demonstrated in several respects. Cardiac arrhythmia may be the first clinical presentation in children with fatty acid oxidation disorders.[25] Experimental models have demonstrated that buildup of acylcarnitines and other intermediates promote dysregulation of calcium resulting in dysrhythmias.[26] Ischemic injury in myocardial infarction has also been associated with the buildup of these intermediates promoting arrhythmogenesis. Meanwhile, shorter chain metabolites such as acetyl-CoA and palmitoyl-CoA do not promote arrhythmogenesis.[26,27]

The potential for statin drugs (HMG-CoA reductase inhibitors) to exert an antiarrhythmic effect on the heart has been an area of research interest. Statins reduce recurrences of supraventricular and ventricular arrhythmias in patients with and without coronary artery disease. Several mechanisms have been proposed for this antiarrhythmic effect, yet none have been proved. Hypotheses include: lowering of LDL cholesterol, improved endothelial function, stabilization of atherosclerosis, anti-inflammatory effects, modulation of membrane ion flux, and improvement of autonomic function.[28,29] Experiments using other antilipidemic agents have not shown similar antiarrhythmic effects; therefore something unique about statins must give them their antiarrhythmic properties, rather than their LDL lowering or atherosclerosis stabilizing effects.

Statin drugs inhibit the effect of the *HMG-CoA reductase* enzyme, leading to an upstream increase in metabolic substrates, especially CoA. It may be that buildup of CoA is responsible, in whole or in part, for the antiarrhythmic effects of statins or for an improvement in autonomic function.

Therapeutic plausibility for the effect of CoA/pantethine/PA on cardiac dysrhythmias is present in the medical literature. Since biochemical and therapeutic plausibility exists for use of either PA/pantethine or choline singly, the potential exists for their combined effect to be greater than the sum of its parts. This is the principle of the MAP.

Protocol, Materials, and Dose Escalation

The principle of the MAP treatment is to give the two essential nutrient precursors for the endogenous production of ACh. These two nutrients are choline and pantothenic acid or pantethine. At various times we have preferred various forms of these two essential ingredients.

Our current preference is to implement the protocol using choline bitartrate and pantethine.

Our preference for choline bitartrate developed due to its high solubility in water, its potency, and the challenges in sourcing a lecithin product that is not genetically modified. Furthermore, a significant number of patients are soy or egg sensitive and most lecithin products in the marketplace are soy or egg derived. Our preference for pantethine over pantothenic acid (PA) comes from our observation that some patients do not respond to PA, though they do respond to pantethine.

We used to begin the protocol with PA due to the fact that it is considerably less expensive than pantethine; if a patient did not respond to PA, we would then switch to pantethine. We now tend to work in the reverse. We know that if we escalate through the dosing stages of MAP using pantethine and the arrhythmia does not come under control, MAP will not likely work for that patient. Conversely, if we can gain control of the arrhythmia using pantethine and choline, we can then try a switch to PA if the patient desires a lower cost option.

Achieving a delivery system which keeps the substrates at constant blood levels is a challenge. As discussed, if we want to ensure that adequate levels of precursors are available to be therapeutic, they must persist at reasonable blood concentrations at all times. We have found only one way to provide this type of steady state and that is to dose the nutrients in a beverage which the patient can drink continuously throughout the day.

We instruct patients to mix their nutrients in a 32 fluid ounce (fl. oz.), drinking bottle with water at the beginning of the day. Assuming that the patient is awake for 16 hours per day, we divide the day into 4-hour segments. During the first 4 hours of the day the patient drinks 4 fl. oz. of the beverage, between hours 5 to 8 they drink 8 fl. oz., during hours 8 to 12 they drink another 8 fl. oz., and during their final 4 hours awake they drink 12 fl. oz., ensuring adequate levels overnight (Table 1).

The MAP dosing works in a three-stage dose escalation (Table 1). At stage 1 we deliver 500 mg of pantethine and 2000 mg of choline per day. Due to the very short half-life of ACh we are able to tell within one week whether this dose is adequate. If the patient achieves complete symptomatic or objective improvement over the course of the first week then the MAP is maintained at stage 1; if not, we escalate to stage 2. Stage 2 dosing is 1000 mg of pantethine and 4000 mg of choline; after one week we reassess. If resolution of symptoms or objective findings is complete or near complete we stop at stage 2, otherwise we escalate to stage 3. Stage 3 dosing is 1500 mg of pantethine and 6000 mg of choline. Reassessment is made after one week in the same manner as previous stages. It is rare that more than 1500 mg of pantethine will demonstrate further benefit, though we have had patients who needed to escalate the initial dose of choline up to 10 grams before coming under rhythm control. After several weeks of a persistent symptom-free/arrhythmia-free period, a down titration can be attempted to find the lowest effective dose that maintains the arrhythmia resolution. When PA is substituted for pantethine, it is used at ➤

Table 1: MAP Dosage Forms, Dose Escalation, and Delivery Method

	Pantothenic acid/Pantethine	Lecithin/Choline Bitartrate
Stage 1	1000 mg/500 mg	2 Tablespoons/2000 mg
Stage 2	2000 mg/1000 mg	4 Tablespoons/4000 mg
Stage 3	3000 mg/1500 mg	6 Tablespoons/6000 mg

*** Mixed with a sufficient quantity of water to make 32 fluid ounces (fl. oz.).
This beverage is drunk throughout the day according to the follow schedule:

Awake Hours	Drink this Amount
Hours 1–4	4 fl. oz.
Hours 5–8	8 fl. oz.
Hours 9–12	8 fl. oz.
Hours 13–16	12 fl. oz.