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Charles F. Babbs

Brief technical note:

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Charles F. Babbs, MD, PhD

Weldon School of Biomedical Engineering, Purdue University
West Lafayette, Indiana 47907-2032, USA E-mail: babbs@purdue.edu
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Abstract

This brief technical note describes a design concept for a low-cost, painless, noninvasive monitor of total placental blood flow during the third trimester of pregnancy. The approach may offer an overlooked solution to a central problem of the human placenta project. A systems level biophysical analysis shows that jets of blood flow emerging from spiral arteries in the placenta generate characteristic 1/f or "pink noise" which is routinely audible, but typically ignored, during fetal phonocardiography. The amplitude of the 1/f noise, recorded at a standardized location in an individual patient, is a measure of total placental blood flow that is potentially useful for monitoring of placental function and better management of third trimester complications such as preeclampsia and maternal diabetes.

Key words: abdominal phonogram, antenatal monitoring, biophysics, fetal cardiotachogram, fetal heart rate, fetal heart sounds, fetal phonocardiogram, fPCG, placental function.

Introduction

The Human Placenta Project is a collaborative research effort sponsored by the U.S. National Institutes of Health to understand the role of the placenta in health and disease. The project supports development of new tools to study the placenta in real time to learn how it functions throughout pregnancy. Ideally such tools would be low cost, noninvasive, and widely applicable. One such tool, which may be hiding in plain sight, is the abdominal phonogram or fetal phonocardiogram (fPCG). The fPCG is a record of the audible sounds recorded from a microphone placed on the maternal abdomen during the antepartum phase (gestational week ≥24)[1,2]. In addition to fetal heart sounds, placental sounds are also routinely heard in pregnant women after 24 weeks gestation and are equally loud[1]. Typically, data processing and analysis of fPCGs focus on the fetus[3,4] and regard the placenta as a source of background noise[2,5]. Here we consider an alternative viewpoint, based on the engineering adage that one person's noise is another person's signal: properly interpreted, placental background noise may be a reliable quantitative indicator of placental blood flow.

[1] These spontaneous, naturally occurring audible sounds are in the range of 10 to 1,000 cycles/sec. They are not the same as the ultrasound generated by piezoelectric transducers in the range of 100,000 to 10,000,000 cycles/sec, and they are also not the same as the synthetic sounds produced by electro-acoustic conversion, when a received ultrasound signal is decoded into audible sound[3].

In the year 1964 South African obstetrician B. G. Beyers[6] eloquently wrote about focusing on placental sounds with an ordinary fetoscope to locate the placenta with good accuracy. He wrote that the "enormous blood mass carried through the uteroplacental circulation causes tremendous … vibrations audible to the examining ear" that were useful "to determine where the placenta was located in the uterus" with a "high degree of certainty". Modern spectral analysis converts an interval of the fPCG from the time domain to the frequency domain by Fourier transformation to better focus on frequencies of the maternal and fetal heartbeats. The frequency spectrum of the background noise in fetal phonocardiography has a broad, 1/f distribution in the shape of a hyperbola, with signal intensity inversely proportional to the frequency[3,5]. This type of noise is called pink noise or colored noise, to distinguish it from white noise that has a uniform distribution in the frequency domain with similarly intense signals over a broad range of frequencies. The swooshing sound of 1/f noise is characteristic of the sound power spectrum resulting from turbulent fluid flow in general, including fluid exiting a nozzle or an orifice in a flat plate[7,8]. The sound pressure level of placental 1/f noise, in particular, is comparable to[9], or often greater[5,8] than that of typical maternal and fetal heart sounds.

The working hypothesis explored here is that the 1/f noise is a direct result of the turbulent flow of blood exiting the spiral arteries of the placenta, and in turn a direct manifestation of total placental blood flow. With proper understanding of the underlying biophysics, it should be possible to record and digitally analyze placental sound to extract a widely applicable measure of placental blood flow, as envisioned by leaders of the Human Placenta Project. The particular objectives of the present investigation are to create and test a simple model of the essential biophysics of sound generation by spiral arteries in the placenta, to relate the intensity of the sound to the amount of placental blood flow, and to define a patient-specific quantitative index of placental function. Such an index would be useful in early detection of preeclampsia, complications of maternal diabetes, small-for-gestational-age babies, and other conditions.

In general, the device design concept imagined here involves future hardware and software to accomplish the following steps: Record the sound pressure level of the fetal phonocardiogram using existing technology, placing the microphone where the placental sound is most prominent in a particular patient. Extract the cardiac signals to get a denoised cardiac signal using standard techniques. Subtract the denoised cardiac signal from the saved raw signal to obtain a time domain noise track, including predominantly placental sounds. Do Fourier transformation on the noise track and look for 1/f pink noise. Remove obvious non-pink noise such as 60 Hz interference from electronic devices. Plot the amplitude of the noise vs. 1/f . The slope of this function should be a figure of merit, which is linearly related to placental blood flow, as shown in the following analytical treatment.

Theory

Table 1: Nomenclature

Variable	Definition	Units
E	Energy of jet of blood exiting one spiral artery in the placenta	Joules
W	Power of jet of blood exiting one spiral artery in the placenta	Watts
L	Length of typical spiral artery	m
r	Inner radius of spiral artery	m
v	Spatial mean velocity of jet of blood exiting one spiral artery	m/sec
Δt	Time increment	sec
m	Mass of blood ejected from spiral artery in time Δt	kg
ρ	Blood density	kg/m^3
μ	Blood viscosity	Pa-sec
N	Total number of spiral arteries in a whole placenta	
i	Blood flow exiting one spiral artery	m^3/sec
i_{tot}	Blood flow exiting N spiral arteries in whole placenta	m^3/sec
ΔP	Spiral artery perfusion pressure (mean arterial pressure minus intervillous pressure in the placenta)	Pa
R	Resistance of one spiral artery to blood flow	$Pa\text{-}sec/m^3$
π	Circle ratio: 3.14159….	
β	Constant of proportionality	

Consider a jet of turbulent blood flow emerging from the end of a spiral artery into the surrounding intervillous space. Here the starting point is the reasonable assumption that sound energy emitted by a jet of turbulent flow during time interval, Δt , is derived from, and proportional to[7], the kinetic energy of the jet, namely

$$E = \frac{1}{2}mv^2 = \frac{1}{2}(\rho \cdot \pi r^2 \cdot v \cdot \Delta t)v^2 \,, \qquad (1)$$

where ρ is blood density, r is the inner radius of the artery, and v is the mean linear velocity of blood flow, which equals the volumetric flow divided by cross sectional area or

$$v = \frac{i}{\pi r^2} = \frac{\Delta P}{R} \cdot \frac{1}{\pi r^2} \,. \qquad (2)$$

Expressing individual spiral artery flow, i , in terms of placental perfusion pressure, ΔP, and vascular resistance, R, of one spiral artery, the jet power, or energy per unit time, is therefore

$$W = \frac{E}{\Delta t} = \frac{1}{2}\left(\rho \cdot \pi r^2 \cdot \frac{\Delta P}{R} \cdot \frac{1}{\pi r^2} \cdot\right)\left(\frac{\Delta P}{R}\right)^2 \frac{1}{\pi^2 r^4} \,. \qquad (3)$$

Next introduce Poiseuille's Law for resistance in the spiral artery (the local "resistance vessel"[10] in this corner of the circulation), namely $R = \frac{8\mu L}{\pi r^4}$, so that

$$\frac{1}{\pi^2 r^4} = \frac{R}{8\pi\mu L}, \tag{4}$$

and in turn,

$$W = \frac{\rho}{2}\left(\frac{\Delta P}{R}\right)^3 \frac{R}{8\pi\mu L} = \frac{1}{16\pi}\left(\frac{\Delta P}{R}\right)^2 \frac{\rho\,\Delta P}{\mu L} = \frac{1}{16\pi}\frac{\rho\,\Delta P}{\mu L}\cdot i^2 . \tag{5}$$

Imagine a sound recording system that produces an output signal, S , that is proportional to the square root of the sound power sensed by the abdominal microphone, so that for lumped empirical constant, β ,

$$S = \beta\sqrt{\frac{\rho\Delta P}{\mu L}}\cdot i , \tag{6}$$

where β is the square root of the small fraction of jet energy converted to sound energy and transmitted to the microphone. Equation (6) states that the output signal, S, is proportional to the individual spiral artery blood flow, i . Now, because the sounds from individual spiral arteries are uncorrelated pink noise, there are no net phase cancellation effects. Hence, for N total spiral arteries in a placental disk roughly centered under the microphone, the combined sound intensity produced by combined flow i_{tot} is

$$S_{tot} \approx \bar{\beta}\sqrt{\frac{\rho\Delta P}{\mu\bar{L}}}\cdot i_{tot} , \tag{7}$$

where $\bar{\beta}$ and $\bar{L}$ represent the average values for the population of N spiral arteries. The dominant term in this expression is the total placental blood flow, i_{tot} . Random individual variations in blood density, blood viscosity, spiral artery length, and physiologically regulated blood pressure (all under the square root sign[2]) would be relatively small. Differences in the individual artery values of β would offset for a microphone centered over the placenta.

[2] If lumped parameter $\theta = \frac{\rho\Delta P}{\mu L}$, and θ_n represents its average normal value of θ, then for a particular patient $\theta = \theta_n + \Delta\theta = \theta_n\left(1 + \frac{\Delta\theta}{\theta_n}\right)$. For the expected small departures from normal, we can use the binomial series expansion $\sqrt{1+\epsilon} \approx 1 + \frac{1}{2}\epsilon$, so that $\theta \approx \theta_n\left(1 + \frac{1}{2}\frac{\Delta\theta}{\theta_n}\right)$, and one would expect the departures from the average normal value to be relatively small, say < 10%, with caveats mentioned in the Discussion.

Discussion

Equation (7) may provide a practical empirical index of total placental blood flow in a particular patient. Although the sampled aggregate signal intensity from the whole placenta, S_{tot} , is not a direct quantitative measure of blood flow in units of ml/min, it may nonetheless have clinical utility as an index for tracking placental blood flow in individual patients in terms of the pattern of progression of sound intensity over time.

As the relative distance of the microphone from the placenta and the relative size of the placenta change during third trimester, some changes in parameter β are to be expected. Further, the placental blood flow itself will increase as the pregnancy matures and the fetus grows. Blood viscosity in pregnant women will be generally be lower than in nonpregnant women on average, owing to hemodilution caused by multiple hormones of pregnancy that results from an increase in red cell mass but an even larger increase in plasma volume. This effect may evolve during the last trimester, changing blood viscosity, μ. However, if the normal time course of changes in the flow index are characterized, then the utility of the index remains. Each individual's chart or curve of blood flow index vs. weeks of pregnancy could be tracked and compared to the normal curve to obtain clinically useful and actionable information.

In human obstetrics, the possibility of reduced placental blood flow is a common concern, with severe consequences, including preeclampsia and intrauterine growth restriction. In cases of pre-eclampsia, pathology does not typically develop until 20 weeks of pregnancy[11], after which placental sounds are audible. One potentially useful signal, therefore, would be a drop in the sonic blood flow index on follow up examinations, either compared to prior measurements for a particular patient or compared to typical normal patients of the same gestational age. Deviations from the expected pattern could be a simple, noninvasive, and timely warning of impending pre-eclampsia. Similarly, the physiology of accelerated placental ageing in cases of maternal diabetes might be detected early in a way that would allow for graceful planning of induced labor, if spontaneous labor has not yet happened. However, if the diabetic mother has a good index of placental blood flow, a preferred spontaneous normal labor could be allowed with less worry. Another potential use for the envisioned technology would be in cases of intrauterine growth restriction, which can develop as a consequence of placental malfunction[12], leading to small-for-gestational-age babies and a large fraction of perinatal deaths[13]. The imagined simple, low cost, and noninvasive monitor of changes in placental blood flow could provide early detection and better clinical management of these and other conditions.

Even at this conceptual stage, however, important caveats are worth consideration, especially those leading to false negative test results. One important caveat is that if in pre-eclampsia spiral artery length is reduced, and simultaneously, blood pressure is increased; then there could be a compounded increase in the lumped constant, $\sqrt{\frac{\rho\Delta P}{\mu \bar{L}}}$, and therefore a falsely high placental flow index. Another uncommon mechanism, perhaps leading to a falsely normal signal, could occur with arterial venous malformations within the uterine wall, which if suspected, could be demonstrated by ultrasonography[14]. Such complexities of human pathology warrant careful consideration in future work.

Nevertheless, follow-on research in computational models, in physical models, and in animal models is justified. In the right technical hands, the theoretical insights presented here could be readily translated into working prototype systems for animal and human testing, with a relatively short journey from bench to bedside.

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