Validation of Mean Arterial Pressure as an Indicator of Acute Changes in Cardiac Output

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Changes in mean arterial pressure (MAP) are often assumed to reflect changes in cardiac output (CO). A linear relationship is postulated to exist between these two quantities based upon the circuit model for systemic circulation. Previous studies have correlated changes in CO and MAP. However, to our knowledge, no studies have tested the relationship between CO and MAP *in vivo* without changes in systemic vascular resistance. Research on baroreceptor stimulation and vasomotor response has shown that vasomotor tone changes 15 to 60 seconds after an acute change in CO. Maximal activation of vasomotor response occurs after approximately 30 seconds. Thus MAP should correlate directly with CO during acute changes (<15 seconds). To test this, we examined the relationship between CO and MAP during 10 second occlusions of the inferior vena cava in anesthetized pigs. A linear relationship existed between CO and MAP in seven pigs (%MAP = 0.60[%CO] − 0.41, $p = 0.0001$). This study validates the use of MAP as an indicator of acute changes in CO. Fluctuations in MAP correlate well with acute changes in CO in the absence of changes in vascular tone. *ASAIO Journal* 2005; 51:22–25.

Important hemodynamic variables of the systemic circulation are cardiac output (CO), systemic vascular resistance (SVR), and arteriovenous pressure gradient (between the left ventricle and right atrium).[1–3] Substituting mean arterial pressure (MAP) for the pressure gradient, these are related by an adapted version of Ohm's Law:[1,2]

$$MAP = CO \cdot SVR$$

This assumes that right atrial pressure is 0. SVR is thus defined as the ratio of MAP to CO. Because MAP represents the mean hydrostatic pressure gradient within the entire vascular tree,[3] it should vary linearly with CO if SVR remains constant.[4] In the clinical setting, fluctuations in MAP are often assumed to directly reflect changes in CO, which is usually measured by invasive means. This relationship, however, has not been verified with intact reflexes and constant SVR.

Previous laboratory studies have assessed the importance of SVR in the MAP/CO relation and have postulated that it is curvilinear. In a study that varied MAP while applying constant positive pressure to the carotid sinuses, CO and MAP were related by a curve convex to the pressure axis.[5] A second study using pump controlled flow of 60–140 ml/min kg^{-1} with intact baroreflex response demonstrated a relation that was also convex to the pressure axis.[6] However, both studies showed that after carotid sinus denervation and bilateral vagotomy, the pressure flow relation was linear. The duration of these studies was 5–30 minutes, and Fick based cardiac output measurements took approximately 30 seconds for each reading.

Both of these studies, however, fail to minimize changes in SVR while testing the CO/MAP relation. Stimulation of the baroreceptors and the carotid sinus receptors has been shown to be the primary effector of changes in MAP.[7] One study reported that under steady state conditions, changes in CO account for less than 10% of changes in blood pressure; the remaining 90% are attributed to baroreceptor activation.[8,9] A study of autoregulation of the total systemic circulation in decapitated dogs demonstrated that during sustained acute changes in MAP of between 25 and 50 mm Hg, changes in SVR facilitated a gradual return to steady state control values of CO, oxygen consumption, and arteriovenous oxygen difference within approximately 35 minutes.[10] A second study showed that before denervation, the vascular bed responded to changes in CO using pressure regulation, whereas after denervation, flow regulation was observed instead.[11] Because SVR can have such drastic effects upon MAP and CO, in determining the true relationship between these variables, changes in vasomotor tone must be minimized while SVR and the nervous reflexes remain intact.

Changes in CO resulting from physical exercise do not affect SVR for at least 15–60 seconds after the onset of muscular stimulation.[12] Studies of hemorrhage and shock have shown that maximal activation of the vasomotor response occurs approximately 30 seconds after a detectable change in CO or MAP.[13] Thus changes in SVR should not be present during the first 15 seconds after a change in CO or MAP.

In this experiment, both MAP and CO were measured during acute decreases in CO in pigs. Trials lasted 10 seconds to avoid any effects of changes in SVR. We sought to determine the relationship between CO and MAP and to verify whether current clinical use of **Equation 1** to predict changes in CO based upon changes in MAP is indeed valid. Such a validation could be of clinical value.

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Submitted for consideration June 2004; accepted for publication in revised form October 2004.

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DOI: 10.1097/01.MAT.0000150506.36603.1B

Materials and Methods

All animals received humane care in compliance with the *Principles of Laboratory Animal Care* developed by the Institute of Laboratory Animal Resources and the *Guide for the Care and Use of Laboratory Animals* written by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication number 85–23, revised 1985).

Surgical Preparation

Seven domestic pigs (35–65 kg) were anesthetized using ketamine hydrochloride (20 mg/kg intramuscular), xylazine hydrochloride (0.5 mg/kg intramuscular), and atropine sulfate (2 mg/kg intramuscular). Pigs were intubated and mechanically ventilated. Anesthesia was maintained with inhalation isoflourane (1.75–2.25%) mixed with 100% oxygen to avoid cardiovascular effects of xylazine. Electrocardiogram leads were attached to the limbs, a 0.9% saline infusion was started, and the left femoral artery was instrumented with an 18 guage angiocatheter attached to a pressure transducer to measure MAP. Midline sternotomy and longitudinal pericardiotomy were performed, and an ultrasonic flow probe (Transonic Systems Inc., Ithaca, NY), validated for measurement of CO by Dean *et al.*,[14] was filled with acoustic coupling gel and placed around the ascending aorta. The inferior vena cava (IVC) was isolated and an umbilical tape snare placed around it proximal to the diaphragm.

Inferior Vena Cava Occlusion

Immediately preceding occlusion of the IVC, all instrumentation was calibrated and checked for accuracy. Mechanical ventilation was stopped to prevent respiratory cycle associated fluctuations in CO and MAP. The snare around the IVC was then tightened, reducing venous return to the heart and causing an acute drop in CO. CO and MAP were measured during the occlusion for a 10 second period (**Figure 1**). The snare was then released, and mechanical ventilation was resumed 5 seconds after occlusion. A minimum of two occlusions were performed on each animal. Following experimentation, all pigs were humanely killed.

Data Recording

Analog data for electrocardiogram, mean arterial pressure, and aortic flow velocity were digitized at 200 Hz using an analog to digital converter (Chart v3.6.3/s software, Powerlab 16SP; ADInstruments Inc., Milford, MA) and recorded on a digital computer (Power Macintosh 7100/66; Apple Computer, Cupertino, CA) (**Figure 1**).

Data Analysis

The aortic flow velocity profile was integrated between R-wave peaks to obtain a measurement of CO, and the arterial pressure waveform was integrated as well to determine the corresponding MAP measurements for each heartbeat during the first 10 seconds after occlusion of the IVC. Baseline MAP and CO data were recorded during the 5–10 seconds immediately preceding each occlusion of the IVC to later calculate percent change in CO and MAP.

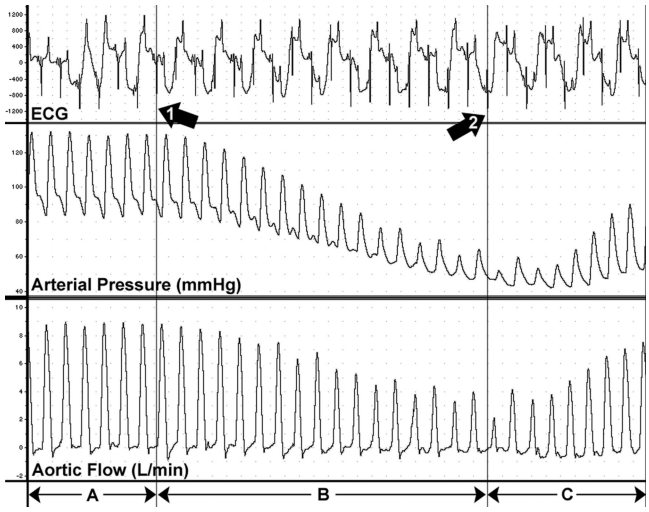

Figure 1. Representative data tracings from Chart 3.6.3/s. Baseline CO and MAP measurements were obtained from interval A. Data collection begins at arrow 1 and ends at arrow 2. Interval B contains the 17 heartbeats analyzed in the experiment. Interval C represents the recovery period. CO, cardiac output; MAP, mean arterial pressure.

Statistical Analysis

Percentage changes in CO *versus* percentage changes in MAP were modeled *via* the PROC MIXED procedure in SAS (SAS Institute Inc., Cary, NC). Because of the fact that repeated measurements within animals may be correlated, this procedure allows one to model this "correlation structure" as a covariance pattern. This accurate estimate will allow for improved estimates of the standard errors of measurement and therefore more powerful tests. A likelihood ratio test or a procedure known as Akaike's information criterion[15] is used to discern which covariance pattern allows for the best fit. We therefore chose the "compound symmetry" structure, for correlations that are constant for any two points in time. Regression equations were then generated with adjusted standard errors.

Results

Representative tracings from an IVC occlusion are presented in **Figure 1**. Section A illustrates baseline values of CO and MAP. At arrow 1, both arterial pressure and aortic flow begin to decrease because of vena caval occlusion. At arrow 2, IVC occlusion stops, establishing interval B, which corresponds to the section of data used for analysis. Interval C represents the recovery period after the vena caval snare was released. Peripheral MAP peaks occur after aortic flow peaks as the pressure catheter is downstream of the aortic flow probe. There is no visible change in heart rate, further supporting the assumption that no systemic reflex responses occurred in the 10 second interval tested. A total of 17 cardiac cycles are present in interval B in **Figure 1**. Neither MAP nor CO is restored to baseline values immediately after release of the IVC snare

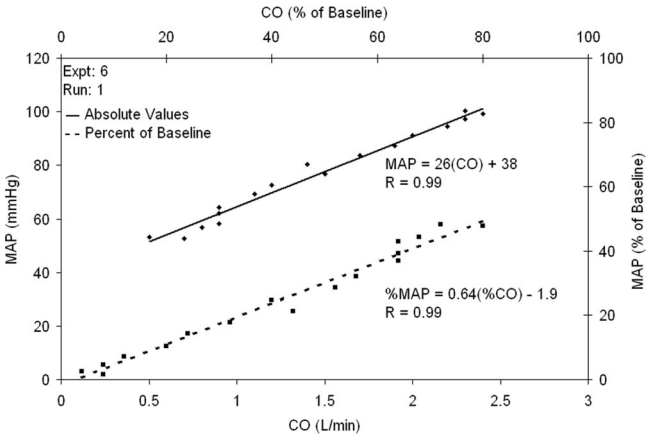

Figure 2. CO/MAP relation from **Figure 1** for 17 beat vena caval occlusion is represented by solid black trendline. CO/MAP data are reexpressed as percentage of baseline value on the axes at the top and right of the graph and are represented by the broken trendline. Linear regression equations and correlation coefficients are provided. CO, cardiac output; MAP, mean arterial pressure.

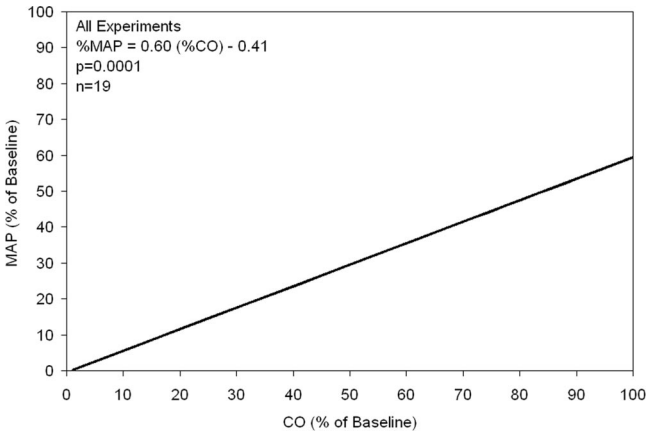

Figure 3. Overall CO/MAP relation for 19 IVC occlusions in seven experiments expressed as a percentage of baseline values. Linear regression equation and *p* values are provided. CO, cardiac output; MAP, mean arterial pressure; IVC, inferior vena cava.

because blood must first travel through the pulmonary circuit before CO and MAP return to normal physiologic values.

Figure 2 illustrates the relation between CO and MAP for each of the 17 heartbeats illustrated in **Figure 1**. The solid trendline represents unaltered, nonnormalized data, found to exist in the relation MAP = 26.14 (CO) + 38.45 (r = 0.99). A linear relation was found in all other experiments as well. The broken trendline in **Figure 2** shows CO and MAP as a percentage of baseline values. These normalized data exist in the relation %MAP = 0.64 (%CO) − 1.86 (r = 0.99). Similar data were recorded for all IVC occlusions in all experiments and underwent the same analysis.

Analyses were performed for all IVC occlusions in all experiments (n = 7) as well as for IVC occlusions 1, 2, and 3 individually. **Table 1** illustrates the corresponding relations that were obtained upon statistical analysis as well as the corresponding error measurements. **Figure 3** illustrates the universally obtained direct relationship found between percentage change in CO and percentage change in MAP. No statistically significant difference was noted between IVC occlusions 1, 2, and 3 in all experiments ($p = 0.0001$).

Discussion

The results of this experiment demonstrate that in the absence of changes in SVR, a clear linear trend exists between CO and MAP during acute decreases in CO in pigs. Statistical analysis reveals that percentage changes in CO are related to percentage changes in MAP by the equation %MAP = 0.60 (%CO) + 0.41. Overall, these data support MAP as a valid indicator of changes in CO when SVR is constant. During the first 10 seconds of fluctuations in CO, MAP should vary with CO. After 15 seconds or more, however, a baroreceptor response is likely to alter this linear relationship.[8,12,13]

Table 1. Linear Regression Equations for Percentage of Baseline Analysis

	Equation	n	*p*
Run 1	%MAP = 0.60 (%CO) + 0.25	7	0.0001
Run 2	%MAP = 0.63 (%CO) − 1.62	7	0.0001
Run 3	%MAP = 0.58 (%CO) + 0.91	5	0.0001
Average	%MAP = 0.60 (%CO) − 0.41	7	0.0001

n = number of animals. MAP, mean arterial pressure; CO, cardiac output.

Previous studies have suggested that the CO/MAP relation is not linear while baroreflex responses are intact. However, the duration of data collection in these experiments was so long (several minutes) that changes in SVR assuredly occurred. This might explain the curvilinear relationship between CO and MAP seen by Sagawa and Eisner[5] and Levy *et al.*[6] during their experimentation.

Studies have also suggested that in the presence of vascular reflex responses, changes in CO account for less than 10% of changes in the arterial blood pressure, with the remaining 90% attributed to changes in vascular tone.[8,9] Experiments in which the baroreceptors are directly stimulated or in which arterial pressure is the controlled variable are thus subject to substantial error because of dynamic changes in SVR.[3,13,16] Our study, however, varied CO and tested the relation before any reflex changes could occur. Additionally, we noted no statistically significant difference in the CO/MAP relation between IVC occlusions in each pig despite the findings of a previous study that indicated that subsequent measurements of the CO and MAP relationship in the same animal over the course of hours can yield curves with significantly different slopes.[4]

Some authors maintain that occlusion of the IVC artificially changes SVR with secondary effects upon CO and MAP. Guyton *et al.*[16] found that the effect of changes in venous resistance upon CO and MAP is eight times less than equivalent changes in arterial resistance. Venous capacitance has been shown to be 18 to 30 times greater than arterial capacitance.[17] Thus occlusion of the IVC during 10 second testing intervals allows for storage of blood in the venous tree without producing noticeable changes in afterload, which would drastically change CO and MAP.[1,17,18]

The data obtained in our experiment imply that changes in MAP within 15 seconds of an intervention can be used to

estimate changes in CO. Examples of such interventions include clinical protocols in which biventricular pacing may be optimized. A variety of atrioventricular and ventricular-ventricular delays can be tested within 15 second time intervals. Acute changes in MAP can be considered to reflect any changes in CO caused by these pacemaker protocol changes. Initial attempts to apply this principle in clinical data on biventricular pacing have shown low correlation coefficients, reflecting scatter in the data and small absolute changes in CO. These studies are continuing.

Clinically, SVR is quite variable. Many patients undergoing cardiac surgery exhibit signs of extremely low SVR immediately after separation from cardiopulmonary bypass that can only be corrected through use of vasoactive drugs.[19] Both patients with diabetes and patients with preoperative ejection fractions of less than 40% often show higher SVR levels postoperatively than patients with less compromised circulatory physiology because of increased preoperative SVR.[19,20] This suggests that acute compensatory fluctuations in SVR are limited in magnitude and duration and that an adaptive mechanism is required to alter SVR for prolonged periods in patients with initially lower SVR levels. Because SVR cannot be changed sufficiently by CO and MAP alone to maintain patient stability in these cases, pharmacologic support is required to keep patients with a need for large changes in vasomotor tone viable.[19,21] Using fluctuations in CO and MAP to predict changes in SVR is therefore not a reliable method because there are confounding factors affecting the body's baroreflex control mechanism.

Future studies would be useful in clarifying whether the CO-MAP relationship is maintained under other physiologic circumstances. These studies most significantly might include an evaluation of the relationship in chronic heart failure to determine whether it is affected by alterations in the renin-angiotensin axis and other feedback mechanisms. A series of IVC occlusions performed in severely hypertensive pigs might also be useful to determine whether increased vascular filling pressures produce an altered relationship in extreme values of CO. Testing at extreme pressures when vessels are distended might reveal a different relationship between the CO-MAP values beyond the values for MAP tested in this experiment. In addition, studies involving acute increases in CO might be valuable in demonstrating that this equation works in the opposite manner in which it was tested in this experiment.

The use of MAP for assessing changes in CO has been validated in this experiment for acute changes (duration < 10 seconds) from baseline vital signs. We feel confident that in the first 10 seconds of fluctuations in CO, MAP will accurately reflect these changes without the interference of SVR.

Acknowledgment

Supported in part by the National Heart, Lung and Blood Institute of the National Institute of Health (RO1 HL 48109 to Dr. Spotnitz) and in part by the Department of Surgery, Columbia University College of Physicians and Surgeons.

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