 15th day. The carnitine series showed the same performance in the occlusion/reperfusion period. However, during the stunning period the segment shortening fraction recovered and reached values close to the basal ones maintained them during the follow-up period. CONCLUSIONS: L-carnitine induces an almost immediate recovery of myocardial contractility, when it has been affected by very brief, repeated coronary occlusions. It limits the myocardial stunning apparition.

MeSH
Animal; Carnitine; Coronary Circulation; Dogs; English Abstract; Female; Male; Myocardial Contraction; Myocardial Ischemia; Myocardial Stunning; Support, Non-U.S. Gov't

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Protein binding of L-carnitine family components.
Eur J Drug Metab Pharmacokinet 1991 Spec No 3:364-8

Abstract

L-carnitine and its short-, medium- and long-chain acyl esters constitute the L-carnitine family. These compounds in the body are equilibrated according to a homeostatic equilibrium preserved and, when impaired, restored by a dynamic inter-exchange between L-carnitine and its esters, catalysed by carnitine acyl transferases, and a tubular reabsorption process with differentiated thresholds for each component. The interaction of these compounds with albumin and plasma proteins of rats, dogs and humans was carefully investigated by means of ultrafiltration and gel filtration techniques. Results obtained demonstrate that L-carnitine and its short-chain esters, namely acetyl-L-carnitine and propionyl-L-carnitine, do not interact with either albumin or plasma proteins; octanoyl-L-carnitine interacts in a measurable even if poor extent (12-30%), whereas palmitoyl-L-carnitine, a molecule with a detergent activity, is completely bound to albumin and plasma proteins.

MeSH
Acetylcarnitine; Animal; Blood Proteins; Carnitine; Chromatography, Gel; Dogs; Human; Palmitoylcarnitine; Protein Binding; Rats; Serum Albumin; Ultrafiltration

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The role of carnitine in the conjugation of acidic xenobiotics.
Quistad GB, Staiger LE, Schooley DA
Drug Metab Dispos 1986 Sep-Oct 14:521-5

Abstract
Conjugation with carnitine is a major metabolic pathway for cyclopropanecarboxylic acid (CPCA). The CPCA-carnitine is cleaved enzymatically (carnitine acetyltransferase) more slowly in vitro than are acetyl- and propionylcarnitines, but also slightly more extensively. When given orally to a rat, CPCA-carnitine is excreted readily in urine as free CPCA and its glycine conjugate. Effects of dietary exposure of rats to CPCA were determined by feeding cycloprate (a CPCA precursor) at 5000 ppm and then assaying tissue levels of carnitine. Both free and total carnitine in the hearts of female rats were depressed by 39% after 3 weeks at this exaggerated dose. We suggest a possible link between sequestration of carnitine and the observed pathology which includes lipid deposition in the hearts of female rats fed cycloprate at high doses. When a rat was given an oral dose of [14C]benzoic acid, benzylocarnitine was a minor urinary metabolite (0.04% of applied dose). This result suggests that many other xenobiotic acids may conjugate with carnitine (albeit at low levels) and this role in xenobiotic metabolism may be more general than presently appreciated.

MeSH
Animal; Carnitine; Carnitine O-Acetyltransferase; Cyclopropanes; Dogs; Esterification; Female; Male; Myocardium; Rats; Rats, Inbred Strains
Effects of dietary fat and L-carnitine on plasma and whole blood taurine concentrations and cardiac function in healthy dogs fed protein-restricted diets.
Sanderson SL, Gross KL, Ogburn PN, Calvert C, Jacobs G, Lowry SR, Bird KA, Koehler LA, Swanson LL

OBJECTIVE: To evaluate plasma taurine concentrations (PTC), whole blood taurine concentrations (WBTC), and echocardiographic findings in dogs fed 1 of 3 protein-restricted diets that varied in fat and L-carnitine content. ANIMALS: 17 healthy Beagles. DESIGN: Baseline PTC and WBTC were determined, and echocardiography was performed in all dogs consuming a maintenance diet. Dogs were then fed 1 of 3 protein-restricted diets for 48 months: a low-fat (LF) diet, a high-fat and L-carnitine supplemented (HF + C) diet, or a high-fat (HF) diet. All diets contained methionine and cystine concentrations at or above recommended Association of American Feed Control Officials (AAFCO) minimum requirements. Echocardiographic findings, PTC, and WBTC were evaluated every 6 months. RESULTS: The PTC and WBTC were not significantly different among the 3 groups after 12 months. All groups had significant decreases in WBTC from baseline concentrations, and the HF group also had a significant decrease in PTC. One dog with PT and WBT deficiency developed dilated cardiomyopathy (DCM). Taurine supplementation resulted in significant improvement in cardiac function. Another dog with decreased WBTC developed changes compatible with early DCM. CONCLUSIONS AND CLINICAL RELEVANCE: Results revealed that dogs fed protein-restricted diets can develop decreased taurine concentrations; therefore, protein-restricted diets should be supplemented with taurine. Dietary methionine and cystine concentrations at or above AAFCO recommended minimum requirements did not prevent decreased taurine concentrations. The possibility exists that AAFCO recommended minimum requirements are not adequate for dogs consuming protein-restricted diets. Our results also revealed that, similar to cats, dogs can develop DCM secondary to taurine deficiency, and taurine supplementation can result in substantial improvement in cardiac function.
Author Address
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Ischemic preconditioning and long-chain acyl carnitine in the canine heart.
Simkhovich BZ, Hale SL, Ovize M, Przyklenk K, Kloner RA
Coron Artery Dis 1993 Apr 4:387-92

Abstract
BACKGROUND: This study investigated the effects of ischemic preconditioning on myocardial carnitine-linked metabolism and high-energy phosphates in the canine model of ischemia and reperfusion. METHODS: Anesthetized dogs underwent 1 hour of coronary artery occlusion and 4.5 hours of reperfusion. The dogs were randomly assigned to a control group (no intervention for 30 minutes), a preconditioned group (four repeated episodes of 3 minutes of mechanical coronary occlusion, each followed by 5 minutes of reperfusion), and a coronary cyclic flow variation (CFV) group (coronary artery stenosis and endothelial injury, resulting in an average of four episodes of platelet thrombosis and dislodgment). After completion of the protocol, ATP, creatine phosphate, and long-chain acyl carnitine concentrations were studied in both nonischemic and previously ischemic myocardium. RESULTS: In Part I of this study (Ovize et al., Circulation 1992, 85:779-789), it was reported that both mechanical occlusion and CFV before sustained occlusion resulted in a decrease in infarct size. In the present paper, we report changes in high-energy phosphates and long-chain acyl carnitine in these groups. Control, preconditioned, and CFV groups showed similar depletion in ATP content and "overshoot" in creatine phosphate stores. Control dogs exhibited a significant accumulation of long-chain acyl carnitine in the previously ischemic tissue (219 +/- 61 vs 131 +/- 38 nmoles/g wet weight in the nonischemic tissue; P < 0.05). No significant increase in long-chain acyl carnitine occurred in the mechanically preconditioned and CFV groups. CONCLUSIONS: These results indicate that brief episodes of transient ischemia before sustained coronary occlusion prevent long-chain acyl carnitine accumulation in the ischemic and reperfused canine myocardium.

MeSH
Acetylcarnitine; Adenosine Triphosphate; Animal; Carnitine; Coronary Circulation; Dogs; Myocardial Ischemia; Myocardial Reperfusion; Myocardium; Phosphocreatine

Author Address
Heart Institute of the Hospital of the Good Samaritan, Los Angeles, CA 90017.
Myocardial carnitine metabolism in congestive heart failure induced by incessant tachycardia.
Pierpont ME, Foker JE, Pierpont GL
Basic Res Cardiol 1993 Jul-Aug 88:362-70

Abstract
Persistent tachycardia induces congestive heart failure (CHF), but the mechanism(s) of progressive ventricular dysfunction is (are) unclear. This study was designed to define possible metabolic causes of myocardial dysfunction in rapid ventricular pacing induced CHF. Twelve adult mongrel dogs were paced to 250 beats/min for 19 days. Plasma carnitine, norepinephrine and renin were measured at 0, 1, 2, and 3 weeks. Myocardial high energy phosphates, carnitine, glycogen, glucose, non-collagenous protein and collagen were measured at 19 days. Cardiac output, arterial pressure and pulmonary wedge pressure, measured at baseline and with CHF, showed a decrease in cardiac output and increase in pulmonary wedge pressure. Neurohumoral activation was evident by progressively increasing plasma norepinephrine and renin activity and depletion of myocardial norepinephrine. Plasma free carnitine rose significantly from 12.6 +/- 2.0 control to 28.3 +/- 3.8 nmol/ml at 19 days (p < 0.001), whereas myocardial total carnitine was lower in paced than in control dogs (6.0 +/- 1.9 vs. 14.1 +/- 3.5 nmol/mg non-collagenous protein, p < 0.001).

Myocardial ATP ATP and ADP were unchanged, while AMP decreased 22%, and creatine phosphate decreased 30% compared to control animals. Myocardial glucose was normal but glycogen was decreased 54% (p < 0.005). The low myocardial carnitine and elevated plasma carnitine in pacing induced CHF suggests altered carnitine transport or membrane integrity.

MeSH
Animal; Cardiac Pacing, Artificial; Carnitine; Catecholamines; Dogs; Energy Metabolism; Heart Failure, Congestive; Hemodynamics; Myocardium; Phosphates; Renin; Tachycardia

Author Address
Department of Pediatrics, University of Minnesota, School of Medicine, Minneapolis.
Studies on experimental coronary insufficiency. Effect of L-carnitine on myocardial ischemia produced by sympathetic-nerve stimulation with high plasma fatty acids.
Adv Myocardiol 1985 6:437-49

Abstract
Our previous studies revealed that sympathetic-nerve stimulation (SNS$t$) plays an important role in the precipitation and the augmentation of myocardial ischemia in dogs with coronary constriction. To clarify the underlying mechanism of the detrimental effect of free fatty acids (FFA) at a high plasma concentration and the beneficial effect of L-carnitine on myocardial ischemia, ischemic changes following SNS$t$ were compared among three groups of dogs with mild or moderate coronary constriction: a saline control group, an intralipid [(IL) 0.1 ml/kg per min + heparin 5 mg/kg] group, and an IL + L-carnitine (200 mg/kg) group. High plasma concentration of FFA aggravated the ischemic changes induced by SNS$t$ in dogs with coronary constriction, in which no signs of increase in myocardial oxygen consumption were seen. L-Carnitine clearly alleviated the mechanical dysfunction, acceleration of anaerobic metabolism, depletion of myocardial contents of high-energy phosphates, myocardial accumulation of lactate, and ECG ischemic changes that were augmented by high plasma FFA in the coronary-constricted dogs with SNS$t$. From these findings, it was suggested that an increased plasma FFA might aggravate myocardial ischemia, at least, produced by SNS$t$ in dogs with mild or moderate coronary constriction and that L-carnitine might improve the ischemia augmented by FFA, presumably by reducing myocardial accumulation of FFA intermediates.

MeSH
Animal; Carnitine; Coronary Circulation; Coronary Disease; Dogs; Electrocardiography; Fat Emulsions, Intravenous; Fatty Acids, Nonesterified; Heart; Heart Ventricle; Heparin; Lactates; Lactic Acid; Myocardium; Oxygen Consumption; Phosphates; Potassium; Sympathetic Nervous System
Myocardial L-carnitine deficiency in a family of dogs with dilated cardiomyopathy.
Keene BW, Panciera DP, Atkins CE, Regitz V, Schmidt MJ, Shug AL

Abstract
Dilated cardiomyopathy in a family of dogs was found to be associated with decreased myocardial L-carnitine concentrations, when compared with those in control dogs. In 2 affected dogs, treatment with high doses of L-carnitine was associated with increased myocardial L-carnitine concentration and greatly improved health and myocardial function. Withdrawal of L-carnitine supplementation from these dogs resulted in development of myocardial dysfunction and clinical signs of dilated cardiomyopathy.

MeSH
Animal; Cardiomyopathy, Congestive; Carnitine; Case Report; Dog Diseases; Dogs; Echocardiography; Male; Support, Non-U.S. Gov't

Author Address
Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin, Madison 53706.
Myocardial preservation in acute coronary artery occlusion with coronary sinus retroperfusion and carnitine.
Katircioglu SF, Iscan HZ, Ulus T, Saritas Z
J Cardiovasc Surg (Torino) 2000 Feb 41:45-50

BACKGROUND: Effectiveness of retrograde coronary sinus perfusion with the use of carnitine supplementation over the severity of ischemia/reperfusion injury, in acute coronary occlusion. METHODS: Eighteen mongrel dogs, divided equally into control, retrograde perfusion (retroperfusion) and carnitine retroperfusion (retrocarnitine) groups. After taking the basal values, the left anterior descending artery was occluded. At the fifteenth minute, without ending the occlusion, retrograde coronary sinus cardioplegia in the retroinfusion group and in the carnitine group, 0.15 mmol/kg of L-carnitine retroperfusion was performed. Then, hemodynamic and biochemical measurements were taken till the end of 120 minutes. The control group had no retroperfusion or medical therapy. RESULTS: Between the three groups, there was a statistically significant difference in cardiac index, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure as hemodynamic parameters and myocardial oxygen extraction, myocardial Lactate extraction, protein thiols and Malonyl dialdehyde (MBA) as biochemical parameters, at different time intervals (p<0.05). CONCLUSION: Coronary sinus retroperfusion with carnitine is found to be very effective in reducing oxygen free radical release and however this advantage did not switch to the hemodynamic function between the retrograde coronary sinus infusion group and retroinfusion carnitine group. In our opinion retrograde coronary sinus perfusion with the use of carnitine supplementation reduces the severity of ischemia/reperfusion injury.

MeSH
Animal; Carnitine; Dogs; Energy Metabolism; Hemodynamics; Myocardial Infarction; Myocardial Reperfusion Injury; Myocardium; Perfusion; Stroke Volume
L-carnitine combined with minimal electrical stimulation promotes type transformation of canine latissimus dorsi.

Dubelaar ML, Glatz JF, De Jong YF, Van der Veen FH, Hülsmann WC

Abstract

In the first part of this study, in four dogs the left latissimus dorsi was equipped to perform in vivo contraction measurements and the right latissimus dorsi served as control. After a control period, the dogs received L-carnitine intravenously for 8 wk. We found that carnitine caused the percentage of type I fibers to increase from 30 to 55% in the left latissimus dorsi but no change in the right latissimus dorsi. In the left latissimus dorsi, the contraction speed (percentage ripple) decreased from 75 to 30% and cytochrome-c oxidase activity increased 1.6-fold. No changes occurred in the right latissimus dorsi. To verify these observations, we performed a second study with placebo control for 8 wk, and only the left latissimus dorsi was subjected to weekly electrical stimulation. In the carnitine-treated dogs, the stimulated muscle showed an increase in the percentage of type I fibers from 16 to 35% and the ripple decreased from 92 to 77%. These measures did not change in the placebo-treated dogs. We concluded that weekly short-term stimulation does not lead to a change in fiber type; however, carnitine combined with minimal stimulation of the muscle leads to a significant shift in muscle fiber type composition toward a muscle with an increased content of type I fibers.

MeSH
Animal; Body Composition; Carnitine; Cytochrome-c Oxidase; Dogs; Electric Stimulation; Electrodes, Implanted; Fatigue; Immunohistochemistry; Male; Muscle Contraction; Muscles; Oxidation-Reduction; Palmitates; Support, Non-U.S. Gov't

Author Address
Department of Physiology, Cardiovascular Research Institute Maastricht, University of Limburg, The Netherlands.
Influence of dietary fish oil on mitochondrial function and response to ischemia.
McMillin JB, Bick RJ, Benedict CR

Abstract
Dietary supplementation with marine oils may reduce the incidence of thromboembolism and decrease cardiac arrhythmias during myocardial ischemia. However, function of subcellular organelles isolated from hearts of these animals is impaired. In contrast to studies where marine oil was the sole source of dietary lipid in rats, menhaden oil was used to supplement standard canine laboratory chow. In mitochondria isolated from hearts of dogs fed this diet for 60 wk, the phospholipid content of arachidonic acid was replaced by the n-3 fatty acids, eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. Mitochondrial levels of linoleic and linolenic acids were not altered. The mitochondrial membrane phospholipid from the menhaden oil-fed dogs demonstrated increased cardiolipin. The respiratory function of heart mitochondria from the menhaden oil-supplemented dogs was not decreased from that of dogs on standard chow only. Increased succinate-supported respiration paralleled increased cytochrome oxidase in mitochondria from menhaden oil-fed dogs. The activity of the cardiolipin-dependent carnitine acylcarnitine translocase was unaffected. Myocardial ischemia decreased mitochondrial respiration in menhaden-fed dogs. Decreased palmitoylcarnitine-carnitine exchange following ischemia resulted from decreased matrix carnitine rather than decreased translocase activity. Normal levels of the essential fatty acids in the n-3-enriched mitochondrial membrane phospholipids appear to eliminate the mitochondrial dysfunction observed in essential fatty acid-deficient membranes.

MeSH
Animal; Carnitine; Cytochrome-c Oxidase; Dogs; Fish Oils; Kinetics; Mitochondria, Heart; Myocardial Ischemia; Oxygen Consumption; Palmitoylcarnitine; Phospholipids; Phosphorylation; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Author Address
Department of Pathology and Laboratory Medicine, University of Texas Health Science Center, Houston.
Effect of propionyl-L-carnitine on experimental myocardial infarction in dogs.
Leasure JE, Kordenat K
Cardiovasc Drugs Ther 1991 Feb 5 Suppl 1:85-95

Abstract
Limitation on infarct size, using propionyl-L-carnitine (Sigma-Tau) by itself and with the calcium entry blocker, tiapamil (Hoffmann-LaRoche), was evaluated in two groups of ten dogs each, during chronic (9 days) myocardial infarction. There were eight dogs that served as the control group. A closed-chest model was used to produce the thrombus by placing a helically shaped copper wire in the LAD by catheter technique, under x-ray visualization. Necrotic tissue in serial transventricular sections were delineated by triphenyltetrazolium chloride and measured by computer technique, using an IBM PC interfaced with a digitizing pad, 9 days following occlusion. The mean total amount of necrosis in the propionyl-L-carnitine (7.4%) and the propionyl-L-carnitine/tiapamil (6.7%) groups were significantly less (p less than .01) than found in the control (14.1%) group, reflecting a difference of 50 and 58%, respectively, between the treated groups and control. A number of significant between-group comparisons (p less than .05 to p less than .001), under the same conditions, were found for various ischemia, hemodynamic, and hematologic variables followed before and at 30, 60, 90, 120, and 180 minutes after occlusion, as well as on the second and ninth day. The results of this study strongly suggest that propionyl-L-carnitine and propionyl-L-carnitine with tiapamil has a protective effect on myocardial function, following thrombotic occlusion of the LAD, as well as limiting the resulting infarct size.

MeSH
Animal; Calcium Channel Blockers; Carnitine; Comparative Study; Creatine Kinase; Dogs; Drug Evaluation, Preclinical; Female; Hemodynamics; Lactate Dehydrogenase; Male; Myocardial Infarction; Propylamines; Support, Non-U.S. Gov’t

Author Address
Cox Heart Institute, Wright State University, School of Medicine, Dayton, OH 45429.
Acute effect of L-carnitine on skeletal muscle force tests in dogs.
Dubelaar ML, Lucas CM, Hülsmann WC

Abstract
Using the mixed type musculus latissimus dorsi of the dog in the present work, we show the effect of carnitine on an in situ fatigue test. L-Carnitine appears to improve force of this muscle by 34% while stimulated in situ. This effect of carnitine is acute and (stereo)specific, since neither D-carnitine nor the structural analogue choline (also a tertiary amine) has a positive effect on contractile force. Because skeletal muscle is rich in carnitine and because carnitine transport is slow, its effect must be exerted outside the striated muscle cells. Insulin (with glucose) administration abolished the carnitine effect. It is speculated that facilitation of fatty acid oxidation in the blood vessel wall is the basis for this positive effect of carnitine.

MeSH
Blood Glucose; Carnitine; Choline; Electric Stimulation; Exercise; Fatty Acids, Nonesterified; Insulin; Lactates; Muscle Contraction; Muscles; Reference Values; Support, Non-U.S. Gov't; Time Factors; Triglycerides

Author Address
Department of Physiology, University of Limburg, Maastricht, The Netherlands.
Kinetics of carnitine-dependent fatty acid oxidation: implications for human carnitine deficiency.
Long CS, Haller RG, Foster DW, McGarry JD
Neurology 1982 Jun 32:663-6

Abstract
The relationship between the concentration of carnitine and the oxidation of oleate was examined in homogenates prepared from skeletal muscle, liver, kidney, and heart of the rat, and from canine and human skeletal muscle. The carnitine content of these tissues in situ spanned a wide range, from about 0.1 mumol per gram in rat liver to about 3.0 mumol per gram in human muscle. The concentration of carnitine required for half-maximal rates of fatty acid oxidation in vitro also varied greatly (10 to 15 microM for rat liver to 200 to 400 microM for human muscle), and in rough proportion to the normal carnitine content of the tissues. For any given tissue, the carnitine content seems to be set at a level necessary for optimal rates of fatty acid oxidation. The data provide a plausible explanation for the fact that muscle fatty acid metabolism is severely impaired in the syndrome of human carnitine deficiency, since measured carnitine levels are in the range expected to limit substantially the capacity for fatty acid oxidation.

MeSH
Animal; Carnitine; Dogs; Fatty Acids; Kidney Cortex; Kinetics; Liver; Male; Muscles; Oleic Acid; Oleic Acids; Oxidation-Reduction; Rats; Rats, Inbred Strains; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Effect of L-carnitine on cardiac hemodynamics.
Suzuki Y, Kamikawa T, Yamazaki N

Abstract
The effect of L-carnitine on cardiac hemodynamics was evaluated in normal closed chest dogs. Extracorporeal circulation was produced to measure coronary blood flow in closed chest dogs. Coronary venous blood was introduced to the extracorporeal circuit through a polyethylene catheter wedged into the coronary sinus under fluoroscopic control and was returned to the animal through the jugular vein. L-carnitine was infused intravenously at a constant rate of 80 mg/Kg/min for 8 min. Hemodynamic responses appeared within 1 to 3 min of carnitine infusion and peak effects were observed nearly after 5 min. Peak effects on cardiac hemodynamics after 5 to 8 min of carnitine infusion were as follows. Heart rate decreased by 17% from control (p less than 0.05). Aortic and left ventricular pressure increased by 20% (p less than 0.05 and p less than 0.01 respectively) and peak positive left ventricular dp/dt increased by 35% (p less than 0.01), the mean rate pressure product as the index of myocardial oxygen consumption remained unchanged. Coronary blood flow increased by 60% (p less than 0.01) and coronary vascular resistance decreased by 25% (p less than 0.01). As the infusion of carnitine was discontinued, the effects promptly disappeared. These data suggest that L-carnitine has direct vasodilating and positive inotropic effects on cardiovascular system.

MeSH
Acetyl Coenzyme A; Adenosine Triphosphate; Animal; Carnitine; Coronary Circulation; Dogs; Fatty Acids; Heart; Hemodynamics; Oxygen Consumption
Effects of carnitine on preconditioned latissimus dorsi muscle at different burst frequencies.
Katircioğlu SF, Grandjean PA, Küçüker S, Saritas Z, Yavas S, Tasdemir O, Bayazit K

Abstract
Exercise and electrical stimulation may result in a decrease in carnitine levels associated with preconditioned latissimus dorsi muscles. Therefore, the effects of exogenous carnitine were studied in a model of latissimus dorsi muscle contraction. Twelve dogs were studied. Under anesthesia, the latissimus dorsi was placed around an implantable mock circulation system. The muscle was made fatigue-resistant with the aid of chronic low-frequency electrical stimulation. Six animals received carnitine 0.15 mmol/kg; the other six served as control. The muscles were stimulated with 20, 43, and 85 Hz pulse training. During the 90-minute stimulation period, the pressure that developed in the mock circulation was measured at 15 minute intervals. The changes in ATP and lactate levels were measured every 30 minutes. Stimulations at 20 and 43 Hz did not result in any change in pressure or metabolic data over the course of 90 minutes of stimulation. When the 85 Hz burst was applied, ATP levels decreased, while lactate levels increased, with an associated drop in pressure in the control group. ATP and lactate levels were, respectively, 13.8 +/- 1.4 mumol/g and 15.0 +/- 4.0 mumol/g in the carnitine group and 10.3 +/- 1.1 mumol/g and 23.0 +/- 3.0 mumol/g in the control group at the end of 90 minutes (p < 0.06). The pressure at the same time interval was 74 +/- 4 mmHg in the control group, and 85 +/- 3 mmHg in the carnitine group (p < 0.05). In this study, we demonstrated that carnitine administration enhances muscle performance in terms of metabolic and pressure changes during high-frequency electrical stimulation at 85 Hz.

MeSH
Adenosine Triphosphate; Animal; Carnitine; Dogs; Follow-Up Studies; Ischemic Preconditioning; Lactic Acid; Muscle Contraction; Respiratory Muscles; Spectrophotometry

Author Address
Cardiovascular Surgery Department at Türkiye Yüksek İhtisas Hastanesi, Ankara, Turkey.
Effect of L-carnitine on mitochondrial acyl CoA esters in the ischemic dog heart.
Kobayashi A, Fujiwara S
J Mol Cell Cardiol 1994 Apr 26;499-508

Abstract
Many studies have shown that L-carnitine has a positive effect on ischemic myocardium, probably by reducing accumulation of long-chain acyl coenzyme A (CoA) esters. Previous studies have involved whole-heart extracts and have not assessed changes of CoA ester levels in mitochondria, the site of translocase inhibition. To more precisely assess L-carnitine effects, we measured long-chain acyl CoA ester levels in cytosol and in mitochondria in the ischemic canine heart. Dogs were divided into four groups: a sham-operated control group; an untreated group; and high- and low-dose L-carnitine-treated groups (30 mg/kg and 100 mg/kg). After 60 min of ischemia, the heart was excised, and the cytosolic and mitochondrial fractions were isolated. CoA esters and the activity of carnitine palmitoylcarnitine transferase (CPT) I and II were measured in both compartments. Approximately 89% of cellular free CoA, 90% of cellular acetyl CoA, 97% of cellular short-chain acyl CoA, and 92% of cellular long-chain acyl CoA were located in the mitochondrial space under the normal condition. Under the ischemic condition, mitochondrial free CoA was significantly decreased. Conversely, mitochondrial acetyl CoA and long-chain acyl CoA were significantly increased. Treatment with L-carnitine significantly decreased acetyl CoA and long-chain acyl CoA in the ischemic mitochondrial space in a dose-dependent manner. These results support the hypothesis that L-carnitine reduces accumulation of long-chain acyl CoA within the ischemic mitochondrial space and thereby improves mitochondrial function and adenine nucleotide translocation.

MeSH
Animal; Carnitine; Coenzyme A; Dogs; Dose-Response Relationship, Drug; Esters; Male; Mitochondria; Myocardial Ischemia; Myocardium; Subcellular Fractions

Author Address
Third Department of Internal Medicine, Hamamatsu University School of Medicine, Japan.
Effect of L-carnitine on the cellular distribution of carnitine and its acyl derivatives in the ischemic heart.
Fujisawa S, Kobayashi A, Hironaka Y, Yamazaki N
Jpn Heart J 1992 Sep 33:693-705

Abstract
The purpose of this study was to investigate the cellular distribution of carnitine and its acyl derivatives in the normal and ischemic myocardium, and the effects of exogenous 1-carnitine on this distribution and mitochondrial function in the ischemic dog heart. Under non-ischemic conditions, about 93% of the total cellular carnitine was located in the cytosolic compartment and 6.5% in the mitochondrial compartment. Sixty minutes of ischemia induced a decrease in the cytosolic free carnitine content, but caused the accumulation of long-chain acylcarnitine in the cytosolic and mitochondrial compartments. Treatment with 1-carnitine (30 or 100 mg/kg, i.v.) inhibited the mitochondrial accumulation of long-chain acylcarnitine. Free fatty acid (FFA) metabolism in the mitochondria differs from that in the cytosol. So, it is necessary to investigate the changes in FFA metabolism in both of these cellular compartments. Our results suggest that 1-carnitine has a protective effect on the ischemic heart by selectively reducing mitochondrial accumulation of long-chain acylcarnitine.

MeSH
Acylation; Animal; Carnitine; Cytosol; Dogs; Fatty Acids, Nonesterified; Male; Mitochondria, Heart; Myocardial Ischemia; Myocardium

Author Address
Third Department of Internal Medicine, Hamamatsu University School of Medicine, J
Control of carnitine-related metabolism during myocardial ischemia.
Shug AL

Abstract
Induction of ischemia in the open-chest dog or isolated rat heart caused a series of critical changes in carnitine-related metabolism. As a result of these metabolic changes, the LCACA/carnitine ratio rapidly increased which, in turn, may have reduced the activity of mitochondrial ANT and a number of other enzyme systems necessary for normal heart function. Carnitine administration apparently reversed these carnitine-linked metabolic changes and protected the ischemic myocardium. Possible mechanisms for the protective action of carnitine were discussed.

MeSH
Aerobiosis; Animal; Anoxia; Biological Transport; Carnitine; Carnitine O-Acetyltransferase; Cell Membrane Permeability; Coronary Disease; Disease Models, Animal; Dogs; Myocardium; Rats; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Effects of L-carnitine on phospholipids in the ischemic myocardium.
Nagao B, Kobayashi A, Yamazaki N
Jpn Heart J 1987 Mar 28:243-51

Abstract
To evaluate the protective effects of L-carnitine on the ischemic myocardium, the effects of its administration on tissue levels of high energy phosphate and phospholipids were studied in ischemic dog hearts. Myocardial ischemia was induced by the ligation of the left anterior descending coronary artery for 40 min. In the experiment, L-carnitine (300 mg/kg) was administered intravenously prior to coronary artery ligation. Mitochondrial phospholipids were extracted from nonischemic and ischemic regions of the myocardium and subsequently analyzed. In ischemic myocardial tissues, levels of adenosine 5′-triphosphate (ATP) were reduced. The decrease was significantly elevated by L-carnitine pretreatment. The mitochondrial fractions obtained from ischemic myocardia had significantly lower levels of phospholipids than those obtained from nonischemic tissues. Moreover, the amounts of phosphatidylcholine, phosphatidylinositol and phosphatidylethanolamine were significantly decreased in ischemic myocardial tissues. L-carnitine-pretreatment prevented the reduction of these phospholipids. Lysophosphatidylethanolamine and sphingomyelin did not show statistically significant decreases. This may explain why the administration of carnitine has beneficial effects on ischemic myocardium.

MeSH
Adenosine Triphosphate; Animal; Carnitine; Coronary Disease; Dogs; Drug Evaluation, Preclinical; Female; Male; Mitochondria, Heart; Myocardium; Phospholipids
Effects of L-carnitine in acute myocardial ischaemia.
Fazekas T, Csáti S, Selmeczi A, Udvary E, Szekeres L

Abstract
Data in the literature suggest that exogenous L-carnitine improves the metabolic function of ischaemic heart cells: it enhances the transport of long-chain fatty acids into the mitochondria, stimulates the slowed beta-oxidation, and moderates the accumulation of amphiphilic acyl esters. A study has therefore been made of the cardiac effects of L-carnitine in dog experiments (n = 8). The left anterior descending coronary artery (LAD) was isolated in anaesthetized, thoracotomized animals in situ. After a control occlusion and equilibration period, the LAD was again ligated at the time of L-carnitine infusion (100 mg/kg iv. during 10 min). The agent diminished the maximal conduction delay and the degree of epicardial ST-segment elevation in the ischaemic myocardial region, and the free fatty acid concentration of the arterial blood, but it did not influence the frequency of ventricular extrasystoles. The anti-ischaemic effect of L-carnitine was manifest only during the infusion, and its discontinuation was immediately followed by an enhanced ST-segment elevation. In the dose applied, the substance did not affect the heart rate, systemic mean arterial pressure, left ventricular end-diastolic pressure (LVEDP), or left ventricular contractility (LV dP/dtmax). In the canine myocardial infarction model employed it was observed that the duration of the anti-ischaemic effect of L-carnitine (100 mg/kg iv.) is very short, and it has no significant antiarrhythmic action.

MeSH
Acute Disease; Animal; Arteries; Blood Pressure; Carnitine; Coronary Disease; Dogs; Fatty Acids, Nonesterified; Heart Rate; Myocardial Contraction
Carnitine distribution in subepicardial and subendocardial regions in normal and ischemic dog hearts.
Suzuki Y, Kamikawa T, Yamazaki N

Abstract
In order to evaluate the role of carnitine on fatty acid metabolism in subepicardial (Epi) and subendocardial (Endo) regions in ischemic heart, tissue levels of carnitine, free fatty acids (FFA), and adenosine triphosphate (ATP) were determined in ischemic, non-ischemic and border areas in dog hearts with acute regional ischemia. Acute regional ischemia was induced by ligation of the left anterior descending coronary artery for 15 min. In normal hearts, tissue carnitine levels were lower in Endo than in Epi. On the other hand, FFA levels were higher in Endo than in Epi. In ATP levels, no significant differences were observed between Endo and Epi. In acute regional ischemia, tissue carnitine levels decreased not only in ischemic and border areas but also in nonischemic area. And the levels were lower in Endo than in Epi in all areas. Tissue ATP levels were also lower in endo than in Epi in all areas. From nonischemic area toward the center of ischemic area, the difference in ATP levels between Endo and Epi became more prominent. Tissue FFA levels increased in ischemic and border areas, while no significant differences were observed between Endo and Epi. These results confirmed that Endo as metabolically more anaerobic than Epi even in normal heart and it became more prominent in the heart with acute regional ischemia.

MeSH
Adenosine Triphosphate; Animal; Carnitine; Coronary Disease; Dogs; Fatty Acids, Nonesterified; Myocardium
Dilated cardiomyopathy in juvenile Portuguese Water Dogs.
J Vet Intern Med 2002 Jan-Feb 16:52-62

Abstract
Dilated cardiomyopathy recently has been recognized in juvenile Portuguese Water Dogs. The purpose of this study was to evaluate unaffected and affected puppies by physical examination, electrocardiogram (ECG), echocardiogram, specific biochemical assays, and ultrastructure to document disease progression and to develop a method of early detection. Results of segregation analysis were consistent with autosomal recessive inheritance. Of 124 puppies evaluated clinically and echocardiographically, 10 were affected. No significant differences were found between unaffected and affected puppies for blood and myocardial carnitine or taurine concentrations, serum chemical variables, results of ophthalmological examinations, ECGs, or measurement of urine metabolites. Ultrastructural examination of myocardium from affected dogs revealed myofibrillar atrophy and small regions of myofibrillar degeneration, most prominently at the region of the intercalated discs. Only echocardiography allowed detection of affected puppies before clinical signs became evident. Echocardiography revealed a significant difference in the shortening fraction, E point to septal separation, and the end systolic and diastolic left ventricular internal diameters. Affected puppies were detected 1-4 weeks before the development of acute congestive heart failure.

MeSH
Animal; Animals, Newborn; Breeding; Cardiomyopathy, Congestive; Carnitine; Case-Control Studies; Disease Progression; Dog Diseases; Dogs; Echocardiography; Electrocardiography; Myocardium; Physical Examination; Retrospective Studies; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.; Taurine

Author Address
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Effect of carnitine on myocardial function and metabolism following global ischemia.

Abstract
Carnitine has therapeutic potential for the postischemic heart by facilitating the oxidation of acylated fatty acid metabolites, the intracellular accumulation of which has a deleterious effect on myocardial function and metabolism. To test this hypothesis, two groups of dogs were given preischemic treatment with carnitine, 50 mg per kilogram of body weight (Group 1) or 100 mg/kg (Group 2), and were compared with untreated controls (N = 12 for all groups). The canine hearts underwent 30 minutes of global 37 degrees C ischemic arrest with reperfusion. Left ventricular systolic and diastolic function was assessed by an intracavitary balloon while metabolic derangements were quantitated by serial myocardial biopsies assayed for adenosine triphosphate (ATP). Comparable 49 to 53% (p less than 0.01) declines in preischemic ATP levels occurred during the study period in the controls and both experimental groups. However, postischemic systolic left ventricular function was better preserved in Group 2: these hearts generated 61 +/- 3% of preischemic peak developed pressure compared with 37 +/- 4% in the controls and 42 +/- 3% in Group 1 (p less than 0.01 for each), and 60 +/- 2% of preischemic maximum rate of rise of left ventricular pressure as opposed to 45 +/- 4% in the controls and 49 +/- 6% in Group 1 (p less than 0.02 for each). (ABSTRACT TRUNCATED AT 250 WORDS)

MeSH
Adenosine Triphosphate; Animal; Blood Pressure; Carnitine; Coronary Disease; Dogs; Fatty Acids; Heart; Myocardial Contraction; Myocardium; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Signalment, survival, and prognostic factors in Doberman pinschers with end-stage cardiomyopathy.
Calvert CA, Pickus CW, Jacobs GJ, Brown J

Abstract
Congestive heart failure (CHF) was evaluated by retrospective review of case records of 66 Doberman Pinschers presenting with overt signs of 2 weeks' duration or less. Left-sided CHF was predominant, the majority of dogs were male, most were 5 to 10 years of age, and CHF tended to occur in females at an older age. Sudden death occurred in 13 dogs (20%). The mean and median survival times of all dogs were 9.65 and 6.5 weeks, respectively. Both atrial fibrillation and bilateral CHF at the time of presentation were associated with significantly shorter survival times.

MeSH
Age Factors; Angiotensin-Converting Enzyme Inhibitors; Animal; Atrial Fibrillation; Cardiomyopathy, Congestive; Cardiotonic Agents; Carnitine; Death, Sudden, Cardiac; Digoxin; Dobutamine; Dog Diseases; Dogs; Female; Furosemide; Heart Failure, Congestive; Hydralazine; Male; Milrinone; Prognosis; Propranolol; Pyridones; Retrospective Studies; Species Specificity; Survival Rate

Author Address
Department of Small Animal Medicine, College of Veterinary Medicine, University of Georgia, Athens 30602, USA.
L-carnitine supplementation in the therapy of canine dilated cardiomyopathy.
Keene BW

Abstract
In evaluating any novel therapeutic agent or intervention, the clinician must question the need for as well as the efficacy and safety of the proposed therapy. In an attempt to address these critical questions with regard to the role of L-carnitine supplementation in the therapy of dilated cardiomyopathy, this article reviews the currently available scientific evidence and clinical experience regarding carnitine metabolism and supplementation in the dog.

MeSH
Animal; Cardiomyopathy, Congestive; Carnitine; Dog Diseases; Dogs

Author Address
North Carolina State University College of Veterinary Medicine, Raleigh.
Interventional nutrition for cardiac disease.
Freeman LM

Abstract
Animals with cardiac disease can have a variety of nutritional alterations for which interventional nutrition can be beneficial. Deviation from optimal body weight, both obesity and cachexia, is a common problem in cardiac patients and adversely affects the animal. Methods for maintaining optimal weight are important for good quality of life in dogs and cats with cardiac disease. Providing proper diets to prevent excess intake of sodium and chloride also is important, but severe salt restriction may not be necessary until later stages of disease. Certain nutrient deficiencies may play a role in the pathogenesis or complications of cardiac disease, but nutrients also may have effects on cardiac disease which are above and beyond their nutritional effects (nutritional pharmacology). Supplementation of nutrients such as taurine, carnitine, coenzyme Q10, and omega-3 polyunsaturated fatty acids may have benefits in dogs or cats with cardiac disease through a number of different mechanisms. By addressing each of these areas maintaining optimal weight, avoiding nutritional deficiencies and excesses, and providing the benefits of nutritional pharmacology, optimal patient management can be achieved.

MeSH
Animal; Antioxidants; Cachexia; Cat Diseases; Cats; Dietary Supplements; Dog Diseases; Dogs; Fatty Acids, Omega-3; Heart Diseases; Magnesium Deficiency; Potassium Deficiency; Taurine; Ubiquinone; Vitamins

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Nutritional therapy in the treatment of heart disease in dogs.
Dove RS

Abstract
A number of diseases affecting the heart are prevalent in canines. Acquired diseases, those which develop over the course of an animal's lifetime (rather than congenital defects present at birth), have recently been the subject of several studies to determine the efficacy of dietary supplementation on symptom presentation, disease severity, and mortality rates. Specifically, coenzyme Q10 (CoQ10), vitamin E (as alpha-tocopherol), L-carnitine, taurine, and fish oil (omega-3 fatty acids) have all been evaluated in the prevention and treatment of many types of heart disease in dogs. Other supplements with preliminary evidence, meriting further investigation, include magnesium, Crataegus, and the B vitamins. Both clinical observation and interventional trials with various breeds have provided clear evidence for the benefit of numerous supplements on canine heart disease. Appropriate levels of certain dietary nutrients have been shown to increase life span, improve life quality, reduce symptoms and physical evidence of disease, and decrease mortality rates in these animals.

MeSH
Animal; Animal Nutrition; Complementary Therapies; Dietary Supplements; Dog Diseases; Dogs; Heart Diseases

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The acetyl group deficit at the onset of contraction in ischaemic canine skeletal muscle.
Roberts PA, Loxham SJ, Poucher SM, Constantin-Teodosiu D, Greenhaff PL

Abstract
Considerable debate surrounds the identity of the precise cellular site(s) of inertia that limit the contribution of mitochondrial ATP resynthesis towards a step increase in workload at the onset of muscular contraction. By detailing the relationship between canine gracilis muscle energy metabolism and contractile function during constant-flow ischaemia, in the absence (control) and presence of pyruvate dehydrogenase complex activation by dichloroacetate, the present study examined whether there is a period at the onset of contraction when acetyl-coenzyme A (acetyl-CoA) availability limits mitochondrial ATP resynthesis, i.e. whether a limitation in mitochondrial acetyl group provision exists. Secondly, assuming it does exist, we also aimed to identify the mechanism by which dichloroacetate overcomes this "acetyl group deficit". No increase in pyruvate dehydrogenase complex activation or acetyl group availability occurred during the first 20 s of contraction in the control condition, with strong trends for both acetyl-CoA and acetylcarnitine to actually decline (indicating the existence of an acetyl group deficit). Dichloroacetate increased resting pyruvate dehydrogenase complex activation, acetyl-CoA and acetylcarnitine by approximately 20-fold (P < 0.01), approximately 3-fold (P < 0.01) and approximately 4-fold (P < 0.01), respectively, and overcame the acetyl group deficit at the onset of contraction. As a consequence, the reliance upon non-oxidative ATP resynthesis was reduced by approximately 40 % (P < 0.01) and tension development was increased by approximately 20 % (P < 0.05) following 5 min of contraction. The present study has demonstrated, for the first time, the existence of an acetyl group deficit at the onset of contraction and has confirmed the metabolic and functional benefits to be gained from overcoming this inertia.