PAPERS AND SHORT REPORTS

Cardiac output during labour

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Abstract

Serial measurements of cardiac output and mean arterial pressure were performed in 15 women during the first stage of labour and at one and 24 hours after delivery. Cardiac output was measured by Doppler and cross sectional echocardiography at the pulmonary valve. Basal cardiac output (between uterine contractions) increased from a prelabour mean of 6·99 l/min to 7·88 l/min at ≥8 cm of cervical dilatation as a result of an increase in stroke volume. Over the same period basal mean arterial pressure also increased. During uterine contractions there was a further increase in cardiac output as a result of increases in both stroke volume and heart rate. The increment in cardiac output during contractions became progressively greater as labour advanced. At ≥8 cm of dilatation cardiac output increased from a basal mean of 7·88 l/min to 10·57 l/min during contractions. There were also further increases in mean blood pressure during contractions. One hour after delivery heart rate and cardiac output had returned to prelabour values, though mean arterial pressure and stroke volume remained raised. By 24 hours after delivery all haemodynamic variables had returned to prelabour values.

Haemodynamic changes of the magnitude found in this series are of considerable clinical relevance in managing mothers with complicated cardiovascular function.

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Introduction

Two thirds of maternal deaths from heart disease occur during or shortly after labour[1] but the changes in cardiac output at these times are uncertain. Some studies have suggested that basal cardiac output (between contractions) increases during the first stage of labour,[2-4] whereas others have found no appreciable change.[5,6] The effect of uterine contractions on cardiac output also remains unclear, reported increases ranging from 1%[7] to 31%.[2] Most studies have used the invasive dye dilution method which assumes stable flow during the period of recording (20-25 seconds), but such an assumption may not be valid during uterine contractions. Serial investigations during labour have been performed on supine subjects in whom caval compression by the gravid uterus may have reduced cardiac output.[7] No serial study of haemodynamic changes has been performed in the lateral position.

Cardiac output may be derived from combined measurement of blood velocity by Doppler ultrasonography and valve area by cross sectional echocardiography. The method has been validated in vivo[8,9] and allows reproducible non-invasive measurement of stroke volume in the lateral position.[9] It has the additional advantage that cardiac output may be measured over short intervals. We have used this technique to reassess in the lateral position serial changes in cardiac output occurring during labour and in the early puerperium.

Subjects and methods

Fifteen healthy women with uncomplicated singleton pregnancies were recruited at random from the antenatal clinic at between 38 and 39 weeks of gestation. The mean age of the group was 26 years (range 21-34) and there were seven primigravidas. The experimental protocol was approved by the ethical committee of Newcastle Health Authority and each subject gave informed consent. We explained that the technique was non-invasive and entailed only placing an ultrasound transducer on the thoracic wall at intervals during labour. In seven women labour was induced by amniotomy and oxytocin because of postmaturity. All women subsequently had an uncomplicated labour and a spontaneous vertex delivery. Pethidine and nitrous oxide and oxygen were given for analgesia. Syntometrine (ergometrine maleate and oxytocin) was given routinely at the time of delivery.

Measurements were performed in the left semilateral position. Women admitted for induction of labour were investigated before amniotomy.

During labour recordings were made at ≤3 cm, 4-7 cm, and ≥8 cm of cervical dilatation both in the basal state (between contractions) and at the peak of a contraction (when maximal haemodynamic changes occurred). Investigations were completed in less than 10 minutes, during which the subject remained in the semilateral position. Further recordings were made one and 24 hours after delivery. During the first stage of labour flow was most easily recorded at the pulmonary valve. During the second stage, however, changes in position and breathing caused lung echoes to override the pulmonary artery so that comparable recordings could not be obtained.

All investigations were performed with a Hewlett-Packard model 77020A echocardiographic system incorporating a 3·5 MHz cross sectional and pulsed Doppler transducer. Doppler velocity output and an electrocardiogram were recorded at a paper speed of 100 mm/s. Pulmonary velocities were obtained from the parasternal short axis plane.[8] Velocity integral was determined by tracing from the baseline around the velocity curve using a digitising tablet linked to a microcomputer.[8] Eight to 10 beats were averaged for each determination.

The diameter of the pulmonary artery was measured during systole at the level of the pulmonary orifice. Measurements were performed at the time of the initial investigation and then after delivery. Diameters from five consecutive beats were averaged and the cross sectional area calculated from the equation $\pi \times (D/2)^2$, where D = mean pulmonary artery diameter. Heart rate was determined directly from the R-R interval of the electrocardiogram. Cardiac output was then calculated according to the formula: cardiac output (l/min) = stroke volume (ml) × heart rate (beats/min)/1000, where stroke volume (ml) = velocity integral (cm) × cross sectional area (cm^2).

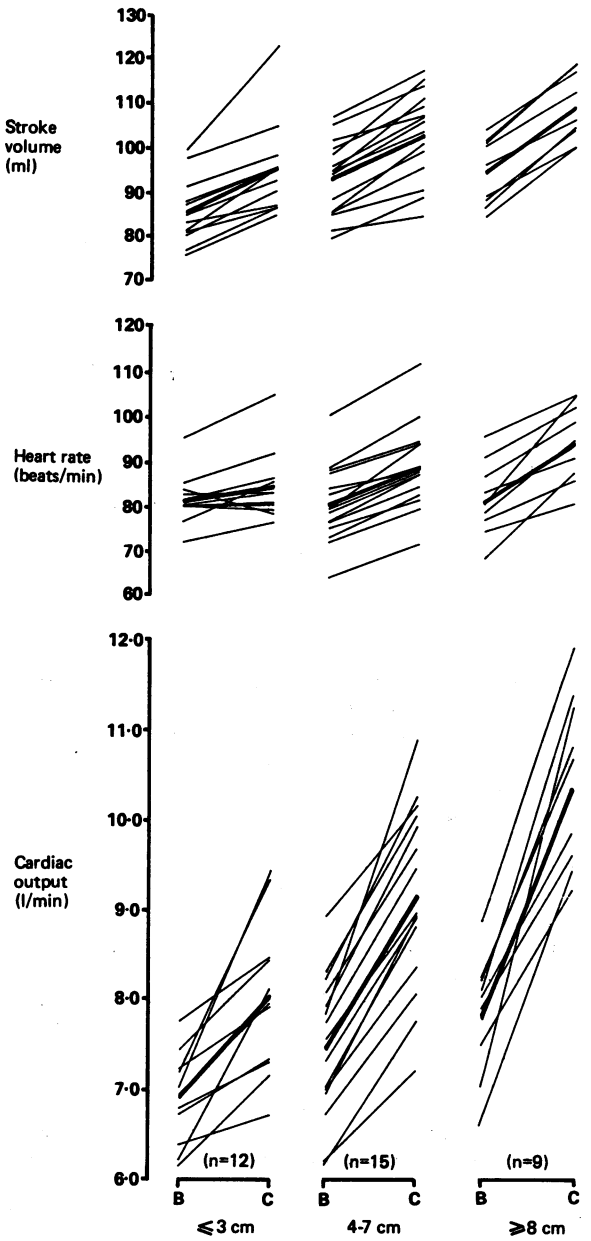
Blood pressure was measured with an automatic sphygmomanometer (Datascope 203Y). Mean arterial pressure was determined by the oscillometric technique.

Analysis of variance was performed for each variable by using the statistical package Genstat. The package estimated individual missing observations with values that minimised the residual sum of squares.[10]

TABLE I—*Haemodynamic findings between contractions*

Case No	Before labour	First stage of labour			After delivery	
		≤3 cm	4-7 cm	≥8 cm	1 Hour	24 Hours
			Stroke volume (ml)			
1	93		95		95	94
2	87		96		97	90
3	81		96	97	102	98
4	82	80	78		80	80
5	75	77	86	87	83	82
6	87	87	95	102	103	102
7	93	99	106	103	104	94
8		83	86	85	111	100
9		81	81	90	96	92
10		76	86	90	90	86
11		97	101	105	96	82
12		85	108	102	110	101
13		88	99		107	96
14		92	102		97	81
15		81	89		104	71
			Heart rate (beats/min)			
1	86		88		84	75
2	76		72		66	86
3	73		65	69	70	69
4	98	95	89		87	100
5	77	79	79	81	82	77
6	81	82	83	78	67	74
7	80	72	77	79	80	86
8		80	84	97	73	73
9		85	98	92	90	77
10		84	73	84	78	74
11		79	76	76	65	64
12		80	77	87	75	70
13		80	79		72	85
14		80	87		74	89
15		76	80		70	91
			Cardiac output (l/min)			
1	8·01		8·34		8·04	6·99
2	6·58		6·88		6·40	7·73
3	6·04		6·22	6·67	7·03	6·80
4	7·99	7·60	6·94		6·99	8·08
5	5·71	6·10	6·93	7·10	6·85	6·30
6	7·01	7·17	7·92	8·06	6·89	7·53
7	7·45	7·15	8·12	8·13	8·29	8·06
8		6·65	7·29	8·29	8·13	7·06
9		6·90	7·74	8·24	8·55	7·06
10		6·32	6·23	7·55	7·04	6·31
11		7·68	7·60	7·96	6·28	5·27
12		6·75	8·25	8·94	8·21	7·10
13		7·01	7·86		7·76	8·16
14		7·37	8·94		7·31	7·24
15		6·16	7·08		7·34	6·50

Because of the problem of multiple significance testing differences between time points were compared by using the studentised range at the 1% level[11] (range = $q_{(v)} \times [s \div \sqrt{n}]$, where $q_{(v)}$ = critical value for comparing two time points and s^2 = residual mean square with v degrees of freedom). Thus any change greater than the studentised range was considered to be significant.



Stroke volume, heart rate, and cardiac output during uterine contractions at ≤3cm, 4-7 cm, and ≥8 cm of cervical dilatation. Change in mean values shown by darker line. B = Basal. C = Contractions.

Results

Three of the patients in whom labour was induced had progressed beyond 3 cm of dilatation by four hours after amniotomy and therefore data at ≤3 cm of dilatation were available from a total of 12 women. Adequate pulmonary velocities were obtained from only nine subjects at ≥8 cm of dilatation. No significant haemodynamic differences were found between primigravidas and multiparas or between induced and spontaneous labours. There were no significant differences between measurements made before labour and those made between contractions at ≤3 cm of dilatation, and therefore basal values were compared with values obtained before labour.

Measurements of diameter were obtained in all patients. Mean calculated pulmonary artery areas (SD) were: before labour or in early labour 7·15

(0·35) cm², one hour after delivery 7·19 (0·32), 24 hours after delivery 7·07 (0·30). These means did not differ significantly when analysed by an F test.

Basal values (between contractions)—Table I gives the individual data for stroke volume, heart rate, and cardiac output in the 15 subjects and table II the corresponding means at each time point. Cardiac output increased during the first stage of labour from a prelabour mean of 6·99 l/min to 7·88 l/min at ≥8 cm of dilatation. This increase in cardiac output was due to an increase in stroke volume, there being no significant change in heart rate. Mean arterial pressure showed a corresponding increase during the first stage of labour. Stroke volume remained raised one hour after delivery, falling between one and 24 hours. Heart rate and cardiac output, however, had returned to prelabour values by one hour after delivery. The increase in mean arterial pressure found at the end of the first stage persisted for at least the first hour after delivery before falling to prelabour values at 24 hours.

During contractions—The figure shows the individual data for stroke volume, heart rate, and cardiac output during contractions and table II the corresponding means at each dilatation. Relative to basal values cardiac output increased during contractions. The increment in cardiac output became progressively greater as labour advanced: 1·14 l/min at ≤3 cm, 1·75 l/min at 4-7 cm, and 2·69 l/min at ≥8 cm of dilatation. At ≤3 cm of dilatation the increase in cardiac output during uterine contractions was primarily due to an increase in stroke volume, whereas later both stroke volume and heart rate increased. Mean arterial pressure increased during contractions at each dilatation.

TABLE II—*Mean haemodynamic values. (Figures in parentheses are mean values during uterine contractions)*

	Before labour	First stage of labour			After delivery		SEM (from analysis of variance)	Studentised range*
		≤3 cm	4-7 cm	≥8 cm	1 Hour	24 Hours		
No of subjects	7	12	15	9	15	15		
Stroke volume (ml)	85·3	85·8 (95·4)	93·8 (103·1)	95·5 (110·5)	97·9	90·0	1·7	6·5
Heart rate (beats/min)	81	80 (84)	80 (89)	83 (96)	76	79	2	6
Cardiac output (l/min)	6·99	6·89 (8·03)	7·49 (9·24)	7·88 (10·57)	7·41	7·08	0·18	0·68
Mean arterial pressure (mm Hg)	82	84 (93)	86 (94)	91 (102)	92	80	2	6

*Changes between any two time points considered statistically significant if difference between means exceeded studentised range (see text).

Discussion

In this study, the first to report the use of Doppler ultrasound for determining maternal cardiac output serially during labour, an attempt has been made to eliminate inaccuracies caused by maternal posture. As methodological factors are likely to be responsible for a substantial proportion of the confusion in existing reports, it is essential that some assessment should be made of the reliability of the data presented here.

Intraobserver and hour to hour coefficients of variation with the technique are less than 5%.[9] Values obtained for resting cardiac output before labour in this study did not differ significantly from those previously reported by us using the same methodology at 38 weeks of gestation[12] and were within the range reported by workers using other techniques in the left lateral position during late pregnancy.[4 13] An important assumption in our study is that there was no change in pulmonary artery area throughout labour. Increases in stroke volume such as we found might have been expected to increase the area slightly[14] but no significant increase was evident after delivery despite a mean increase in stroke volume of 15%. The maximum increase in stroke volume detected during the first stage of labour was 29%, and thus it seems likely that underestimates arising from this assumption were small.

Basal cardiac output in this study increased by 12% towards the end of labour. Other studies performed in the supine position have had conflicting results, some agreeing with these findings[3 4] and others showing no appreciable change.[5 6] Maruta was the only worker to shown an increase in basal heart rate during the first stage of labour.[6] His investigations were performed at 7-8 cm of dilatation in mothers who had received no analgesia.

Most workers have reported an increase in cardiac output in the supine position during uterine contractions. There is, however, no unanimity about the magnitude and timing of these increments. Ueland and Hansen found similar increments early and late in the first stage of labour.[3] On the other hand, Kjeldsen reported an increase in the increments of cardiac output up to 7 cm of dilatation but no further increase thereafter.[4] Both studies showed that cardiac output increased as a result of increases in stroke volume, though Kjeldsen suggested that the increment in stroke volume was smaller after 7 cm of dilatation. In our study the maximum increase in cardiac output and stroke volume during contractions occurred at ≥8 cm of dilatation. The increment in cardiac output was greater than any previously reported in the first stage of labour. This may be explained by the effect of posture.[7] Two studies have investigated small numbers of subjects in the lateral position early in labour. Kjeldsen reported increases in cardiac output during contractions of comparable magnitude to those found here[4] but Ueland and Hansen reported smaller increases in stroke volume and cardiac output.[15] Surprisingly, their results appeared to show that haemodynamic changes during contractions were considerably greater in the supine position.

Conversely, in our study changes in cardiac output and stroke volume one hour after delivery, as compared with prelabour values, were smaller than those previously reported.[3-5] Once again this may be attributable to the effect of posture.[16] By 24 hours after delivery cardiac output and stroke volume were no longer significantly increased. Other studies using the same methods of investigation have suggested that stroke volume and cardiac output remain at values similar to those found before labour for at least 48 hours after delivery.[17]

The changes in mean arterial pressure in our series confirm reports of a progressive rise in blood pressure during the first stage of labour[4 18] and a further increase during uterine contractions.[3-5] Few studies have repeated blood pressure measurements after delivery. An increase in blood pressure, relative to the prelabour value, one hour after delivery was also reported by Ueland and Hansen but no other puerperal measurements were performed.[3]

Haemodynamic changes of the magnitude described are of considerable clinical relevance in managing women with complicated cardiovascular function. Presumably they are in part a consequence of displacement of blood from the extensive choriodecidual reservoir which is present during late pregnancy. This is clearly a subject for detailed investigation in the future.

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SHORT REPORTS

Cyclical sequential hormonochemotherapy in advanced breast cancer

Endocrine treatment or chemotherapy is widely used for patients with breast cancer, and the response rate remains more or less constant at about 30-40%. Using hormonal treatment to render the cancer cells more susceptible to cytotoxic chemotherapy was proposed by Lippman[1] and Allegra *et al.*[2] We report using oestrogen at a physiological concentration to bring stem cells out of the resting phase and to stimulate cell division into partial synchrony. High dose progestogen is then given, which, by reducing the receptor state of the cancer cells, is designed to enhance their susceptibility to the subsequent cytotoxic chemotherapy. This was administered cyclically and sequentially at three week intervals in accordance with the stem cell kinetic data of Skipper[3] and Hill.[4]

Patients, methods, and results

Forty women presenting with advanced breast cancer were treated with our regimen. All were postmenopausal (mean age 63 (SD 11) years), with the exception of two patients aged 30 and 36. The diagnosis of advanced breast cancer was based on finding one or more of the following: metastases in bone (eight cases), lung (six), or liver (seven) or fixity of axillary lymph nodes (17) and large tumour size (mean 7·5 (SD 3·9) cm).

Patients received three double cycles of hormonochemotherapy. Hormonal treatment was initiated with ethinyloestradiol for one week (10 μg/day) followed by medroxyprogesterone acetate for two weeks (500 mg/day intramuscularly). At the end of the first three week period of hormonal treatment the patient received a bolus injection of vincristine (2 mg intravenously) and an infusion of doxorubicin (50 mg intravenously). The hormonal treatment was then repeated for a further three weeks—that is, one week of oestrogen, two weeks of progestogen—at the end of which an infusion of cyclophosphamide (500 mg), methotrexate (50 mg), and 5-fluorouracil (500 mg) was given. This constituted one double cycle, and patients received three of these cycles. Response to treatment was assessed according to criteria of the International Union Against Cancer.[5]

Thirty four of the 40 patients completed three double cycles of treatment. Of these, 16 showed a complete response, 15 a partial response, and only three no response, giving an overall response rate of 91%. The six patients who did not complete the treatment died of their disease before they had finished one cycle. The mean disease free interval for patients showing a complete response was 22·0 months and was significantly longer ($p<0·05$) than the 11·6 months for partial responders.

The table shows the response by metastatic site together with the average duration of disease free interval for patients achieving a complete or partial response. The overall response at these sites approached 90%.

Response in metastatic sites

Site	No	No (%) showing complete response	Mean duration (months)	No (%) showing partial response	Mean duration (months)	Overall response (%)
Advanced local disease or lymph node fixity, or both	17	7 (41)	22	8 (47)	6	89
Bone	8	2 (25)	23	6 (75)	5	100
Lung	6	2 (33)	21	3 (50)	7	83
Liver	7	1 (14)	24	5 (71)	6	85

Comment

The results of this study in which women with advanced metastatic breast cancer were treated with three double cycles of sequential hormonochemotherapy are very encouraging. Over 90% of the women showed some degree of objective response. Furthermore, the 16 (47%) patients who obtained a complete response by established criteria[5] had a disease free interval of 22 months. The response to hormonal treatment alone in unselected patients is usually about 30%, which may improve to about 60% in patients selected on the basis of their oestrogen receptor state. The response to chemotherapy may be higher but is usually between 30% and 60%. The disease free interval in patients treated with either hormonal treatment or chemotherapy is usually less than one year.

As hormones and drugs are thought to act by different mechanisms and against different cell populations, we have combined hormonal treatment with chemotherapy. We have not, however, simply used these two forms of treatment in an adjuvant synchronous manner but have attempted to use the hormones in such a way as to bring the stem cells out of their resting phase and make them more susceptible to cytotoxic drugs: hence cyclical sequential hormonochemotherapy.

Our results suggest that using hormonal and cytotoxic treatment in a cyclical sequential combination may significantly improve the response rate compared with using either treatment alone and provides a useful prolongation of life.

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